Articles

Boron Analogs of Phenylalanine, Valine, Leucine, and Isoleucine: Syntheses of Amine–Alkyl[(ethylimino)alkoxymethyl]boranes

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A series of amine–alkyl[(ethylimino)alkoxymethyl]boranes (alkyl = *i*-Pr, *i*-Bu, *s*-Bu, and benzyl; alkoxy = MeO, EtO, and benzyl–O) were synthesized by two different methods. The first method consisted of reacting an (amine–alkyl(*N*-ethylcarbamoyl)borane with an excess of Et_3OBF_4 in CH_2Cl_2, followed by deprotonation of the resulting amine–alkyl[(ethyliminiumylidene)ethoxymethyl]borane tetrafluoroborate with aqueous sodium hydroxide. In one case the intermediate amine–alkyl[(ethyliminiumylidene)alkoxymethyl]borane tetrafluoroborate was stable enough to be fully characterized. The second more direct method involved reacting an amine–alkyl[(ethylnitrilio)methyl]-borane tetrafluoroborate with a sodium alkoxide in alcohol.

Introduction

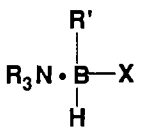
In 1968 Borch reported the conversion of organic alkylamides to *C*-ethoxy imino ethers by reaction of the parent amide with Et_3OBF_4, followed by deprotonation of the intermediate iminium salt with aqueous base.[1] These imino ethers were shown to hydrolyze to the ethyl ester upon prolonged exposure to moisture. In 1989 Mittakanti and Morse reported that the reaction of $[(pyridine)\cdot BH_2C{\equiv}NEt]BF_4$ with MeOH over a 24-h period yielded the corresponding *N*-ethyl, *C*-methoxy iminium salt. Upon workup with aqueous base the free imino ether, $(pyridine)\cdot BH_2C(OMe){=}NEt$, was obtained.[2] No *B*-alkyl versions of these species have been reported to date. Following our development of a convenient high-yield synthesis of amine–alkylcyanoboranes[3] and amine–alkyl(*N*-ethylcarbamoyl)boranes,[4] we have investigated the synthesis of *B*-alkyl iminoboranes. Two new rapid methods of synthesis of imino ethers containing the –RBH– moiety were developed, the second of which saves a substantial amount of time over the method of Mittakanti and Morse.[2] This paper summarizes the isolation and full characterization of representative iminoboranes with several different alkyl side chains, as illustrated in Scheme I, as well as a study of some chemical properties of these interesting imino ether derivatives.

Experimental Section

Techniques. Unless otherwise noted, all reactions were performed under an atmosphere of N_2 using methods described by Brown[5] and Shriver.[6] Nitrogen gas was dried by passage through a glass column 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).[7] 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[8] using 230–400-mesh silica gel (Aldrich 60 Å or Merck grade 60).

Reagents. Triethyloxonium tetrafluoroborate was synthesized according to the Meerwein protocol.[9] 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.

Scheme I



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

1. R' = benzyl 2. R' = *i*Bu 3. R' = *i*Pr 4. 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

(1) (a) Borch, R. F. *Chem. Commun.* **1968**, 442. (b) Borch, R. F. *Tetrahedron Lett.* **1968**, 61.
(2) (a) Morse, K. W.; Mittakanti, M. *Abstr. Pap.—Am. Chem. Soc.* **1989**, *197*, INOR 144. (b) Morse, K. W.; Mittakanti, M. *Inorg. Chem.* **1990**, *29*, 554.
(3) Mills, W. J.; Sutton, C. H.; Libby, E.; Todd, L. J. *Inorg. Chem.* **1990**, *29*, 302.
(4) Mills, W. J.; Sutton, C. H.; Baize, M. W.; Todd, L. J. *Inorg. Chem.* **1991**, *30*, 1046.
(5) Brown, H. C. *Organic Synthesis via Boranes*; Wiley and Sons: New York, 1975.
(6) Shriver, D. F. *The Manipulation of Air-Sensitive Compounds*; McGraw-Hill: New York, 1969.
(7) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon: Oxford, U.K., 1980.
(8) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(9) Meerwein, H. *Org. Synth.* **1966**, *46*, 113.

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Alcohols used as reactants were fractionally distilled from over calcium hydride or sodium alkoxide generated in situ by addition of elemental sodium to the alcohol prior to distillation.[7] In some syntheses anhydrous methanol was used as purchased.

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 ($I_{[^{11}B]} = 3/2$; $I_{[^{10}B]} = 3$) 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, *206.0, 29.8*; chloroform-d, *77.0*.

Other Characterization Techniques. Infrared spectra were recorded in inverse centimeters 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.[10] 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–Benzyl[(ethyliminiumylidene)ethoxymethyl]borane Tetrafluoroborate (1d). Carbamoylborane **1c** (100 mg, 0.40 mmol) and Et_3OBF_4 (0.13 g, 0.67 mmol) were combined under N_2. Dry CH_2Cl_2 (0.40 mL) was added by syringe. The resulting solution was stirred at room temperature for 24 h. Afterward the organic solution was stirred with an aqueous buffer (pH 3.0, 0.40 mL) and ethylene glycol (0.40 mL) for 96 h in an unsuccessful attempt to hydrolyze the product to an acid or ester derivative. The homogeneous mixture was then washed with $CHCl_3$ (3 × 1 mL). These combined extracts were dried ($MgSO_4$) and evaporated to give a solid (90.0 mg, 56.0%). Recrystallization from warm $CHCl_3$ and hexane yielded small, flocculent needles (60.0 mg, 37.3%): mp 154–154.5 °C; ^{11}B NMR (CD_3CN) δ –0.62 (s, BF_4^-), –5.64 (d, J = 90 Hz); ^1H NMR (CD_3CN) δ 8.71 (v br N–H), 7.15 and 7.02 (m, J = 7.54 and 7.44 Hz, Ph–H), 4.35 (complex m, –O–CH_2–CH_3), 3.46 and 3.26 (septet, m, J = 6.93, complex Hz, diastereotopic =NH–CH_2–CH_3), 3.11 and 3.00 (2d order m, diastereotopic N–[CH_2]$_3$–), 2.23 (br dist m, B–CH_2–Ph), 2.01 (septet, J = 3.29 Hz, HC–[CH_2]$_3$–), 1.80 (td, J = 7.77, 3.29 Hz, HC–[CH_2]$_3$–), 1.09 (t, J = 7.30 Hz, =NH–CH_2–CH_3), 0.94 (t, J = 7.06 Hz, –O–CH_2–CH_3); ^{13}C NMR (CD_3CN) δ 1.97 (v br, B–C(=NH$^+$)–O–), 144.04 (–CH_2–C[Ph]), 129.65 (*m*-Ph–C), 128.99 (*o*-Ph–C), 125.00 (*p*-Ph–C), 70.93 (–O–CH_2–CH_3), 52.34 (N–[CH_2]$_3$–), 38.11 (=NH–CH_2–CH_3), 25 (v br, B–CH_2–Ph), 24.77 (HC–[CH_2]$_3$–), 20.55 (HC–[CH_2]$_3$–), 14.98 and 13.54 (–CH_2–CH_3); IR (KBr) ν_{max} 3330 m (=N(Et)–H$^+$), 3020 (m), 2980 (s) (alkyl C–H), 2940 (s), 2880 (m), 2420 (m) (B–H), 1605 (s) (B–C(OEt)=NHEt$^+$), 1325 (m), 1070 (vs br) (BF_4^-), 755 (m), 700 (m), 520 (m) cm^{-1}. Anal. Calcd for $C_{19}H_{32}B_2F_4N_2O$: C, 56.75; H, 8.02; N, 6.97. Found: C, 56.73; H, 8.14; N, 6.80.

Quinuclidine–Benzyl[(ethylimino)ethoxymethyl]borane (1f). The iminium ether salt **1d** (35 mg, 0.087 mmol) in $CHCl_3$ (0.5 mL) was vigorously stirred in aqueous NaOH (1 N × 0.5 mL) for 2 h. The organic layer was separated, and the aqueous layer was washed with fresh $CHCl_3$ (3 × 0.5 mL). The combined organic layers were dried (Na_2CO_3) and evaporated to give a colorless, crystalline solid (20 mg, 0.063 mmol, 73.1%): ^{11}B NMR ($CDCl_3$) δ –5.79 (br d); ^1H NMR ($CDCl_3$) δ 7.09 (t, J = 7.52 Hz, *m*-Ph–H), 7.00 (d, J = 6.86 Hz, *o*-Ph–H), 6.92 (t, J = 7.20 Hz, *p*-Ph–H), 3.97 and 3.91 (dq, dq, J_{gem} = 17.65, 17.66 Hz, $J_{H-C-C-H}$ = 7.14, 7.07, 7.03, and 7.33 Hz, diastereotopic –O–CH_2–CH_3), 3.26 and 2.93 (complex multiplets, diastereotopic N–[CH_2]$_3$–), 3.069 and 3.064 (nearly coincident q, q {other expected quartets not observed due to quinuclidine signals} J = 7.23, 7.17 Hz, diastereotopic =N–CH_2–CH_3), 1.97 (septet, J = 3.17 Hz, HC–[CH_2]$_3$–), 1.90 (br distorted m, B–CH_2–Ph), 1.70 (td, J = 7.86, 3.03 Hz, HC–[CH_2]$_3$–), 1.26 (t, J = 7.07 Hz, –O–CH_2–CH_3), 0.63 (t, J = 7.22 Hz, =N–CH_2–CH_3); ^{13}C NMR ($CDCl_3$) δ 180.1 (br, B–C(=N–)–O–), 146.64 (–CH_2–C[Ph]), 128.53 (*m*-Ph–C), 127.50 (*o*-Ph–C), 122.80 (*p*-Ph–C), 57.35 (–O–CH_2–CH_3), 50.61 (N–[CH_2]$_3$–), 43.50 (=N–CH_2sbdCH_3), 26.96 (br, B–CH_2–Ph), 24.75 (HC–[CH_2]$_3$–), 20.41 (HC–[CH_2]$_3$–), 16.88 (=N–CH_2–CH_3), 14.97 (–O–CH_2–CH_3); IR (NaCl) ν_{max} 3023 (m) (aryl C–H stretch), 2965 (vs) (alkyl C–H stretch), 2940 (s, sh), 2878 (s), 2396 (m) (B–H stretch), 1624 (vs) (–C=N–), 1599 (s sh) (aryl distortion) 1493 (m), 1464 (s), 1451 (s), 1167 (vs), 1119 (s), 1114 (s), 1092 (s), 1034 (vs), 831 (s), 816 (s), 737 (vs), 700 (s) cm^{-1}; HRMS (+CI, NH_3) 315.2619/214.1751 (M^+ + H calcd for $C_{19}H_{32}{}^{11}BN_2O$, 315.2608/M^+ – –C(=NEt)–OEt calcd for $C_{14}H_{21}{}^{11}BN$, 214.1767).

Quinuclidine–Isobutyl[(ethylimino)ethoxymethyl]borane (2f). Freshly recrystallized amide **2c** (0.510 g, 2.02 mmol) was dissolved in 2 mL of CH_2Cl_2 and added to 0.774 g (4.08 mmol) Et_3OBF_4, followed by two more 1-mL rinses via cannula, for a total volume of 4 mL. This was allowed to react according to the above procedure for 30 h. Darkening upon exposure to ambient light was observed along with some accompanying decomposition. Subsequently, the reaction vessel was wrapped in aluminum foil for the duration of the alkylation. Upon extractive workup, discolored crystalline material (0.595 g, 1.93 mmol), presumably the iminium salt, was isolated. By infrared analysis, the reaction was complete; the amide carbonyl stretching absorbance (1580 cm^{-1}) had been replaced by a slightly narrower absorbance at 1605 cm^{-1}, assigned to the iminium C=N stretch. This salt was not characterized but was dissolved in a homogeneous mixture of 2 mL of acetonitrile and 2.0 mL of 1.0 N aqueous NaOH. This was allowed to stir for 2 h, during which time the reaction reached completion. A yellowish oil was isolated (0.487 g, 1.74 mmol, 85.8%) that solidified to crystalline material overnight in a freezer (–15 °C). This remained solid upon warming to room temperature. Infrared analysis revealed that a new band had appeared at 1620 cm^{-1} and that nearly all N–H associated bands (these were present with the iminium salt, except shifted somewhat relative to the amide values) were no longer present. A ^{11}B NMR (THF) spectrum of this material revealed that the tetrafluoroborate peak was no longer present and a new resonance (–6.9 ppm, d, J = 66.7 Hz) was present. There was a small resonance (approximately 5%) due to some unreacted ethylamide. Spectroscopic and characterization data were identical to that of the purer *C*-ethoxy, *N*-ethyl imino ether obtained by direct attack of ethoxide on the nitrilium salt and are summarized below in that section.

Quinuclidine–Isopropyl(*N*-ethylcarbamoyl)borane (3c). Unpurified solid **3b** (0.654 g, 2.12 mmol) was dissolved in 2.5 mL of MeCN and reacted with 2.5 mL of 1.0 N aqueous NaOH by the general procedure.[4] After 40 h, the reaction was worked up to afford a faintly yellowish oil (0.460 g). This was shown by ^{11}B NMR analysis to consist of about 2% starting cyanoborane and 98% amide. This was flash chromatographed (e.g., 100 g, R_f = 0.57, THF; 0.19, EtOAc) and a colorless oil was obtained that solidified (0.288 g, 1.21 mmol, 57%) upon cooling (–15 °C) to long needlelike crystals which remained solid at room temperature: ^{11}B NMR (CH_2Cl_2) δ –0.85 (br d, J = 83.5 Hz); ^1H NMR ($CDCl_3$) δ 5.58 (br s, C(=O)–NH–, 1 H), 3.39 and 2.98 (2d order multiplets, diastereotopic N–[CH_2]$_3$–, 6 H), 3.31 and 3.12 (2d order multiplets, J = 6.0, 5.8 Hz, diastereotopic NH–CH_2–CH_3, 2 H), 1.94 (br septet, J = 2.4 Hz, HC–[CH_2]$_3$–, 1 H), 1.69 (2d order multiplet, HC–[CH_2]$_3$–), 1.05 (t, J = 7.22 Hz, NH–CH_2–CH_3), 0.89 and 0.76 (br d, s, J = 4.12, 0 Hz, diastereotopic B–CH–[CH_3]$_2$), ca. 0.84 (br {nearly obscured}, BH–CH–[CH_3]$_2$); ^{13}C NMR ($CDCl_3$) δ 195 (br, B–C(=O)–NH–), 51.2 (N–[CH_2]$_3$–), 31.3 (NH–CH_2–CH_3), 25.2 and 21.6 (diastereotopic –CH–[CH_3]$_2$), 24.3 (HC–[CH_2]$_3$–), 20.1 (HC–[CH_2]$_3$–), 15.2 (NH–CH_2–CH_3), 14.7 (br, BH–CH–[CH_3]$_2$); IR (neat, NaCl) ν_{max} 3435 (m sh), 2935 (s), 2875 (ms), 2855 (ms), 2302 (m), 1585 (s) (–C(=O)–), 1475 (s), 1460 (s), 1372 (w m), 1348 (w m), 1314 (w m), 1279 (w m), 1260 (w), 1204 (m), 1127 (w), 1090 (m), 1030 (ms), 1004 (w), 975 (m), 902 (w), 836 (m), 810 (m sh) cm^{-1}; HRMS (+CI, CH_4), 237.2155 (M^+ – H calcd for $C_{13}H_{26}{}^{11}BN_2O$, 237.2138).

Quinuclidine–Isopropyl[(ethylimino)ethoxymethyl]borane (3f). Freshly prepared **3c** (0.19 g, 0.80 mmol) was dissolved in dry CH_2Cl_2 (5 mL),

(10) Durkin, T.; DeHayes, L.; Glore, J. *J. Chem. Educ.* **1971**, *48* (7), 452.
(11) Mills, W. J. The Synthesis of Alkylcyano-, Alkylcarbamoyl-, and Alkylimino- Boranes: Analogs of Amino Acids Derivatives. Doctoral Dissertation, Indiana University, February 1989.

and the solution was transferred by cannula to a N_2-purged round-bottomed flask which contained Et_3OBF_4 (0.18 g, 0.96 mmol). This was allowed to react for 24 h until all signs of starting material had disappeared by infrared. A new band (1605 cm^{-1}) signaled the appearance of the iminium salt. A crystalline solid was isolated by extractive workup. This solid was briefly exposed to aqueous NaOH and reextracted to yield a yellowish-white crystalline material. The entire mass was recrystallized from $CHCl_3$/hexane to yield white crystals (0.11 g, 0.41 mmol, 52%): mp 60–61.5 °C; ^{11}B NMR (CH_2Cl_2) δ −3.83 (d, J = 68.6 Hz); ^1H NMR ($CDCl_3$) δ 3.94 and 3.89 (nearly coincident dq, dq, J_{gem} = 17.59, 17.64 Hz, $J_{H-C-C-H}$ = 7.09, 7.06, 7.04, 7.13 Hz, diastereotopic –O—CH_2—CH_3), 3.45 and 3.36 (dq, dq, J_{gem} = 11.85, 12.17 Hz, $J_{H-C-C-H}$ = 7.26, 7.18, 7.23, 7.30 Hz, diastereotopic =N—CH_2—CH_3), 3.31 and 2.94 (complex 2d order multiplets, diastereotopic N—[CH_2]$_3$–), 1.95 (septet, J = 3.16 Hz, –[CH_2]$_3$—CH), 1.69 (td, J = 7.7, 3.0 Hz, –[CH_2]$_3$—CH), 1.19 (t, J = 7.07 Hz, –O—CH_2—CH_3), 1.04 (t, J = 7.23 Hz, =N—CH_2—CH_3), 0.89 (2d order m, J = 3.0 Hz, half of diastereotopic –CH—[CH_3]$_2$), 0.73 (s, coincident other half diastereotopic –CH—[CH_3]$_2$, and –CH—[CH_3]$_2$); ^{13}C NMR ($CDCl_3$) δ 181.1 (br, B—C(=N–)—O–), 56.92 (–O—CH_2—CH_3), 50.45 (N—[CH_2]$_3$–), 43.84 (=N—CH_2—CH_3), 24.81 (HC—[CH_2]$_3$–), 24.99 and 22.38 (diastereotopic –CH—[CH_3]$_2$), 20.50 (HC—[CH_2]$_3$–), 17.49 (=N—CH_2—CH_3), 15.4 (br, B—CH—[CH_3]$_2$), 14.90 (–O—CH_2—CH_3); IR (KBr) ν_{max} 2950 (s) (alkyl C—H), 2842 (m), 2360 (m) (B—H), 1620 (ms) (–C=N–), 1455 (m), 1260 (s), 1164 (m), 1090 (s) cm^{-1}. Anal. Calcd for $C_{15}H_{31}N_2BO$: C, 67.42; H, 12.07. Found: C, 67.54; H, 11.87.

Quinuclidine–Isobutyl[(ethylimino)methoxymethyl]borane (2e). Clean quinuclidine–isobutyl[(ethylnitrilio)methyl]borane tetrafluoroborate (**2b**) (0.966 g, 3.00 mmol) was reacted with 0.103 g of Na (4.50 mmol) dissolved in 4.5 mL of anhydrous MeOH. Precipitate appeared approximately 5 s after addition of the first portion of **2b**. This reaction mixture was allowed to stir for 22 h before workup. The methanol was removed under vacuum, and the residues were treated with 10 mL of water. The aqueous mixture was extracted six times with 5 mL of CH_2Cl_2 and the extracts were dried over Na_2CO_3. After evaporation of the CH_2Cl_2, the colorless oil solidified to an oily crystalline mass (0.767 g, 2.88 mmol, 96%) when cooled in a freezer (–15 °C). This was recrystallized from pentane at –15 °C to produce large colorless crystals: mp 48–50 °C; ^{11}B NMR (CH_2Cl_2) δ −7.07 (br d, J = 71.9 Hz); ^1H NMR ($CDCl_3$) δ 3.48 (s, resonance superimposed over N-methylene multiplet –O—CH_3), 3.51, 3.45 (exactly centered partially obscured resonance {average 3.48} dq, dq, J_{gem} = 11.6, 12.0 Hz, $J_{H-C-C-H}$ = 7.25, 7.45, 7.30, 7.28 Hz, diastereotopic =H—CH_2—CH_3), 3.15 and 2.86 (complex 2d order multiplet, diastereotopic N—[CH_2]$_3$–), 1.94 (septet, J = 3.17 Hz, HC—[CH_2]$_3$–), 1.68 (td, J = 7.89, 3.07 Hz, HC—[CH_2]$_3$–), 1.28 (septet of t, J = 6.51, 2.15 Hz, –CH_2—CH—[CH_3]$_2$), 1.06 (t, J = 7.24 Hz, =N—CH_2–CH_3), 0.81 (d, J = 6.46 Hz, –CH—[CH_3]$_2$), 0.46 and 0.13 (2d order septets, diastereotopic BH—CH_2—CH–); ^{13}C NMR (acetone-d_6) δ 180.8 (br, B—C(=N–)—O–), 51.21 (N—[CH_2]$_3$–), 49.45 (–O—CH_3), 44.30 (=N—CH_2—CH_3), 28.2 (br, B—CH_2—CH–), 27.52 and 25.25 (diastereotopic –CH—[CH_3]$_2$), 27.47 (–CH_2—CH—[CH_3]$_2$), 25.21 (HC—[CH_2]$_3$–), 21.29 (HC–[CH_2]$_3$–), 18.17 (=N—CH_2—CH_3); IR (KBr) ν_{max} 2958 (ms), 2932 (vs), 2862 (s), 2796 (m) (C—H), 2396 (m), 2356 (mw) (B—H), 1623 (vs) (–C=N–), 1466 (s), 1416 (w), 1370 (mw), 1363 (w), 1354 (mw), 1336 (w), 1325 (wm), 1313 (mw), 1244 (m), 1206 (m), 1170 (s), 1144 (ms), 1128 (m), 1111 (ms) 1083 (mw), 1059 (mw), 1031 (ms), 1003 (ms), 975 (mw), 915 (mw), 909 (m), 895 (w), 825 (s), 810 (ms), 697 (mw), 644 (w) cm^{-1}; HRMS (+CI NH_3) 267.2589 (M^+ + H, calcd for $C_{15}H_{32}{}^{11}BN_2O$, 267.2607). Anal. Calcd for $C_{15}H_{31}N_2BO$: C, 66.14; H, 12.29. Found: C, 67.78; H, 11.81.

Quinuclidine–Isopropyl[(ethylimino)methoxymethyl]borane (3e). Crystalline **3b** (0.62 g, 2.0 mmol) was reacted with 0.069 g of Na (3.0 mmol) dissolved in 3.0 mL of MeOH. Precipitate appeared less than 2 s after **3b** was added as a powder to the reaction mixture. The reaction was allowed to continue for 14 h before being worked up as described for **2e** to afford a colorless oil which rapidly solidified to a slightly oily crystalline mass (0.49 g, 1.96 mmol, 98%). A portion of this was recrystallized from cold pentane (–15 °C) over a 3-week period to yield large white translucent crystals: mp 52–53 °C; ^{11}B NMR (CH_2Cl_2) δ −3.62 (d, J = 85.75); ^1H NMR ($CDCl_3$) δ 3.49 (s, –O—CH_3), 3.46 and 3.42 (partially obscured dq, dq, J_{gem} = 12.1, 12.0 Hz, $J_{H-C-C-H}$ = 7.30, 7.32, diastereotopic =N—CH_2—CH_3), 3.28 and 2.92 (complex 2d order multiplets, diastereotopic N—[CH_2]$_3$–), 1.95 (2d order septet, HC—[CH_2]$_3$–), 1.70 (2d order td, HC—[CH_2]$_3$–), 1.06 (t, J = 7.22 Hz, =N—CH_2—CH_3), 0.90 and 0.71 (d, br s, J = 6.65, 0 Hz, diastereotopic –CH—[CH_3]$_2$), 0.73 (partially obscured 2d order multiplet, BH—CH—[CH_3]$_2$); ^{13}C NMR ($CDCl_3$) δ 180.9 (br, B—C(=N–)—O–), 50.47 (N—[CH_2]$_3$–), 49.10 (–O—CH_3), 43.72 (=N—CH_2—CH_3), 24.95 and 22.42 (diastereotopic –CH—[CH_3]$_2$), 24.72 (HC—[CH_2]$_3$–), 20.38 (HC—[CH_3]$_2$), 17.45 (=N—CH_2—CH_3), 15.51 (br, B—CH—[CH_3]$_2$); IR (KBr) ν_{max} 2950 (ms), 2932 (s), 2895 (m), 2875 (m), 2851 (ms) (C—H), 2370 (ms) (B—H), 1624 (s) (–C=N–), 1461 (s), 1374 (mw), 1354 (w), 1339 (mw sh), 1313 (mw), 1289 (w), 1261 (m), 1207 (m), 1171 (s), 1165 (s), 1137 (mw), 1110 (m), 1091 (m), 1071 (w), 1043 (mw), 1032 (ms), 1019 (mw), 999 (ms sh), 972 (w), 912 (ms), 831 (ms), 813 (ms sh), 742 (w), 699 (w), 572 (w) cm^{-1}. Anal. Calcd for $C_{14}H_{29}N_2BO$: C, 65.01; H, 12.17. Found: C, 66.96; H, 11.79.

Quinuclidine–*sec*-Butyl[(ethylimino)methoxymethyl]borane (4e). Clean solid **4b** (1.606 g, 4.99 mmol) was reacted with 0.174 g of sodium (7.59 mmol) dissolved in 7.5 mL of anhydrous methanol for 4 h. After workup as described for **2e**, a colorless oil was obtained which solidified at –15 °C and remained solid upon warming to room temperature (1.085 g, 4.26 mmol, 85%): ^{11}B NMR (CH_2Cl_2) δ −3.62, −4.28 (br d, d, diastereomers); ^1H NMR ($CDCl_3$) δ 3.475 and 3.470 (diastereomeric –O—CH_3), 3.45 and 3.40 (partly obscured complex 2d order pattern, diastereotopic and diastereomeric =N—CH_2—CH_3), 3.264 and 2.914 (complex 2d order pattern, diastereotopic N—[CH_2]$_3$–), 1.942 (septet, J = 3.10 Hz, HC—[CH_2]$_3$–), 1.684 (td, J = 7.71, 2.89 Hz, HC—[CH_2]$_3$–), 1.38, 1.09, ca. 0.85 (complex multiplets, diastereomeric and diastereotopic CH_3—CH—CH_2–), 1.040 and 1.036 (t, t, J = 7.17, 7.11 Hz, diastereomeric =N—CH_2—CH_3), 0.9–0.7 (complex t, t, d, diastereomeric CH_3—CH—CH_2—CH_3), 0.446 (br 2d order multiplet, BH—CH–); ^{13}C NMR ($CDCl_3$) δ 181.4 (br, B—C(=N–)—O–), 50.3 (N—[CH_2]$_3$–), 49.07 and 48.93 (diastereomeric –O—CH_3), 43.56 and 43.51 (diastereomeric =N—CH_2–CH_3), 30.68 and 27.91 (diastereomeric –CH—CH_2—CH_3), 24.66 (HC—[CH_2]$_3$–), 23.06 (CH_3—CH–CH_2–), 20.36 (HC—[CH_2]$_3$–), 20.19 and 18.57 (diastereomeric (BH—CH—CH_3), 17.39 and 17.35 (diastereomeric =N—CH_2—CH_3), 13.484 (CH—CH_2—CH_3); IR ν_{max} 2920 (vs), 2850 (s), 2380 (ms), 2295 (m) (B—H), 1625 (vs) (–C=N–), 1467 (s), 1373 (m), 1345 (s sh), 1320 (m), 1286 (m), 1240 (ms), 1212 (ms), 1170 (vs), 1120 (s), 1088 (s), 1038 (ms), 1088 (ms), 980 (m), 922 (ms), 832 (s), 820 (ms sh), 701 (m), 588 (m) cm^{-1}; HRMS (+CI, CH_4) 267.2597 (M^+ + H calcd for $C_{15}H_{32}{}^{11}BN_2O$, 267.2607).

Pyridine–*sec*-Butyl[(ethylimino)methoxymethyl]borane (4e′). Recently prepared **4b′** (2.8677 g, 9.8913 mmol) was reacted with 0.285 g of sodium (12.4 mmol) dissolved in 12.0 mL of methanol in a 25-mL three-necked flask for 20 min before being worked up. Infrared analysis indicated a completed reaction. Using the workup procedure described for **2e**, a dark yellow oil (2.020 g, 8.62 mmol, 87%) was obtained which remained liquid at –15 °C: ^{11}B NMR (CH_2Cl_2) δ −3.47 (d, J = 78.3 Hz); ^1H NMR ($CDCl_3$) δ 8.706 (d, J = 5.79 Hz, *o*-pyr—H), 7.948 (t, J = 7.68, *p*-pyr—H), 7.508 (t, J = 6.32 Hz, *m*-pyr—H), 3.49 (complex 2d order multiplet, diastereomeric and diastereotopic =N—CH_2—CH_3), 3.454 and 3.448 (s, s diastereomeric –O—CH_3), 1.33, 1.2, 1.1 (complex br multiplets, diastereomeric and diastereotopic B—CH—CH_2–), 1.028 (t, J = 7.68 Hz, =N—CH_2—CH_3), 0.97–0.69 (complex multiplets, diastereomeric CH_3—CH—CH_2—CH_3), 0.61 (br multiplet, BH—CH–), 0.481 (d, J = 5.16 Hz, diastereomeric B—CH—CH_3); ^{13}C NMR ($CDCl_3$) δ 181.0 (br, B—C(=N–)—O–), 146.8 and 146.6 (diastereomeric *o*-pyr—C), 139.9 (*p*-pyr—C), 124.9 (*m*-pyr—C), 50.0 (–O—CH_3), 43.3 (=N—CH_2—CH_3), 28.0 (br, BH—CH–), 27.5 and 27.3 (diastereomeric –CH—CH_2—CH_3), 17.4 (=N—CH_2—CH_3), 16.5 (BH—CH—CH_3), 13.0 (CH—CH_2—CH_3); IR (NaCl) ν_{max} 3125 (w), 3110 (w), 3083 (2), 3055 (mw), 2930 (vs), 2865 (s), 2383 (ms) (B—H), 1627 (s) (–C=N–), 1491 (m), 1466 (s), 1372 (m), 1343 (m), 1257 (m), 1216 (m sh), 1180 (vs), 1140 (ms), 1120 (s), 1090 (vs), 1052 (ms), 1021 (ms), 1003 (ms), 957 (mw), 919 (m), 778 (ms), 770 (m), 728 (m), 693 (ms), 649 (w) cm^{-1}; HRMS (+CI, CH_4) 235.2003 (M^+ + H calcd for $C_{13}H_{24}{}^{11}BN_2O$, 235.1981).

Quinuclidine–Isobutyl[(ethylimino)ethoxymethyl]borane (2f). Solid quinuclidine–isobutyl[(ethylnitrilio)methyl]borane tetrafluoroborate (**2b**) (0.381 g, 1.18 mmol) was reacted with sodium (0.059 g, 2.57 mmol), dissolved in 2.4 mL of ethanol in a reaction vial, for 7 h before isolation by the procedure described for **2e**. A colorless oil was obtained which slowly solidified in a freezer (–15 °C) to colorless oily crystals (0.29 g, 1.03 mmol, 87%), which did not remelt upon warming to room temperature (25 °C). Another reaction was run with 0.156 g (0.485 mmol) of **2b**, 0.05 g of Na, and 2 mL of EtOH for only 2 min. The recovered **2f** in this case was 90% imino ether by ^{11}B NMR and 10% amide **2c** upon aqueous workup. This second recovered oil (0.1165 g, 0.415 mmol, 85.7%) also

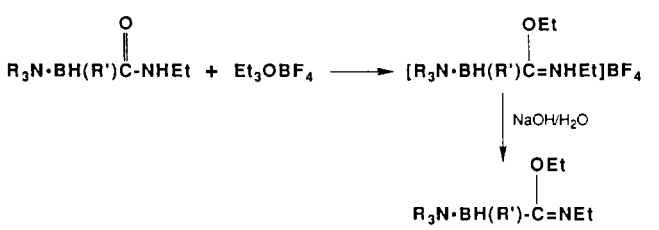
solidified on cooling: ^{11}B NMR (THF) δ −6.9 (br d, J = 66.7 Hz); ^{11}B NMR (CH_2Cl_2) δ −7.17 (br d, J = 68.5 Hz); ^{1}H NMR ($CDCl_3$) δ 3.88 (q, J = 7.04 Hz, –O—CH_2—CH_3), 3.46, 3.40 (dq, dq, J_{gem} = 11.81, 11.78 Hz, $J_{H-C-C-H}$ = 7.30, 7.29, 7.24, 7.24 Hz, diastereotopic =N—CH_2—CH_3), 3.15 and 2.83 (complex multiplets, diastereotopic N—[CH_2]$_3$–), 1.91 (septet, J = 3.17 Hz, HC—[CH_2]$_3$–), 1.65 (td, J = 7.9, 3.03 Hz, HC—[CH_2]$_3$–), 1.24 (complex multiplet, –CH_2—CH—[CH_3]$_2$), 1.14 (t, J = 7.05 Hz, –O—CH_2—CH_3), 1.01 (t, J = 7.25 Hz, =N—CH_2—CH_3), 0.78 (d, J = 6.50 Hz, –CH—[CH_3]$_2$), 0.46 and 0.09 (2d order septets, diastereotopic BH—CH_2—CH–); ^{13}C NMR ($CDCl_3$) δ 181.3 (br, B—*C*(=N–)—O–), 56.82 (–O—CH_2—CH_3), 50.17 (N—[CH_2]$_3$–), 43.63 (=N—CH_2—CH_3), 28.05 (br, B—CH_2—CH–), 26.83 and 24.71 (diastereotopic –CH—[CH_3]$_2$), 26.41 (–CH_2—CH—[CH_3]$_2$), 24.59 (HC—[CH_2]$_3$–), 20.26 (H*C*—[CH_2]$_3$–), 17.39 (=N—CH_2—CH_3), 14.65 (–O—CH_2—CH_3); IR (NaCl) ν_{max} 2935 (s), 2865 (s), 2807 (m) (C—H), 2393 (ms) (B—H), 1625 (s) (–C=N–), 1480 (m sh), 1465 (s), 1378 (ms), 1358 (m sh), 1340 (m sh), 1327 (mw sh), 1316 (m sh), 1283 (m), 1250 (ms), 1228 (m), 1208 (ms), 1170 (s), 1111 (s), 1087 (ms), 1028 (s), 979 (ms sh), 946 (m), 894 (ms), 830 (s), 817 (ms), 777 (w), 696 (w) cm^{-1}; HRMS (+CI, CH_4) 281.2766 (M^+ + H calcd for $C_{16}H_{34}{}^{11}BN_2O$, 281.2764).

Quinuclidine–Isobutyl[(ethylimino)(benzyloxy)methyl]borane (2g). Purified solid **2b** (3.23 g, 10.04 mmol) was placed under dynamic vacuum for 10 min to dry prior to use. Dried benzyl alcohol (10 mL) was placed in a reaction vial with a magnetic stirrer. Elemental Na (0.36 g, 15.9 mmol) was added and allowed to react to completion. The nitrilium salt was added in one portion as a solid which rapidly dissolved. The reaction mixture became cloudy after about 10 s and a white precipitate fell out of solution over 5 min. After 2 h the reaction mixture was added to water in an attempt to separate the benzyl alcohol from **2g**. After six extractions with CH_2Cl_2 from water, the imino ether was still significantly contaminated with benzyl alcohol. This mixed product was purified by flash chromatography on silica gel (R_f = 0.0–0.1, THF), and **2g** was eluted with the ethyl acetate fraction; a later fraction included the (*N*-ethylcarbamoyl)borane **2c**, accounting for the majority of the remaining boron. A colorless crystalline solid material was isolated (1.63 g, 4.76 mmol, 47.4%), part of which was recrystallized from pentane (–15 °C) over 1 h to produce analytical quality crystals (0.295 g, 0.862 mmol, 8.6%): mp 82–84 °C; ^{11}B NMR (CH_2Cl_2) δ −7.12 (br d, J = 70.0 Hz); ^{1}H NMR ($CDCl_3$) δ 7.40–7.22 (complex m, Ph—*H*), 5.04 and 4.95 (d, d, J_{gem} = 12.94, 12.96 Hz, diastereotopic –O—CH_2—Ph), 3.60 and 3.51 (dq, dq, J_{gem} = 11.83, 11.83 Hz, $J_{H-C-C-H}$ = 7.22, 7.27, 7.22, 7.21 Hz, diastereotopic =N—CH_2—CH_3), 3.18 and 2.89 (complex multiplets, diastereotopic N—[CH_2]$_3$–), 1.93 (septet, J = 3.13 Hz, *H*C—[CH_2]$_3$–), 1.65 (td, J = 7.9, 3.02 Hz, HC—[CH_2]$_3$–), 1.36 (septet of t, J = 6.50, 2.45 Hz, –CH_2—CH—[CH_3]$_2$), 1.12 (t, J = 7.23 Hz, =N—CH_2—CH_3), 0.87 and 0.86 (d, d, J = 6.47, 6.42 Hz, diastereotopic –CH—[CH_3]$_2$), 0.63 and 0.18 (ddd, ddd, J_{gem} = 12.3, 11.9 Hz, $J_{H-B-C-H}$ = 8.36, 9.38 Hz, $J_{H-C-C-H}$ = 4.08, 2.38 Hz, BH—CH_2—CH–); ^{13}C NMR ($CDCl_3$) δ 180.7 (br, –C=N–), 140.05 (–O—CH_2—*C*(Ph)), 127.85 (*m*-Ph—*C*), 127.27 (*o*-Ph—*C*), 126.44 (*p*-Ph—*C*), 63.53 (–O—CH_2—Ph), 50.32 (N—[CH_2]$_3$–), 43.90 (=N—CH_2—CH_3), 28.06 (br, B—CH_2—CH–), 27.07 and 24.71 (diastereotopic –CH—[CH_3]$_2$), 26.57 (–CH_2—CH—[CH_3]$_2$), 24.60 (HC—[CH_2]$_3$–), 20.24 (H*C*—[CH_2]$_3$–), 17.53 (=N—CH_2—CH_3); IR (KBr) ν_{max} 3026 (wm), 2093 (wm) (aryl C—H), 2930 (vs), 2860 (vs) (alkyl C—H), 2406 (m), 2365 (wm), 2297 (w) (B—H), 1626 (vs) (–C=N–), 1604 (wm) (aryl distortion), 1499 (w sh), 1466 (s), 1378 (wm sh), 1359 (m sh), 1345 (wm sh), 1320 (wm), 1285 (w), 1248 (wm), 1232 (wm), 1211 (m), 1160 (s), 1112 (ms), 1083 (m), 1036 (m), 996 (ms), 940 (m), 906 (wm sh), 852 (wm), 827 (m), 817 (wm), 750 (mw), 728 (m), 698 (ms), 605 (wm), 559 (w), 504 (wm) cm^{-1}; Anal. Calcd for $C_{21}H_{35}N_2BO$: C, 73.68; H, 10.31. Found: C, 74.59; H, 10.56.

Results and Discussion

In our previous report, the syntheses of several amino–alkyl-(*N*-ethylcarbamoyl)boranes were described.[4] Attempts to hydrolyze amine–alkyl(*N*-ethylcarbamoyl)boranes directly to carboxylic acids by use of aqueous base or acid failed, so an alternative means of obtaining esters and other related derivatives was pursued. The amine–alkyl(*N*-ethylcarbamoyl)boranes were reacted with triethyloxonium tetrafluoroborate and then with aqueous sodium hydroxide to form amine–alkyl[(ethylimino)-ethoxymethyl]boranes (Scheme II).

Scheme II



Synthesis of Amine–Alkyl[(ethylimino)ethoxymethyl]boranes. First Method. In the work of Borch[1] it became apparent that to activate certain amides to further reaction, it was necessary to alkylate the oxygen with Meerwein's reagent.[9] It was noted in the studies of Borch[1] that an undesired side product of such a reaction was the ethyl ester derivative of the alkylamide produced whenever moisture at neutral pH was inadvertently introduced to a reaction mixture containing imino ethers. In an attempt to produce the ethyl ester by this technique, **2c** was reacted with Et_3OBF_4 in excess. A product was isolated with an infrared band at 1605 cm^{-1}. This was of lower intensity and higher energy than the parent carbamoylborane. The N–H band was still present, but the B–H frequency was shifted 50 cm^{-1} higher in energy than in the case of **2c**, implying the presence of a positive charge and a boronium salt. A very broad and strong absorbance at 1050–1100 cm^{-1} indicated the presence of BF_4^- in the compound. A ^{11}B NMR (THF) spectrum revealed a BF_4^- resonance at –1.3 ppm and a broadened boron signal at –6.0 ppm, indicating that a previously unobserved derivative had been synthesized. The reaction mixture was also observed to darken upon exposure to light.

Iminium salt **1d** was isolated in analytical purity by recrystallization from hot water and was observed to be a high-melting solid (154–154.5 °C). This demonstrated the excellent stability of the this salt at pH 7.

An alternate route to the iminium salts involves the reaction of nitrilium salts with alcohols, paralleling the work of Mittakanti and Morse.[2] A sample of nitrilium salt **1b** was dissolved in MeOH at room temperature, and the reaction progress was monitored by ^{11}B NMR. The nitrilium salt ^{11}B NMR resonance at –7.38 ppm (MeOH) was observed over time to first develop a shoulder at lower field, which totally replaced the nitrilium salt signal in 3 days, the reaction being approximately half-way completed in ca. 22 h at room temperature. A new resonance at –6.08 ppm (MeOH), assigned to the iminium salt, totally replaced the former nitrilium salt signal.

This addition reaction for –RBH– containing derivatives, though it does occur, is about 3 times slower than the reaction of MeOH with [(pyridine)–BH_2CNEt]BF_4.[2] After the MeOH was removed, pH 7 buffer and some MeCN was used as a cosolvent to test the salt's stability to water. A ^{11}B NMR spectrum taken of the new solution 20 min after dissolving the salt looked identical with a second spectrum obtained 53 h later. After 1 month in this solution at room temperature, during which time this salt partially crystallized as the MeCN evaporated, there was no evidence by ^{11}B NMR of reversion to the nitrilium salt or hydrolysis to carbamoylborane.

Aqueous base deprotonation of **2d** resulted in the disappearance of the BF_4^- absorbance in the infrared spectrum, a new band at 1625 cm^{-1}, loss of the N–H absorbance, and a shift in the B–H band to a position more typical of neutral –RBH– species. This implied that imino ether **2f** had been produced, presumably in accordance with the mechanism in Scheme II.

The ^{11}B NMR (THF) spectrum of this new derivative revealed the presence of only one boron atom, whose resonance was split into a broad doublet by the borane proton, with a chemical shift of –6.9 ppm, intermediate between cyanoborane **2a** (–9.0 ppm) and amide **2c** (–3.9 ppm). Proton NMR analysis of this derivative revealed two ethyl signals which were unambiguously assigned

Scheme III

to the *C*-ethoxy and the *N*-ethyl groups by their multiplicity and chemical shifts. As no N–*H* proton was in evidence, it was concluded that the amide proton had been rendered acidic enough by the transfer of positive charge by the added ethyl group from Et_3OBF_4 to be removed completely by a brief reaction with 1 N aqueous NaOH. A molecular ion confirming the existence of **2f** was observed by mass spectroscopy.

A molecular ion was also observed for **1f** in the mass spectrum. In the case of **3d**, the solid salt was not characterized but was instead immediately converted to **3f** in high yield. As it was possible to cleanly recrystallize **3f**, a good elemental analysis was obtained.

Synthesis of Amine–Alkyl[(ethylimino)ethoxymethyl]boranes. Second Method. Upon analysis, it became apparent that attack of alkoxide on a nitrilium salt would more directly produce the *C*-alkoxy iminoboranes as illustrated in Scheme III.

As this method proved to have a superior yield from the parent cyanoborane, it superseded the first method.

In general, the reactions tended to go to completion even with the most hindered derivatives in a matter of minutes. This was especially apparent for reactions run in methanol. Addition of the parent nitrilium salt to a methanol solution containing sodium methoxide resulted in rapid precipitation of $NaBF_4$ from the formerly clear solutions. Usually less than 5 min passed before apparent settling of the precipitate indicated completion of the reaction. Upon working up the reactions, using distilled water in the process, solid products usually appeared upon removal of possible contaminants such as silicon grease or excess solvents.

As mentioned earlier, only quinuclidine adducts were solids at room temperature. So despite the relative ease of synthesizing amine–alkyl[(ethylimino)alkoxymethyl]boranes of other amine adducts (i.e. Me_3N, *N*,*N*-dimethylbenzylamine, pyridine), the lack of a means of separating the contaminating carbamoylborane from the crude products has thus far prevented full characterization of these derivatives. Imino ethers **1f** and **2g** were stable to silica gel column chromatography. Most other imino ether boranes quantitatively decomposed upon attempted flash chromatography.

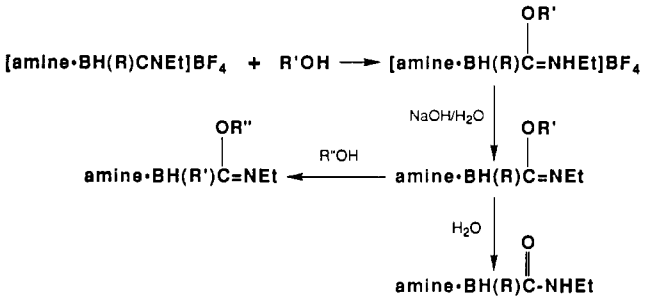
Spectroscopic Considerations

Infrared. The infrared stretching frequency of the imino –C=N– bond for derivatives **1–4e,e′,f,g** was usually found in a narrow range of 1623–1627 cm^{-1}, about 40–60 cm^{-1} lower in frequency than *C*-alkyl, *C*-alkoxy imino ethers.[12] Mittakanti and Morse[2] reported the –C=N– band of the (pyridine)·BH_2C(OMe)=NEt product to have an absorbance at 1619 cm^{-1}, similar to our derivatives. This change relative to the organic imino ether derivatives could be attributed to strong inductive electron donation to the –C=N– double bond by the amine–borane group in the molecule.

NMR. Generally, the imino ether ^{11}B NMR spectra revealed doublets that were broader than the parent carbamoyl- or cyanoboranes, probably due to slower tumbling in solution because of a larger molecular weight. Their ^{11}B chemical shifts were generally intermediate between that of the parent cyanoboranes and carbamoylboranes. Proton NMR revealed the asymmetric boron center, in the form of complex diastereotopic signals for various methyl and methylene groups, as was the case in the parent derivatives.[3,4] The *B*-alkyl group α carbon protons were shifted upfield by about 1 ppm relative to the equivalent protons of the analogous organic imino ether derivatives.

The less electron withdrawing nature of the (amine)–B(R)H– group of these imino ether borane derivatives compared to

Scheme IV



corresponding alkyl groups of typical organic imino ethers, such as EtC(OEt)=NEt, is evident in the proton chemical shift data. The *C*-methoxy resonance of EtC(OMe)=NEt occurred at δ = 3.63 ppm ($CDCl_3$).[12] The corresponding *C*-methoxy signals of borane imino ether derivatives **1–4e** and **4e′** were observed ($CDCl_3$) at an average δ = 3.48 ppm. Other slightly shielded proton signals in boron derivatives relative to the proton resonances of all carbon analogs have been seen in this work and previous reports[3,4] as well.

The unique B—*C*(O—R)=N—Et carbon usually was observed by ^{13}C NMR at δ 180–181 ppm. This was deshielded relative to other organic R—*C*(=N–)—X– species (145–165 ppm).[13,14] This signal was also quite broadened, as was the cyano group carbons[3] and the *N*-ethylcarbamoyl carbonyl carbons[4] of the parent derivatives, and is ascribed to the influences of primarily the nearby boron nucleus. Other ^{13}C resonances of nucleii adjacent to either the boron or the imino functionality were shielded relative to analogous organic species.

Some General Observations. Originally intended to be little more than reactive intermediates on the way to the synthesis of $R_3N{\cdot}R'BHC(O)OR''$, these imino ethers proved to be unusually stable and resistant to hydrolysis relative to purely organic derivatives. Quinuclidine adducts were solids with melting points near 50–80 °C. Their stability to aqueous acid was markedly higher than the parent carbamoylboranes, presumably reprotonating to the iminium salt, but they decomposed, for the most part, when column chromatography was attempted on less-pure derivatives. Invariably, thin-layer chromatography revealed very dark, low R_f smeared spots regardless of eluting solvent.

These imino ethers were very soluble in all solvents of intermediate polarity. Recrystallizations from cold pentane, pentane/Et_2O, or pentane/CH_2Cl_2 (–15 °C) resulted in analytical purity crystals. Since the parent ions were observed in the mass spectra of the two *s*-Bu derivatives **4e** and **4e′**, the *C*-methoxy quinuclidine and pyridine adducts, respectively, their characterization data are included as well for comparison with the other better characterized iminoboranes.

No reaction was observed with amine–alkyl[(ethylimino)-alkoxymethyl]boranes dissolved in aqueous NaOH/MeCN or aqueous KOH/EtOH over periods of up to 3 weeks except occasionally for some trace attack at the boron center. This was consistent with the observations of Pilotti[12] and Borch[1] that organic imino ethers, though very hydrolytically unstable to neutral or acidic water, tended to be relatively unaffected by exposure to aqueous base.

Under neutral conditions in mixed water/MeCN or water/MeOH, nearly quantitative hydrolysis of **2f** (see Scheme IV) to the amine–alkyl(*N*-ethylcarbamoyl)borane **2c** was observed to occur at room temperature over a period of 1 week.

(12) Pilotti, A.; Reuterhäll, A.; Torssell, K.; Lindblad, C-G. *Acta Chem. Scand.* **1969**, *23*, 818.
(13) Silverstein, R. M.; Bassler, G. C.; Morril, T. C. *Spectrometric Identification of Organic Compounds*, 4th ed.; Wiley and Sons: New York, 1981.
(14) Deyrup, J. A.; Gingrich, H. L. *J. Org. Chem.* **1977**, *42* (6), 1015.

Mattakanti and Morse[2] had observed that if (pyridine)·BH_2C(OMe)=NEt was dissolved in a small volume of water and heated to 50 °C for 8 h, in addition to some starting imino ether, a 40% yield of (pyridine)·BH_2C(O)OMe was realized. Upon heating **1f** in 1/1 water/MeCN (55 °C) for 6 h, amide **1c** was present in a 1:1 ratio with **1f**. Further heating to 63 °C for 18 h resulted in ca. 95% conversion of **1f** to the amide. In no experiment run to date has there been any spectroscopic evidence for the presence of esters.

Imino ether **2g** was dissolved in excess MeOH for 6 days at room temperature (22 °C), during which time imino ether **2e** was produced. A proton NMR spectrum revealed over 95% conversion to **2e** had been achieved. Free benzyl alcohol was also observed in the same spectrum. Imino ether **2f** was dissolved in excess MeOH for 6 days at room temperature. The integrated proton NMR spectrum revealed that alkoxy group exchange of **2f** to **2e** had reached 55%.

The lone pair on the nitrogen of the imino ether is quite nucleophilic, so further reaction with Et_3OBF_4 yielded C-alkoxy, *N*,*N*-diethyl iminium salts. The studies of Borch[1] indicated that there was a strong tendency for the organic analogs of these *N*,*N*-dialkyl salts to hydrolyze exclusively to the ester.

The amine–alkyl[(diethyliminiumylidene)alkoxymethyl]borane tetrafluoroborates, upon hydrolysis with aqueous base, yielded both amine–alkyl(*N*,*N*-diethylcarbamoyl)boranes and amine–alkyl(alkoxycarbonyl)boranes in varying ratios, depending on the boron R group and the alkoxy group. A detailed report on the synthesis of these amide and ester derivatives, plus some preliminary results of biological testing on a few of the ester derivatives will be published in the near future.

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