JOC Notes

Grignard Reactions in Imidazolium Ionic Liquids

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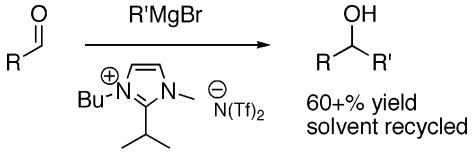
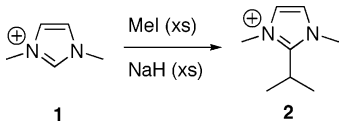


A new, base-stable, imidazolium room-temperature ionic liquid (RTIL) has been prepared and applied to the addition of Grignard reagents to carbonyl compounds. These reactions occur readily at ambient temperature to afford the alcohol products in good to excellent yield. The RTIL can be recycled and reused numerous times without any difficulty.

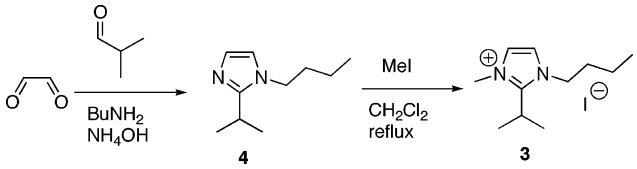
The range of uses and applications of room-temperature ionic liquids continues to grow at a rapid rate.[1] Indeed, it is difficult to find an organic reaction that has not been tried in these solvents. In many cases, there is little difference between the same chemistry in room-temperature ionic liquids (RTILs) and conventional solvents, but that is not always the case. The most popular of the RTILs, those based on the imidazolium cation, can have a very substantial effect on the chemistry carried out in them.[2] In particular, transition-metal-catalyzed reactions in imidazolium ionic liquids often result in the formation of N-heterocyclic carbene (NHC) modified transition-metal catalysts via generation of the NHCs in situ.[3] These catalysts can demonstrate enhanced reactivity and/or stability, rendering both these catalysts and their use in RTILs very valuable to the synthetic community.

At the same time, the ease with which the 2-position of the imidazolium cation can be deprotonated can result in problems with base-mediated reactions. In particular, reports by Aggarwal and ourselves have demonstrated that there are practical limitations.[4,5] Further studies from this lab have shown that the 2-position can be deprotonated under surprisingly mild conditions.[6] As a result, it is of clear interest to generate more base-stable RTILs.

SCHEME 1. Alkylation Studies of Begtrup



SCHEME 2. Condensation Route to Imidazolium Salt 3



One obvious method for solving this problem is to simply avoid the imidazolium cation. RTILs with cations based on tetraalkylammonium or phosphonium salts are well-known and certainly expected to be less sensitive to a base. At the same time, though, these nonimidazolium RTILs are generally less well characterized than the imidazolium RTILs and certainly less well-known outside of the ionic liquid community. Further, particularly in the case of the phosphonium RTILs, they are much more viscous, which can make working with them more difficult.

A second option is to render the 2-position of the imidazolium cation less acidic. The simple addition of a methyl group at this position does render the imidazolium salts somewhat less base sensitive, but we have noted that this methyl group can still be deprotonated under surprisingly mild conditions.[6] As a result, it appears that greater substitution will be required. Indeed, a report by Begtrup provides a guide as to what substitution might avoid issues with deprotonation (Scheme 1).[7] In this report, it was noted that treatment of salt **1** with excess sodium hydride and methyl iodide resulted in the formation of isopropyl-substituted salt **2**. No product of further alkylation could be detected, even after prolonged reaction times. As a result, it appears that the 2-isopropyl group cannot be deprotonated, at least under those particular conditions.

Armed with this information, our first goal was the preparation of imidazolium salt **3**. This salt was prepared via two methods. The first method was part of an effort targeting a general approach for the concise synthesis of 2-substituted imidazolium salts (Scheme 2). Thus, glyoxal was treated sequentially with butylamine, isobutyraldehyde, and ammonium hydroxide in a manner similar to that reported by Nakamura and co-workers for the synthesis of a 2-substituted imidazole.[8] Unfortunately, this route was highly capricious, even on a small scale (1 mmol), and did not scale-up well.

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(1) Welton, T. *Chem. Rev.* **1999**, *99*, 2071−2083. Freemantle, M. *C&E News* **2000**, 37−50. Wasserscheid, P., Welton, T., Eds. *Ionic Liquids in Synthesis*; Wiley-VCH: Weinheim, 2002.

(2) Wilkes, J. S. *J. Mol. Catal. A* **2004**, *214*, 11−17. Zhao, H. *Phys. Chem. Liq.* **2003**, *41*, 545−557. Handy, S. T. *Curr. Org. Chem.* **2005**, *9*, 959−988.

(3) 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.

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

(5) Handy, S. T.; Okello, M. *J. Org. Chem.* **2005**, *70*, 2874−2877.

(6) Handy, S. T.; Okello, M. *J. Org. Chem.* **2005**, *70*, 1915−1918.

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

(8) Nakamura, T.; Sato, M.; Kakinuma, H.; Miyata, N.; Taniguchi, K.; Bando, K.; Koda, A.; Kameo, K. *J. Med. Chem.* **2003**, *46*, 5416−5427.

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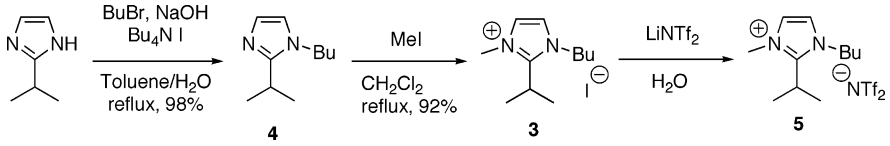
SCHEME 3. Alkylation Route to Imidazolium Salt 3



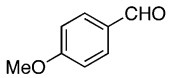
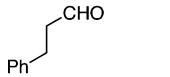
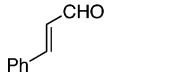
A more satisfactory, though longer, route employed standard imidazole alkylation chemistry (Scheme 3). Thus, alkylation of 2-isopropylimidazole with *n*-butyl bromide in the presence of sodium hydroxide under phase-transfer conditions afforded imidazole **4** in 98% yield.[9] A second alkylation with methyl iodide in refluxing methylene chloride then afforded the desired iodide salt in 92% yield. Using this strategy, 10−20 g scale reactions could be easily carried out with good reproducibility.

With the desired iodide salt in hand, standard anion metathesis afforded the triflimide salt **5** as a very pale yellow liquid in essentially quantitative yield. Qualitatively, this RTIL is slightly more viscous than BMIM NTf_2 but still readily poured and transferred via pipet.

At this point, the use of RTIL **5** in main group organometallic chemistry could be studied. There have been very few reports of main group organometallic chemistry in RTILs. Most have dealt with the use and/or generation of organozinc reagents in imidazolium or pyridinium RTILs.[10] These species are generally less basic and less reactive, which may account for the greater number of successful reports of their use in RTILs. Beyond these reports, there have been only two reports of the use of main group organometallic reagents in RTILs.[11,12] In both cases, Grignard reagents were employed. Clyburne and co-workers reported that Grignard reagents could be successfully used in tetraalkylphosphonium RTILs; the products could be separated, and the RTIL could be reused in a relatively simple fashion.[11] More recently, Wilhelm and co-workers have reported a new class of RTILs (2-phenylimidazolinium salts) that are also compatible with Grignard reagents.[12] Again, the products of the addition of these reagents to carbonyl compounds could be readily separated from the RTIL and the RTIL could be recycled using simple extraction methods.

Our own efforts also targeted the addition of Grignard reagents to aldehydes. The first aldehyde that was employed was *p*-anisaldehyde. The reaction of this aldehyde with both methylmagnesium chloride and vinylmagnesium bromide was conducted in RTIL **5**. The Grignard reagents were both used as solutions in THF as supplied by commercial sources. Because of the nonvolatile nature of the RTIL, no external cooling was applied, although subsequent efforts have shown that the reactions can also be carried out using an ice bath with no solidification of the RTIL. The reaction vessels did become slightly warm to the touch after addition of the Grignard reagent. After 3 h, the reactions were quenched by the addition of dilute (0.1 N) hydrochloric acid. The organic products were then extracted using 10% ether in hexanes to afford, after purification,

TABLE 1. Grignard Reactions in RTIL 5[a]

Entry	Carbonyl	Grignard	Yield[b]
1		MeMgCl	78%[c]
2			81%[13]
3		PhMgBr	69%[c]
4		MeMgCl	75%[c]
5			82%[14]
6		MeMgCl	67%[c]
7			94%[15]

[a] Reaction conditions: 0.5 mmol of the carbonyl compound in 2 mL of RTIL **5** and 0.55 mmol of the Grignard reagent. [b] Isolated yield. [c] Identity confirmed by comparison to commercially available material.

the anticipated addition products in good yield (Table 1, entries 1 and 2). A similar reaction with phenylmagnesium bromide also afforded the anticipated addition product in good yield (Table 1, entry 3).

For the product extraction stage, pure ether could also be employed. However, RTIL **5** does exhibit slight solubility in ether, meaning that, over the course of several recyclings, the volume of the RTIL remaining will decrease. On the other hand, the use of the 10% ether in hexane solution was sufficient to completely extract the products from the RTIL because NMR analysis of the recovered RTIL layer showed no traces of either the addition products or the starting aldehyde. At the same time, NMR analysis of the concentrated crude organic extract layer showed no trace of RTIL **5**, indicating that the use of 10% ether in hexanes avoids leaching of the RTIL during product extraction.

For the recycling of the RTIL layer, two options were explored. In one case, the aqueous layer was simply removed following the extraction of the organic products. The remaining RTIL was then dried under vacuum for 36−48 h prior to use in the next Grignard addition. Although this option may leave some magnesium salts in the RTIL layer, it worked satisfactorily. The other option was to employ a method akin to that reported by both Clyburne and Wilhelm.[11,12] In this case, after extraction of the organic products, the RTIL layer was diluted with methylene chloride, the aqueous layer was separated, and the RTIL layer was washed with water. This organic layer was then dried with magnesium sulfate, concentrated, and dried under vacuum overnight. Because there did not appear to be any significant difference between the two recycling methods, both were used interchangeably during the following studies. It should also be noted that the same two ionic liquid samples that were used in the first two reactions (Table 1, entries 1 and 2) were recycled repeatedly and used as the solvent for all of the experiments reported in this paper.[16]

(9) Khabnadideh, S.; Rezaei, Z.; Khalafi-Nezhad, A.; Bahrinajafi, R.; Mohamadi, R.; Farrokhroz, A. A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2863−2865.

(10) Law, M. C.; Wong, K.-Y.; Chan, T. H. *J. Org. Chem.* **2005**, *70*, 10434−10439. Law, M. C.; Wong, K.-Y.; Chan, T. H. *Green Chem.* **2004**, *6*, 241−242. Sirieix, J.; Ossberger, M.; Betzemeier, B.; Knockel, P. *Synlett* **2000**, 1613−1615.

(11) Ramnial, T.; Ino, D. D.; Clyburne, J. A. C. *Chem. Commun.* **2005**, 325−327.

(12) Jurcik, V.; Wilhelm, R. *Green Chem.* **2005**, *7*, 844−848.

(13) Chang, C.; Kumar, M. P.; Liu, R. *J. Org. Chem.* **2004**, *69*, 2793−2796.

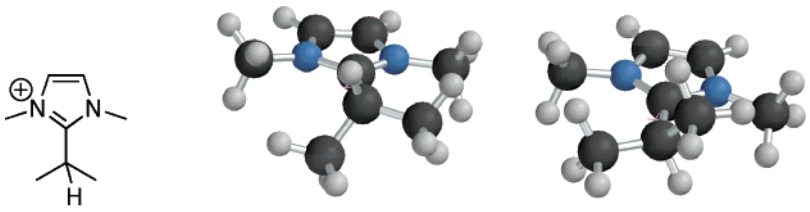
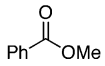


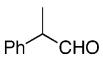
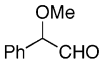
FIGURE 1. Conformations of the 2-isopropyl-1,3-dimethylimidazolium cation.

TABLE 2. Grignard Reactions with Ketones and Esters in RTIL 5[a]

Entry	Carbonyl	Grignard	Yield[b]
1		MeMgCl	80%[c]
2		PhMgBr	74%[c]
3		PhMgBr[d]	83%[c]

[a] Reaction conditions: 0.5 mmol of the carbonyl compound in 2 mL of RTIL **5** and 0.55 mmol of the Grignard reagent. [b] Isolated yield. [c] Identity confirmed by comparison to commercially available material. [d] 1.1 mmol of Grignard reagent was employed.

TABLE 3. Felkin−Ahn and Cram Chelate Studies[a]

Entry	Carbonyl	Grignard	Yield[b]	Ratio[c]
1		MeMgCl	92%	2.7:1[17]
2			92%	2.9:1[17]
3		MeMgCl	63%	1:4.2[18]
4			82%	1:3.9[18]

[a] Reaction conditions: 0.5 mmol of the carbonyl compound in 2 mL of RTIL **5** and 0.55 mmol of the Grignard reagent. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] 1.1 mmol of Grignard reagent was employed.

The addition to other aldehydes was equally effective, affording good to excellent yields of the addition products. Modest yields (as found in entry 6) were not due to incomplete extraction of the product from RTIL **5** and appear to be the result of loss during purification because the weight of the crude extracted product (prior to purification) was near quantitative. In all cases, the identity of the products was confirmed by comparison of their spectral data with that reported in the literature.

Also noteworthy is the fact that these conditions are applicable to the addition of Grignard reagents to ketones and esters (Table 2). Again, yields are good and the products could be readily extracted from RTIL **5** using 10% ether/hexanes.

Another area of study was the influence of the RTIL solvent on the facial selectivity of the addition of Grignard reagents to aldehydes such as **6** and **7** (Table 3). In the case of aldehyde **6**, the anticipated Felkin−Ahn selectivity for the syn isomer was obtained, with ratios similar to those obtained using THF as the solvent.[17] Aldehyde **7**, on the other hand, offered an opportunity to determine if good Cram chelate selectivity would still be observed in the highly ionic environment of the RTIL. In the event, selectivity for the Cram (anti) isomer was observed, again similar to that reported for the corresponding addition in THF.[18] Thus, it appears that the highly ionic nature of RTIL **5** does not interfere in the formation of the chelated intermediate reported to be responsible for the anti selectivity of these additions.

One obvious question from these studies is why the isopropyl group is sufficient to afford an imidazolium cation that is stable to deprotonation, particularly because a potentially acidic proton still remains (Figure 1). Upon further reflection, the answer appears to at least partially lie in the conformation of the imidazolium cation of RTIL **5**. Focusing on the bond between the isopropyl group and the imidazolium ring, it is assumed that the hydrogen would be required to be in a position aligned with the π system (conformation **8**) to be readily removed because the forming anion can be delocalized, and thus stabilized, by the imidazolium π system. However, the preferred conformation is **9**, in which the proton is nearly orthogonal to the π system (−15.7° dihedral angle with respect to the imidazolium ring vs the dihedral angle of −75.7° in conformation **8**), thereby eliminating this stabilizing effect and rendering it significantly less acidic. Molecular modeling of the 2-isopropyl-1,3-dimethylimidazolium cation supports this rationale, with a calculated energy difference of 2.266 kcal/mol between conformations **8** and **9**.[19]

In conclusion, we have reported the first base-stable imidazolium RTIL that can be employed in the addition of Grignard reagents to carbonyl compounds.[20] The products can be readily separated by extraction and could, in theory, also be separated by distillation due to the nonvolatile nature of the RTIL. The RTIL can be recycled a number of times with negligible loss

(14) Ueki, H.; Chiba, T.; Yamazaki, T.; Kitazum, T. *J. Org. Chem.* **2004**, *69*, 7616−7627.

(15) Bertus, P.; Laroche, C.; Drouin, L.; Szymoniak, J. *Tetrahedron* **2004**, *60*, 1375−1383.

(16) It is also worth noting that ionic liquid **5** affords comparable yields for these Grignard reactions, even after numerous recyclings. For example, the addition of vinylmagnesium bromide to *p*-anisaldehyde after roughly 10 recyclings through other Grignard reactions still afforded the anticipated product in 80% yield.

(17) For the methyl addition product: Spino, C.; Granger, M.; Tremblay, M. *Org. Lett.* **2002**, *4*, 4735−4737. For the vinyl addition product: Koerner, T.; Slebocka-Tilk, H.; Brown, R. S. *J. Org. Chem.* **1999**, *64*, 196−201.

(18) For the methyl addition product: Shibata, I.; Yoshida, T.; Kawakami, T.; Baba, A.; Matsuda, H. *J. Org. Chem.* **1992**, *57*, 4049−4051. For the vinyl addition product: Iio, H.; Mizobuchi, T.; Tsukamoto, M.; Tokoroyama, T. *Tetrahedron Lett.* **1986**, *27*, 6373−6476.

(19) Semiempirical calculations were performed using Spartan 2004 for the Macintosh using the AM1 force field.

(20) It should be noted that attempts to add butyllithium to anisaldehyde in ionic liquid **5** afforded only very modest (10%) yields of the carbonyl addition product. It appears that butyllithium is capable of readily metalating the imidazolium ring itself. Thus, the use of these highly basic and reactive organometallic reagents is not yet within the reach of ionic liquid chemistry.

of the RTIL, even over 10 recyclings. Efforts are currently underway to utilize RTIL **5** in other base-mediated chemistry and to develop further base-stable RTILs.

Experimental Section

2-Isopropyl-1,3-dimethylimidazolium Iodide (3). To a solution of 10 g (90.8 mmol) of 2-isopropylimidazole in 90 mL of toluene was added 11.8 mL (109 mmol) of butyl bromide, 3.3 g (9.0 mmol) of tetrabutylammonium iodide, and finally 110 mL (110 mmol) of 1 M sodium hydroxide. The solution was heated to reflux for 20 h and then cooled to room temperature. The organic layer was separated, washed with brine, dried with magnesium sulfate, filtered, and concentrated in vacuo. The resulting residue was then chromatographed (silica gel) using a gradient of 20% ether in hexane to straight ether. This afforded 14.8 g (98%) of 1-butyl-2-isopropylimidazole as a clear liquid. A portion of 14.8 g (89.2 mmol) of the butylated imidazole was dissolved in 100 mL of methylene chloride, and 6.11 mL (98.1 mmol) of methyl iodide was added. The solution was heated to reflux for 18 h and then cooled to room temperature, and the solvent was removed in vacuo to afford 25.3 g (92%) of **3** as a pale yellow oil. IR ($CDCl_3$) 3058, 2930, 1585, 1450, 1364, 725. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.64 (s, 1H), 4.33 (t, J = 8.0 Hz, 2H), 4.11 (s, 3H), 3.73 (septet, J = 7.1 Hz, 1H), 2.18 (s, 3H), 1.90−1.78 (m, 2H), 1.55 (d, J = 7.2 Hz, 6H), 1.45 (hextet, J = 8.0 Hz, 2H), 1.00 (t, J = 8.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.8, 124.0, 121.6, 49.0, 37.3, 32.4, 30.8, 24.8, 19.4, 13.4. HRMS (EI) calcd for $C_{11}H_{21}N_2$, 181.6494; found, 181.6492.

2-Isopropyl-1,3-dimethylimidazolium Triflimide (5). IR ($CDCl_3$) 2963, 1516, 1462, 1342, 1179, 1049, 726. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (s, 1H), 7.19 (s, 1H), 4.11 (t, J = 7.1 Hz, 2H), 3.0 (s, 3H), 3.53 (septet, J = 7.1 Hz, 1H), 1.85−1.74 (m, 2H), 1.48 (d, J = 7.4 Hz, 6H), 1.40 (hextet, J = 7.2 Hz, 2H), 0.97 (t, J = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.1, 123.8, 121.4, 119.9 (q, J = 320 Hz), 49.0, 36.5, 32.4, 25.1, 19.6, 18.9, 13.5. HRMS (EI) calcd for $C_{11}H_{21}N_2$, 181.6494; found, 181.6495.

General Procedure for Grignard Reactions in RTIL 5. To a stirred solution of 68 mg (0.50 mmol) of *p*-anisaldehyde in RTIL **5** was added 183 μL (0.55 mmol) of a 3.0 M solution of methylmagnesium chloride in THF. The reaction vessel was sealed and stirred for 2 h. The reaction was then quenched by the addition of 2 mL of 0.2 M hydrochloric acid and extracted with 10% ether in hexanes (4 × 3 mL). The combined organic extracts were dried with magnesium sulfate, filtered, and concentrated in vacuo. The crude residue was purified on silica (50% ether/hexanes as eluent) to afford 59 mg (78%) of 1-(4-methoxyphenyl)ethanol as a clear liquid. IR ($CDCl_3$) 2954, 2892, 1657, 1627, 1381. ^{1}H NMR (360 MHz, $CDCl_3$): δ 2.34−2.28 (m, 8H), 2.23 (s, 4H), 1.98 (s, 6H), 1.89−1.87 (m, 4H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 198.8, 156.1, 135.0, 37.7, 32.7, 24.5, 22.2, 21.2. HRMS (EI) calcd for $C_{16}H_{22}O_2$, 246.1801; found, 246.1799.

RTIL 5 Recycling Options. The RTIL/aqueous layers, after extraction of the Grignard addition product, were directly separated, and the RTIL was dried in vacuo for 48 h prior to use in the next reaction.

In the other option, to the RTIL/aqueous layers, after extraction of the Grignard addition product, was added 5 mL of methylene chloride. The aqueous layer was separated, and the organic layer was washed a second time with 2 mL of water. The combined aqueous extracts were then extracted with 2 mL of methylene chloride, and the combined organic layers were dried with magnesium sulfate, filtered, and concentrated in vacuo. The RTIL was then dried on a vacuum line for 20 h prior to use in the next reaction.

Acknowledgment. We thank Middle Tennessee State University for financial support of this work.

Supporting Information Available: Spectra (^{1}H and ^{13}C) for all new compounds (**3**−**5**). This material is available free of charge via the Internet at http://pubs.acs.org.

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