Research Article

Journal of Labelled Compounds and Radiopharmaceuticals

Received 20 January 2011, Accepted 22 February 2011 Published online 25 April 2011 in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/jlcr.1884

Synthesis of sequentially deuterated 1-*n*-Butyl-3-methylimidazolium ionic liquids

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Deuterium isotopologues of the ionic liquid (IL) 1–*n*-butyl-3-methylimidazolium chloride ([C_4mim]Cl) sequentially labeled on the C-1″, C-1′, C-2′, C-3′, and C-4′ positions of the *N*-alkyl groups were prepared following a strategy that minimizes the number of distinct reactions through the use of analogous synthetic routes. In several cases, good yields after the initial deuterium incorporation reaction were achieved by combining well-established chemical transformations into efficient single-step processes.

Keywords: deuteration; deuterium isotope effects; imidazolium cations; ionic liquids

Introduction

Arbitrarily defined as organic salts with melting points below 100°C, ionic liquids (ILs) have gained considerable notoriety in the past decade. Owing to their negligible vapor pressure, thermal stability, and tunable solvent properties, these materials have found applications in a wide range of laboratory and industrial processes.[1] As part of efforts aimed at better understanding the liquid structure of imidazolium-based ILs, we have shown that intraionic hydrogen-bonding (H-bonding) interactions in 1-*n*-butyl-3-methylimidazolium chloride ([C_4mim]Cl (**1**), Figure 1) are evidenced by sizable deuterium isotope effects on the chloride ion $^{35/37}$Cl NMR signal (i.e. $\Delta^{35/37}$Cl(H,D)).[2] Measurements obtained on the [C_4mim]Cl isotopologues [2-d_1]-[C_4mim]Cl and [2,4,5-d_3]-[C_4mim]Cl led to $\Delta^{35/37}$Cl(H,D) values of up to 2 ppm, and corroborated the presence of H-bonds between the anion and the imidazolium cation protons on the C-2, C-4, and C-5 positions.

Recent theoretical studies indicate that H-bonding between the anion and protons along the *N*-alkyl groups could also have an impact on the structure and dynamics of this class of ILs.[3,4] Based on our previous results, these anion–cation interactions could be detected experimentally by measurement of deuterium isotope effects on the $^{35/37}$Cl NMR signal of the chloride ion. For this purpose, we decided to synthesize a series of [C_4mim]Cl deuterium isotopologues sequentially labeled along the *N*-alkyl group carbons (Figure 1a–e). These could also be easily converted by metathesis to the corresponding tetrafluoroborate and hexafluorophosphate imidazolium salts (i.e. [C_4mim]BF_4 and [C_4mim]PF_6), which would be suitable for the study of interionic H-bonds through analysis of deuterium isotope effects on the $^{10/11}$B, ^{19}F, and ^{31}P signals of the BF_4^- and BF_6^- anions. In this manuscript we describe a strategy which uses similar routes to minimize the number of distinct reactions needed to prepare these compounds. As detailed below, good yields after the initial deuterium incorporation reaction were achieved in several cases through the combination of well-established chemical transformations into efficient single-step processes.

Experimental

Deuterated starting materials were purchased from Sigma-Aldrich, Inc. (St. Louis, MO, USA) and Cambridge Isotopes, Inc. (Andover, MA, USA), and used as received. THF and diethyl ether were distilled from sodium benzophenone ketyl prior to use. 1-Methylimidazole used in *N*-alkylation reactions was freshly distilled through a Vigreux column at ~20 mm Hg. Flash column chromatography was carried out using 230–450 mesh silica gel. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Thermo Electron Nicolet Avatar 370 DTGS FT-IR spectrophotometer. NMR experiments were performed on a Bruker AVANCE 400 spectrometer operating at 1H and ^{13}C frequencies of 400.13 and 100.61 MHz, respectively, using $CDCl_3$ as solvent. Chemical shifts (δ) are in ppm relative to the residual solvent signal (7.28 ppm), and coupling constants (*J*) are reported in Hz. MS and HR-MS spectra were recorded on Varian Saturn 2100 T and Thermo Scientific Exactive Orbitrap mass spectrometers using EI and ASAP ionization,[5] respectively.

[1′,1′,1′-d_3]-1-Methylimidazole (**2**): To a round-bottom flask containing a solution of imidazole (10.6 g, 0.16 mol) in diethyl ether (200 mL) was added 18-crown-6 (4.1 g, 16 mmol) and potassium *tert*-butoxide (19.3 g, 0.17 mol) under an argon atmosphere. The resulting slurry was stirred for 20 min, and a solution of [d_3]-iodomethane (23.8 g, 0.16 mmol) in diethyl ether (100 mL) was added dropwise over 30 min at 0°C. After an additional 4 h, the reaction mixture was filtered and the solid residue was washed with diethyl ether (5 × 100 mL). The combined organic phases were concentrated *in vacuo*, and the

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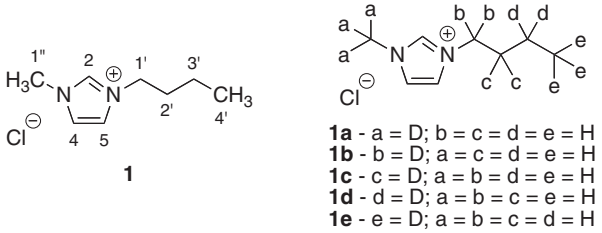

Figure 1. Structure and numbering of [C_4mim]Cl (**1**) and its deuterium isotopologues (**1a**–**e**).

crude product was distilled through a Vigreux column at ~20 mm Hg to yield **2** as a colorless oil (11.8 g, 84%). IR (NaCl plate, cm^{-1}): 3392, 3106, 2136, 2078, 1508, 1286, 1233, 1118, 1076, 910, 818, 743, 664. ^{1}H NMR: δ 10.53 (1H, bdd, J = 1.2, J = 1.0, H2), 7.64 (1H, dd, J = 1.2, J = 1.0, H4), 7.47 (1H, dd, J = 1.2, J = 1.2, H5). ^{13}C NMR: δ 137.7 (C2), 129.3 (C5), 120.0 (C4), 32.5 (hep, $^1J_{CD}$ = 21.4, C1′). HR-MS (ASAP): *m/z* calcd for $C_4H_4D_3N_2$ ($[M+H]^+$): 86.0793, found: 86.0809.

[1,1-d_2]-1-Butanol (***3a***): THF (50 mL) and $LiAlD_4$ (4.5 g, 0.11 mol) were carefully combined in an argon-flushed 2-neck round-bottom flask. Methyl butyrate (22.2 mL, 0.20 mol) was added dropwise over 10 min at 0°C, and the resulting slurry was refluxed for 1 h. The mixture was cooled to room temperature and diluted with diethyl ether (200 mL), and the reaction was then quenched with 1 M HCl (100 mL). After 30 min the mixture was filtered, and the filtrate was extracted with diethyl ether (2 × 200 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to yield the title compound as a colorless oil (12.2 g, 82%). IR (NaCl plate, cm^{-1}): 3351, 2960, 2932, 2875, 2197, 2100, 1465, 1380, 1081, 1067, 968. ^{1}H NMR: δ 1.56 (2H, tquin, J = 7.5, $^3J_{HD}$ = 0.9, H2), 1.41 (2H, tq, J = 7.5, J = 7.3, H3), 1.27 (1H, bs, OH), 0.96 (3H, t, J = 7.3, H4). ^{13}C NMR: δ 61.9 (quin, $^1J_{CD}$ = 21.6, C1), 34.6 (C2), 18.8 (C3), 13.8 (C4). MS (EI): *m/z* (rel. int.): 58 (100, $[M\text{-}H_2O]^+$), 43 (45).

(±)-[2,2-d_2]-Methyl-3-hydroxybutyrate (***5***): Methyl acetoacetate (30.0 g, 0.27 mol) and D_2O (30 mL) were combined in a round-bottom flask and stirred under argon for 10 min at 70°C. The solution was then cooled to room temperature and solid NaCl (9 g) was added. The mixture was extracted with D_2O-saturated diethyl ether (300 mL), and the solvent evaporated *in vacuo*. After repeating this process twice, the crude product was redissolved in D_2O (60 mL) at 70°C, cooled to −5°C, and treated with a chilled solution of $NaBH_4$ (3.3 g, 88 mmol) in D_2O (30 mL) added in one portion. Stirring was continued for 30 min at 0°C, 1 M HCl (60 mL) and NaCl (40 g) were then added, and the mixture was extracted with chilled dichloromethane (300 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure to yield **5** as a colorless oil (24.9 g, 80%). IR (NaCl plate, cm^{-1}): 3435, 2972, 2957, 2932, 2240, 1736, 1437, 1270, 1118, 1064, 1028, 921. ^{1}H NMR: δ 4.20 (1H, tquin, J = 6.4, $^3J_{HD}$ = 1.2, H3), 3.73 (3H, s, OCH_3), 2.94 (1H, bs, OH), 1.24 (3H, d, J = 6.4, H4). ^{13}C NMR: δ 173.3 (C1), 64.2 (C3), 51.7 (OCH_3), 42.0 (quin, $^1J_{CD}$ = 19.6, C2), 22.4 (C4). HR-MS (ASAP): *m/z* calcd for $C_5H_9D_2O_3$ ($[M+H]^+$): 121.0829, found: 121.0827.

(±)-[2,2-d_2]-Methyl-3-(p-toluenesulfonyloxy)butyrate (***6***): Compound **5** (21.5 g, 0.18 mol) was dissolved in anhydrous pyridine (72 mL, 0.90 mol) in a round-bottom flask and cooled to 0°C. *p*-Toluenesulfonyl chloride (51.1 g, 0.27 mol) was then added, and the solution was stirred under argon for 22 h at 0°C. The reaction was quenched by addition of water (10 mL), which was done slowly to avoid layer separation and to maintain the temperature below 10°C. The resulting mixture was diluted with diethyl ether (300 mL), and extracted with 3 M HCl (3 × 60 mL), 1 M NaOH (30 mL), 3 M HCl (30 mL), and brine (20 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to yield the title compound as white solid (46.3 g, 94%). M.p.: 40–43°C. IR (KBr disc, cm^{-1}): 3068, 3002, 2984, 2960, 2936, 1751, 1597, 1436, 1366, 1348, 1272, 1191, 1177, 1079, 1019, 897, 732, 659, 575, 556. ^{1}H NMR: δ 7.81 (2H, d, J = 8.3, Ar), 7.36 (2H, d, J = 8.3, Ar), 4.98 (1H, bq, J = 6.4, H3), 3.61 (3H, s, OCH_3), 2.47 (3H, s, Ar-CH_3), 1.37 (3H, d, J = 6.4, H4). ^{13}C NMR: δ 169.7 (C1), 144.7 (Ar), 134.0 (Ar), 129.8 (Ar), 127.8 (Ar), 75.7 (C3), 51.8 (OCH_3), 40.7 (quin, $^1J_{CD}$ = 19.8, C2), 21.6 (Ar-CH_3), 20.9 (C4). HR-MS (ASAP): *m/z* calcd for $C_{12}H_{15}D_2O_5S$ ($[M+H]^+$): 275.0917, found: 275.0908.

[2,2-d_2]-1-Butanol (***3b***): THF (300 mL) and $LiAlH_4$ (7.4 g, 0.20 mmol) were carefully combined in an argon-flushed two-neck round-bottom flask. A solution of compound **6** (46.2 g, 0.20 mmol) in THF (100 mL) was then added dropwise over 30 min at 0°C. The resulting slurry was warmed to room temperature, stirred for 1 h, and heated to reflux for an additional 15 min. The reaction was then quenched with 6 M HCl (130 mL), and extracted with diethyl ether (3 × 400 mL). The combined organic layers were concentrated *in vacuo*, re-dissolved in dichloromethane, and washed with brine (60 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure to yield **3b** as a pale yellow oil (7.8 g, 61%). IR (NaCl plate, cm^{-1}): 3344, 2960, 2933, 2874, 2191, 2131, 1465, 1379, 1049, 1027, 982. ^{1}H NMR: δ 3.66 (2H, quin, $^3J_{HD}$ = 1.0, H1), 1.58 (1H, bs, OH), 1.39 (1H, qquin, J = 7.4, $^3J_{HD}$ = 1.1, H3), 0.95 (3H, t, J = 7.4, H4). ^{13}C NMR: δ 62.6 (C1), 33.9 (quin, $^1J_{CD}$ = 19.2, C2), 18.7 (C3), 13.8 (C4). MS (EI): *m/z* (rel. int.): 57 (100, $[M\text{-}HDO]^+$), 42 (72).

4-(tert-Butyldimethylsilyloxy)-2-butanone (***7***): 4-Hydroxy-2-butanone (10.0 g, 0.11 mol) and imidazole (9.3 g, 0.13 mol) were dissolved in dichloromethane (500 mL) in an argon-flushed round-bottom flask. *tert*-Butyldimethylsilyl chloride (18.0 g, 0.11 mol) was quickly added and the resulting mixture was stirred at room temperature for 1.5 h. The reaction mixture was then extracted with saturated aqueous NH_4Cl (3 × 100 mL), and the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude oil was purified by flash chromatography using hexanes-EtOAc (95:5) as eluting solvent to yield the title compound as a colorless oil (21.6 g 94%). IR (NaCl plate, cm^{-1}): 2957, 2930, 2885, 2858, 1717, 1473, 1361, 1257, 1104, 867, 837, 778. ^{1}H NMR: δ 3.89 (2H, t, J = 6.4, H4), 2.62 (2H, t, J = 6.4, H3), 2.18 (3H, s, H1), 0.88 (9H, s, $SiC(CH_3)_3$), 0.05 (6H, s, $Si(CH_3)_2$). ^{13}C NMR: δ 207.8 (C2), 58.8 (C4), 46.5 (C3), 30.7 (C1), 25.8 ($SiC(\underline{C}H_3)_3$), 18.1 ($Si\underline{C}(CH_3)_3$), −5.6 ($Si(CH_3)_2$). HR-MS (ASAP): *m/z* calcd for $C_{10}H_{23}O_2Si$ ($[M+H]^+$): 203.1462, found: 203.1456.

(±)-[2-d_1]-4-(tert-Butyldimethylsilyloxy)-2-butanol (***8a***): $NaBD_4$ (2.4 g, 58 mmol) was added to a solution of compound **7** (21.6 g, 0.11 mol) in methanol (200 mL), and the resulting mixture was refluxed for 15 min. The reaction mixture was then concentrated *in vacuo*, redissolved in dichloromethane (300 mL), washed with saturated aqueous NH_4Cl (75 mL), and brine (75 mL). The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure to yield **8a** (21.7 g, 99%). IR (NaCl plate, cm^{-1}): 3403, 2957, 2930, 2885, 2858, 2134, 1473, 1361, 1257, 1154, 1104, 837, 776. ^{1}H NMR: δ 3.91 (1H, ddd, J = 10.2, J = 4.8, J = 4.6, H4), 3.83 (1H, ddd, J = 10.2, J = 8.5, J = 4.4, H4), 3.05 (1H, bs, OH), 1.69 (1H, dddt, J = 14.3, J = 8.5, J = 4.6, $^3J_{HD}$ = 1.2, H3), 1.64 (1H, ddd, J = 14.3, J = 4.8, J = 4.4, H3), 1.21 (3H, t, $^3J_{HD}$ = 0.8, H1),

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0.92 (9H, s, $SiC(CH_3)_3$), 0.10 (6H, bs, $Si(CH_3)_2$). ^{13}C NMR: δ 67.8 (t, $^1J_{CD}$ = 21.6, C2), 62.7 (C4), 39.9 (C3), 25.8 ($SiC(\underline{C}H_3)_3$), 23.2 (C1), 18.1 ($Si\underline{C}(CH_3)_3$), −5.5 & −5.6 ($Si(CH_3)_2$). HR-MS (ASAP): m/z calcd for $C_{10}H_{24}DO_2Si$ ($[M+H]^+$): 206.1682, found: 206.1707.

(±)-[2-d_1]-4-(tert-Butyldimethylsilyloxy)-2-(p-toluenesulfonyloxy)butane (***9a***): Compound **8a** (21.5 g, 0.10 mol) and anhydrous pyridine (25 mL, 0.30 mol) were dissolved in dichloromethane (50 mL) in a round-bottom flask. *p*-Toluenesulfonyl chloride (29.9 g, 0.16 mol) was then added, and the solution was stirred under argon at room temperature for 20 h. The mixture was subsequently cooled to 0°C, and the reaction was quenched by addition of water (10 mL), which was done slowly to avoid layer separation and to maintain the temperature below 10°C. The resulting mixture was diluted with dichloromethane (350 mL) and extracted with 3 M HCl (3 × 40 mL), 1 M NaOH (20 mL), 3 M HCl (20 mL), and brine (20 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to yield the title compound as a pale yellow oil (36.7 g, 98%). IR (NaCl plate, cm^{-1}): 2955, 2929, 2884, 2857, 2194, 1472, 1361, 1257, 1189, 1093, 910, 839, 777, 664. ^1H NMR: δ 7.80 (2H, d, *J* = 8.4, Ar), 7.34 (2H, d, *J* = 8.4, Ar), 3.55 (1H, ddd, *J* = 10.4, *J* = 6.1, *J* = 6.1, H4), 3.50 (1H, ddd, *J* = 10.4, *J* = 6.8, *J* = 5.9, H4), 2.45 (3H, s, Ar-CH_3), 1.85 (1H, ddd, *J* = 14.2, *J* = 6.1, *J* = 5.9, H3), 1.67 (1H, ddd, *J* = 14.2, *J* = 6.8, *J* = 6.1, H3), 1.32 (3H, s, H1), 0.86 (9H, s, $SiC(CH_3)_3$), 0.00 & −0.00 (6H, s, $Si(CH_3)_2$). ^{13}C NMR: δ 144.4 (Ar), 134.6 (Ar), 129.7 (Ar), 127.7 (Ar), 77.8 (t, $^1J_{CD}$ = 22.9, C2), 58.8 (C4), 39.4 (C3), 25.8 ($SiC(\underline{C}H_3)_3$), 21.6 (Ar-CH_3), 20.9 (C1), 18.1 ($Si\underline{C}(CH_3)_3$), −5.5 & −5.6 ($Si(CH_3)_2$). HR-MS (ASAP): *m/z* calcd for $C_{17}H_{30}DO_4SSi$ ($[M+H]^+$): 360.1770, found: 360.1815.

[3,3-d_2]-1-Butanol (***3c***): Diethyl ether (150 mL) and $LiAlD_4$ (7.3 g, 0.17 mol) were carefully combined in an argon-flushed two-neck round-bottom flask. A solution of compound **9a** (56.5 g, 0.15 mol) in diethyl ether (60 mL) was added dropwise over 5 min, and the resulting slurry was refluxed for 4 h. The reaction was then quenched slowly by addition of 6 M HCl (200 mL). The organic solvent was distilled off under vacuum, and the remaining aqueous solution was stirred for an additional 30 min at room temperature. The solution was then extracted with diethyl ether (3 × 500 mL), and the combined organic layers were concentrated *in vacuo*, redissolved in diethyl ether (150 mL), and washed with water (10 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure to yield **3c** as a pale yellow oil (8.3 g, 69%). IR (NaCl plate, cm^{-1}): 3345, 2957, 2931, 2873, 2179, 2115, 1457, 1378, 1061, 1042, 991. ^1H NMR: δ 3.67 (2H, t, *J* = 6.7, H1), 3.20 (1H, bs, OH), 1.56 (2H, tquin, *J* = 6.7, $^3J_{HD}$ = 1.1, H2), 0.93 (3H, quin, $^3J_{HD}$ = 1.1, H4). ^{13}C NMR: δ 62.5 (C1), 34.3 (C2), 18.1 (quin, $^1J_{CD}$ = 19.1, C3), 13.6 (C4). MS (EI): *m/z* (rel. int.): 58 (100, $[M\text{-}H_2O]^+$), 43 (74).

3-(tert-Butyldimethylsilyloxy)-1-propanol (***10***): 1,3-Propanediol (13.9 g, 0.18 mol) was added dropwise over 15 min to a stirred suspension of NaH (4.4 g, 0.18 mol) in THF (300 mL) under argon. After 45 min, *tert*-butyldimethylsilyl chloride (25.0 g, 0.17 mol) was added over 15 min and stirred for an additional 45 min. The reaction was quenched by slow addition of 10% aqueous Na_2CO_3 (40 mL), and water (80 mL). The clear aqueous phase was extracted with diethyl ether (100 mL), and the combined organic layers were concentrated *in vacuo*, redissolved in dichloromethane (150 mL), and washed with water (3 × 20 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to yield the title compound as a colorless oil (30.3 g, 96%). IR (NaCl plate, cm^{-1}): 3352, 2955, 2929, 2985, 2858, 1473, 1257, 1098, 964, 837, 776. ^1H NMR: δ 3.83 (2H, td, *J* = 5.6, *J* = 0.4, H3), 3.79 (2H, td, *J* = 5.6, *J* = 0.4, H1), 2.69 (1H, bs, OH), 1.77 (2H, quin, *J* = 5.6, H2), 0.92 (9H, s, $SiC(CH_3)_3$), 0.10 (6H, s, $Si(CH_3)_2$). ^{13}C NMR: δ 62.7 (C3), 62.2 (C1), 34.2 (C2), 25.8 ($SiC(\underline{C}H_3)_3$), 18.2 ($Si\underline{C}(CH_3)_3$), −5.5 ($Si(CH_3)_2$). HR-MS (ASAP): *m/z* calcd for $C_9H_{23}O_2Si$ ($[M+H]^+$): 191.1462, found: 191.1487.

3-(tert-Butyldimethylsilyloxy)propanal (***11***): Dimethylsulfoxide (32.7 mL, 0.46 mol) was added over 20 min to a stirred solution of oxalyl chloride (19.5 mL, 0.23 mol) in dichloromethane (250 mL) at −78°C. A solution of compound **10** (29.2 g, 0.14 mol) in dichloromethane (150 mL) was then added over 40 min, and the mixture was stirred for an additional 15 min. Triethylamine (106 mL, 0.77 mol) was then added dropwise over 10 min, and the resulting slurry diluted with dichloromethane (200 mL). After stirring for 15 min, the reaction mixture was allowed to warm to room temperature and water (150 mL) was added. The aqueous layer was extracted with dichloromethane (100 mL), and the combined organic layers were washed with brine (100 mL), concentrated *in vacuo*, diluted with diethyl ether (100 mL), extracted with water (3 × 100 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford **11** as a yellow oil that was used in the next step without further purification. IR (NaCl plate, cm^{-1}): 2657, 2930, 2885, 2857, 2728, 1729, 1475, 1389, 1256, 1098, 814, 778. ^1H NMR: δ 9.82 (1H, t, *J* = 2.1, H1), 4.01 (2H, t, *J* = 6.0, H3), 2.62 (2H, td, *J* = 6.0, *J* = 2.1, H2), 0.90 (9H, s, $SiC(CH_3)_3$), 0.09 (6H, s, $Si(CH_3)_2$). ^{13}C NMR: δ 202.1 (C1), 57.40 (C3), 46.6 (C2), 25.80 ($SiC(\underline{C}H_3)_3$), 18.2 ($Si\underline{C}(CH_3)_3$), −5.5 ($Si(CH_3)_2$). HR-MS (ASAP): *m/z* calcd for $C_9H_{21}O_2Si$ ($[M+H]^+$): 189.1306, found: 189.1330.

(±)-[1,1,1-d_3]-4-(tert-Butyldimethylsilyloxy)-2-butanol (***8b***): Magnesium turnings (4.0 g, 0.17 mol) were added to an argon-flushed two-neck round bottom flask containing a solution of [d_3]-iodomethane (24.0 g, 0.17 mol) in anhydrous diethyl ether (400 mL) at 0°C. The mixture was allowed to warm to room temperature, refluxed for 30 min, and cooled to 0°C. A solution of compound **11** (27.9 g, 0.15 mol) in diethyl ether (100 mL) was then added dropwise over 15 min, and the resulting mixture was refluxed for an additional 15 min. After cooling to room temperature, the reaction was quenched with saturated aqueous NH_4Cl (50 mL) and diluted with water (250 mL). The aqueous layer was extracted with diethyl ether (150 mL), the organic layers were combined and dried over $MgSO_4$, and the solvent evaporated *in vacuo*. The remaining crude oil was purified by flash chromatography using hexanes-EtOAc (95:5) as eluting solvent to yield the title compound as a colorless oil (40.0 g, 65% from **10**). IR (NaCl plate, cm^{-1}): 3393, 2956, 2929, 2885, 2858, 2223, 1472, 1361, 1257, 1141, 1095, 836, 776. ^1H NMR: δ 4.02 (1H, bdd, *J* = 8.4, *J* = 2.6, H2), 3.90 (1H, ddd, *J* = 10.3, *J* = 4.7, *J* = 4.7, H4), 3.82 (1H, ddd, *J* = 10.3, *J* = 8.7, *J* = 4.0, H4), 3.28 (bs, OH), 1.68 (1H, ddd, *J* = 14.3, *J* = 8.7, *J* = 4.7, H3), 1.64 (1H, dddd, *J* = 14.3, *J* = 8.4, *J* = 4.7, *J* = 4.0, H3), 0.91 (9H, s, $SiC(CH_3)_3$), 0.09 (6H, bs, $Si(CH_3)_2$). ^{13}C NMR: δ 68.1 (C2), 62.8 (C4), 39.9 (C3), 25.8 ($SiC(\underline{C}H_3)_3$), 22.5 (hep, $^1J_{CD}$ = 19.2, C1), 18.1 ($Si\underline{C}(CH_3)_3$), −5.5 & −5.6 ($Si(CH_3)_2$). HR-MS (ASAP): *m/z* calcd for $C_{10}H_{22}D_3O_2Si$ ($[M+H]^+$): 208.1807, found: 208.1799.

(±)-[1,1,1-d_3]-4-(tert-Butyldimethylsilyloxy)-2-(p-toluenesulfonyloxy)butane (***9b***): Obtained from **8b** in 94% yield following the procedure described for the preparation of **9a**. IR (NaCl plate, cm^{-1}): 2956, 2929, 2884, 2857, 2231, 1472, 1363, 1257, 1189, 1098, 918, 837, 777, 662. ^1H NMR: δ 7.81 (2H, d, *J* = 8.3, Ar), 7.24 (2H, d, *J* = 8.3, Ar), 4.77 (1H, bdd, *J* = 7.2, *J* = 5.5, H2), 3.54

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(1H, ddd, $J = 10.4$, $J = 6.2$, $J = 6.0$, H4), 3.50 (1H, ddd, $J = 10.4$, $J = 6.8$, $J = 5.9$, H4), 2.46 (3H, s, Ar-CH_3), 1.86 (1H, dddd, $J = 14.1$, $J = 7.2$, $J = 6.2$, $J = 5.9$, H3), 1.68 (1H, dddd, $J = 14.1$, $J = 6.8$, $J = 6.0$, $J = 5.5$, H3), 0.86 (9H, s, $SiC(CH_3)_3$), 0.00 & −0.00 (6H, s, $Si(CH_3)_2$). ^{13}C NMR: δ 144.4 (Ar), 134.5 (Ar), 129.7 (Ar), 127.7 (Ar), 78.0 (C2), 58.8 (C4), 39.5 (C3), 25.8 ($SiC(\underline{C}H_3)_3$), 21.6 (Ar-CH_3), 20.1 (hep, $^1J_{CD} = 19.8$, C1), 18.2 ($Si\underline{C}(CH_3)_3$), −5.5 & −5.6 ($Si(CH_3)_2$). HR-MS (ASAP): *m/z* calcd for $C_{17}H_{28}D_3O_4SSi$ ($[M+H]^+$): 362.1895, found: 362.1903.

[4,4,4-d_3]-1-Butanol (***3d***): Obtained from **9b** in 60% yield by reduction of **9b** with $LiAlH_4$ following the procedure described for the preparation of **3c**. IR (NaCl plate, cm^{-1}): 3351, 2934, 2867, 2220, 2124, 2076, 1461, 1380, 1051, 1020, 951. ^{1}H NMR: δ 3.67 (2H, t, $J = 6.7$, H1), 1.66 (bs, 1H, OH), 1.57 (2H, tt, $J = 7.6$, $J = 6.7$, H2), 1.38 (2H, thep, $J = 7.6$, $^3J_{HD} = 1.1$, H3). ^{13}C NMR: δ 62.7 (C1), 34.4 (C2), 18.6 (C3), 12.9 (hep, $^1J_{CD} = 19.1$, C4). MS (EI): *m/z* (rel. int.): 59 (100, $[M\text{-}H_2O]^+$), 41 (48).

Chlorination of 1-butanol isotopologues

To a solution of the appropriate 1-butanol isotopologue (15 g, 0.20 mol) and anhydrous pyridine (0.02 eq), thionyl chloride (1.1 eq) was added dropwise over 30 min at 0°C. The mixture was refluxed until gas ceased to evolve for at least 15 min. The solution was then cooled to room temperature and the reaction was quenched with water (5 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (5 mL), dried over $MgSO_4$, and distilled through a Vigreux column to yield the different 1-chlorobutane isotopologues as colorless oils.

[1,1-d_2]-1-Chlorobutane (***4a***): Obtained from **3a** in 77% yield. IR (NaCl plate, cm^{-1}): 2963, 2935, 2876, 2251, 2244, 2161, 1466. ^{1}H NMR: δ 1.76 (2H, tquin, $J = 7.5$, $^3J_{HD} = 1.1$, H2), 1.48 (2H, tq, $J = 7.5$, $J = 7.4$, H3), 0.95 (3H, t, $J = 7.4$, H4). ^{13}C NMR: δ 44.2 (quin, $^1J_{CD} = 22.8$, C1), 34.4 (C2), 20.0 (C3), 13.3 (C1). MS (EI): *m/z* (rel. int.): 58 (100, $[M\text{-}HCl]^+$), 43 (30).

[2,2-d_2]-1-Chlorobutane (***4b***): Obtained from **3b** in 63% yield. IR (NaCl plate, cm^{-1}): 2962, 2935, 2875, 2203, 2130, 2107, 1460. ^{1}H NMR: δ 3.55 (2H, quin, $^3J_{HD} = 1.0$, H1), 1.47 (2H, qquin, $J = 7.4$, $^3J_{HD} = 1.1$, H3), 0.95 (3H, t, $J = 7.4$, H4). ^{13}C NMR: δ 44.7 (C1), 33.8 (quin, $^1J_{CD} = 19.5$, C2), 19.8 (C3), 13.3 (C4). MS (EI): *m/z* (rel. int.): 57 (100, $[M\text{-}DCl]^+$), 42 (42).

[3,3-d_2]-1-Chlorobutane (***4c***): Obtained from **3c** in 54% yield. IR (NaCl plate, cm^{-1}): 2969, 2932, 2874, 2217, 2184, 2116, 1459. ^{1}H NMR: δ 3.56 (2H, t, $J = 6.7$, H1), 1.76 (2H, tquin, $J = 6.7$, $^3J_{HD} = 1.1$, H2), 0.94 (3H, quin, $^3J_{HD} = 1.1$, H4). ^{13}C NMR: δ 44.8 (C1), 34.4 (C2), 19.3 (quin, $^1J_{CD} = 19.3$, C3), 13.1 (C4). MS (EI): *m/z* (rel. int.): 58 (100, $[M\text{-}HCl]^+$), 43 (33).

[4,4,4-d_3]-1-Chlorobutane (***4d***): Obtained from **3d** in 74% yield. IR (NaCl plate, cm^{-1}): 2957, 2935, 2869, 2216, 2126, 2078, 1463. ^{1}H NMR: δ 3.56 (2H, t, $J = 6.8$, H1), 1.77 (2H, tt, $J = 7.4$, $J = 6.8$, H2), 1.46 (2H, thep, $J = 7.4$, $^3J_{HD} = 1.0$, H3). ^{13}C NMR: δ 44.9 (C1), 34.5 (C2), 19.8 (C3), 12.4 (hep, $^1J_{CD} = 19.2$, C4). MS (EI): *m/z* (rel. int.): 59 (100, $[M\text{-}HCl]^+$), 41 (32).

Alkylation of 1-methylimidazole isotopologues

The appropriate 1-methylimidazole (5 g, 60 mmol) and 1-chlorobutane (1.2 eq) isotopologues were combined in a 20 mL scintillation vial and sealed with a Teflon-lined cap. The vial was then immersed in an oil bath at 95°C, and the solution was stirred vigorously for 16–20 h. The resulting biphasic mixture was subsequently cooled to room temperature and the top layer, consisting mainly of unreacted 1-chlorobutane, was decanted. The remaining residue was washed with EtOAc (3 × 5 mL), discarding the solvent after each wash. The residual EtOAc was removed under reduced pressure to yield the different 1-*n*-butyl-3-methylimidazolium chloride isotopologues as pale yellow viscous oils.

[1′,1′,1′-d_3]-1-n-Butyl-3-methylimidazolium chloride (***1a***): Obtained from **2** and 1–chlorobutane in quantitative yield. IR (NaCl plate, cm^{-1}): 3384, 3130, 3052, 2959, 2935, 2874, 2257, 2129, 2076, 1564, 1466, 1174. ^{1}H NMR: δ 10.53 (1H, bdd, $J = 1.8$, $J = 1.7$, H2), 7.64 (1H, dd, $J = 1.8$, $J = 1.7$, H4), 7.47 (1H, dd, $J = 1.8$, $J = 1.8$, H5), 4.25 (2H, t, $J = 7.4$, H1′), 1.82 (2H, tt, $J = 7.6$, $J = 7.4$, H2′), 1.29 (2H, tq, $J = 7.6$, $J = 7.4$, H3′), 0.87 (3H, t, $J = 7.4$, H4′). ^{13}C NMR: δ 137.8 (C2), 123.7 (C4), 122.0 (C5), 49.7 (C1′), 35.8 (hep, $^1J_{CD} = 22.0$, C1″), 32.1 (C2′), 19.4 (C3′), 13.4 (C4′). HR-MS (ASAP): *m/z* calcd for $C_8H_{12}D_3N_2$ ($[M\text{-}Cl]^+$): 142.1419, found: 142.1437.

[1′,1′-d_2]-1-n-Butyl-3-methylimidazolium chloride (***1b***): Obtained from 1-methylimidazole and **4a** in quantitative yield. IR (NaCl plate, cm^{-1}): 3385, 3132, 3052, 2959, 2934, 2873, 2237, 2146, 2117, 1571, 1467, 1182. ^{1}H NMR: δ 10.58 (1H, bdd, $J = 1.8$, $J = 1.8$, H2), 7.64 (1H, dd, $J = 1.8$, $J = 1.8$, H4), 7.48 (1H, dd, $J = 1.8$, $J = 1.8$, H5), 4.06 (3H, s, H1′), 1.82 (2H, bt, $J = 7.6$, H2′), 1.31 (2H, tq, $J = 7.6$, $J = 7.4$, H3′), 0.89 (3H, t, $J = 7.4$, H4′). ^{13}C NMR: δ 137.8 (C2), 123.7 (C4), 122.0 (C5), 49.1 (quin, $^1J_{CD} = 21.6$, C1′), 36.5 (C1″), 31.9 (C2′), 19.3 (C3′), 13.4 (C4′). HR-MS (ASAP): *m/z* calcd for $C_8H_{13}D_2N_2$ ($[M\text{-}Cl]^+$): 141.1356, found: 141.1352.

[2′,2′-d_2]-1-n-Butyl-3-methylimidazolium chloride (***1c***): Obtained from 1-methylimidazole and **4b** in quantitative yield. IR (NaCl plate, cm^{-1}): 3385, 3138, 3052, 2959, 2933, 2873, 2201, 2135, 2109, 1572, 1465, 1175. ^{1}H NMR: δ 10.54 (1H, bdd, $J = 1.8$, $J = 1.7$, H2), 7.64 (1H, dd, $J = 1.8$, $J = 1.7$, H4), 7.47 (1H, dd, $J = 1.8$, $J = 1.8$, H5), 4.25 (2H, bs, H1′), 4.05 (3H, s, H1′), 1.28 (2H, bt, $J = 7.4$, H3′), 0.88 (3H, t, $J = 7.4$, H4′). ^{13}C NMR: δ 137.6 (C2), 123.7 (C4), 122.0 (C5), 49.5 (C1′), 36.4 (C1″), 31.3 (quin, $^1J_{CD} = 19.6$, C2′), 19.1 (C3′), 13.3 (C4′). HR-MS (ASAP): *m/z* calcd for $C_8H_{13}D_2N_2$ ($[M\text{-}Cl]^+$): 141.1356, found: 141.1352.

[3′,3′-d_2]-1-n-Butyl-3-methylimidazolium chloride (***1d***): Obtained from 1-methylimidazole and **4c** in quantitative yield. IR (NaCl plate, cm^{-1}): 3383, 3137, 3046, 2957, 2933, 2870, 2178, 2137, 2110, 1572, 1459, 1172. ^{1}H NMR: δ 10.42 (1H, bdd, $J = 1.8$, $J = 1.8$, H2), 7.62 (1H, dd, $J = 1.8$, $J = 1.8$, H4), 7.45 (1H, dd, $J = 1.8$, $J = 1.8$, H5), 4.18 (2H, t, $J = 7.4$, H1′), 3.98 (3H, s, H1′), 1.74 (2H, dt, $J = 7.4$, H2′), 0.78 (3H, bs, H4′). ^{13}C NMR: δ 137.6 (C2), 123.7 (C4), 122.0 (C5), 49.7 (C1′), 36.4 (C1″), 31.9 (C2′), 18.6 (quin, $^1J_{CD} = 19.3$, C3′), 13.1 (C4′). HR-MS (ASAP): *m/z* calcd for $C_8H_{13}D_2N_2$ ($[M\text{-}Cl]^+$): 141.1356, found: 141.1355.

[4′,4′,4′-d_3]-1-n-Butyl-3-methylimidazolium chloride (***1e***): Obtained from 1-methylimidazole and **4d** in quantitative yield. IR (NaCl plate, cm^{-1}): 3385, 3138, 3052, 2983, 2935, 2865, 2220, 2124, 2075, 1571, 1460, 1170. ^{1}H NMR: δ 10.62 (1H, bdd, $J = 1.8$, $J = 1.8$, H2), 7.64 (1H, dd, $J = 1.8$, $J = 1.8$, H4), 7.47 (1H, dd, $J = 1.8$, $J = 1.8$, H5), 4.28 (2H, t, $J = 7.4$, H1′), 4.07 (3H, s, H1′), 1.84 (2H, $J = 7.7$, $J = 7.4$, H2′), 1.30 (2H, bt, $J = 7.7$, H3′). ^{13}C NMR: δ 137.9 (C2), 123.7 (C4), 122.0 (C5), 49.7 (C1″), 36.5 (C1′), 32.1 (C2′), 19.2 (C3′), 12.5 (hep, $^1J_{CD} = 19.2$, C4′). HR-MS (ASAP): *m/z* calcd for $C_8H_{12}D_3N_2$ ($[M\text{-}Cl]^+$): 142.1419, found: 142.1417.

Results and discussion

Our previous deuterium isotope effect studies employed [C_4mim]Cl labeled on the C-2 or C-2,4,5 positions. Given the labile nature of the imidazolium protons, the preparation of

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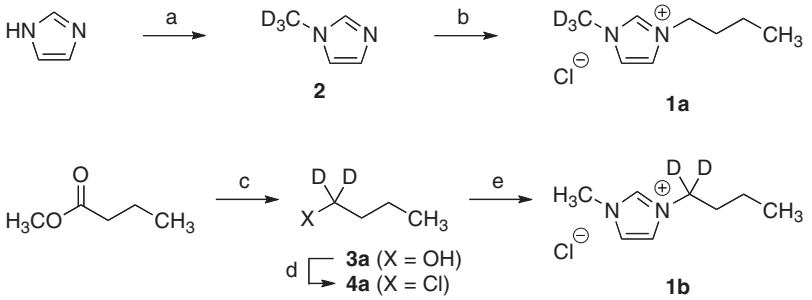
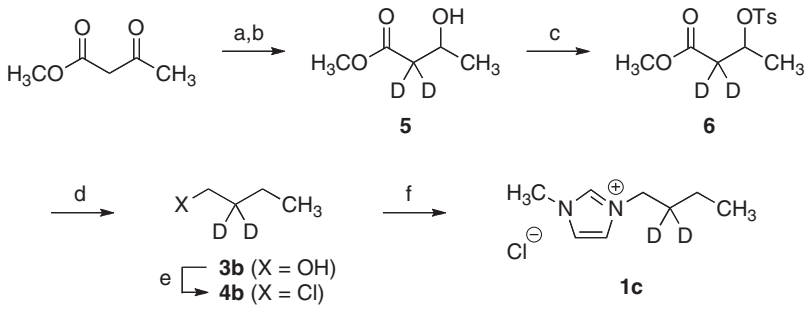
these isotopologues only requires an H/D exchange of the IL with D_2O, either pure or in the presence of a weak base.[2,6] In order to use established literature methods,[6,7] the synthesis of [C_4mim]Cl bearing sequential labels along the *N*-alkyl groups requires suitable deuterated 1-chlorobutane precursors. While similar compounds have been reported in the literature, their preparation employed relatively low-yielding reactions and expensive starting materials which are no longer commercially available.[8] Furthermore, an approach that uses analogous transformations to obtain the different 1-chlorobutane isotopologues was desirable.

As shown in Scheme 1, the preparation of **1a** and **1b** was straightforward. The former involved *N*-methylation of imidazole with [d_3]-iodomethane using potassium *tert*-butoxide as base and a catalytic amount of 18-crown-6,[9,10] followed by *N*-alkylation of **2** with 1-chlorobutane to afford the imidazolium salt in 84% combined yield. In the case of **1b**, methylbutyrate was first reduced to alcohol **3a** with $LiAlD_4$,[11] which was then converted to the corresponding chloroalkane with thionyl chloride. A slight excess of **4a** was then used to *N*-alkylate 1-methylimidazole and obtain the desired product in 63% overall yield (Scheme 1).

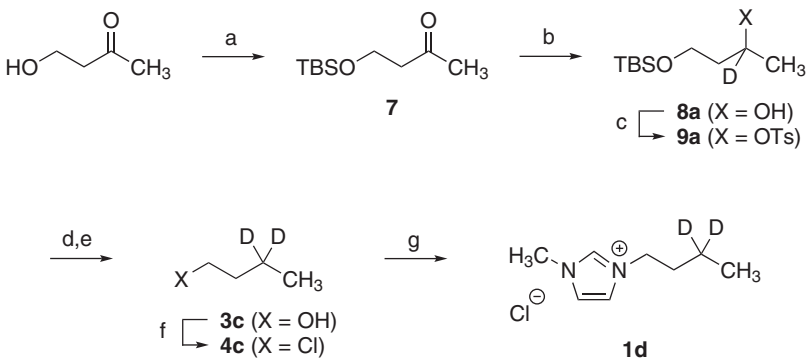
The preparation of **1c** required a 1-chlorobutane isotopologue deuterated in the C-2 position. An appropriately labeled precursor of this chloroalkane could be easily and inexpensively obtained by successive H/D exchange reactions on methyl acetoacetate. Owing to the labile nature of the C-2 protons of the b-ketoester,[12] the final deuterium content at this position is higher than 98% after three exchange cycles. Furthermore, the ketone in the C-3 position of the deuterated intermediate can be reduced to alcohol **5** using $NaBH_4$ without isolation from the D_2O solution after the last H/D exchange step (Scheme 2). The resulting β-hydroxyester was treated with *p*-toluenesulfonyl chloride to afford **6**, which after simultaneous reduction of the ester and tosylate functionalities with $LiAlH_4$ produced alcohol **3b**.[13] The next steps in the preparation of imidazolium chloride **1c**, which was obtained from **5** in 36% overall yield, were identical to those used in the synthesis of **1b**.



Scheme 1. (a) CD_3I, tBuOK, 18-crown-6, Et_2O (84%); (b) 1-Chlorobutane (quantitative); (c) $LiAlD_4$, THF (82%); (d) $SOCl_2$ (77%); and (e) 1-Methylimidazole (quantitative).



Scheme 2. (a) D_2O; (b) $NaBH_4$, D_2O (84% over both steps); (c) TsCl, pyridine (94%); (d) $LiAlH_4$, THF (61%); (e) $SOCl_2$ (63%); and (f) 1-Methylimidazole (quantitative).



Scheme 3. (a) TBDMSCl, imidazole (94%); (b) $NaBD_4$, MeOH (99%); (c) TsCl, pyridine, CH_2Cl_2 (98%); (d) $LiAlD_4$, Et_2O; (e) HCl/H_2O (69% over both steps); (f) $SOCl_2$ (54%); and (g) 1-Methylimidazole (quantitative).

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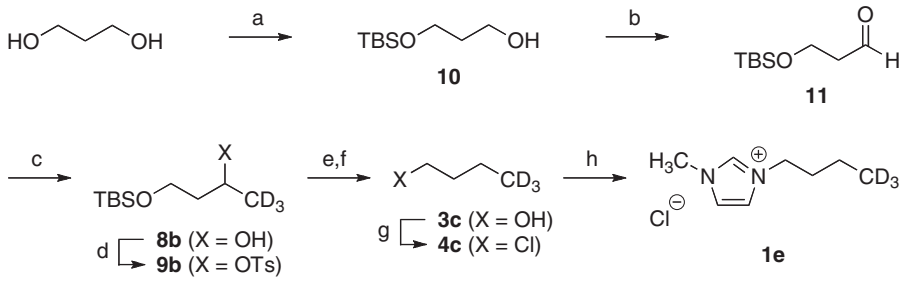
The synthesis of the 1-chlorobutane isotopologue needed to obtain **1d** started with the reduction of TBDMS-protected ketone **7** with $NaBD_4$ to yield monodeuterated alcohol **8a**. This intermediate was converted into tosylate **9a**, which was reduced with $LiAlD_4$ and deprotected under acidic conditions to afford **3c** (Scheme 3). After this point, the same transformations described



Scheme 4. (a) TBDMSCl, NaH, THF (96%); (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (c) CD_3I, Mg, Et_2O (65% over both steps); (d) TsCl, pyridine, CH_2Cl_2 (94%); (e) $LiAlH_4$, Et_2O; (f) HCl/H_2O (60% over both steps); (g) $SOCl_2$ (74%); and (h) 1-Methylimidazole (quantitative).

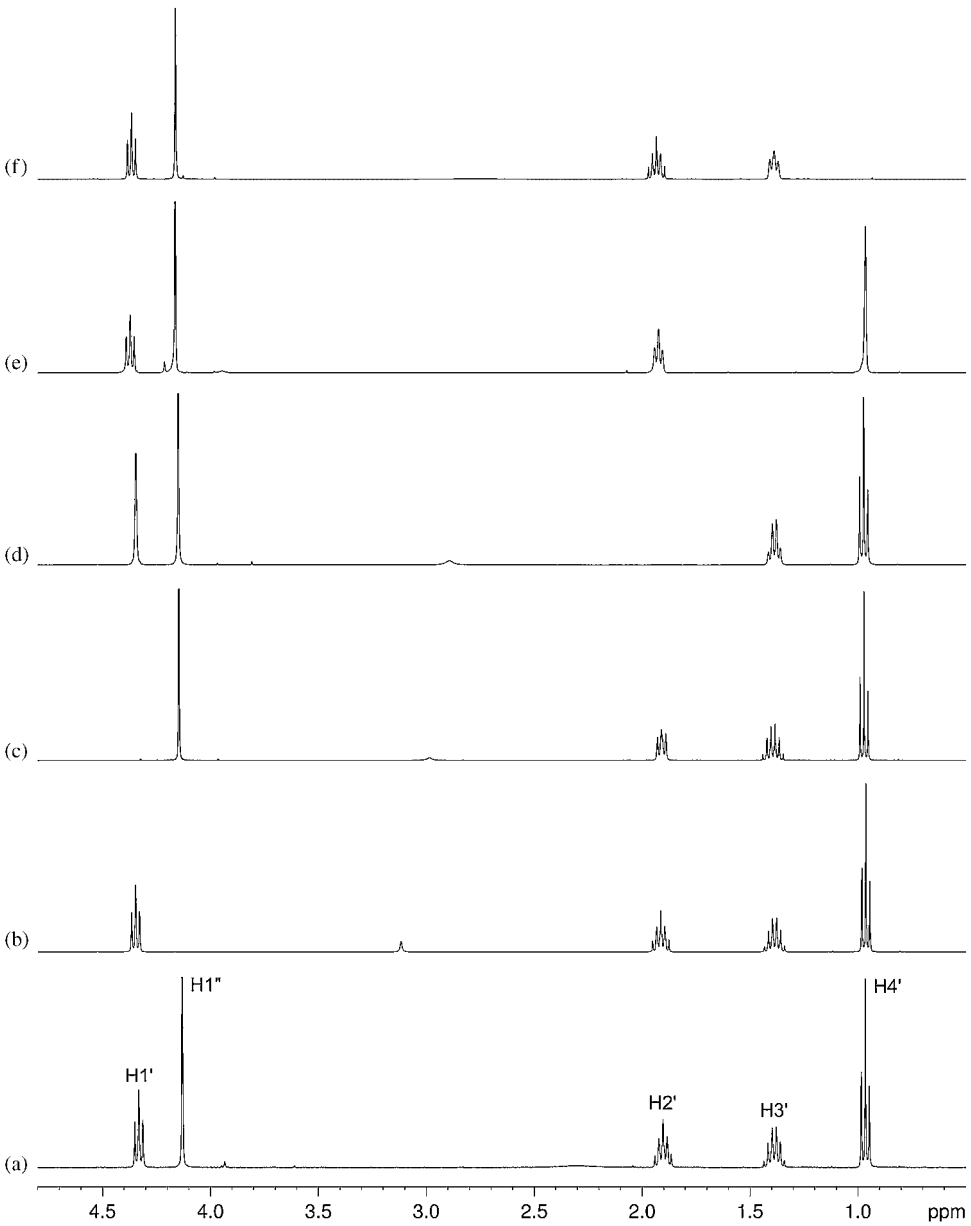


Figure 2. Aliphatic region of the ^1H NMR spectra of **1**(**a**) and its deuterium isotopologues **1a**–**e** (**b**–**f**).

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for the preparation of the previous imidazolium salts were employed to obtain **1d** in 36% combined yield following the initial deuterium incorporation reaction.

It is important to mention that the choice of solvent for the reduction of **9a** with $LiAlD_4$ is critical. While using either THF or diethyl ether leads to the elimination of the tosylate group almost quantitatively, performing the reaction in the former generates a 2:1 mixture of [3,3-d_2]-1-butanol and [4-d_1]-1-butanol after removal of the TBDMS protecting group. Interestingly, this apparent scrambling of the deuterium label is not observed in the reduction of butyrate **6** with $LiAlH_4$ in THF described earlier. Based on these results and on other preliminary experiments (data not shown), we believe that the formation of the side product is due to reductive cleavage of the THF ring by the metal hydride with participation of the silyl group present in compound **9a**.[14]

The last [C_4mim]Cl isotopologue in the series was prepared using singly protected propanediol **10** as a precursor. This alcohol was oxidized using standard Swern conditions to afford TBDMS-protected aldehyde **11**,[15] which was then converted to alcohol **8b** by treatment with [d_3]-methylmagnesium iodide (Scheme 4). The remaining steps were analogous to those detailed above for the preparation of **1d**, and led to imidazolium salt **1e** in 42% overall yield following the Grignard reaction.

Conclusions

To summarize, we described the preparation of deuterium isotopologues of [C_4mim]Cl sequentially labeled along the *N*-alkyl groups. The aliphatic region of their ^{1}H NMR spectra is presented in Figure 2.

As stated earlier, the approach employs a limited number of distinct reactions, and in several cases combines them efficiently into single-step processes. This is best exemplified in the preparation of imidazolium salt **1c**, which combines an H/D exchange reaction with a reduction in aqueous media as well as the reduction of tosylate and ester functionalities into single steps. It is also worth noting that all deuterium incorporation reactions were carried out using few and relatively inexpensive reagents (D_2O, $LiAlD_4$, $NaBD_4$, and CD_3I). As a result, we have been able to obtain the deuterated ILs in sufficient quantities to carry out a variety of Δ(H,D) measurements at a moderate cost. The results from these ongoing studies will be reported elsewhere in due course.

Acknowledgements

Funding from the National Science Foundation is acknowledged (Awards DUE-9952264 and CHE-0845026).

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