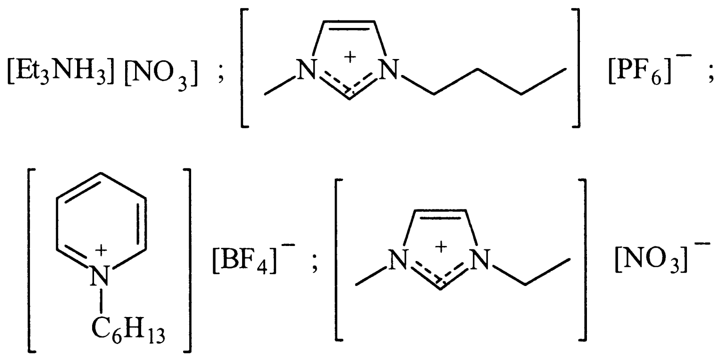
14. Versatile Ionic Liquids as Green Solvents

14.1 Green Solvents

The commonly used solvents like benzene, toluene, methylene chloride etc. for organic synthesis, particularly in industrial production, are known to cause health and environmental problems. In view of this, the search for alternatives to the damaging solvent is of highest priority. This is particularly important as solvents are used in huge amounts (in industrial production) and these are mostly volatile liquids, which are difficult to contain.

The ionic liquids, comprising entirely of ions were and mainly of interest to the electrochemists.[1] It is possible, by careful choice of starting materials, to prepare ionic liquids that are liquid at and below room temperature. Different aspects of ionic liquids have been reviewed by a number of authors.[2] The first ionic liquid [EtNH$_3$] [NO$_3$] (m.p. 12 °C) was discovered in 1914.[3]

Broadly speaking, ionic liquids are of two types: simple salts (made up of a single anion and cation) and binary ionic liquids; the latter are salts where an equilibrium is involved. It is the binary ionic liquids that are used as green solvents. Some examples of simple salt are given (Scheme 1).



Scheme 1

An example of a binary ionic liquid system is a mixture of aluminium (III) chloride and 1,3-dialkylimidazolium chloride. It contains several different ionic species and their m.p. and properties depend upon the mole fractions of AlCl$_3$

and 1,3-dialkyl imidazolium chloride present. For the binary systems, the m.p. depends upon the composition[4] and is designated as [emin]Cl-$AlCl_3$, where $[emin]^+$ is 1-ethyl-3-methyl imidazolium.

The above binary system, [emin]Cl-$AlCl_3$ can be basic, acidic or neutral in nature. The composition of the binary ionic liquid is described by the apparent mole fraction of $AlCl_3$ [$X(AlCl_3)$] present. Ionic liquids with $X(AlCl_3) < 0.5$ contain an excess of Cl^- ions over $[Al_2Cl_7]^-$ ions are called 'basic'. On the other hand, those with $X(AlCl_7) > 0.5$ contain an excess of $(Al_2Cl_7)^-$ ions over Cl^- and are called 'acidic'. Mixtures with $X(AlCl_3) = 0.5$ are called 'neutral'. These ionic liquids (basic, acidic or neutral) are used in different types of reactions. Thus, the properties such as m.p., viscosity and hydrophobicity and misicibility with water can be varied by changing the structure and composition of the ions.

The most common salts in use are those with alkylammonium, alkylphosphonium, N-alkylpyridinium and N,N′-dialkyl imidazolium cation (Scheme 1).

The reactions in ionic liquids are easy to perform and need no special apparatus or methodologies. Also, the ionic liquids can be recycled and this leads to reduction of the costs of the processes.

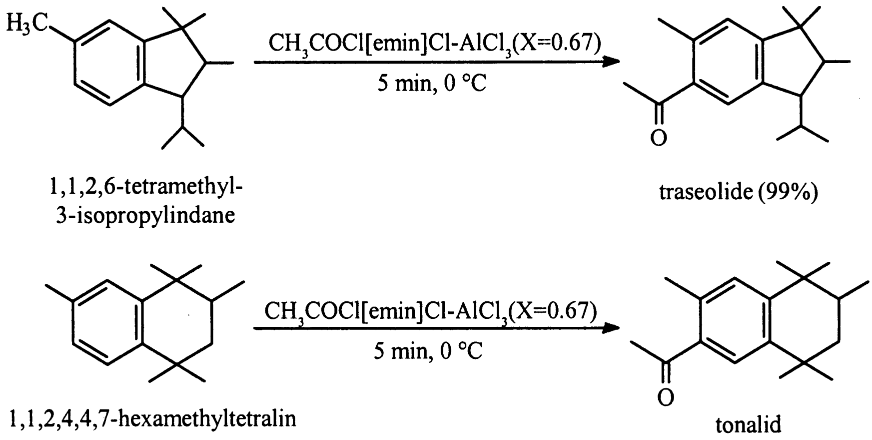
14.2 Reactions in Acidic Ionic Liquids

The chloroaluminate (III) ionic liquids (where $X(AlCl_3) > 0.50$) behave like powerful Lewis acid and promote reactions that are usually promoted by $AlCl_3$. In fact, chloroaluminate ionic liquids are powerful solvents and can be prepared by mixing the appropriate organic halide salt with $AlCl_3$ and heating to form the ionic liquid. This synthesis should be performed in inert atmosphere.

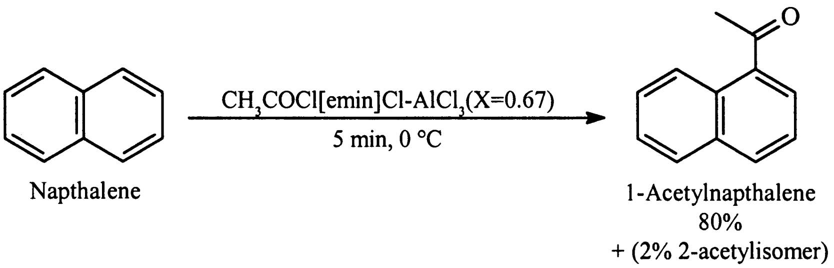
The well known Friedel-Crafts reaction works very well with the chloroaluminate (III) ionic liquids.[5] Thus, using this methodology, traseolide (5-acyl-1,1,2,6-tetramethyl-3-isopropylindane) and tonalid (6-acetyl-1,1,2,4,4,7-heaxmethyltetralin have been synthesised in high yield in the ionic liquid [emin]Cl-$AlCl_3$ ($X = 0.67$) (Scheme 2).

Similarly Friedel-Crafts reaction of naphthalene gives 1-acetyl derivative as the major product (Scheme 3).

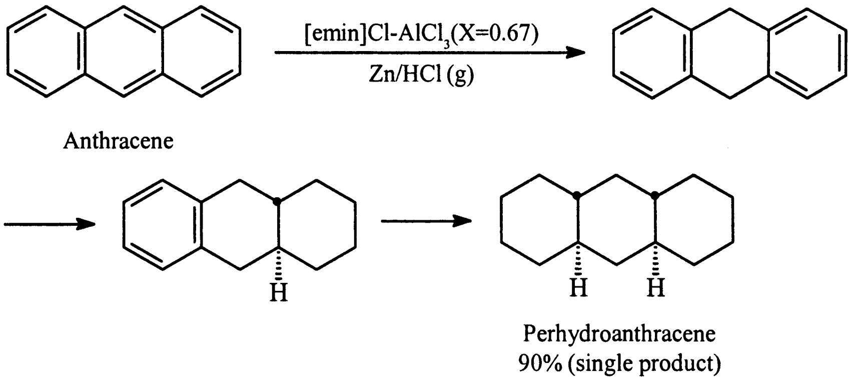
Another interesting application in the use of ionic liquids is in the hydrogenation of polycyclic aromatic hydrocarbons, which are soluble in chloroaluminate (III) ionic liquids to form highly coloured paramagnetic solutions[6], which on treatment with a reducing agent such as an electropositive metal and a proton source results in selective hydrogenation of the aromatic compound. Using this method, the anthracene can be reduced to perhydroanthracene at normal temperature and pressure to give the most stable isomer (the sequence of reduction of anthracene is depicted in Scheme 4).[7]



Scheme 2



Scheme 3



Scheme 4

The above reduction is in contrast to catalytic hydrogenation reaction, which requires high temperature and pressure and expensive platinum oxide catalyst and gives a mixture of products.[8] In the above case (Scheme-4) the sequence of chemical reduction can be determined by careful monitoring of the reduction in ionic liquid.

Using the above procedure (Scheme-4) pyrene can be reduced to perhydro pyrene.

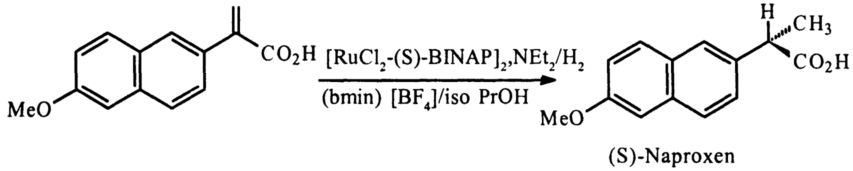
14.3 Reactions in Neutral Ionic Liquids

As already stated, chloroaluminate (III) ionic liquids are excellent solvents in many reactions. The main problem arises due to their moisture sensitivity and difficulty in separation of products (containing heteroatoms) from the ionic liquid. In view of this, water-stable ionic liquids have been developed. One example of this is the ionic liquid [bmin][PF_6] [$(bmin)^+$ = 1-butyl-3-methylimidazolium)].[9] The ionic liquid [bmin][PF_6] forms triphasic mixture with water and alkanes, which makes it useful for clean synthesis. Such ionic liquids can be used without any special conditions needed to exclude moisture and the isolation of the reaction products is convenient.

Some applications in the use of neutral ionic liquids are discussed here.

14.3.1 Hydrogenations

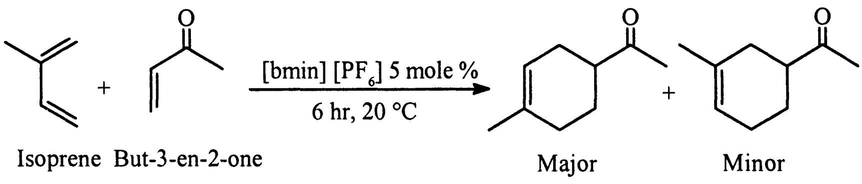
The most important advantage of using neutral ionic liquids is that the reaction products can be easily separated from the ionic liquids and the catalyst.[10] Using the neutral ionic liquids, cyclohexene can be reduced to cyclohexane.[11] Even benzene could be reduced to cyclohexane.[12] An interesting asymmetric hydrogenation using a chiral catalyst $[RuCl_2\text{-(S)-BINAP}]_2,NEt_2$ has enabled the synthesis of (S)-Naproxen (Scheme 5).[13]



Scheme 5

14.3.2 Diel's-Alder Reaction

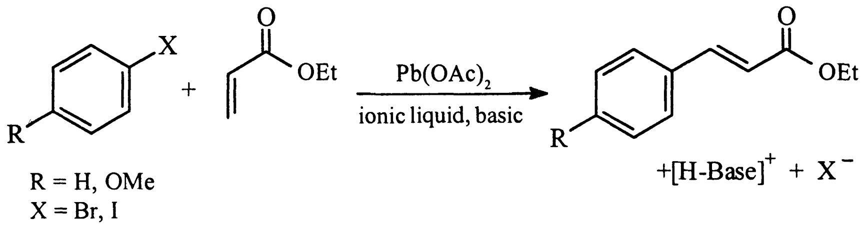
The neutral ionic liquids are excellent solvents for the Diels-Alder reaction[14] and are better than the conventional solvents and even water (see Section 12.2). Addition of a mild Lewis acid like ZnI_2 increases the selectivities in this reaction. A special advantage of this system is that the ionic liquid and catalyst can be recycled and reused after extraction or direct distillation of the product from the ionic liquid. A typical Diel's-Alder reaction is given (Scheme 6).



Scheme 6

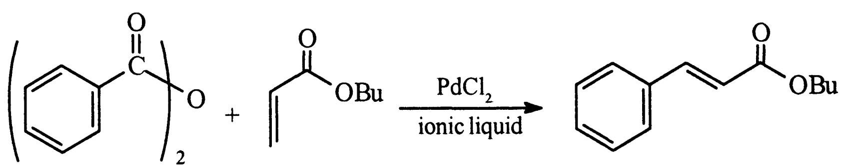
14.3.3 Heck Reaction

Neutral ionic liquids are excellent solvents for the palladium catalysed coupling of alkyl halides with alkenes (Heck reaction). The special advantage of using neutral ionic liquids is that many palladium complexes are soluble in ionic liquids[15] and that the products or product of the reaction can be extracted with water or alkane solvents. So the expensive catalyst can be recycled compared to the routine Heck reaction in which the catalyst is lost at the end of the reaction (see Section 12.11). A typical Heck reaction is given (Scheme 7).



Scheme 7

An alternative Heck reaction uses aromatic anhydrides as a source of the aryl group (Scheme 8).



Scheme 8

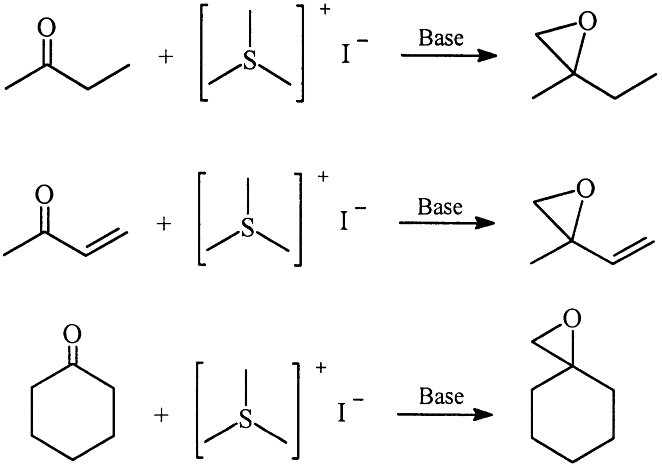
In the above method (Scheme 8) the by-product of the reaction is benzoic acid (which can be converted back to the anhydride for reuse) and the halide containing waste is not formed.

14.3.4 O-Alkylation and N-alkylation

A common reaction in organic synthesis is the nucleophilic displacement reaction. Thus 2-naphthol undergoes alkylation to give O-alkyl ether on treatment with a haloalkane and base (NaOH or KOH) in [bmin][PF_6].[16] Similarly indol undergoes N-alkylation. Though both the above O- and N-alkylations occur with similar rates to those carried out in dipolar solvents (e.g. DMF or DMSO), but the advantage of ionic liquid process is that the reaction products can be extracted into an organic solvent such as toluene leaving behind the ionic liquid, which can be recycled after separation from sodium or potassium halide by extraction with water.

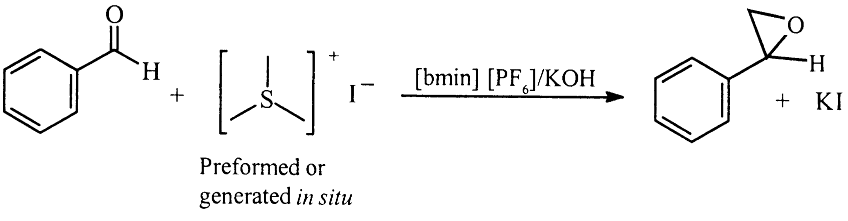
14.3.5 Methylene Insertion Reactions

Aldehydes and ketones are known to react with sulphur ylides to give epoxide (Scheme 9).



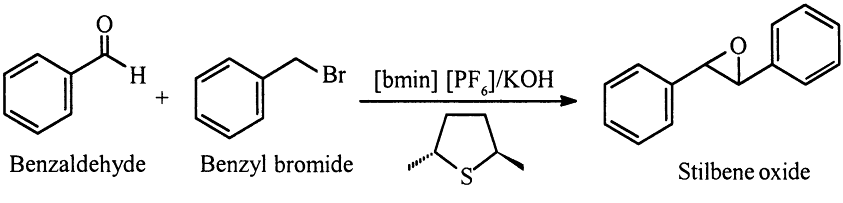
Scheme 9

The methylene insertion reactions have been found to proceed better in ionic liquids such as [bmin] [PF_6] or [bmin] [BF_4] on treatment with sulphur ylides. Sulphur ylides are obtained *in situ* by the reaction of alkyl halides with sulphides. The reaction works equally well with preformed sulphonium salts (Scheme 10).



Scheme 10

It is also possible to carry out asymmetric methylene insertion reaction in good enantiomeric excess by using a chiral sulphide such as 2R,5R-tetrahydrothiophene (Scheme 11).

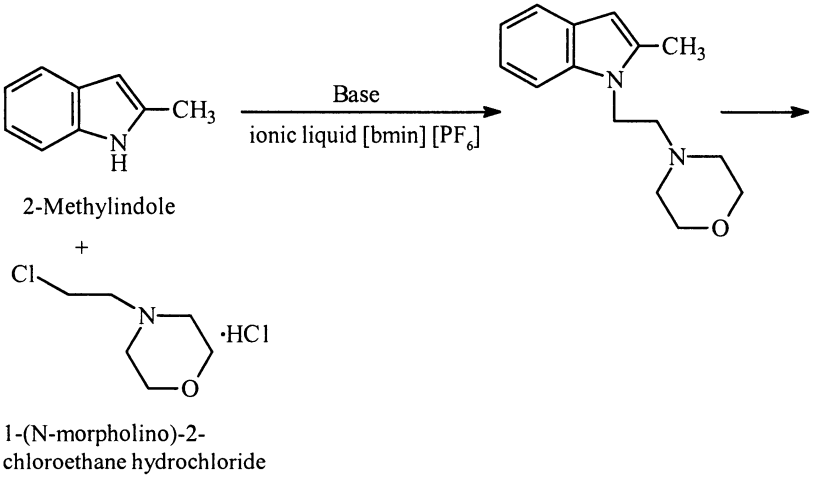


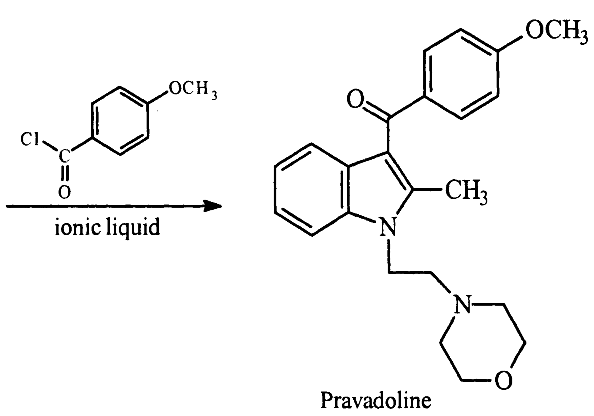
Scheme 11

14.3.6 Miscellaneous Applications

14.3.6.1 Synthesis of Pharmaceutical Compounds

Ionic liquids have been extensively used in the synthesis of pharmaceutical compounds. A representative example is the synthesis of pravadoline.[17] The method consists the alkylation of 2-methylindole with 1-(N-morpholino)-2-chloroethane in [bmin] [PF$_6$] to give 95% yield of the corresponding N-alkyl derivative. Subsequent Friedel Craft reaction with p-methoxybenzoyl chloride in chloroaluminium (III) ionic liquid gives pravadoline (Scheme 12).





Scheme 12

References

1. C.L. Hussey, *Adv. Molten Salt Chem.*, 1983, **5**, 185.
2. T. Welton, *Chem. Rev.*, 1999, 2071-2083; J. Holbrey and K.R. Seddon, *Clean Prod. Proc.*, 1991, **1**, 223-236; K.R. Seddon, *J. Chem. Tech. Biotech.*, 1997, **68**, 351-356; K. Sheldon, *Chem. Commun.*, 2001, 2399-2407; M.J. Earle and K.R. Seddon, *Pure Appl. Chem.*, 2000, **72**, 1391-1398; P. Wasserscheid and W. Keim, *Angew. Chem. Int. Ed. English*, 2002, 3773-3784.
3. P. Walden, *Bull. Acad. Imper. Sci.* (St. Petesburg), 1914, 1800.
4. C.L. Hussey, J.B. Scheffler, J.S. Wilkes and A.A. Fannin, Jr., *J. Electrochem. Soc.*, 1986, **133**, 1389.
5. J.A. Boon, J.A. Levosky, J.L. Pfung and J.S. Wikes, *J. Org. Chem.*, 1998, **51**, 480.
6. P. Tarakeshwar, J.Y. Lee and K.S. Kim, *J. Phys. Chem.*, 1998, **102A**, 2253.
7. C.J. Adams, M.J. Earle and K.R. Seddon, *Chem. Commun.*, 1999, 1043.
8. D.K. Dalling and D.M. Grant, *J. Am. Chem. Soc.*, 1974, **96**, 1827.
9. J.D. Huddlesten, H.D. Willauer, R.P. Swatloski, A.E. Visser and R.D. Rogers, *Chem. Commun.*, 1998, 1765.
10. T. Welton, *Chem. Rev.*, 1999, **99**, 2071-2083.
11. P.A.Z. Suarez, J.E.L. Dullius, S. Einloft, R.F. de Souza and J. Dupont, *Inorg. Chim. Acta.*, 1997, **225**, 207.
12. P.J. Dyson, D.J. Ellis, D.G. Parker and T. Welton, *Chem. Commun.*, 1999, 25.
13. A.L. Monterio, K.F. Zinn, R.F. de Souza and J. Dupont, *Tetrahedron Asymmetry*, 1997, **8**, 177.
14. M.J. Earle, P.B. McCormac and K.R. Seddon, *Green Chem.*, 1999, **1**, 23; T. Fisher, A. Sethi, T. Welton and J. Woolf, *Tetrahedron Lett.*, 1999, **40**, 793.
15. W.A. Herrmann and V.P.W. Bohn, *J. Organomet. Chem.*, 1999, **572**, 141.
16. M.J. Earle, P.B. McCormac and K.R. Seddon, *Chem. Commun.*, 1998, 2245.
17. M.J. Earle and K.R. Seddon, *Pure Appl. Chem.*, 2000, **7**, 1397.