Ionic liquids as catalytic green solvents for nucleophilic displacement reactions

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We demonstrate the use of room-temperature ionic liquids as a catalytic, environmentally benign solvent for the cyanide displacement on benzyl chloride, replacing phase-transfer catalyzed biphasic systems and thus eliminating the need for a volatile organic solvent and hazardous catalyst disposal.

Ionic liquids have recently gained recognition as possible environmentally benign alternative chemical process solvents. Because of their vanishingly low vapor pressures, ionic species do not contribute to VOC emissions as do most organic solvents. Examples of their application in both reactions[1,2] and separations[3,4] have been demonstrated. Although many types of reactions have been investigated in ionic liquids, examples of nucleophilic substitution reactions are absent from the literature.

Nucleophilic displacement reactions are often carried out using phase-transfer catalysis (PTC) to facilitate the reaction between the organic reactants and the inorganic ionic salts that provide the nucleophiles.[5] The phase-transfer catalyst, often a tetraalkylammonium salt, acts as a shuttle for the reactant anion between a polar phase that contains the salt reactant and a non-polar phase that contains the organic reactant. This technique not only overcomes the problem of contacting the reactants, but also provides activation of the nucleophilic anion, since it is much less tightly bound to a tetraalkylammonium cation than it would be to a metal cation. In conventional PTC typical organic solvents are environmentally undesirable species such as methylene chloride or o-dichlorobenzene, and catalyst separation and recovery are significant challenges. With ionic liquids as both the solvent and the catalyst, there are zero VOCs, and it has been shown that product recovery is facile by CO_2 stripping.[3]

Because ionic liquids are comprised of bulky organic cations, they seem well suited for the types of reactions for which PTC is effective. There even exists the possibility that the solvent itself can act as a catalyst to activate the anion for reaction. The ionic liquid cation might not be as effective a catalyst as most PTCs; however, as a solvent, its high concentration should overcome this limitation, yielding a high reaction rate.

We chose the cyanide displacement on benzyl chloride to yield phenylacetonitrile, depicted in Scheme 1, as a model reaction. For the solvent, we selected the ionic liquid 1-n-butyl-3-methylimidazolium hexafluorophosphate (**1**), often called
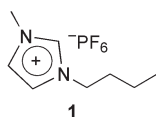
[bmim][PF$_6$]. The reaction was chosen because it has been well characterized in a variety of other systems. The choice of

Scheme 1 Cyanide displacement on benzyl chloride.

solvent was motivated by its being one of the most widely used, and therefore the most widely available, ionic liquids.

These reactions were carried out in a 25 ml volumetric flask set in a recirculating heated bath and stirred with a magnetic stir bar. The concentration of benzyl chloride in the ionic liquid was 1 M, and the amount of potassium cyanide was three times the stoichiometric amount of benzyl chloride. While all of the benzyl chloride was visually observed to be soluble, solid potassium cyanide was present in the systems at all times. Before introduction of benzyl chloride, the salt was stirred overnight in the liquid so that the uniform particle sizes would form and the salt would reach an equilibrium concentration.[6] After the introduction of benzyl chloride, samples were drawn and dissolved in cold acetonitrile before being analyzed by HPLC equipped with a UV-Vis detector.

Reactions were carried out at 40, 60, and 80 °C, and conversion is plotted in Fig. 1. Reaction rates were high, with the reaction at 80 °C reaching complete conversion in less than half an hour. Although the reactions at 60 and 80 °C show the expected pseudo-first-order kinetic behavior (since the amount of cyanide available for reaction should be constant), the reaction at 40 °C appears to be zero order. This behavior indicates that mass transfer of potassium cyanide into the solvent is probably the rate-limiting step at the lower temperature, which is consistent with the fact that the viscosity of the ionic liquid is observed to decrease steeply with an increase in temperature. Although solid salt is always present in the reacting systems, the transfer into the liquid at higher temperatures is apparently faster than the reaction step itself, such that an equilibrium concentration of cyanide is achieved and pseudo-first-order behavior is exhibited.

The rate constants for each temperature are listed in Table 1. An effective activation energy of 19 kcal mol^{-1} is calculated using the data at 60 and 80 °C. Because the nature of the solvent changes with temperature, this activation energy includes several factors other than the temperature dependence of the intrinsic reaction rate, most especially the solubility of potassium cyanide.
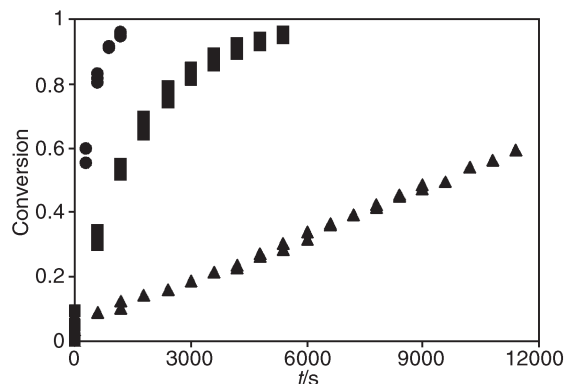

Fig. 1 Conversion of benzyl chloride to benzyl cyanide (● 80 °C, ■ 60 °C, ▲ 40 °C).

Table 1 Rate constants for reaction of benzyl chloride with potassium cyanide. Uncertainty is represented by 95% confidence intervals

| Temperature/°C	Rate constant
40	[a]$(4.76 \pm 0.12) \times 10^{-5}$ mol L^{-1} s^{-1}
60	[b]$(5.45 \pm 0.38) \times 10^{-4}$ s^{-1}
80	[b]$(2.54 \pm 0.10) \times 10^{-3}$ s^{-1}

[a] Zero order. [b] Pseudo-first order.

Another reaction that has been demonstrated in a similar system is the base-promoted cyclo-alkylation of phenylacetonitrile with 1,4-dibromobutane, shown in Scheme 2. Kinetic data were not taken, but the reaction was complete in less than three hours. As in the previous example, the organic reactants were dissolved in the ionic liquid, and excess solid potassium hydroxide was present at all times.
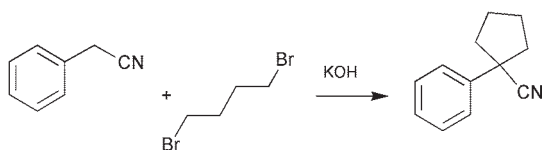
Scheme 2 Cyclo-alkylation of phenylacetonitrile with 1,4-dibromobutane.

Once the reaction is complete, we must turn our attention to product recovery and solvent recycle. As demonstrated by Blanchard *et al.*, supercritical CO$_2$ can be incorporated to extract non-volatile organic compounds from ionic liquids.[3,7] Heating is sufficient to remove more volatile compounds from the solvent. Fig. 2 illustrates a proposed environmentally benign reaction and separation solvent system for reactions of organic compounds with inorganic salts. The low solubility of ionic liquids in water and in CO$_2$ allows for facile separation steps that should result in minimal solvent loss, although loss of ionic liquid in a water extraction must be considered when selecting the ionic liquid.

In conclusion, we have demonstrated the viability of ionic liquids as a solvent for reactions between organic compounds and inorganic salts. This opens many opportunities for environmentally friendly processing, especially when combined with the benign separations techniques that have already been demonstrated.
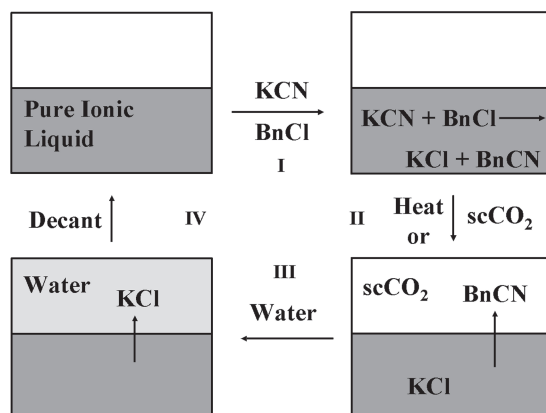
Fig. 2 A recyclable ionic liquid solvent system for nucleophilic substitution reactions. In step I, the reactants are added to the ionic liquid and the reaction is allowed to proceed. Step II involves the removal of the organic reactant *via* vaporization or supercritical fluid extraction. Washing with water, as in step III, will remove the salt product and after decantation, step IV, the purified ionic liquid is obtained and available for another reaction cycle.

Notes and references

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6 The [bmim][PF$_6$] was obtained from SACHEM, Inc., and used as received. Two separate bottles were used in these experiments, one labeled 97% pure, with the balance water, and the other without indication of water content. However, the results obtained with each were the same. The overnight heating of the solvent prior to reaction should allow the water content to come to an equilibrium level.
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