ORGANIC LETTERS

2003
Vol. 5, No. 14
2513−2515

Solvents from Biorenewable Sources: Ionic Liquids Based on Fructose

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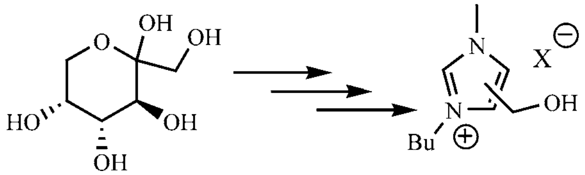
Received May 7, 2003

ABSTRACT



Fructose has been used as the starting material for the preparation of a new class of room-temperature ionic liquids (RTILs). These liquids exhibit tunable solvent properties much like conventional imidazole-based RTILs. They have been applied as recyclable solvents for the Heck reaction of aryl iodides.

In the ongoing quest to improve the environmental compatibility of chemical synthesis, alternatives to conventional organic solvents have attracted increasing attention.[1] Among the numerous alternatives that have been or are being explored (including water, supercritical fluids, and fluorous solvents), a particularly promising option is room-temperature ionic liquids (RTILs). A number of RTILs based on large organic cations (particularly dialkylimidazolium) in combination with weakly coordinating anions such as tetrafluoroborate, hexafluorophosphate, and bis(trifluoromethanesulfonyl)imide (triflimide) have been reported.[2] These compounds are all reasonably air and moisture stable and are capable of dissolving a wide range of organic, organometallic, and inorganic compounds. Further, as salts, they exhibit no detectable vapor pressure under ambient conditions and are nonflammable. Finally, while the toxicity has yet to be determined for many of these materials, the lack of volatility greatly reduces any chance of exposure other than by direct physical contact through spills or intentional ingestion.

Another potential problem with most conventional solvents and alternative solvents is the fact that they are based on petroleum. As this resource continues to be consumed at a prodigious pace, alternative materials based on biorenewable resources are of considerable interest.[3] Within the area of RTILs, only a few of these new solvent alternatives have been based on biorenewable natural products.[4] In this communication, we report our initial studies of a family of RTILs based on fructose.

Using chemistry developed many years ago by Trotter and Darby, fructose can be readily converted into hydroxymethyleneimidazole **1** (Scheme 1).[5] From imidazole **1**, double alkylation of this core generates the corresponding imida-

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[1] For a recent volume reviewing many of these alternatives, see: Knochel, P., Ed. *Topics in Current Chemistry*; Springer: New York, 1999; Vol. 206.

[2] For recent reviews, see: Welton, T. *Chem. Rev.* **1999**, *99*, 2071−2083. Rogers, R. D., Seddon, K. R., Eds.; *Ionic Liquids: Industrial Applications to Green Chemistry*; American Chemical Society: Washington, DC, 2002. 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.

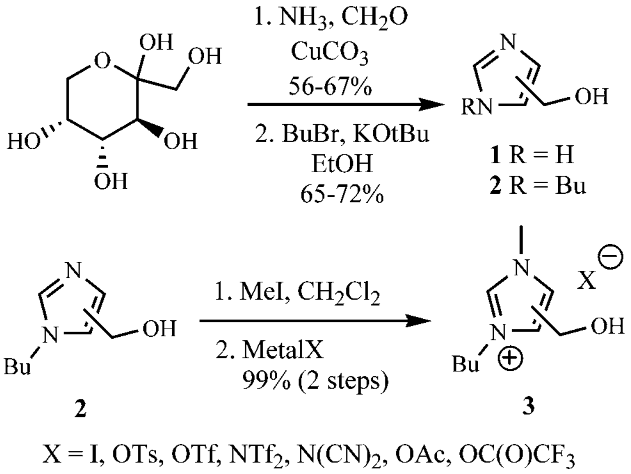
[3] For examples, see: Descotes, G., Ed.; *Carbohydrates as Organic Raw Materials II*; VCH: Weinheim, 1993. Stevens, E. S. *Green Plastics: An Introduction to the New Science of Biodegradable Plastics*; Princeton University Press: Princeton, 2002.

[4] For examples, see: Abbott, A. P.; Capper, G.; Davies, D. L.; Munro, H. L.; Rasheed, R. K.; Tambyrajah, V. *Chem. Commun.* **2001**, 2010. Abbott, A. P.; Capper, G.; Davies, D. L.; Rasheed, R. K.; Tambyrajah, V. *Green Chem.* **2002**, *4*, 24. Abbott, A. P.; Capper, G.; Davies, D. L.; Rasheed, R. K.; Tambyrajah, V. *Chem. Commun.* **2003**, 70. Wasserscheid, P.; Boesmann, A.; Bolm, C. *Chem. Commun.* **2002**, 200.

[5] Trotter, J.; Darby, W. In *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 460. We have optimized the workup and isolation conditions of this original report by replacing the use of hydrogen sulfide to decompose the copper salts with thioacetimide and isolating the final product **1** by chromatography instead of precipitation as a perchlorate salt. Preparations of **1** on a 0.5 mmol scale have been routinely carried out using these modifications. Details can be found in Supporting Information.

10.1021/ol034778b CCC: $25.00

Scheme 1. Synthesis of Fructose-Derived Ionic Liquids



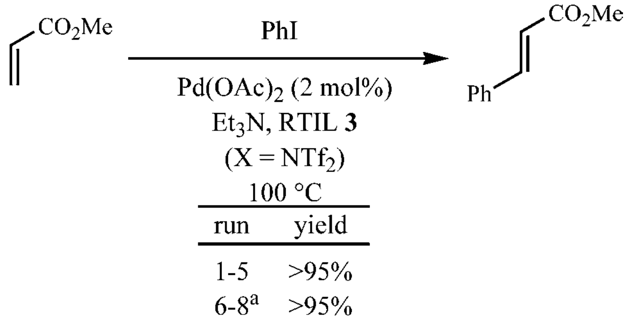
zolium cation. For the first alkylation, the ultrasound-promoted conditions of Diez-Barra were most effective on a small scale.[6] Increasing the reaction scale above 1 g of **1**, however, resulted in poor reproducibility. For larger-scale alkylations, conventional solution-phase alkylations in ethanol with potassium *tert*-butoxide as the base afforded reproducible results.[7] As a result, 10−20 g scale reactions afforded 65−72% yields of the monoalkylation product **2**. It is worth noting that this first alkylation is not entirely regiospecific but instead affords an inseparable 9:1 mixture of the two regioisomers. On the basis of the observation of a NOE enhancement between the butyl group and the methylene group in the minor isomer, the major isomer is that of alkylation at the nitrogen more distant from the hydroxymethylene group. At this point, the second alkylation with methyl iodide in methylene chloride proceeded uneventfully to afford the final iodide salt **3** in nearly quantitative yield.

Standard anion metathesis was employed to afford a range of new RTILs. The tosylate, trifluoroacetate, and acetate salts were all extremely viscous, while the tetrafluoroborate, triflimide, and dicyanimide salts were less viscous (qualitatively similar to the corresponding simple *N*-butyl, *N*-methylimidazolium [bmim] salts).

Another physical property that was investigated was the solubility/miscibility properties of the different salts. Attention was focused on the least viscous RTILs, those with triflimide and dicyanimide anions. These two salts displayed complementary properties. The triflimide salt was completely immiscible in water and poorly miscible in methanol. At the same time, it was completely miscible with acetonitrile, acetone, methylene chloride, ethyl acetate, and even ether. Only upon reaching simple hydrocarbons such as hexane and toluene was immiscibility again noted, and even here, toluene was partially miscible. The dicyanimide salt, on the other hand, was completely miscible with water and methanol, as well as acetonitrile, acetone, and methylene chloride. With ethyl acetate, a small degree of immiscibility was noted, while this salt was completely immiscible with ether, toluene, and hexane.

One important question was if these protic RTILs could be effective solvents for the same types of reactions that have been performed in conventional imidazolium RTILs. Initial investigations have focused on the Heck reaction (Scheme 2).[8] The reaction of methyl acrylate with iodobenzene was examined using a simple catalyst (palladium acetate).[9] The reaction was quite rapid, being complete in under 1 h at 100 °C, and methyl cinnamate was isolated as the only product in >95% yield. The solvent and catalyst could be recycled several times. Indeed, the catalyst/solvent could be recycled up to five times by simply extracting the cinnamate product with cyclohexane. By the fifth reaction, however, the medium had become relatively viscous, doubtless due to the buildup of triethylammonium salts. Fortunately, washing with water and drying in vacuo at 80 °C for 5 h was sufficient to return the ionic liquid to its original state. This restored solvent/catalyst could then be reused at least another three times.

Scheme 2. Heck Reaction of Methyl Acrylate and Iodobenzene



a. Recycling after washing RTIL/catalyst layer with water

Additional substrates were explored under these conditions (Scheme 3). In terms of aryl iodides, both electron-rich and

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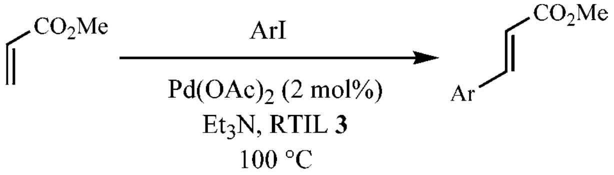
(6) Diez-Barra, E.; de la Hoz, A.; Sanchez-Migallon, A.; Tejeda, J. *Synth. Commun.* **1993**, *23*, 1783.

(7) Interestingly, despite the fact that the use of potassium *tert*-butoxide in ethanol should generate sodium ethoxide in situ, attempts to use a solution of sodium ethoxide in ethanol generated by the addition of sodium metal to ethanol have not led to satisfactory results.

(8) For reports of the Heck reaction in RTILs, see: Calo, V.; Nacci, A.; Lopez, L.; Napola, A. *Tetrahedron Lett.* **2001**, *42*, 4701. Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Synlett* **2002**, 439. Calo, V.; Nacci, A.; Monopoli, A.; Lopez, L.; Cosmo, A. *Tetrahedron* **2001**, *57*, 6071. Boelm, V. P. W.; Herrmann, W. A. *Chem. Eur. J.* **2000**, *6*, 1017. Calo, V.; Nacci, A.; Lopez, L.; Mannarini, N. *Tetrahedron Lett.* **2000**, *41*, 8973. Herrmann, W. A.; Boehm, V. P. W. *J. Organomet. Chem.* **1999**, *572*, 141. Kaufmann, D. E.; Nouroozian, M.; Henze, H. *Synlett* **1996**, 1091. Xu, L.; Chen, W.; Ross, J.; Xiao, J. *Org. Lett.* **2001**, *3*, 295. Okubo, K.; Shirai, M.; Yokoyama, C. *Tetrahedron Lett.* **2002**, *43*, 7115. See also ref 10.

(9) **Representative Reaction Conditions.** A solution of 0.045 g (0.20 mmol) of $Pd(OAc)_2$ in 4 mL of 3-butyl-(4)5-hydroxymethyl-1-methyl-3*H*-imidazol-1-ium triflimide salt was heated while stirring to 60 °C, whereupon a dark reddish solution formed. The mixture was cooled to room temperature, and a combination of 2.04 g (10.0 mmol, 1.119 mL) of iodobenzene, 1.1257 mL (12.5 mmol) of methyl acrylate, and 1.51 g (15.0 mmol, 2.010 mL) of triethylamine were added. The reaction mixture was heated to 100 °C under argon for 30 min. The cooled solution was extracted with 10 × 10 mL portions of cyclohexane. The combined organic extracts were concentrated in vacuo to afford 1.6086 g (99.2%) of methyl cinnamate (pure by ^{1}HNMR in $CDCl_3$).

Scheme 3. Other Heck Reactions



Ar = *p*-MeOPh

run	yield
1	98%
2	96%
3	97%
4	95%

Ar = *p*-AcPh

run	yield
1	96%
2	97%
3	93%
4	95%

electron-deficient compounds worked well. In both cases, the catalyst/RTIL layer could be recycled three or four times with no detectable loss in activity.

With aryl bromides, the case was somewhat different. Using bromobenzene as the substrate, no reaction was observed at 100 °C. Even attempts at 140 °C afforded only traces of the desired product after 12 h. Finally, the same reaction was attempted using a combination of palladium acetate and tri-(*ortho*-tolyl)phosphine. Seddon and coworkers have noticed that, in conventional imidazole-derived RTILs, the addition of phosphine ligands improves the rate of reaction with aryl bromides.[10] In the fructose-derived RTILs, however, no reaction was observed, even after 24 h at 140 °C.

Given the failure with aryl bromides, there is a significant question regarding the effect of the hydroxyl group present in the fructose-derived RTILs on the rate of the Heck coupling. Initially, we suspected that it might enhance the reactivity of aryl iodides since these couplings could be readily performed at temperatures much lower than those reported for [bmim][BF$_4$] (60 versus 100 °C). Subsequently, it was observed that even the [bmim] salts were effective at 60 °C. With respect to the rate of the Heck reaction, there are two main differences between the fructose-derived RTIL and [bmim][BF$_4$]: the anion and the hydroxyl group. To dissect the relative effects of these two modifications, a study of the kinetics of the reaction of methyl acrylate and iodobenzene in [bmim][BF$_4$], [bmim][NTf$_2$], and RTIL **3** (X = NTf$_2$) was undertaken. These reactions were conducted under pseudo first-order conditions using a 10-fold excess of methyl acrylate with 1-methylnaphthalene as the internal standard. They were monitored by removing aliquots at the specified times and analyzing the ratio using GC/MS. The results are seen in Figure 1.

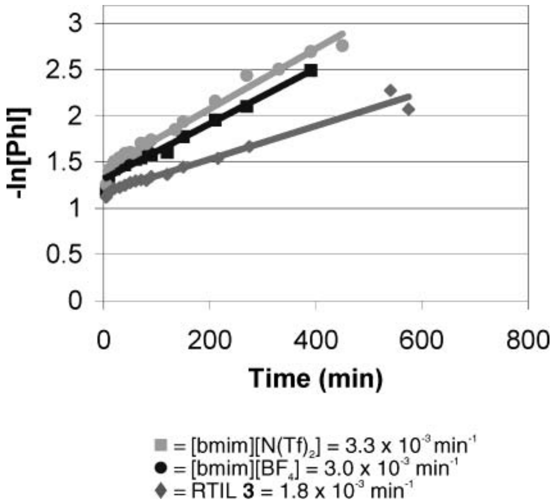


Figure 1. Reaction rates and pseudo first-order rate constants for the Heck reaction of methyl acrylate and iodobenzene

From these results, it is apparent that in the normal [bmim] series, the Heck reaction in the triflimide salt is slightly faster than in the tetrafluoroborate salt, presumably due to poorer coordination of the triflimide anion with any vacant coordination sites on the palladium metal than is observed with the tetrafluoroborate anion. In keeping with the hypothesis that coordination of the solvent with the palladium metal will slow the reaction rate, RTIL **3** was observed to have an even slower reaction rate than either of the [bmim] salts, although the magnitude of this difference is not great (less than a factor of 2).

On the basis of even the current efforts, it seems likely that a number of other transition metal-catalyzed reactions could be performed equally well in the fructose-derived RTILs instead of the conventional [bmim] series. At the same time, the protic nature of this new solvent affords the opportunity to explore other features not accessible using conventional RTILs. Efforts along these lines are currently underway and will be reported in due course.

Acknowledgment. The authors thank the State University of New York at Binghamton, the Research Foundation, and the New York State Energy Research and Development Authority (NYSERDA) for financial support of this work.

Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[10] Carmichael, A. J.; Earle, M. J.; Holbrey, J. D.; Seddon, K. *Org. Lett.* **1999**, *1*, 997.