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Base-promoted reactions in ionic liquid solvents. The Knoevenagel and Robinson annulation reactions

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Abstract—When used in place of classical organic solvents, ionic liquids offer a new and environmentally benign approach toward solvation in modern synthetic chemistry. Two classical named reactions, the Knoevenagel condensation and Robinson annulation, have been studied using the ionic liquid 1-hexyl-3-methyl imidazolium hexafluorophosphate, [6-mim]PF_6 as solvent. Yields for each reaction were moderate to excellent. In each system the ionic liquid was successfully recycled for reuse in subsequent reaction runs, a factor of key importance to the 'green' nature of solvation with ionic liquids. © 2001 Published by Elsevier Science Ltd.

With vanishingly small vapor pressures and the capacity to solvate an array of organic and inorganic substrates, ionic liquids are promising substitutes for volatile organic solvents (VOCs).[1] Already these versatile liquids have been used in place of traditional molecular solvents in a variety of organic reactions, and recent developments have been ably reviewed.[2] Despite the surging pace of research in the use of ILs as organic reaction solvents, the preponderance of this research has centered upon reactions that are metal catalyzed.[2]

Among organic reaction types that are not metal catalyzed, but which have been achieved in ionic liquids are the alkylation of phenolic oxygen and the benzoin condensation.[3,4] Both of these reactions are carried out under basic conditions, yet remain isolated examples of the genre despite the vast number of organic reactions that are similarly base-promoted. Given our earlier success with IL solvation–catalysis of the benzoin condensation, we decided to further investigate the use of ionic liquids in other base-promoted reactions. These continuing efforts are complimentary to our other, ongoing work on various aspects of ionic liquids chemistry and synthetic methods development.[5–10]

We report here the successful 'proof-of-concept' execution in ionic liquids of two related reactions, the unifying features of which are their base dependence and the use in them of substrates with activated methylene groups. Specifically, these are the Knoevenagel and Robinson annulation reactions. Both of these fundamentally important synthetic transformations are typically carried out in a volatile organic solvent.

The model reactions were both conducted in a common ionic liquid (Fig. 1), 1-hexyl-3-methyl imidazolium hexafluorophosphate, [6-mim]PF_6.[11] This ionic liquid was chosen for its ease of preparation as well as its good balance of desirable physical and chemical properties. These include thermal stability, relatively low viscosity and a good capacity for solubilizing organic substrates.

Both reactions proceed in a straightforward fashion (Scheme 1), in air and without any rigorous drying of the ionic liquid.[12] In the case of the model Knoevenagel reaction, glycine was used as the base. The glycine and the reaction substrates malononitrile and benzaldehyde dissolved readily in the ionic liquid. After stirring for 22 h at room temperature, the reaction product was extracted from the ionic liquid phase using an immiscible co-solvent, toluene. Significantly, it has been demonstrated that dissolved organic substrates can be separated from an ionic liquid system by extraction with a 'green' cosolvent, supercritical CO_2.[12] The unoptimized yield of chromatographed product was excellent (77%), and the ionic liquid was readily re-used for repeat runs of the reaction. The latter consideration is of particular significance given that a key rationale for

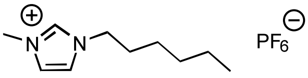

Figure 1.

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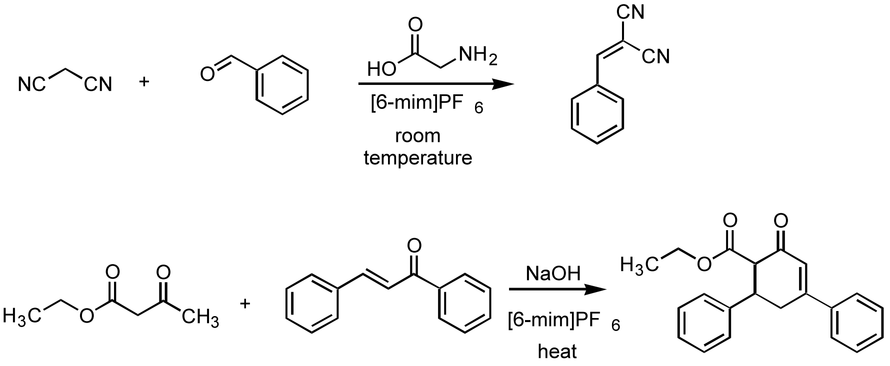

Scheme 1.

pursuing studies in ionic liquids is to develop 'greener' syntheses through suppressing solvent evaporative loss.

Likewise, the Robinson annulation of ethyl acetoacetate and *trans*-chalcone was uncomplicated. The reaction procedure deviates somewhat from that used in the Knoevenagel reaction in that pulverized NaOH was used as the base, and the reaction mixture heated to 100°C for 1.5 h. Workup by neutralization of the reaction mixture with aqueous acid followed by extraction with toluene then silica gel chromatography gave 6-ethoxycarbonyl-3,5-diphenyl-2-cyclohexenone in modest (48%) unoptimized yield. Again, the ionic liquid could be recycled for repeat reaction runs with no diminution of product yield.

The acidity of the C(2)–H in imidazolium cations is well known, and the pK_a is such that the proton readily exchanges with D_2O at room temperature and pH 7.[13] Consequently, the reaction of these cations with base is facile, and gives rise to imidazolidene carbenes.[14] Indeed, when the substituents on the ring nitrogen atom are sufficiently bulky, the reactive species may be isolated, and it is just such materials that constitute the only isolable examples of free carbenes.[14] Given this behavior, it is likely that the active base in the Knoevenagel and Robinson annulation reactions are carbenes. This possibility has been raised in earlier reactions involving base in ionic liquids as well.[3,4] If current studies in our laboratory bear out the case for carbenes as the actual base in these reactions, considerable opportunities exist for exploiting ionic liquids as customized basic reaction media. Suitably functionalized imidazolium cations might control the degree of medium basicity and potentially even the stereochemistry of deprotonations, possibilities we plan to investigate.

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12. **Representative procedure for the preparation of benzylidenemalonitrile**: To a 5 mL flat-bottomed flask containing a magnetic stir bar was added, in the following order, 0.5 mL 1-hexyl-3-methyl imidazolium hexafluorophosphate ([6-mim]PF_6), 40 mg malononitrile (0.61 mmol, 1.0 equiv.), 62 μL benzaldehyde (0.61 mmol, 1.0 equiv.) and 9 mg glycine (0.12 mmol, 0.2 equiv.). The reaction mixture was kept at room temperature for a period of 22 h at

which time the reaction mixture was extracted with toluene (3×2.0 mL). Analysis of the crude reaction mixture revealed that 98% of the organic residues introduced to 1-hexyl-3-methyl imidazolium hexafluorophosphate ([6-mim]PF_6) are removed after performing three 2.0 mL washes with toluene. The organic extracts were then combined and concentrated in vacuo. The resulting viscous oil was immediately purified via silica gel chromatography [hexane/EtOAc, 1/1, 10×30 mm SiO_2, 3 mL fractions] to afford 72.3 mg (77% yield) of the title compound. Spectral and physical data obtained are in agreement with those previously reported.

Recycling of 1-hexyl-3-methyl imidazolium hexafluorophosphate ([6-mim]PF_6) for the preparation of benzylidenemalonitrile: Analysis of the crude reaction mixture revealed that nearly all of the organic materials introduced to the ionic liquid solvent were removed (98%) after washing the ionic liquid solvent with toluene (3×2.0 mL). Upon completion of the toluene washes, a second run using the ionic liquid solvent, as is without any further manipulation, was performed under identical reaction conditions and resulted in the formation of the title compound in 39% yield. The spectral data (NMR and TLC) obtained with this material was in agreement to that obtained in the first.

Representative procedure for the preparation of 6-ethoxycarbonyl-3,5-diphenyl-2-cyclohexenone: To a 10 mL round-bottomed flask containing a magnetic stir bar was added, in the following order, 2.0 mL 1-hexyl-3-methyl imidazolium hexafluorophosphate ([6-mim]PF_6), 120 mg *trans*-chalcone (0.57 mmol, 1.0 equiv.), 73 μL ethyl acetoacetate (0.57 mmol, 1.0 equiv.) and 50 mg of pulverized sodium hydroxide (1.0 mmol, 1.7 equiv.). The reaction mixture was warmed and kept at 100°C for a period of 1.5 h at which time it was cooled to 60°C and allowed to stir for an additional 1.5 h. The crude reaction mixture was then cooled to room temperature, neutralized with aqueous hydrochloric acid (v/wt) and washed with toluene (3×4.0 mL). This workup procedure does afford a triphasic system. Control experiments revealed that 90% of the organic residues are removed after performing three 4.0 mL washes with toluene. The organic extracts were then combined and concentrated in vacuo. The resulting viscous oil was immediately purified via silica gel chromatography [hexane/EtOAc, 8/1, 10×30 mm SiO_2, 3 mL fractions] to afford 88 mg (48% yield) of the title compound. Spectral data obtained are in agreement with those previously reported.

Recycling of 1-hexyl-3-methyl imidazolium hexafluorophosphate ([6-mim]PF_6) for the preparation of 6-ethoxycarbonyl-3,5-diphenyl-2-cyclohexenone: Analysis of the crude reaction mixture revealed that nearly all of the organic materials introduced to the ionic liquid solvent were removed (90%) after the triphasic workup procedure, that is, aqueous neutralization and subsequent toluene washings of the ionic liquid solvent. Upon completion of the toluene washes (3×4.0 mL), the resulting ionic liquid solvent was concentrated in vacuo (1.0 Torr for 3 h at room temperature). Using this ionic liquid solvent, as is without any further manipulation, a second run was performed under identical reaction conditions and resulted in the formation of the title compound in 47% yield. The spectral data (NMR, TLC and GC) obtained with this material was in agreement to that obtained in the first.

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