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The 2-Position of Imidazolium Ionic Liquids: Substitution and Exchange

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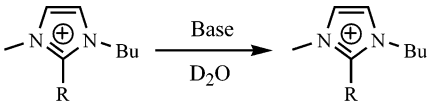

The 2-position of imidazolium cations is known to be relatively acidic, leading to the useful Arduengo-type carbenes. At the same time, the acidity of this site can lead to undesired side reactions when using imidazolium-based ionic liquids as solvents. In this note, we describe the surprisingly facile deuterium exchange at this position and also the synthesis and exchange under modestly basic conditions (triethylamine) of a series of 2-methyl-substituted compounds.

Interest in room temperature ionic liquids (RTILs) continues to grow.[1] These materials, once an object of scientific curiosity, are making their mark as solvents for a variety of applications, including organic and inorganic synthesis, battery applications, chromatographic stationary phases, and separation science. One of the attributes of this class of materials that has been widely publicized is the potential to generate a wide range of types of RTILs by the combination of various organic cations with numerous organic and inorganic anions. At the same time, the vast majority of the research in this area continues to focus on materials derived from imidazole. In part this is due to the simplicity in preparing these compounds and the generally lower melting points and viscosities of the RTILs derived from imidazole as compared to other classes (such as pyridinium and tetraalkylammonium RTILs). Under most circumstances, the imidazole-derived RTILs are considered to be "inert" solvents, but this is not always the case.[2] It is well-established that the 2-position can be deprotonated to form a stabilized carbene.[3] Indeed, this Arduengo-type carbene has been implicated in a number of the advantageous applications of RTILs, particularly in the area of transition metal catalyzed reactions.[4] Most typically the deprotonation of the imidazolium cation is conducted with an alkoxide base.

Despite all of these positive applications, this facile deprotonation can also be detrimental (Scheme 1). This was clearly noted by Aggarwal in his studies of the Baylis−Hillman reaction in imidazolium RTILs.[5] The basic catalysts employed in these reactions (such as DABCO) resulted in deprotonation at C2 on the butylmethylimidazolium (BMIM) salt. The resulting carbene was then responsible for a number of side reactions with the aldehyde component of the reaction mixture, considerably reducing the yield of the desired Baylis−Hillman product.

We have made a similar observation in our efforts exploring RTILs as homogeneous supports.[6] Attempts to acylate a fructose-derived RTIL under basic conditions at ambient temperature led to considerable darkening of the reaction. The isolated, acylated RTIL was a dark brown liquid that was actually a complex mixture of compounds, including some that appeared to be C2-modified RTILs. In the final cleavage of the supported product from the ionic liquid, it was also noted that the pale yellow reaction mixture became dark brown upon treatment with either aqueous sodium hydroxide or sodium methoxide in methanol. In either case, the recovered RTIL was again a dark brown liquid that contained a number of imidazolium byproducts. In both cases (acylation and cleavage), the darkening could be avoided by employing less basic conditions.

These observations raised two questions: (1) Could a 2-substituted fructose-derived ionic liquid be readily prepared that would avoid this deprotonation problem and (2) how acidic is this 2-position? Both of these issues have been addressed and are the central topic of this note.

2-Substituted imidazolium RTILs are certainly known. Indeed, a few of the 2-methyl compounds are commercially available.[7] Most typically, such compounds are used to demonstrate that Arduengo carbenes are likely intermediates in various transition metal catalyzed reactions in RTILs. At the same time, there is a report that employs a 2-methylimidazolium RTIL as a solvent for some organozinc reagents.[8] More recently, Chu and coworkers have also investigated a 2-substituted imidazolium ionic liquid as a solvent for the Baylis−Hillman reaction and found that it avoids the problems encountered by Aggarwal with the simple BMIM salts.[9] As a result, it certainly appears that these compounds are

(1) Welton, T. *Chem. Rev.* **1999**, *99*, 2071−2083. Freemantle, M. *C&E News* **2000**, 37−50. Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772−3789. Dupont, J.; de Souza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, *102*, 3667−3692.

(2) Dupont, J.; Spencer, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 5296−5297.

(3) Arduengo, A. J., III; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361−363

(4) In addition to the many applications of these carbene species found in the reviews in ref 1, specific study and characterization of these complexes can be found in the following two articles. Xu, L.; Chen, W.; Xiao, J. *Organometallics* **2000**, *19*, 1123−1127. Mathews, C. J.; Smith, P. J.; Welton, T.; White, A. J. P.; Williams, D. J. *Organometallics* **2001**, *20*, 3848−3850.

(5) Aggarwal, V. K.; Emme, I.; Mereu, A. *Chem. Commun.* **2002**, 1612−1613.

(6) Handy, S. T.; Okello, M. *Tetrahedron Lett.* **2003**, *44*, 8399−8402.

(7) Companies such as Aldrich, Strem, and EMD all sell 2-methylimidazolium ionic liquids.

(8) Sirieix, J.; Ossberger, M.; Betzemeier, B.; Knochel, P. *Synlett* **2000**, 1613−1615.

(9) Hsu, J.-C.; Yen, Y.-H.; Chu, Y.-H. *Tetrahedron Lett.* **2004**, *45*, 4673−4676.

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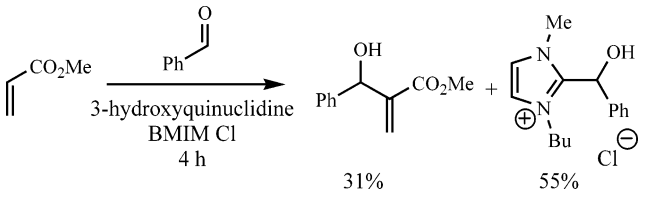
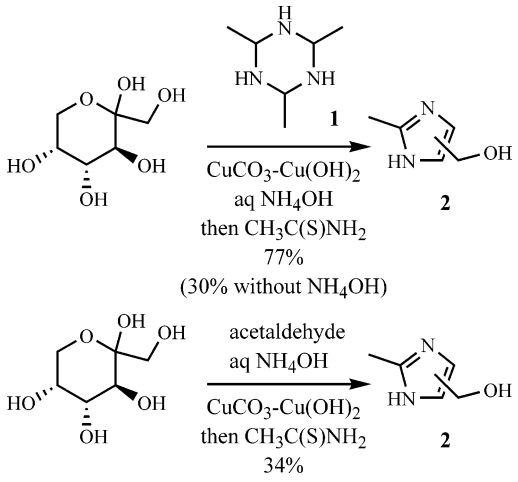
SCHEME 1. Aggarwal's Baylis–Hillman Reaction in a RTIL



SCHEME 2. C2-Substituted Fructose-Derived Imidazole Preparation



considerably less acidic and more base tolerant than the simple 2-unsubstituted compounds.

For the preparation of a 2-methylfructose-derived ionic liquid, the most promising route was based on the historical route to 2-methylimidazole, which involves the condensation of glyoxal with the acetaldehyde ammonia trimer **1**.[10] Armed with this information, the degradation/condensation reaction of fructose with trimer **1** in place of formaldehyde and ammonium hydroxide was attempted (Scheme 2). Much to our delight, this did afford the desired C2 methyl product **2**, although in modest yield (30%). After reexamining the literature surrounding the use of trimer **1**, one distinct possible reason for this low yield was that trimer **1** was dissociating under the reaction conditions and evolving ammonia.[10] To compensate for this loss of ammonia, the same reaction was attempted again, but this time with the addition of ammonium hydroxide. Indeed, the yield of **2** did improve to 77%, or nearly the same as we reported earlier for the 2-unsubstituted compound.[6]

On the basis of this success, one further variation was attempted, this time with ammonium hydroxide and acetaldehyde instead of trimer **1**. Although this did also afford the desired imidazole **2** in 34% yield, the reaction afforded numerous products and the isolation of **2** required extensive chromatography. It is likely that further optimization of these reaction conditions can improve upon this result, including pregeneration of an equilibrating mixture of acetaldehyde/ammonia adducts including trimer **1**.

With imidazole **2** in hand, the next step leading to imidazolium salt **3** involved alkylation of the nitrogens (Scheme 3). In previous work on the 2-unsubstituted series, the use of potassium *tert*-butoxide in ethanol had proved to be the optimal method on large scale.[6] Application of these same conditions to **2** resulted in the formation of very modest amounts of **4** (35%) along with significant amounts of the product of N and O alkylation (38%). After considerable experimentation, it was discovered that the use of potassium hydroxide in DMF at 55 °C afforded imidazole **4** in reasonable (60%) yield with only a small amount of double alkylation (<5%). With **4** in hand, the remaining imidazole nitrogen was then alkylated with methyl iodide to afford the iodide salt **3**. This salt turned out to be a highly viscous, orangish liquid at room temperature. Following anion metathesis with either silver dicyanimide or lithium triflimide, the triflimide and dicyanimide salts were obtained as clear liquids which were qualitatively slightly more viscous than the corresponding 2-unsubstituted fructose-derived compounds.

With a synthetic route to the 2-methyl ionic liquids in hand, the way was paved to address the question of how acidic this position is.[11] To that end, a series of deuterium-exchange experiments were initiated (Table 1). To establish a point of comparison, the 2-unsubstituted RTILs were examined first. Although it was expected that the 2-position in these compounds would be relatively acidic, it was surprising to note that the dicyanimide salt of 2-unsubstituted fructose-derived RTIL underwent exchange quite rapidly in the absence of any added base (entry 1). Indeed, a similar result was obtained for the corresponding simple BMIM dicyanimide salt (entry 2). One possible explanation for these observations is the fact that aqueous solutions of sodium dicyanimide are reported to be slightly basic (pH of roughly 8).[12] As a result, the anion may be serving as the base in these salts. To test this hypothesis, a similar exchange experiment was conducted on BMIM tetrafluoroborate (entry 3). In this case, no exchange was observed for up to 72 h without the addition of some base.

The 2-methyl RTILs were expected to be much less susceptible to exchange. As a result, it was not surprising that these salts failed to undergo any detectable exchange in the absence of added base. What was more surprising was the observation that even a very mild base such as triethylamine was sufficient to induce a slow but measurable exchange at the 2-methyl group. Thus, both the fructose-derived compound **6** and the 3-butyl-1,2-dimethylimidazolium salts[13] (with either the dicyanimide or chloride anion) would eventually undergo complete exchange of the three protons at this position (entries 5, 7, and 9). The presence of a stronger base such as potassium hydroxide greatly increased this rate, but still resulted in little difference in terms of rate of exchange on the three compounds (entries 4, 6, and 8).

Further evidence that the 2-unsubstituted and 2-methyl-substituted positions are reasonably acidic came from a series of attempted alkylation reactions on RTIL **7**

(10) Radziszewski, B. *Chem. Ber.* **1886**, *15*, 2706–2708.

(11) There has been a single report measuring the pK_a of the 2-position on an imidazolium salt. Kim, Y.-J.; Streitwieser, A. *J. Am. Chem. Soc.* **2002**, *124*, 5757–5761.

(12) Sodium dicyanimide, Merck Safety Data Sheet, catalog no. 490015.

(13) The 2-methyl BMIM salts were prepared in the same fashion as the simple BMIM salts, except starting with 1,2-dimethylimidazole.

SCHEME 3. Imidazolium Cation Preparation

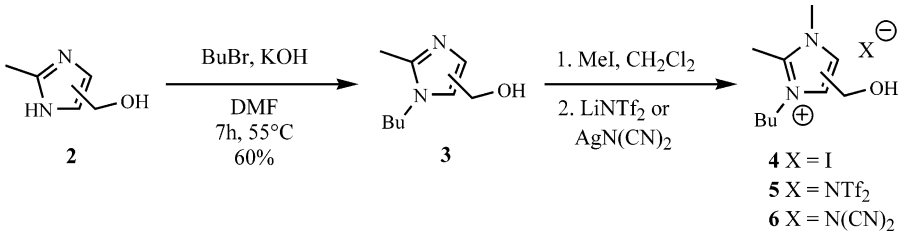
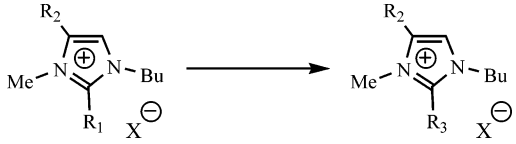


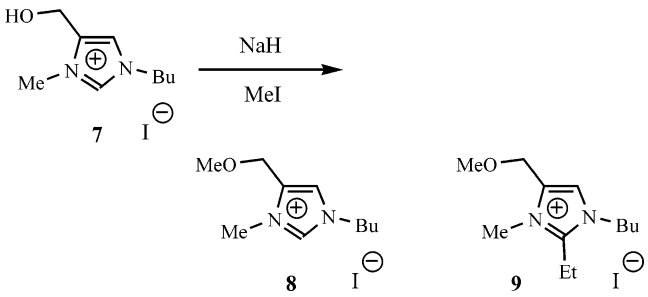
TABLE 1. Deuterium Exchange Results for Imidazolium RTILs



entry	R_1	R_2	R_3	X	base	rate (min^{-1})[a]
1	H	$HOCH_2$	D	$N(CN)_2$	none	3.0×10^{-3}
2	H	H	D	$N(CN)_2$	none	4.1×10^{-2}
3	H	H	D	BF_4	none	no exchange
4	CH_3	$HOCH_2$	CD_3	$N(CN)_2$	KOH	2.3×10^{-3}
5	CH_3	$HOCH_2$	CD_3	$N(CN)_2$	Et_3N	0.04×10^{-3}
6	CH_3	H	CD_3	$N(CN)_2$	KOH	1.0×10^{-3}
7	CH_3	H	CD_3	$N(CN)_2$	Et_3N	0.04×10^{-3}
8	CH_3	H	CD_3	Cl	KOH	2.1×10^{-3}
9	CH_3	H	CD_3	Cl	Et_3N	0.04×10^{-3}

[a] Determined by ^1H NMR integration. Average of 3 exchange reactions.

TABLE 2. Alkylation Reactions on Imidazolium Salt 7



entry	equiv of NaH	equiv of MeI	time (h)	ratio of products[a] (**7**:**8**:**9**)
1	0	3	12	all **7**
2	0.5	3	1	1.85:1.0:0.0
3	6	10	12	all **9**

[a] Determined by ^1H NMR.

(Table 2). Treatment of **7** with an excess of sodium hydride and methyl iodide resulted in the formation of 2-ethyl methyl ether **9** as the sole product (entry 3). A similar result was obtained starting with RTIL **4**. This differs slightly from the observation of Begtrup on 1,3-dimethylimidazolium iodide, in which treatment under the same conditions resulted in the formation of 2-isopropyl-1,3-dimethylimidazolium iodide.[14] The effective acidity of the 2-position is also apparent from alkylation studies on RTIL **7**. Treatment with a limiting amount of sodium hydride and excess methyl iodide results in the formation of only methyl ether **8** and recovered starting material, indicating that the alkoxide is being formed first and then subsequent deprotonations occur at the 2-position (entry 2). Thus, the acidity of the 2-position is less than that of the hydroxyl group.

The result of these studies indicates that the 2- position of imidazolium ILs can be rendered less acidic by replacing the hydrogen with a methyl group. Even this methyl group is not completely inert, however, and can be subject to deprotonation under surprisingly mild conditions. Still, this added stability is sufficient to avoid some of the competing reactions that are so common in the simple imidazolium series.[9] Efforts are underway to employ these 2-methyl-substituted ILs derived from fructose as more base-stable supports and to explore the preparation of even more base-stable derivatives. These efforts will be reported in due course.

Experimental Section

2-Methyl-1*H*-imidazol-4(5)-ylmethanol [2]. To 11.1 g (0.0500 mol) of copper carbonate basic was added 75 mL of water, followed by 11.4 mL (0.600 mol) of 28−30% aqueous ammonium hydroxide. During this addition, the green suspension became a homogeneous deep blue solution. To this solution was added 11.9 g (0.0600 mol) of acetaldehyde/ammonia trimer **1** and 4.5 g (0.024 mol) of D-fructose. The resulting mixture was swirled and then placed in a boiling water bath. After 30 min of heating and occasional swirling, a moderate current of air was bubbled through the solution with continued heating for 2 h. The reaction mixture was then chilled in an ice bath for 3 h and the olive-brown precipitate was filtered off. The filter cake was washed with 50 mL of chilled water or until no more blue color was observed. The residue was then suspended in 200 mL of water and 4.5 g (0.060 mol) of thioacetamide was added. The resultant brown-black suspension was stirred at 50 °C for 2 h. The precipitated CuS was removed via filtration and the reddish/brown filtrate was concentrated in vacuo. The resulting residue was purified on silica gel with use of aqueous ammonium hydroxide/methanol/ethyl acetate (5:35:60) to afford 2.06 g (77%) of **2** as an off-white solid (mp 112−113 °C). IR (Nujol) 3213, 2972, 2928, 1664, 1540, 1419, 1118, 1037, 993, 757 cm^{-1}; ^1H NMR (360 MHz, D_2O) δ 6.89 (s, 1H), 4.44 (s, 2H), 2.27 (s 3H); ^{13}C NMR (90 MHz, D_2O with a dioxane reference) δ 146.4, 137.0, 117.49, 56.7, 13.2. Mass spec (EI) calcd for $C_5H_8N_2O$ 112.0634, found 112.0633.

1-Butyl-2-methyl-1*H*-imidazol-4(5)-ylmethanol [3]. To a stirred solution of 0.1072 g (0.9559 mmol) of **2** in 2.4 mL of anhydrous DMF was added 0.2676 g (4.7793 mmol) of finely powdered potassium hydroxide, followed by 114 μL (1.0515 mmol) of butyl bromide. The mixture was heated to 55 °C for 7 h. Once TLC indicated complete consumption of starting material, the reaction was quenched by the addition of powdered sodium bicarbonate. The mixture was filtered through Celite, the filter cake rinsed with ethanol, and the filtrate concentrated in vacuo. The crude product was purified on silica gel with use of ammonium hydroxide/methanol/ethyl acetate (1:10:89) to afford 0.096 g (60%) of **3** as a pale yellow oil. IR (neat) 3305, 2959, 1659, 1632, 1546, 1518, 1460, 1425, 1380, 1335, 1232, 1165, 1116, 1040, 1010, 824, 736 cm^{-1}; ^1H NMR (360 MHz,

(14) Begtrub, M. *Bull. Soc. Chim. Belg.* **1988**, *97*, 573−577.

$CDCl_3$) δ 7.1 (s, 1H), 4.7 (s, 2H), 4.0 (t, 2H) 2.7 (s 3H), 1.8 (m, 2H), 1.4 (m, 2H), 1.0 (t, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 142.8, 132.9, 118.3, 53.7, 47.5, 31.6, 19.5, 13.5, 11.2. Mass spec (EI) calcd for $C_9H_{16}N_2O$ 168.1258, found 168.1259.

3-Butyl-4(5)-hydroxymethyl-1,2-dimethyl-3*H*-imidazolium Iodide [4]. To a solution of 0.9284 g (5.4844 mmol) of **3** in 3.7 mL of methylene chloride under argon was added 0.3759 mL (6.0345 mmol) of iodomethane. This solution was heated to reflux and stirred overnight. After cooling, the solvent was removed in vacuo. The residual material was extracted with ether (5 × 5 mL) and the ether layer decanted. The remaining ionic liquid layer was dissolved in 5 mL of methylene chloride and filtered through Whatman #1 filter paper. Removal of the solvent in vacuo afforded 1.6051 g (94%) of iodide **4** as a pale orange liquid. IR (neat) 3318, 3088, 2958, 2932, 2872, 1664, 1621, 1536, 1463, 1418, 1382, 1156, 1128, 1064, 1028, 808, 732 cm^{-1}; ^{1}H NMR (360 MHz, acetone-d_6) δ 7.76 (s, 1H), 4.66 (s, 2H), 4.32 (t, 2H), 3.92 (s 3H), 2.85 (s, 3H), 1.82 (m, 2H), 1.41 (m, 2H), 0.92 (t, 3H); ^{13}C NMR (90 MHz, acetone-d_6) δ 145.6, 134.3,120.2, 52.9, 48.7, 33.9, 32.5, 20.0, 13.9, 11.4. Mass spec (EI) calcd for $C_{10}H_{19}N_2O$ 183.1492, found 183.1490.

3-Butyl-4(5)-hydroxymethyl-1,2-dimethyl-3*H*-imidazolium Triflimide [5]. Lithium triflimide (0.19 g, 0.66 mmol) of was dissolved in 0.33 mL of water. In a separate flask, 0.2054 g (0.6619 mmol) of iodide **4** was dissolved in 0.66 mL of water. Both solutions were heated to 70 °C and then combined. The combined solution was allowed to cool to room temperature while stirring was continued for 3 h. The top aqueous layer was decanted and extracted with methylene chloride (2 × 5 mL). These washes were combined with the original remaining ionic liquid layer and washed with water (2 × 5 mL). The organic layer was filtered through a short plug of basic alumina and the solvent removed in vacuo. The residue was dried on a vacuum line overnight to afford 0.2193 g (72%) of **5** as a pale yellow liquid. IR (neat) 3523, 3137, 2967, 2939, 2879, 1624, 1590, 1539, 1467, 1420, 1351, 1191, 1136, 1056, 789, 762, 740, 654, 616 cm^{-1}; ^{1}H NMR (360 MHz, acetone-d_6) δ 7.19 (s, 1H), 4.58 (s, 2H), 3.99 (t, 2H), 3.72 (s 3H), 2.56 (s, 3H), 1.70 (m, 2H), 1.30 (m, 2H), 0.88 (t, 3H); ^{13}C NMR (90 MHz, acetone-d_6) δ 144.4, 133.4, 119.7 (q, $J^{C,F}$ = 315 Hz), 119.2, 118.0, 144.4, 53.2, 38.2, 32.2, 31.4, 19.4, 13.3, 9.6. Anal.: C 39.12 (39.09), H 5.20 (5.28), N 11.4 (11.44).

3-Butyl-4(5)-hydroxymethyl-1,2-dimethyl-3*H*-imidazolium Dicyanimide [6]. To a solution of 0.2010 g (0.6477 mmol) of 3-butyl-4(5)-hydroxymethyl-1,2-dimethyl-3*H*-imidazol-1-ium iodide **4** in 1.5 mL of methanol was added 0.1127 g (0.6477 mmol) of silver dicyanimide. The resultant mixture was left to stir overnight at room temperature. The reaction was worked up by filtration of the reaction mixture through a Hirsch funnel under vacuum. The filtrate was concentrated in vacuo, to afford 0.1700 g of the crude salt. Further purification was achieved by dissolving the crude in about 4 mL of dichloromethane, drying with MgSO4, gravity filtration, and concentration in vacuo to afford 0.1424 g (88%) of **6** as a pale yellow liquid. IR (neat) ν_{max} 3522, 3366.33, 3135, 2965, 2939, 2878, 2245, 2201, 2142.26, 1624, 1539, 1465, 1420, 1351, 1193, 1136, 1057, 789, 762, 740, 654, 617 cm^{-1}. ^{1}H NMR (360 MHz, acetone-d_6) δ 7.54 (s, 1H), 4.72 (s, 1H), 4.25 (t, 2H), 3.89 (s, 3H), 2.78 (s, 3H), 1.84 (m, 2H), 1.40 (m, 2H), 0.94 (t, 3H). ^{13}C NMR (90 MHz, acetone-d_6) δ 146.1, 134.7, 119.9, 53.8, 48.7, 32.8, 32.5, 20.1, 13.8, 10.0. Anal.: C 57.81 (57.77), H 7.68 (7.70), N 28.09 (28.01).

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Supporting Information Available: Methods for deuterium exchange studies and spectra for compounds **2**, **3**, **4**, **5**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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