THE SYNTHESIS AND APPLICATION OF ROOM TEMPERATURE IONIC LIQUIDS

XIAOMEI HU

Doctor of Philosophy

ASTON UNIVERSITY

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Aston University

The Synthesis and Application of Room Temperature Ionic Liquids

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Summary

There is an urgent need to develop alternative solvents and technologies for synthetic chemistry due to the increasing need for protecting the environment. Room temperature ionic liquids (RTILs) as "green solvents" have gained wide popularity in recent years for their increasing applications in the areas of synthetic and biological chemistry. Moreover, their properties such as solubility, density and viscosity can be adjusted to suit the requirements simply by changing the nature of the cations or anions. Due to all the benefits, RTILs are applied in many organic reactions.

This research project is concerned with the development and use of these eco-friendly reaction media for a variety of organic transformations in the preparation of organic chemicals with potential pharmaceutical applications. These chemicals will then be investigated for their anti-cancer, anti-bacterial and anti-inflammation properties.

In this project, different methods were used to synthesize various kinds of ionic liquids. Some new ionic liquids were prepared. In addition, Knoevenagel condensation reactions were investigated in RTILs. For the first time, some 'neutral' ionic liquids such as $[BMIM]^+[BF_4]^-$, $[MeOEtMIM]^+[CF_3COO]^-$ acted as both catalysts and solvents to promote Knoevenagel reactions. All these experiments indicated that RTILs have a great potential as alternative solvents in synthetic chemistry.

Furthermore, nucleoside chemistry is an important research area in drug discovery. Various chemical modified nucleosides have therapeutic activities. However, these compounds usually have poor solubility in common organic solvents. RTILs such as $[MeOEtMIM]^+[CH_3SO_3]^-$ have good dissolving capability for these chemicals. A range of thio-substituted nucleobases and nucleosides with potential pharmaceutical applications have been synthesized in several RTILs. These chemicals will then be investigated for their anti-cancer properties.

Keywords: room temperature ionic liquids, Knoevenagel condensation reactions, nucleoside chemistry, thionucleobase, thionucleoside.

To my parents

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Abbreviations

RTILs	Room temperature ionic liquids
DMSO	Dimethyl sulfoxide
DMF	Dimethylformamide
THF	Tetrahydrofuran
DMAP	4-Dimethylaminopyridine
TFSI	Bis((trifluoromethyl)sulfonyl)amide
TBAH	Tetrabutylammonium hydroxide
$[RMIM]^+$	1-Alkyl-3-methylimidazolium
$[MMIM]^+$	1,3-Dimethylimidazolium
$[EMIM]^+$	1-Ethyl-3-methylimidazolium
$[BMIM]^+$	1-Butyl-3-methylimidazolium
$[PMIM]^+$	1-Propyl-3-methylimidazolium
$[iPMIM]^+$	1-Isopropyl-3-methylimidazolium
$[HMIM]^+$	1-Hexyl-3-methylimidazolium
$[OctMIM]^+$	1-Octyl-3-methylimidazolium
$[DecMIM]^+$	1-Decyl-3-methylimidazolium
$[MeOEtMIM]^+$	1-Methoxyethyl-3-methylimidazolium
$[PhOPMIM]^+$	1-Phenoxypropyl-3-methylimidazolium
$[MeOMeOEtMIM]^+$	1-Methoxymethoxyethyl-3-methylimidazolium
$[MPhMIM]^+$	1-(1-Methylbenzyl)-3-methylimidazolium
$[BMMIM]^+$	1-Butyl-2,3-dimethylimidazolium
$[PhOPMMIM]^+$	1-Phenoxypropyl-2,3-dimethylimidazolium
$[DecMMIM]^+$	1-Decyl-2,3-dimethylimidazolium
$[1\text{-Et-2,3-Me}_2\text{IM}]$	1-Ethyl-2,3-dimethylimidazolium
$[EtOEtBuIM]^+$	1-Ethoxy-ethyl-3-butyl-imidazolium
$[PhOPBuIM]^+$	1-Phenoxypropyl-3-butylimidazolium
Bis(MIM)butane	1,4-Bis(3-methylimidazole)butane
$[DecMBzIM]^+$	1-Decyl-3-methylbenzimidazole
$[Epy]^+$	*N*-ethylpyridinium
$[Bpy]^+$	*N*-butylpyridinium

$[BF_4]^-$	Tetrafluoroborate
$[PF_6]^-$	Hexafluorophosphate
$[SbF_6]^-$	Hexafluoroantimonate
$[CH_3COO]^-$	Acetate
$[CF_3COO]^-$	Trifluoroacetate
$[CF_3SO_3]^-$	Trifluoromethansulfonate
$[CF_3CF_2COO]^-$	Pentafluoropropionate
$[CF_3CF_2CF_2COO]^-$	Heptafluorobutyrate
$[CH_3SO_3]^-$	Methanesulfonate
$[CF_3SO_3]^-$	Trifluomethanesulfonate
$[(CF_3SO_2)_2N]^-$	Bis((trifluoromethyl)sulfonyl)amide

Chapter 1

Introduction

One big challenge in modern society is the prevention of environment pollution. A large amount of organic solvents is employed by industrial production. The usage of industrial volatile organic compounds (VOCs) is over $5 billion every year worldwide (US Patent 6924341, 2005). Because of their inherent volatility, a significant quantity of VOCs evaporates into the atmosphere. This causes environmental pollutions. Problems are also encountered with the disposal and recycling of the used solvents.

Today, green chemistry attracts much interest and it represents the chemistry for the future. Green chemistry aims to design safer and cleaner methods to reduce hazardous processes with the maximum use of raw materials and minimize energy requirements. Most conventional organic solvents are volatile, flammable, and harmful. Green chemistry requires the solvents to have low volatility, be physically and chemically stable and be easy to handle and recycle. Chemists have made great efforts to seek alternative reaction media to organic solvents. Many solvents are now being used to replace traditional organic solvents such as water, supercritical fluids and perfluorinated solvents (Wasserscheid and Keim, 2000; Tzschucke et al., 2002; Dzyuba and Bartsch, 2003). All of them have some advantages and disadvantages. For example, water is readily available, cheap, non-toxic and recyclable. However, it is limited by the low solubility of most organic compounds, its high vapor pressure and its incompatibility with some products and catalysts. Many useful reactions carried out in organic solvents are ineffective or impossible in water. Supercritical fluids are non-toxic solvents, which leave no harmful residues. Their gas and liquid form can be controlled by pressure and temperature. Supercritical fluids are limited for many applications due to their narrow range of solvating properties. More complex process design and higher energy are required in processes involving supercritical fluids. The limitations of perfluorinated solvents are cost, toxicity, poor thermal stability and poor solubility of reactants. Special ligands are always required to dissolve most catalysts and this causes product contamination (Poole, 2004).

Recently, room temperature ionic liquids (RTILs) have attracted a great deal of attention in many organic reactions. RTILs have been a good choice in many important reactions because of their favorable properties in relation to green chemistry such as high thermal stability, high electrochemical stability, good solubility of organic, inorganic and polymeric materials, negligible vapor pressure and ease of recycling. In addition, their physical and chemical properties can be easily altered by changing the nature of the cations and anions. For example, using two cations with two different alkyl side chain and two anions, we can make eight ionic liquids with varying properties. RTILs have a wide range of applications; especially for the use as solvents for many organic reactions. The increasing numbers of applications of ionic liquids are shown in Figure 1.1. Ionic liquids were initially used as electrolytes in electrochemistry, but now they are widely employed as solvents for organic synthesis. Currently, they are being designed for specific uses with different purposes.

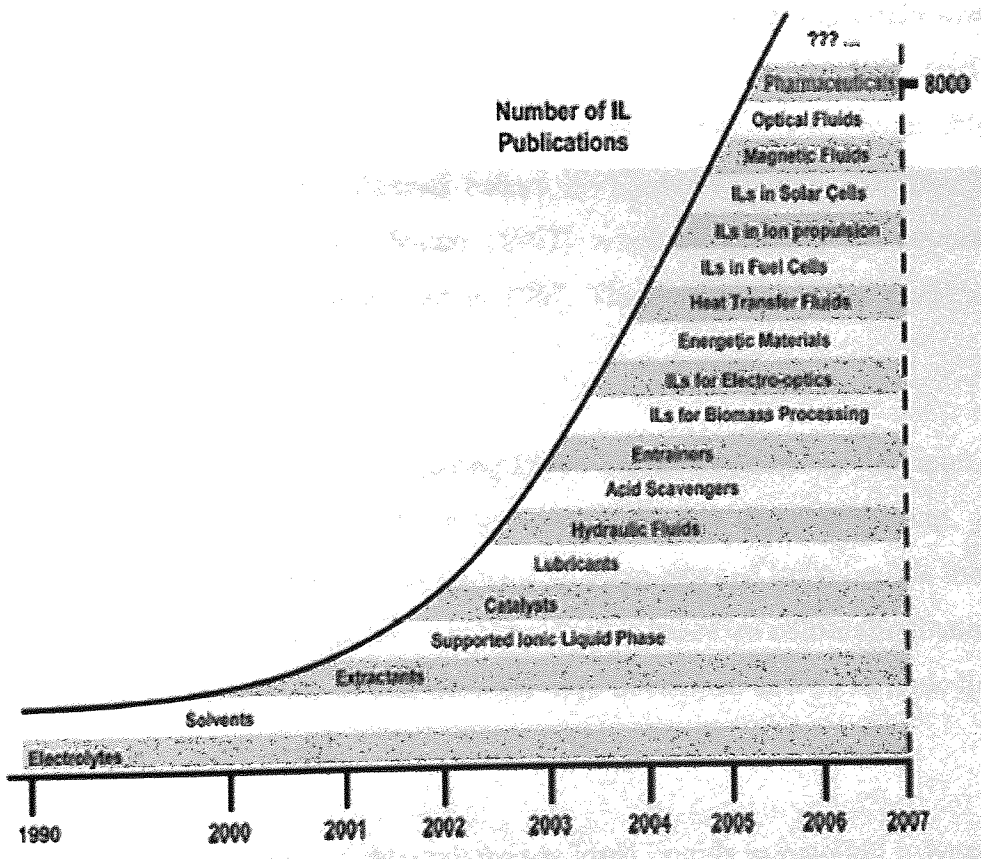


Figure1.1 Growth in the number of ionic liquids publications and representative areas of interest (Smiglak, 2007)

1.1 History of ionic liquids

What are ionic liquids? Ionic liquids, also called molten salts, consist typically of organic cations and inorganic anions. Ionic liquids generally refer to the organic salts which have the melting points below 100 °C. Room temperature ionic liquids have the melting points at or below room temperature (Wasserscheid and Keim, 2000).

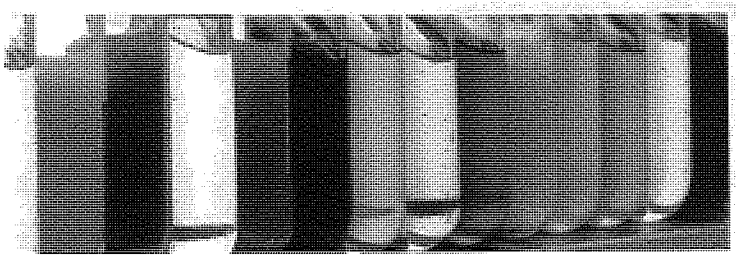


Figure 1.2 Ionic liquids (Davey, 2007)

The history of ionic liquids started in 1914. The first ionic liquid was synthesized by Walden (1914), which was ethylammonium nitrate formed from nitric acid and ethylamine. In 1948, an ionic liquid 1-ethyl-pyridinium bromide/aluminium chloride was synthesized and used in a thermal battery by Hurley and Wier (Hurley, 1948; Hurley and Wier, 1951). Later, Swain (1967) reported tetra-n-hexyl-ammonium benzoate as an electrochemical solvent in 1967. There were very few publications during that time.

Ionic liquids received much attention during 1970s-1980s, when chloroaluminate salts were employed for electrochemical applications (Robinson and Osteryoung, 1979; Wilkes et al., 1982). Many researchers focused on these types of ionic liquids for their use as electrolytes in batteries. A series of ionic liquids based on chloroaluminate salts with the cations of pyridinium or imidazolium were developed and these ionic liquids are commonly used even today.

One of the early applications of chloroaluminate ionic liquids as reaction solvents for organic synthesis was reported in 1986 (Boon et al., 1986). These ionic liquids acted as both solvents and catalysts in Friedel–Crafts reactions. In 1990, Chauvin et al. (1990) reported the dimerisation of propene by nickel complexes in acidic

chloroaluminate melts. In the same year, Osteryoung reported the polymerization of ethylene by Ziegler–Natta catalysts in chloroaluminate salts (Carlin and Osteryoung, 1990).

Chloroaluminate salts have many successful applications, especially in electrochemistry. However, there are some problems associated with these kinds of ionic liquids in organic synthesis. For example, they are very sensitive to water and oxygen and they are incompatible with many organic compounds such as ketones. Significant progress in the development of ionic liquids was made in 1992 when the ionic liquids based on anions such as $[BF_4]^-$ and $[PF_6]^-$ were synthesized by Wilkes' group (Wilkes and Zaworotko, 1992). These ionic liquids were air and water stable and they were widely used as solvents for organic reactions. Since then, numerous ionic liquids have been reported.

Task specific ionic liquids (TSILs) were defined in the year 2000 (Wasserscheid and Welton, 2003). A chemical containing a functional group was converted to a cation or an anion and this led to a specific function of the ionic liquid for a certain application. For example, a TSIL, 1-(3-aminopropyl) imidazole, is commercially available now. The appended amino group is a versatile reactive site which can be converted by various substitutions to give different functionality. For example, the treatment of 1-(3-aminopropyl) imidazole with isocyanates or isothiocyanates afforded the urea and thiourea derivatives as shown in Figure 1.3 (Visser et al., 2001). To date, a large number of ionic liquids have been constructed for specific purposes.

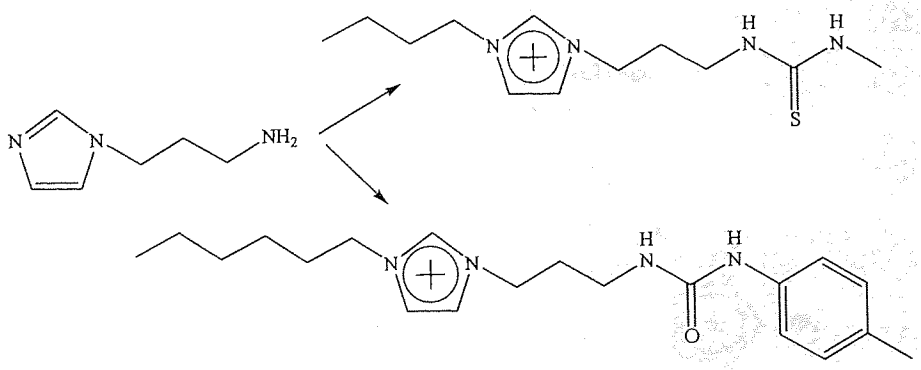


Figure 1.3 1-(3-Aminopropyl) imidazole and its derivations

1.2 Synthesis of ionic liquids

A large range of ionic liquids have been synthesized. Various types of cations have been employed for the formation of ionic liquids such as 1,3-dialkylimidazolium, N-alkylpyridinium, tetraalkylammonium and tetraalkylphosphonium (Figure 1.4). Meanwhile, many types of anions can be used to prepare the ionic liquids, for example, $[AlCl_4]^-$, $[NO_3]^-$, $[CH_3CO_2]^-$ have been used to prepare water soluble ionic liquids and $[PF_6]^-$, $[(CF_3SO_2)_2N]^-$ have been employed for water insoluble ones. The general synthetic process is presented in Scheme 1.1.

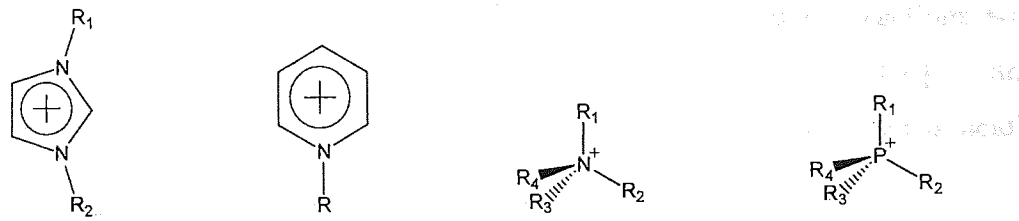
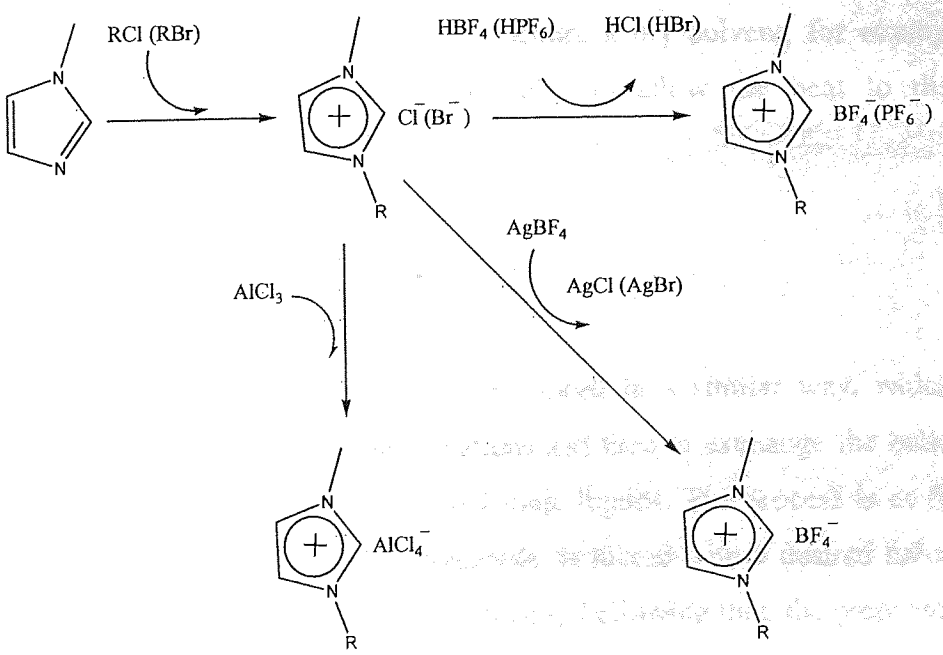


Figure 1.4 Structures of commonly used cations of ionic liquids



Scheme 1.1 General scheme for the synthesis of ionic liquids

1.2.1 Lewis acid-based ionic liquids

Generally, alkylimidazoles or pyrimidines react with haloalkanes to form halide salts and then the prepared halide salts are mixed with Lewis acids, such as $AlCl_3$, BCl_3, CuCl and $SnCl_2$, to give Lewis acid-based ionic liquids (Parshall, 1972; Williams et al., 1987; Chauvin and Olivier-Bourbigou, 1995). The ionic liquids prepared by this approach may contain more than one anion species depending on the relative molar proportions of the halide salts and Lewis acids. For example, if the molar ratio of $[RMIM]^+Cl^-$ is equal or in excess over $AlCl_3$, the reaction occurs as $[RMIM]^+Cl^- + AlCl_3 \rightleftharpoons [RMIM]^+[AlCl_4]^-$, so the ionic liquid is neutral or basic repectively. If the molar ratio of $AlCl_3$ is in excess over $[RMIM]^+Cl^-$, the following reactions will predominate, $[RMIM]^+[AlCl_4]^- + AlCl_3 \rightleftharpoons [RMIM]^+[Al_2Cl_7]^-$ and $[RMIM]^+[Al_2Cl_7]^- + AlCl_3 \rightleftharpoons [RMIM]^+[Al_3Cl_{10}]^-$, thus the ionic liquid is acidic (Oye et al., 1991).

These Lewis acid-based ionic liquids were prepared in the early development of ionic liquids for electrochemistry. The reaction is exothermic, so it is usually carried out with efficient cooling in order to avoid the decomposition and discoloration of the ionic liquid resulting from the excess heat. Moreover, the reaction should proceed under anhydrous conditions because both the starting materials and products are moisture sensitive. For industrial-scale production, a dry solvent, for example, an alkane is used to prevent hydrolysis and also to allow the heat to dissipate (Wasserscheid and Welton, 2003).

1.2.2 Moisture stable ionic liquids

Moisture stable ionic liquids can also be produced in a similar way, which is to synthesize the halide salts with suitable cations and then to exchange the halide ions with appropriate anions to form the desired ionic liquids. The process is as follows, the amine, such as pyridine and alkylimidazole, is mixed with a desired haloalkane. The reaction mixture is then refluxed with stirring. Following that, the prepared halide salt react with an acid or a metal salt, so the halide ion is exchanged with the desired

anion via anion metathesis. More details on the synthesis of moisture stable ionic liquids are discussed in Chapter 2.

For both Lewis acidic ionic liquids and moisture stable ionic liquids, the common experimental apparatus is a round-bottomed flask fitted with a reflux condenser for the preparation of halide salts. Reactions involving short chain alkyl halides such as chloroethane are carried out in an autoclave especially for large-scale production (Wasserscheid and Welton, 2003). Another alternative method to produce ionic liquids is the use of microwave irradiation. This approach can give high yields of the products with short reaction times. However, this method is limited to the preparation of small amounts of ionic liquids for laboratory research, and it is difficult to be employed for large-scale production (Varma and Namboodiri, 2001).

1.2.3 Purification of ionic liquids

Ionic liquids have low vapour pressure, so they are difficult to be purified by distillation. However, it is possible that some impurities can be removed by distillation. For instance, starting materials such as imidazoles and haloalkanes are always potential impurities in the halide salts during the first step of the synthesis, thus after the completion of the reactions, the unreacted reagents can be removed by rotary evaporation under high vacuum.

For chloroaluminate ionic liquids, impurity $[AlOCl_2]^-$ is usually formed by water and oxygen, which can be removed by bubbling with phosgene ($COCl_2$) to produce CO_2 (Abdul-Sada et al., 1993). Triphosgene is used as well and it is less toxic than phosgene (Dent et al., 1996). Other impurities in these types of ionic liquids can be removed by using rotary evaporation under high vacuum.

Moisture stable ionic liquids can always contain some impurities, such as halide ions and acidic ions, which depend on the synthetic method used. The presence of such impurities can affect the performance of ionic liquids in their applications. For example, for some transition metal catalytic reactions, halide ions can deactivate the

catalyst. Additionally, physical properties can also be changed by the presence of halide ions (Seddon et al. 2000). The viscosity increases and the density decreases with a high concentration of halides. These impurities can be removed by washing with water. Additionally, some residual water is often present in most ionic liquids even in the hydrophobic ionic liquids. Karl Fischer titration is used to check the water content. For anhydrous reactions, ionic liquids should be dried under vacuum before being used.

1.3 Properties of ionic liquids

Ionic liquids contain organic cations and inorganic anions. Their physical and chemical properties vary with the different cations and anions. Ionic liquids have many characteristic properties that are suitable for chemical reactions.

1.3.1 Melting points

Most ionic liquids have low melting points and many of them are liquids at room temperature. They are decomposed rather than volatilized at very high temperatures. In general, as the size of cations and anions increases, the melting points of ionic liquids decrease (Table 1.1). In contrast, when the symmetry of cations increases, the melting points of ionic liquids usually increase, for example, the melting point of $[BMIM]^+[(CF_3SO_2)_2N]^-$ is -15 °C, while the melting point of $[MMIM]^+[(CF_3SO_2)_2N]^-$ is 22 °C.

Table 1.1 Melting points of some commonly used ionic liquids

Ionic liquid	Mp (°C)	Ionic liquid	Mp (°C)
$[EMIM]^+Cl^-$	89	$[iPMIM]^+[PF_6]^-$	102
$[BMIM]^+Cl^-$	65	$[BMIM]^+[PF_6]^-$	-8
$[BMIM]^+[BF_4]^-$	11	$[MMIM]^+[(CF_3SO_2)_2N]^-$	22
$[PMIM]^+[BF_4]^-$	-17	$[1\text{-Et-}2,3\text{-}Me_2IM]^+[(CF_3SO_2)_2N]^-$	20
$[EMIM]^+[PF_6]^-$	62	$[EMIM]^+[(CF_3SO_2)_2N]^-$	-15
$[PMIM]^+[PF_6]^-$	40	$[BMIM]^+[(CF_3SO_2)_2N]^-$	-4

1.3.2 Density and viscosity

Ionic liquids usually have a density of >1. Most ionic liquids are quite viscous compared with conventional organic solvents. The viscosity range is from 10 cP (centipoise) to 600 cP with a typical range of 30-50 cP, which depends on the type of cations or anions. Ionic liquids with the anion $[(CF_3SO_2)_2N]^-$ have relatively low

viscosity. The structural difference in the cations or anions can dramatically influence the viscosity and density of the ionic liquids as shown in Table 1.2. The density decreases, but the viscosity increases as the length of the alkyl chain substituent on the imidazolium ring increases.

Table 1.2 Density and viscosity of some typical ionic liquids (Gordon, 2001)

Ionic liquid	**Density at 20 °C**	**Viscosity at 20 °C**
$[BMIM]^+[PF_6]^-$	1.37 g/cm^{-3}	330 cP
$[BMIM]^+[BF_4]^-$	1.24 g/cm^{-3}	154 cP
$[EMIM]^+[(CF_3SO_2)_2N]^-$	1.52 g/cm^{-3}	34 cP
$[BMIM]^+[(CF_3SO_2)_2N]^-$	1.43 g/cm^{-3}	52 cP
$[EMIM]^+[CF_3SO_3]^-$	1.39 g/cm^{-3}	45 cP
$[BMIM]^+[CF_3SO_3]^-$	1.29 g/cm^{-3}	90 cP

As usual, density and viscosity are temperature dependent. As temperature increases, the viscosity decreases. Examples are 1-ethyl-3-methylimidazolium bis((trifluoro-methyl)sulfonyl)amide (EMITFSI) and 1-ethyl-3-methylimidazolium tetrafluoro borate ($EMIBF_4$) as shown in Figure 1.5. Impurities also have a significant effect on the viscosity. The presence of halide ions increase while water decreases the viscosity of ionic liquids.

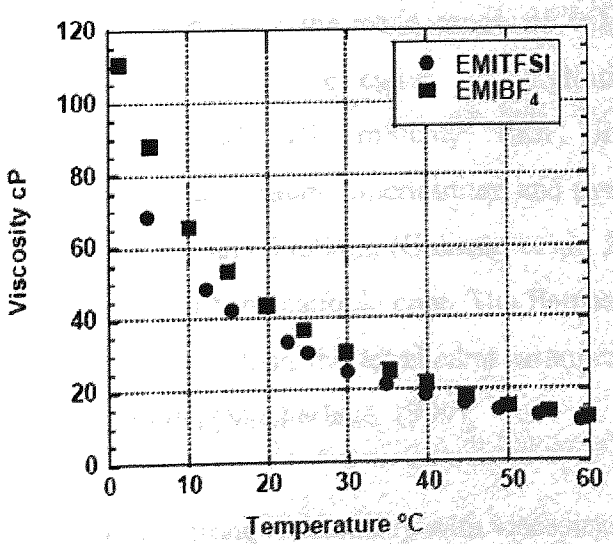


Figure 1.5 Variation of viscosity with temperature for EMITFSI and $EMIBF_4$ (Garcia et al., 2004)

1.3.3 Polarity and conductivity

As expected, ionic liquids are polar solvents. Carmichael and Seddon (2000) tested the polarity of several ionic liquids based on 1-alkyl-3-methylimidazolium using solvatochromic Nile Red. When Nile Red was dissolved in the increasingly polar solvents, the visible absorption maximum wavelength moved to a longer wavelength. Nile Red study showed that the value of maximum wavelength from ionic liquids was similar to those from the short chain alcohols. Another solvatochromatic study using [Cu(acac)(tmen)][X] (X = BPh_4 or ClO_4) (Figure 1.6) was described by Muldoon et al. (2001). It indicated that absorption maximum of [Cu(acac)(tmen)][X] was entirely dependent on the type of anions and the cations played a limited role. Both of the two studies showed that the polarity of ionic liquids was similar to that of the short chain alcohols and other polar solvents such as DMSO and DMF.

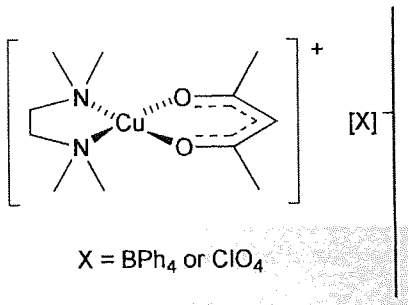


Figure 1.6 Structure of [Cu(acac)(tmen)][BPh_4] (Muldoon et al., 2001)

Conductivity of ionic liquids σ is in the wide range of 0.1–18 mS/cm at room temperature. Ionic liquids based on the cation of alkylimidazole have higher conductivities, typically around 10 mS/cm, than ionic liquids with dialkylpyrrolidinium, tetraalkylammonium, piperidinium and pyridinium which are in the range of between 0.1 mS/cm and 5 mS/cm (Galinski et al., 2006). The reason for this is the decrease in planarity of the cationic core. The flatness of the imidazolium ring confers a higher conductivity than the tetrahedral arrangement of alkyl groups displaced by the ammonium salts (MacFarlane, 1999).

Ionic liquid conductivity has a strong relationship with viscosity and temperature. The conductivity increases as viscosity decreases. High temperature results in relatively high conductivity. Examples are 1-ethyl-3-methylimidazolium bis[(trifluoro-methyl)-

sulfonyl] amide (EMITFSI) and 1-ethyl-3-methylimidazolium tetrafluoro borate ($EMIBF_4$) as shown in Figure 1.7.

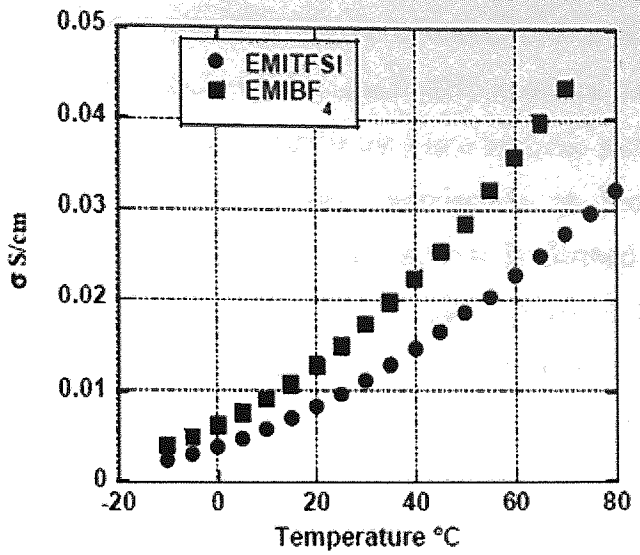


Figure1.7 Variation of conductivity with temperature for EMITFSI and $EMIBF_4$ (Garcia et al., 2004)

1.3.4 Solubility

Ionic liquids have a good solubility for a wide range of materials including inorganic, organic and even polymeric materials. A broad range of polymers can be dissolved in ionic liquids, which is beneficial for the polymer synthesis. Moreover, ionic liquids are also good solvents for transition metal-catalyzed organic reactions, because the transition metal complexes are usually difficult to dissolve in common solvents and special ligands are often needed, whereas ionic liquids can dissolve these transition metal catalysts without the chemical modification.

Miscibility of ionic liquids with other solvents depends on the type of cations and anions. In general, ionic liquids are miscible with most organic solvents such as methanol, acetone, acetonitrile and they are immiscible with ether, ethyl acetate or toluene. The immiscible organic solvents can be used to extract products in organic reactions where an ionic liquid is used as the reaction medium. The miscibility of ionic liquids with water is much dependant on the type of anions. Most ionic liquids are very hygroscopic. Ionic liquids with the anions $[NO_3]^-$, $[CF_3COO]^-$ and Lewis

acid-based ionic liquids are water miscible. Others based on the anions $[PF_6]^-$, $[(CF_3SO_2)_2N]^-$ are water immiscible. Cations also have some effect. The alkyl chain length of the cations will influence the water solubility of ionic liquids. Long chains lead to a decrease in water solubility of ionic liquids (Seddon, et al., 2000). It has also been reported that water miscibility of ionic liquids based on anion of $[BF_4]^-$ can be controlled thermally. This property can be used in a biphasic system. For example, an ionic liquid $[OctMIM]^+[BF_4]^-$ is water immiscible at room temperature. By controlling the temperature, a monophasic system is formed to achieve efficient mixing of reactants at 80 °C and then the biphasic system is formed on cooling to room temperature to achieve the separation of the resulting products (Dullius et al., 1998). Water/water-immiscible ionic liquid and non-polar solvent/ionic liquid can also be also used in the biphasic system.

Furthermore, gas solubility in ionic liquids has been investigated by many researchers. CO_2 has a high solubility in an ionic liquid $[BMIM]^+[PF_6]^-$. High solubility of gases, such as C_2H_4, C_2H_6 and CH_4, are also observed in $[BMIM]^+[PF_6]^-$. Other gases, such as H_2, O_2 and CO, have a relatively low solubility. Additionally, different solubility is found with different ionic liquids. At a given pressure, CO_2 solubility is twice in $[BMIM]^+[PF_6]^-$ as in $[EMIM]^+[EtSO_4]^-$. H_2 solubility has been found to be four times greater in $[BMIM]^+[BF_4]^-$ than in $[BMIM]^+[PF_6]^-$ (Wasserscheid and Welton, 2003). Some gas-involving reactions, such as hydroformylation, hydrogenation and oxidation, have been tested in the ionic liquids. Supercritical CO_2 and ionic liquids have been used in biphasic reactions (Murielle et al. 2001; Liu et al. 2001).

1.3.5 Toxicity

Ionic liquids have been used in a wide range of areas. If large quantities of ionic liquids are used for industrial-scale production, workers will be exposed to them daily. Moreover, ionic liquids are not only used for laboratory and industry work, they exist in normal consumer products. For example, $[BMIM]^+Cl^-$ is included as a suitable quaternary ammonium salt for skin and hair cleansing and conditioning formulations by L'Oreal France (Giroud, 2003). Scott et al. (2002) reported that $[BMIM]^+[PF_6]^-$

was an efficient plasticizer for poly-methyl methacrylate. Wallace (2003) suggested the incorporation of ionic liquids as electrolytes in artificial muscles. Thus ionic liquids have potential exposures to people's daily life. Although ionic liquids are considered environmentally friendly because of their non-volatility and low vapor pressure, they still need to be tested with regards to toxicity and safety issues.

Hassoun and his colleagues (2002) investigated the toxicity of $[BMIM]^+Cl^-$. In J774A.1 macrophage cells, cultures were incubated with $[BMIM]^+Cl^-$ (0.05-1.0 mg/mL) for up to 72 hours. Cellular viabilities were reduced in a time- and dose-dependent manner. A dose of 0.75 mg/mL at 24 hours; 0.50 mg/mL at 48 hours and 0.20 mg/mL at 72 hours (incubation times) caused 50% cellular death. Bailey et al. (2008) studied the effects of prenatal exposure of mice to $[BMIM]^+Cl^-$. After exposure to this ionic liquid, fetal weight was significantly decreased and malformations were also induced in mice, which indicated that $[BMIM]^+Cl^-$ was possibly teratogenic. Maternal toxicity was also found. Maternal morbidity and mortality were dose-dependent. $[BMIM]^+Cl^-$ has potentially adverse effects on humans.

It was reported by Merck (2003), $[BMIM]^+Cl^-$ was irritating to the eyes, skin, and respiratory system. If swallowed, it could cause irritation to the mouth mucous membranes, pharynx, esophagus, and gastrointestinal tract. Inhalation of the compound might result in irritation of the mucous membranes, coughing, and dyspnea.

Furthermore, for an ionic liquid $[BMIM]^+[PF_6]^-$, an oral LD_{50} ranging from 300 to 500 mg/kg and a dermal LD_{50} of > 2000 mg/kg for $[BMIM]^+[PF_6]^-$ were reported in rats. In rabbits, minimal irritation was seen when the compound was tested in the eyes, while no irritation was observed when applied dermally. It was not a skin sensitizer when tested on guinea pigs. Additionally, $[BMIM]^+[PF_6]^-$ was not mutagenic in the Ames test (Chemada Fine Chemicals, 2003).

However, based on my working experience, if HPF_6 was used for the synthesis of $[BMIM]^+[PF_6]^-$, HF was easily produced due to the hydrolysis of $[PF_6]^-$. Swatloski et

al. (2003) also reported the formation of HF in the process of purification of $[BMIM]^+[PF_6]^-$. Other research reported that HF would be produced if $[BMIM]^+[PF_6]^-$ was kept for a long time. This means that not only ionic liquids, but also some byproducts produced during the synthetic process may have toxicity issues. Toxicity data of some ionic liquids are illustrated in Table 1.3.

Table 1.3 Toxicity data of some ionic liquids (Masten, 2004)

Name	Irritation				Burns
	Oral	Skin	Eye	Inhal	
1-Butyl-3-methylimidazolium hexafluorophosphate		X	X		
1-Butyl-3-methylimidazolium methylsulfate		X	X		
1-Butyl-3-methylimidazolium tetrafluoroborate		X	X	X[2]	
1-Butyl-3-methylimidazolium trifluoromethanesulfonate				X[2]	X[3]
1-Butyl-3-methylimidazolium hexafluorophosphate				X[2]	X[3]
N-Butylpyridinium hexafluorophodphate				X[2]	X[3]
1, 3-Dimethylimidazolium methylsulfate		X	X		
1, 3-Dimethylimidazolium trifluoromethanesulfonate		X	X		
1-Butyl-2, 3-dimethylimidazolium hexafluorophosphate	X[1]	X	X	X[2]	
1-Butyl-2, 3-dimethylimidazolium trifluoromethanesulfonate				X[2]	X[3]
1-Butyl-4-methylpyridinium chloride		X	X		
1-Butyl-4-methylpyridinium hexafluorophosphate		X	X		
1-Butyl-4-methylpyridinium tetrafluoroborate		X	X	X[2]	
1-Ethyl-3-methylimidazolium bromide	X[1]	X	X	X[2]	
1-Ethyl-3-methylimidazolium chloride		X	X	X[2]	
1-Ethyl-3-methylimidazolium hexafluorophosphate		X	X		
1-Ethyl-3-methylimidazolium tetrafluoroborate	X[1]	X	X	X[2]	
1-Ethyl-3-methylimidazolium trifluoromethanesulfonate	X[1]	X	X	X[2]	
1-Hexyl-3-methylimidazolium chloride	X[1]	X	X	X[2]	
1-Hexyl-3-methylimidazolium hexafluorophosphate	X[1]	X	X	X[2]	
1-Hexyl-3-methylimidazolium tetrafluoroborate	X[1]	X	X	X[2]	
1-Methyl-3-octylimidazolium chloride		X	X		
3-Methyl-1-Octylimidazolium tetrafluoroborate		X	X		

[1]Irritation of the mucous membrane in the mouth, pharynx, esophagus and gastrointestinal tract after swallowing
[2]Irritation of the mucous membrane, coughing and dyspnea
[3]Eyes and skin and the mouth throat esophagus and gastrointestinal tract after swallowing

1.4 Application of ionic liquids

Ionic liquids have been applied to a wide range of areas. They have covered diverse fields such as electrochemistry (Hussey et al., 1994), polymer synthesis (Ambler et al., 1993), photochemistry (Gordon and McLean, 2000) and biochemistry (Yang and Pan, 2005). Ionic liquids have attracted much interest for their applications in organic synthetic chemistry.

1.4.1 The use of RTILs in electrochemistry

Early applications of ionic liquids were found in electrochemistry. The first publication was in 1948. Hurley and Wier (1948) reported a mixture of $AlCl_3$ and 1-ethyl pyridinium bromide used in thermal batteries. At that time, this work did not receive much attention. Much more work has been done by US Air Force Academy in this field.

Normal molten salts as electrolytes usually have high melting points. Although LiCl/KCl has a relatively low melting point of 355 °C, this temperature still causes problems inside batteries. The aim of one project from the US Air Force Academy was to find a new material to replace LiCl/KCl electrolyte in thermal batteries. Initial work was done using $NaCl/AlCl_3$ as the electrolyte. $NaCl/AlCl_3$ has a melting point of 107 °C and this is much lower than classical LiCl/KCl electrolyte. Major progress was made in 1968, when 1-ethylpyridinium bromide/$AlCl_3$ was prepared and used as the electrolyte in batteries. This salt is liquid at room temperature. Following this, a number of alkylimidazolium and alkylpyridinium ionic liquids based on chloroaluminate anions were developed and used as electrolytes in electrochemistry. In 1990, Mike Zaworotko from the US Air Force Academy synthesized a series of ionic liquids based on water stable anions such as nitrate, acetate, tetrafluoroborate and hexafluorophosphate. Later, Joan Fuller continued this work to develop a broad range of water stable ionic liquids with the anions such as cyanide, tosylate and trifluoromethanesulfate (Wikes, 2002).

Ionic liquids have advantages such as non-volatility and low vapor pressure. Here, the discussion will focus on some unique properties of ionic liquids for electrochemistry.

Conductivity

Pure ionic liquids as electrolytes have lower conductivity than the traditional aqueous electrolytes. Conductivity of the aqueous electrolyte is about 500 mS/cm. For example, the conductivity of an aqueous KOH (29.4 wt %) solution used in alkaline batteries is 540 mS/cm.

Ionic liquids are composed of ions and would be expected to have high conductivity. However, pure ionic liquids show low to moderate conductivity in the range of 0.1-15 mS/cm. This is because ionic liquids consist of large cations or anions and are viscous and these ions tend to have low mobility. Fortunately, ionic liquids based on cations of alkylimidazolium have conductivity typically at 10 mS/cm, which is comparable to that of conventional lithium electrolytes. In a lithium-ion battery, the conductivity of a solution of $LiN(CF_3SO_2)_2$ (1 mol/dm^3) in ethylene carbonate with 1,2-dimethoxyethane (1:1) is 13.3 mS/cm (Morita et al., 1998). Dialkyl imidazolium salts have higher conductivity than tetraalkylammonium salts.

In addition, increased conductivity has also been observed when ionic liquids are mixed with a small amount of organic solvent. For instance, the conductivity of pure $[EtMIM]^+[BF_4]^-$ is 14 mS/cm, while the conductivity of a 2 mol/dm^3 solution of $[EtMIM]^+[BF_4]^-$ in acetonitrile is 47 mS/cm. In a double layer capacitor, an ionic liquid Et_4NBF_4 in acetonitrile (1 mol/dm^3) shows a high conductivity σ = 60 mS/cm. When an ionic liquid is diluted, the viscosity is reduced and this can result in significant increase in conductivity (Galinski et al., 2006).

Electrochemical stability

One requirement for the ionic liquids to be used as electrolytes is that they should be electrochemically stable. Many studies show that ionic liquids are electrochemically stable in various electrodes.

Electrochemical stability of ionic liquids have been studied in several electrodes such as Pt, W, glassy carbon (GC), graphite (G). Their electrochemical stability is in a wide range from 2 V to 6 V, commonly up to 4.5 V (Table1.4). Halide salts with the anion of F^- or Br^- are oxidized at lower anodic potentials. These types of ionic liquids have a relatively narrow stability of 2–3 V. In contrast, $[N(CF_3SO_2)_2]^-$ is oxidized at higher anodic potentials. Ionic liquids based on this anion have stability up to 5.7 V. In addition, ionic liquids based on tetraalkylammonium cations show cathodic reduction at negative potentials and have a relatively high stability of 4.0–5.7 V (Galinski et al., 2006).

Table 1.4 The room temperature electrochemical potential windows for some ionic liquids

Ionic liquids	**Working electrode**	**Window (V)**	**Ref.**
$[EMIM]^+F^-$	Pt	3.1	(Hagiwara, 1999)
60.0-40.0mol% $[EMIM]^+Cl^-/AlCl_3$	W	2.8	(Lipsztajn, 1983)
50.0-50.0mol% $[EMIM]^+Cl^-/AlCl_3$	W	4.4	(Lipsztajn, 1983)
45.0-55.0mol%$[EMIM]^+Cl^-/AlCl_3$	W	2.9	(Lipsztajn, 1983)
$[EMIM]^+[BF_4]^-$	Pt	4.5	(Fuller, 1997)
$[EMIM]^+[CF_3SO_3]^-$	Pt	4.3	(Cooper, 2000)
$[EMIM]^+[(CF_3SO_3)_2N]^-$	Pt	4.5	(Bonhote, 1996)
$[BMIM]^+[BF_4]^-$	Pt	4.1	(Schroder, 2000)
$[(n\text{-}C_3H_7(CH_3)_3N)]^+[(CF_3SO_3)_2N]^-$	GC	5.7	(Matsumoto, 2000)
$[(n\text{-}C_8H_{17}(C_2H_5)_3N)]^+[(CF_3SO_3)_2N]^-$	GC	5.0	(Sun, 1998)

To date, ionic liquids have been used in electrochemical devices such as batteries, capacitors, sensors, fuel cells. Selected applications are discussed below.

1.4.1.1 Lithium battery

Early studies focused on the use of ionic liquids as electrolytes in lithium batteries. A classical electrolyte involves a salt dissolved in an organic solvent such as ethylene

carbonate. Organic solvents may cause problems due to their volatile and flammable nature. An ionic liquid electrolyte, however, contains a room temperature ionic liquid and no other solvents are added (Sakaebe et al., 2007). Ionic liquids based on the cations of alkylimidazolium and pyridinium and the anions of $[BF_4]^-$, $[PF_6]^-$ or $[(CF_3SO_2)_2N]^-$ are widely used as electrolytes in batteries. This is because these ionic liquids have moderate viscosity and good electrochemical stability and conductivity.

Garcia et al. (2004) reported 1-ethyl-3-methyl-imidazolium bis(trifluoromethane-sulfonyl) imide (EMI-TFSI) as an electrolyte used in the lithium battery. Its thermal stability, viscosity, conductivity and electrochemical properties were measured. EMI-TFSI was stable up to 400 °C. The viscosities of EMI-TFSI and EMI-BF4 were 30 cP and 36 cP and their conductivities were 10 mS/cm and 15 mS/cm respectively at room temperature. EMI-TFSI had the larger potential window (4.3 V). The solution of lithium bis(trifluoromethanesulfonyl)imide (LiTFSI) in EMI-TFSI was studied as the electrolyte in the lithium battery with $LiCoO_2$ cathode and $Li_4Ti_5O_{12}$ anode. Cyclic and power studies were compared with those obtained with LiTFSI/EMI-BF_4 and a conventional organic solution of LiTFSI/ethylene carbonate/1,2-dimethoxyethane as electrolytes. The LiTFSI/EMI-TFSI electrolyte provided the highest performance and delivered up to 106 mAh/g after 200 cycles.

Xu et al (2006) described the use of an ionic liquid *N*-methyl-*N*-propylpiperidinium bis(trifluoromethanesulfonyl)imide (PP13-TFSI) in lithium batteries. The electrochemical window of PP13-TFSI was 5.8 V(Li/Li+), which was broader than the commonly used ionic liquids $[BMIM]^+[BF_4]^-$ (4.7 V) and $[BMIM]^+[PF_6]^-$ (4.5 V). The cathodic limit of the PP13-TFSI was about -0.3 V, while it was about 0.7 V for both $[BMIM]^+[PF_6]^-$ and $[BMIM]^+[BF_4]^-$. Therefore PP13-TFSI can be used as the electrolyte in lithium batteries. The charge–discharge cycling efficiency of lithium plating/striping on nickel substrate was tested and measured using 0.4 M LiTFSI/PP13-TFSI electrolyte. Enhanced lithium cycling efficiency was observed when 5% (wt/wt) ethylene carbonate was added to the electrolyte. Lithium cycling efficiency of ionic liquid electrolyte with ethylene carbonate was higher than an organic electrolyte.

Sakaebe et al (2007) also tested several ionic liquids with the cations of N-methyl-N-propyl piperidinium (PP13), tetrapentylammonium, 1-ethyl-3-methyl imidazolium and with the anion of bis(trifluoromethanesulfonyl)imide (TFSI). These ionic liquids had a good stability for $Li/LiCoO_2$. For PP13[TFSI], Li cycling efficiency was over 95%. Halide impurities and water were found to reduce the average cycling efficiency. The thermal stability of PP13[TFSI] was up to 300 °C.

1.4.1.2 Capacitor

Double layer electrochemical capacitors are high power-density energy storage devices. They are based on the capability of the double layer at the electrode/electrolyte interface. Ionic liquids are electrochemically stable up to 4 V, conductivity of 10 mS/cm and double layer specific capability of 10 $\mu F/cm^2$. Thus they are suitable electrolytes for double layer capacitors (Galinski et al., 2006).

Sato and co-workers (Sato et al., 2004) prepared several ionic liquids to be used in electric double layer capacitor (EDLC). Three ionic liquids were evaluated: *N*,*N*-diethyl-*N*- methyl-*N*-(2-methoxyethyl)ammonium tetrafluoroborate (DEME-BF_4), *N*,*N*-diethyl- *N*-methyl-*N*-(2-methoxyethyl)ammonium bis(trifluoromethylsulfonyl)-imide DEME-TFSI (Figure 1.8) and 1-ethyl-3-methylimidazolium tetrafluoroborate (EMIM-BF_4).

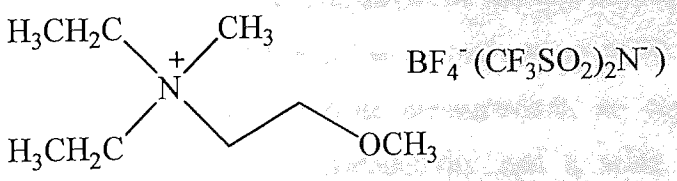


Figure 1.8 Structures of DEME-BF_4 and DEME-TFSI

DEME-BF_4 had the highest ionic conductivity of 4.8 mS/cm at 25 °C of the three ionic liquids and it also had the widest potential window of 6.0 V. Thus DEME-BF_4 has a particular potential to be used as the electrolyte in electrochemical capacitors. An EDLC (Figure 1.9) was prepared with a pair of activated carbon electrodes and

DEME-BF_4 as the electrolyte. This electrolyte working voltage 2.5 V had a high capacity and good charge–discharge cycle durability even at temperatures over 100 °C. However, high viscosity resulted in the lower capacity of EDLC using DEME-BF_4 compared with the classical EDLC using tetraethylammonium tetrafluoroborate (TEA-BF_4)/propylene carbonate (PC) (Sato et al., 2004).

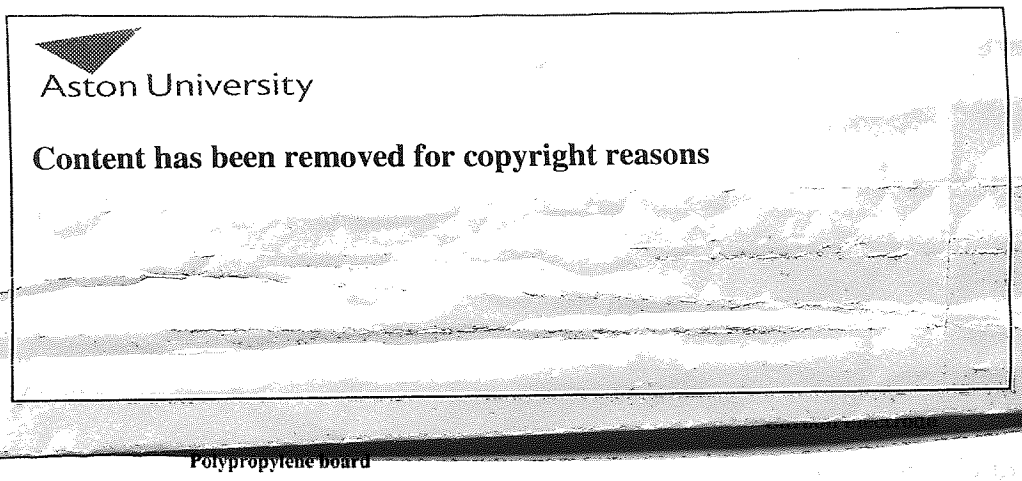


Figure 1.9 An electric double layer capacitor (Sato et al., 2004)

A supercapacitor was prepared by Liu et al. (2006). It was a 3 V sandwich asymmetrical supercapacitor. It consisted of a positive Mesopore nickel-based mixed rare-earth oxide (NMRO), a negative activated carbon (AC) electrode and an ionic liquid $[BMIM]^+[PF_6]^-$ as the electrolyte. The electrode worked well in this ionic liquid. It showed a real power density of 458 Wkg^{-1} and a real energy of 50 $Whkg^{-1}$. During 500 cycles of galvanostatic charge/discharge measurement, no capacity loss was observed. $[BMIM]^+[PF_6]^-$ had a good conductivity and a wide electrochemical window. The use of $[BMIM]^+[PF_6]^-$ as the electrolyte increased the supercapacitor duration.

1.4.1.3 Sensor

Ionic liquids have been used to develop new sensors. Ionic liquids are widely used in electrochemical gaseous sensors such as O_2, CO_2, and NH_3. For example, the

superoxide radical (O_2^-) is formed by the reduction of O_2 and it was found to be stable in the ionic liquids at glassy carbon, gold (Au) or platinum (Pt) electrodes (Wei and Ivaska, 2008). Wang et al (2004) made a solid state O_2 gas sensor on supported 1-ethyl-3-methylimidazolium tetrafluoroborate $[EMIM]^+[BF_4]^-$ porous polyethylene membrane-coated electrodes. The $[EMIM]^+[BF_4]^-$ membrane-coated electrode as an O_2 gas sensor can be readily constructed and miniaturized when compared to a solid electrolyte gas sensor and the classic Clark-type gas sensor. This O_2 gas sensor had a wide detection range, a high sensitivity and an excellent reproducibility (Wang et al., 2004).

The normal design of a gas sensor involves a gas permeable membrane that is used to separate the gaseous sample and the electrolyte. The membrane is usually poly(tetrafluoethylene) or polyethylene with a thickness ranging from 1 to 20 μm. The thickness of the membrane has a significant effect on the rate of transport of analyte to the electrode surface. Gas sensors with low volatile RTILs as electrolytes can be used without the sensor membranes. A membrane-free gas sensor involving a two-electrode cell was designed by Buzzeo et al. (2004). The surface of the working microelectrode was modified with a thin layer of a RTIL. The non-volatility of ionic liquids gives these types of gas sensors a wide range of potential applications especially in high temperature or high pressure conditions (Buzzeo et al., 2004).

Furthermore, gas solubility has also been studied in ionic liquids by many researchers. Ionic liquids were used to detect organic vapors via a Quartz crystal microbalance (QCM). QCM measures the frequency changes between a reference state and its state when quartz crystal is exposed to the vapor sample. Usually, the only change in frequency is due to the change of mass loaded on the surface of the vibrating crystal (Wei and Ivaska, 2008). Liang and co-workers, however, found that the frequency change was due to the viscosity change rather than mass change of ionic liquids film. Thus ionic liquid QCM sensors worked on the viscosity change due to gas absorption. The viscosity change depended on the vapor of chemicals and the type of ionic liquids, which resulted in the frequency shift of the quartz crystal. Viscosity change was temperature dependant (Liang et al., 2002).

1.4.2 The use of RTILs in organic chemistry

The most important area for the application of ionic liquids is organic chemistry. The first report about organic synthesis in an ionic liquid was for Friedel–Crafts reactions. Following that, progress was made using chloroaluminate ionic liquids as reaction solvents, however, chloroaluminate salts are sensitive to moisture and they are not compatible with certain organic solvents such as acetone. With the development of air and water stable room temperature ionic liquids, many chemists have made great efforts to use these types of ionic liquids in organic synthesis instead of using traditional volatile and flammable organic solvents. A large number of reactions have been investigated in RTILs, for instance, acid-catalyzed reactions such as Friedel-craft reaction; transition metal-catalyzed reactions, and also gas-involved reactions such as hydroformylation, hydrogenation and oxidation.

There are a number of features of ionic liquids that make them attractive in organic chemistry. Most ionic liquids have low melting points and high thermal stabilities. The thermal stability of ionic liquids is particularly useful for reactions that require relatively high temperatures.

Moreover, ionic liquids are non-volatile and non-flammable. They have low vapor pressure and decompose rather than evaporate at very high temperatures. These properties make them safer to handle and also reduce air pollution compared with organic solvents. In addition, low vapor pressure and high thermal stability of ionic liquids can make the product separation procedure easier after the completion of an organic reaction. It is possible to isolate and purify products by distillation from the ionic liquid. For example, in our laboratory, the purification of ethyl-2-cyano-3-cyclohexanyl-2-propenoate was readily achieved by distillation using a Buchi Kugelrohr apparatus instead of flash column chromatography.

Furthermore, when selecting a solvent for an organic reaction, one often considers two factors. One is the solvation ability for the reactants such as starting materials and catalysts. The other is their capability to promote reaction reactivity and product

selectivity. A wide range of organic, inorganic compounds is soluble in ionic liquids. Transitional metal complexes are usually difficult to dissolve in common organic solvents, but they are soluble in many ionic liquids, which benefits transition metal catalysis. A large number of cases have shown that organic reactions can proceed more efficiently in ionic liquids than in traditional organic solvents. Ionic liquids have the capability to catalyze the reactions, enhance the conversion rate and improve the selectivity of the products. Another important advantage of ionic liquids is that they can be recycled and reused.

Some representative examples of Lewis acid-based ionic liquids and moisture stable ionic liquids are discussed according to the roles of ionic liquids in organic reactions.

Lewis acid-based ionic liquids can act as the solvent and the catalyst or co-catalyst in organic synthesis. Acidity and basicity of Lewis acid-based ionic liquids can be controlled by changing the ratio of Lewis acid. This unique property makes these types of ionic liquids capable of catalyzing reactions or coordinating to the catalyst complex to enhance its catalytic activity.

1.4.2.1 Lewis acid-based ionic liquids as solvents and catalysts

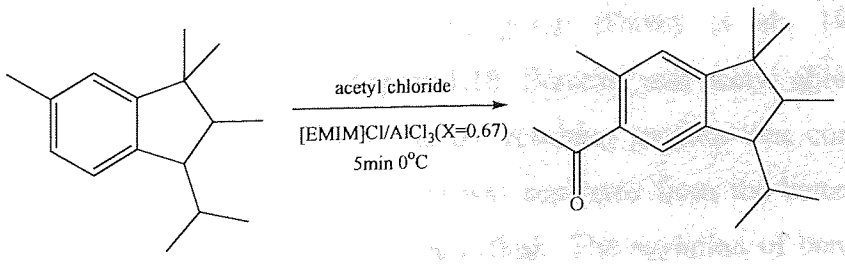
The first use of an ionic liquid, [EMIM]Cl/$AlCl_3$, as a solvent and a catalyst in Friedel-Crafts reaction was reported in 1986. The reactions of aromatic compounds with alkyl halides, or acyl halides are catalyzed by strong Bronsted acids or Lewis acids. The reactions often produce a range of products such as polyalkylated or isomerized products.

Imidazole cation based chloroaluminate salts have been successfully used for Friedel–Crafts alkylation reactions. Boon et al. (1986) reported the reaction of benzene with alkyl halide in an ionic liquid [EMIM]Cl/$AlCl_3$ ($Cl^-/AlCl_3$ = 0.6 or 0.67). For the methylation of benzene with methyl chloride, dimethylbenzene (xylenes) and tetramethylbenzene were predominant. Hexamethylbenzene (10%) was also produced.

In the butylation of benzene with 1-butyl chloride, isomerization of butyl side chain occurred and the main product was sec-butyl benzene.

DeCastro et al. (2000) described the alkylation of aromatic compounds with dodecene catalyzed by chloroaluminate ionic liquids. Good yields of products were obtained and a high selectivity was observed towards monoalkylated products. A reduction in the yields was found when the catalyst was recycled. The author gave the possible reasons, the water content of the ionic liquid could deactivate the catalyst and the oligomerization of dodecene on the catalyst surface would deactivate the catalyst as well.

Friedel–Crafts acylation reactions were also investigated in chloroaluminate ionic liquids. Adams et al. (1998) carried out Friedel–Crafts acylation reactions in [EMIM]Cl/$AlCl_3$ (X=0.67). High yields of the products were obtained. When acetylation of naphthalene was carried out in [EMIM]Cl/$AlCl_3$, 1-acetylnaphthalene was predominant. Only 2% of 2-acetylnaphthalene was obtained. In contrast, when the reaction was carried out in nitrobenzene or nitromethane, 2-acetylnaphthalene was predominant. It was proposed that when nitrobenzene was used as the reaction solvent, the complex of AcCl-$AlCl_3$-nitrobenzene acted as the acylating agent, but when the ionic liquid was used as the solvent, the free acylium ion was the acylating agent which is smaller than the complex. Thus it was easier to attack at a sterically more hindered position. Rearrangement of 1- or 2-acetylnaphthalene was not found in the ionic liquid. Moreover, in the acetylation of toluene, chlorobenzene and anisole, 4-acetylated products were predominant for all three agents. In the acetylation of 1,1,2,6-tetramethyl-3-isopropyl indane (Scheme 1.2), a commercially available fragrance traseolide (5-acetyl-1,1,2,6-tetramethyl-3-isopropyl indane) was produced in a high yield of 99% as a single isomer.

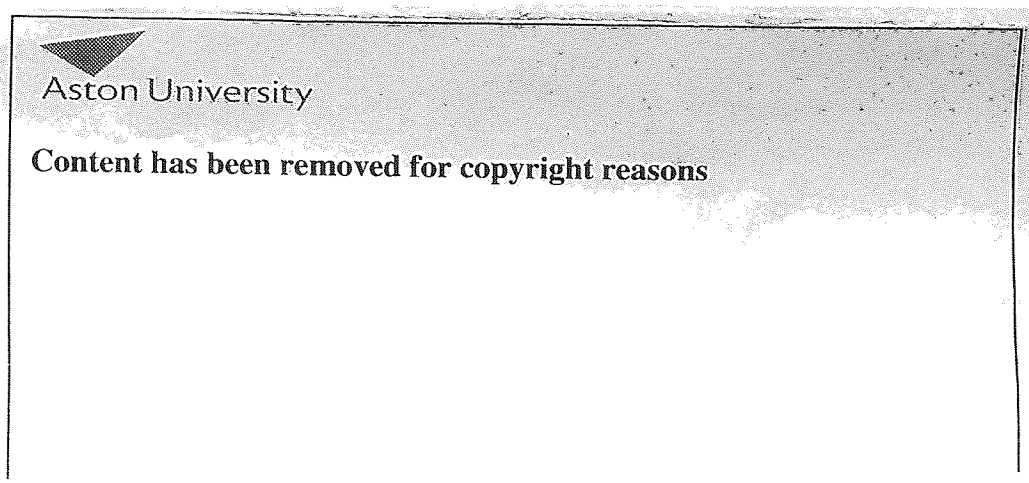


Scheme 1.2 Acetylation of 1,1,2,6-tetramethyl-3-isopropylindane in [EMIM]Cl/$AlCl_3$

In the acetylation of anthracene, 9-acetylanthracene was obtained when carbon disulfide was used as the reaction solvent and 1-acetylanthracene was found when nitrobenzene was employed as the solvent. In contrast, different products were detected when [EMIM]Cl/$AlCl_3$ was used with the increase of the reaction time (Scheme 1.3). After 5 min, the initial product was 9-acetylanthracene (b). This monoacetylation of anthracene was reversible. 1-Acetylanthracene (d) and 2-acetylanthracene (c) were then produced and after 24 hr, the 1,5- and 1,8-diacetyl-anthracenes were found to be the final products.

Scheme 1.3 Acetylation of anthracene in [EMIM]Cl/$AlCl_3$ (Adams et al. 1998)

An important patent of Friedel-Crafts acylation reactions in an ionic liquid [EMIM]Cl/$AlCl_3$ was reported by Seddon's group (Davey et al., 1999). The experimental apparatus is shown in Figure 1.10. Benzene and acetyl chloride were added dropwise to the reaction vessel and the resulting product was continuously removed by an extractor. The acetophenone was separated from the benzene/acetyl chloride in the column and was collected in a flask. The acylation of benzene with acetyl chloride afforded acetophenone in a high yield.



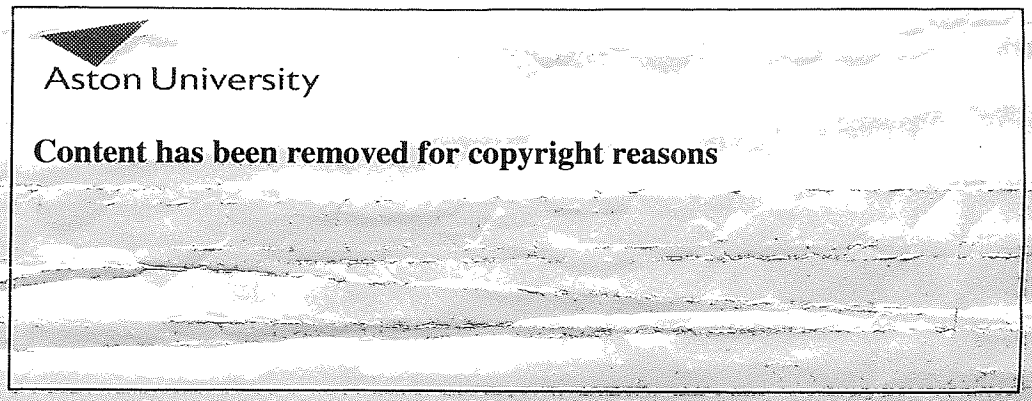


Figure 1.10 Experimental apparatus of acetylation of benzene (Davey et al., 1999)

1.4.2.2 Lewis acid-based ionic liquids as solvents and co-catalysts

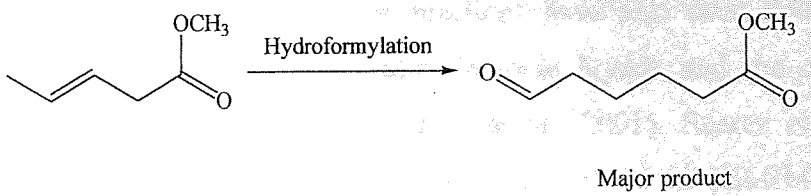
An ionic liquid interacts with a catalyst to activate it or improve its catalytic activity leading to acceleration of the reaction rate. In most cases, ionic liquids interact with the electron rich parts of the catalyst complex and this results in a lower electron density at the catalytic center.

Not only chloroaluminate ionic liquids are used in organic synthesis, other Lewis acid-based ionic liquids are also employed. Hydroformylation reactions have been investigated in ionic liquids by many researchers. Some successful reports were based on RTILs with the anion of chlorostannate.

Wasserscheid and Waffenschmidt (2001) described the platinum-catalyzed hydroformylation of olefins using chlorostannate ionic liquids as a solvent. Chlorostannate ionic liquids were prepared by following a similar procedure to that used for chloroaluminate salts.

$$[\text{cation}]^+ Cl^- + SnCl_2 \rightleftharpoons [\text{cation}]^+ SnCl_3^-$$
$$[\text{cation}]^+ SnCl_3^- + SnCl_2 \rightleftharpoons [\text{cation}]^+ Sn_2Cl_5^-$$

In Wasserscheid experiment, a Pt-catalyst was easily dissolved in ionic liquids. Hydroformylation of 1-octene showed a high selectivity to give linear nonanal in both dichloromethane and ionic liquids. Hydroformylation of methyl-3-pentenoate (Scheme 1.4) showed that the activity of the catalyst was higher in chlorostannate ionic liquids than in dichloromethane. They suggested that the catalyst was deactivated when the reaction was carried out in dichloromethane. The acidic ionic liquid could enhance Pt catalytic activity in the hydroformylation of methyl-3-pentenoate and 1-octene compared with the organic solvent under the same reaction conditions.



Scheme 1.4 Hydroformylation of methyl-3-pentenoate in ionic liquids

Generally, ionic liquids provide a polar reaction medium and good solubility for the catalysts, starting materials and products. In a large number of cases, ionic liquids have a beneficial effect on organic reactions. The reaction rates are accelerated and the product yields are improved in ionic liquids compared with organic solvents. Thus ionic liquids not only act as "pure" solvent, but also have some interaction with reactants/catalysts and therefore promote organic reactions.

1.4.2.3 Moisture stable ionic liquids as solvents and co-catalysts

As described previously, Friedel–Crafts reactions, which normally use $AlCl_3$ as a catalyst, can successfully proceed in chloroaluminate ionic liquids. They can also be carried out in water stable ionic liquids such as $[BMIM]^+[PF_6]^-$. Song and co-workers (2000) used scandium (III) triflate as a Lewis acidic catalyst for the alkylation of benzene and 1-hexene. Various ionic liquids were investigated. They found that the alkylation reactions were successful in $[BMIM]^+[PF_6]^-$, $[HMIM]^+[PF_6]^-$, $[EMIM]^+[SbF_6]^-$, $[BMIM]^+[SbF_6]^-$. The desired products were obtained in high quantities. However, the reactions were unsuccessful when the anions of the above ionic liquids were changed to $[BF_4]^-$ and $[CF_3COO]^-$. Those reactions did not proceed in organic solvents either. Song explained that it was due to the hydrolysis of ionic liquids with the anion $[PF_6]^-$ or $[SbF_6]^-$ producing a small amount of HF which could promote the alkylation reactions. The catalyst and ionic liquids from those reactions could be recycled and reused (Adams et al., 1998; Song et al., 2000).

Transition metal-catalyzed hydrogenation reactions have also been investigated in ionic liquids. Alkenes have good solubility in ionic liquids and the diffusion of hydrogen into ionic liquids is rapid (Medved et al., 2001). Suarez et al. (1996) reported that the hydrogenation of cyclohexene proceeded in $[BMIM]^+[BF_4]^-$ or $[BMIM]^+[PF_6]^-$ at room temperature for 120 hours at 10 atm H_2 (1 atm = 101.325 kPa). Wilkinson's catalyst $RhCl(PPh_3)_3$ was readily dissolved in both of these ionic liquids. After the completion of the reaction, the catalyst remained in the ionic liquids and the products were isolated without the contamination of the catalyst.

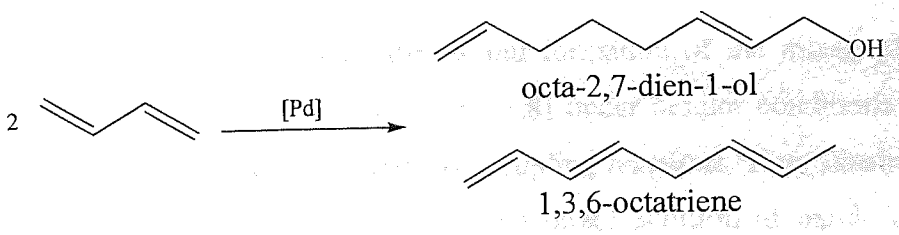
Steines et al. (2000) reported hydrogenation of sorbic acid to *cis*-3-hexenoic acid in an ionic liquid $[BMIM]^+[PF_6]^-$/MTBE. Over a threefold enhanced activity for the production of *cis*-3-hexenoic acid was observed in $[BMIM]^+[PF_6]^-$/MTBE compared with polar organic solvents. The reason given by the authors for the failure of the reactions in organic solvents was that the polar organic solvents had poor solubility and they deactivated the Ru catalyst, while ionic liquids which they used had high

solvation capability and relatively weak coordination preventing the deactivation of the catalyst. In this process, a biphasic system was established and ionic liquids were easily recovered.

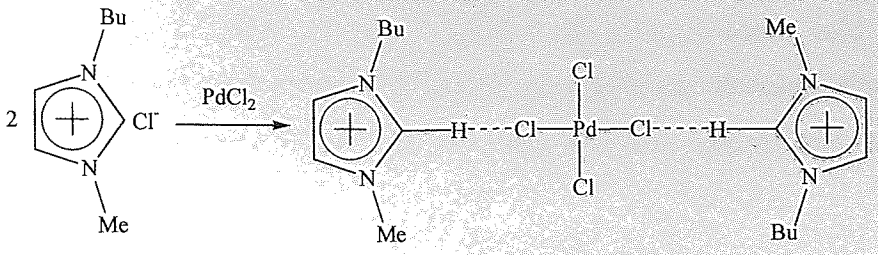
As described previously, the miscibility of ionic liquids with water can be controlled by temperature and pressure. Dyson et al. (2001) took advantage of this property to carry out hydrogenation of 2-butyne-1,4-diol in the $[OctMIM]^+[BF_4]^-$/water system. At room temperature, a biphasic system was formed. The ionic liquid layer contained the Rh catalyst and water phase contained the reagent. The reaction was carried out in a stirred autoclave at 80 °C with hydrogen pressure of 60 atm, under which a monophasic system was established. After the completion of the reaction, the biphasic system reformed on cooling to room temperature. The product butane-1,4-diol remained in water phase could be easily separated without the catalyst contamination.

1.4.2.4 Moisture stable ionic liquids as solvents and ligands

Dullius et al., (1998) reported the hydrodimerization of 1,3-butadiene (Scheme 1.5) catalyzed by Palladium (II) complex in $[BMIM]^+[BF_4]^-$/water. 1,3-Butadiene dimer 1,3,6-octatriene and octa-2,7-dien-1-ol were produced. The conversion rate of 1,3-butadiene was 28%, with a turnover frequency (TOF) of 118 h^{-1} and the selectivity was 94% on octa-2,7-dien-1-ol. The conversion rate increased as the temperature increased. The products were easily separated due to the formation of two layers when the temperature was below 5 °C and the catalyst could be recovered and reused with no decreased catalytic activity. The catalyst formed a $(BMIM)_2PdCl_4$ complex with the ionic liquid and the structure of this complex was determined by X-ray diffraction analysis (Scheme 1.6)

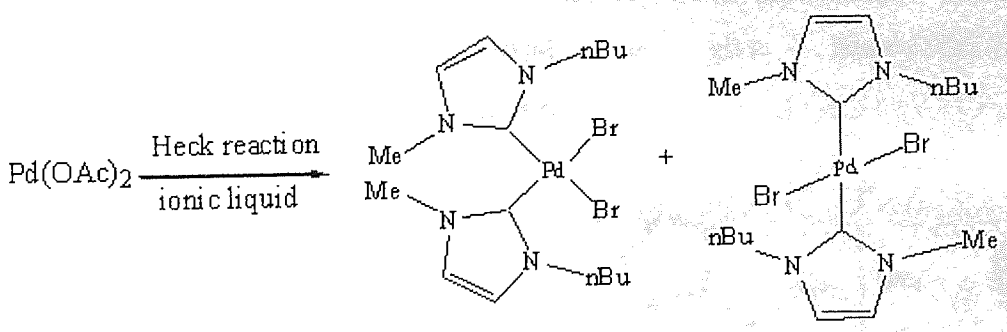


Scheme 1.5 Hydrodimerization of 1,3-butadiene in $[BMIM]^+[BF_4]^-$/water



Scheme 1.6 Catalyst complex $(BMIM)_2PdCl_4$

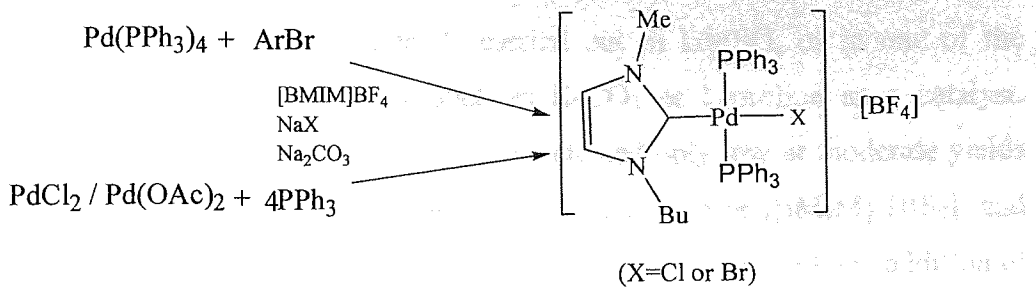
Xu et al. (2000) found that the Heck reaction with a catalyst $Pd(OAc)_2$ proceeded effectively in $[BMIM]^+Br^-$, while it did not proceed well in $[BMIM]^+[BF_4]^-$. For instance, when the reaction of iodobenzene with styrene was carried out in $[BMIM]^+Br^-$, the reaction conversion rate was 100% and the selectivity was 99% to *trans*-stilbene. In contrast, when the reaction was carried out in $[BMIM]^+[BF_4]^-$, the conversion was only 21% and the selectivity was 92%, significantly lower than $[BMIM]^+Br^-$. Subsequently, N-heterocyclic carbine complexes of palladium were identified. These complexes were produced by $Pd(OAc)_2$ reacting with $[BMIM]^+Br^-$ in $[BMIM]^+Br^-$ (Scheme 1.7). The higher activity of palladium in the Heck reaction in $[BMIM]^+Br^-$ than in $[BMIM]^+[BF_4]^-$ was due to the formation of palladium carbine complexes in $[BMIM]^+Br^-$.



Scheme 1.7 Catalyst complex $(BMIM)_2PdBr_2$

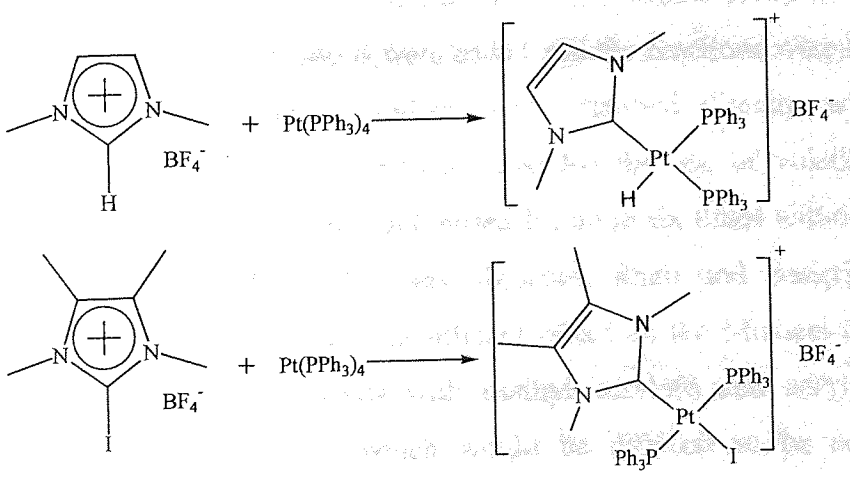
Mathew et al. (2001) have detected the in situ formation of the mixed phosphine imidazolylidene palladium complex (Scheme 1.8) under similar conditions in ionic liquids which promoted palladium-catalyzed coupling reactions. They illustrated that the catalyst could be synthesized by either the direct addition of halide or halide contamination in the ionic liquids. They tested the activity of the catalyst complex for

a Suzuki reaction. Bromobenzene was reacted with phenylboronic acid to afford biphenyl with the conversion rate of 95% without significant decomposition of the catalyst. They also repeated the reaction using this recycled catalyst and no reduced activity was found.



Scheme 1.8 Catalyst complex [(BMIM)Pd(PPh_3)$_2$X (X=Cl or Br)][BF_4]

Metal-carbene complexes can also be formed by oxidative addition of the imidazolium cation to the metal center. McGuinness et al. (2001) carried out a reaction of equimolar $[BMIM]^+[BF_4]^-$ with $Pt(PPh_3)_4$ in refluxing THF (Scheme 1.9). This gave 15% of the oxidative addition product *cis*-[PtH(1,3-dimethylimidazolin-2-ylidene)(PPh_3)$_2$][BF_4], the identity of which was confirmed by ^{1}H NMR and ^{31}P NMR. The oxidative addition of 2-iodo-1,3,4,5-tetramethylimidazolium tetrafluoborate was also achieved to give *trans*-[PtI(1,3,4,5-tetramethylimidazolin-2-ylidene)(PPh_3)$_2$][BF_4]$^-$.



Scheme 1.9 Catalyst complexes *cis*-[PtH(1,3-dimethylimidazolin-2-ylidene)(PPh_3)$_2$][BF_4] and *trans*-[PtI(1,3,4,5- tetramethylimidazolin-2-ylidene)(PPh_3)$_2$][BF_4]

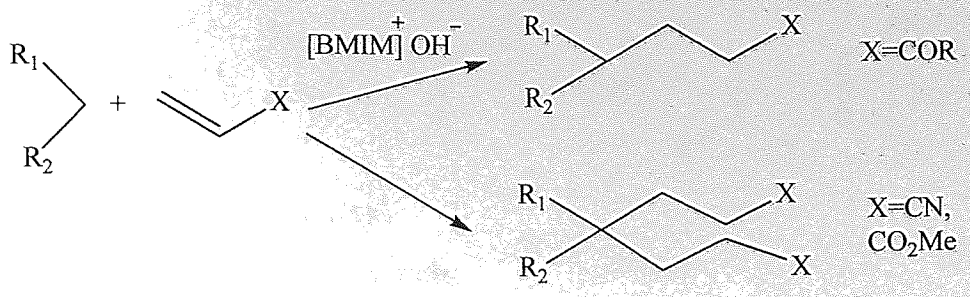
1.4.2.5 Moisture stable ionic liquids as solvents and catalysts

In this case, no other catalysts are added and ionic liquids act as catalysts and solvents. Michael reaction is a representative example.

The Michael reactions are conventionally carried out in DMSO, or in one of the excess starting materials with a base such as K_2CO_3 or L-proline as a catalyst. However, some reactions take long time to complete and only low or moderate yields are achieved using the traditional approach. Ionic liquids such as $[BMIM]^+[BF_4]^-$ and $[BMIM]^+[PF_6]^-$ have been used as solvents for Michael reactions with the addition of a catalyst such as L-proline. Recently, several ionic liquids have been investigated as both a solvent and a catalyst to promote Michael reactions.

One successful task specific ionic liquid $[BMIM]^+[OH]^-$ was prepared by Ranu and Banerjee (2005). $[BMIM]^+[OH]^-$ was used as a catalyst to promote the Michael addition of a wide range of 1,3-dicarbonyl compounds, cyano esters and nitro alkanes to conjugated ketones, carboxylic esters and nitriles.

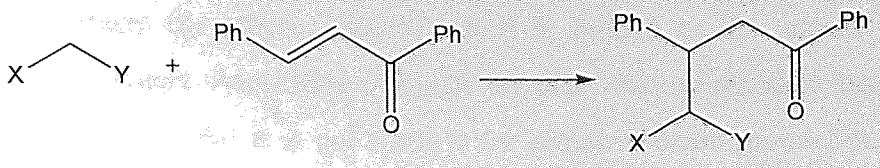
$[BMIM]^+[OH]^-$ was used to catalyze the addition reaction of α,β-unsaturated ketones. Monoaddition products were obtained for most reactions. In addition, $[BMIM]^+[OH]^-$ was found to catalyze the reaction of open-chain 1,3-dicarbonyl compounds with α,β-unsaturated esters to afford bis-adducts in one step (Scheme 1.10). In the whole process, no other catalysts and solvents were added. All the reactions were completed within 0.5-4 hours. The resulting products were distilled directly without the extraction of organic solvents. This approach avoided the use of volatile organic solvents. $[BMIM]^+[OH]^-$ was recycled and reused for up to six times without reduced reactivity, but loss of $[BMIM]^+[OH]^-$ was observed. Ranu and Banerjee (2005) emphasized that $[BMIM]^+[OH]^-$ had a significant effect on the Michael addition of open-chain 1,3-dicarbonyl compounds with methyl acrylate and acrylonitrile to produce the bis-addition products, which would be difficult to be achieved in traditional solvents in one step.



Scheme 1.10 Michael addition of 1,3-dicarbonyl compounds in $[BMIM]^+[OH]^-$

Ionic liquids can be specifically designed to produce a catalytic activity. Non-specifically designed ionic liquids have also been observed to promote organic reactions at various levels. However, up to date, there have been very few reports to describe these types of catalytic activity.

In 2007, Meciarova and Toma (2007) reported Michael addition of methylene compounds to chalcone (Scheme 1.11) in various ionic liquids (Figure 1.11) without the presence of other catalysts. Some promising results were obtained for the catalyst-free addition of malononitrile to chalcone. The reactions proceeded very well in acidic IL 7 and basic IL 8. High yields of the products were also obtained in neutral ionic liquids IL3 and IL1. However, low yields of products were obtained in IL 4, IL 6. No reaction occurred in IL 5. Michael addition of malononitrile catalyzed by HCl in dichloromethane did not proceed, which indicated that the catalytic activity of IL 7 was due to the special properties of IL 7, rather than because of its acidity. Meciarova and co-workers extended the range of methylene compounds for Michael reactions. Not all the reactions proceeded at room temperature and some of them required a relatively high temperature. This study demonstrated that ionic liquids had a certain capability to catalyze Michael reactions. The mechanism was not fully understood. One suggestion was that the catalytic activity was due to the formation of H bond on C(2) proton of the imidazole ring with certain starting materials, resulting in the catalytic activity (Meciarova and Toma, 2007).



X = CN, $COOCH_3$, $COCH_3$, COPh

Y = CN, $COOCH_3$, $COOCH_2CH_3$, COPh

Scheme 1.11 Michael addition reactions in various ionic liquids

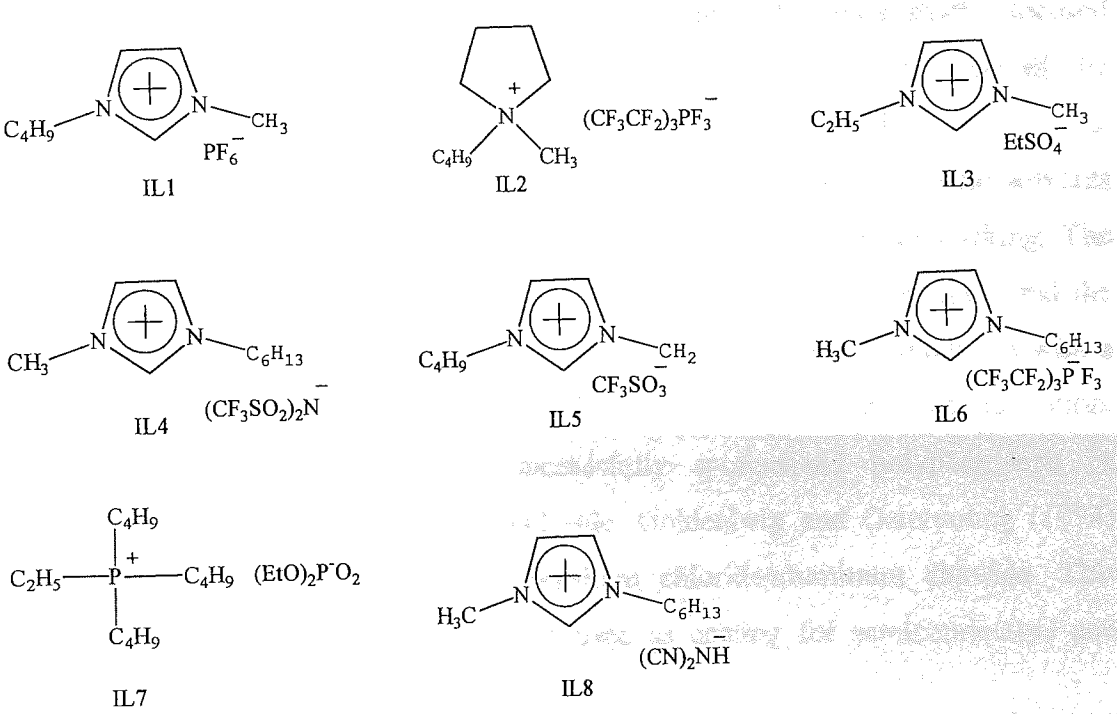


Figure 1.11 Structures of ionic liquids for Michael addition reactions

1.4.3 The use of RTILs in polymer synthesis

Polymer production is an important industry. Thirty million tons of polymers are produced annually (US Patent 6924341, 2005). Common organic solvents such as THF, DMF and DMSO are widely used for the synthesis of polymers. The use of large amount of volatile organic solvents has become a serious environmental problem. Chemists have started to seek safe and environmental benign reaction media. Water is

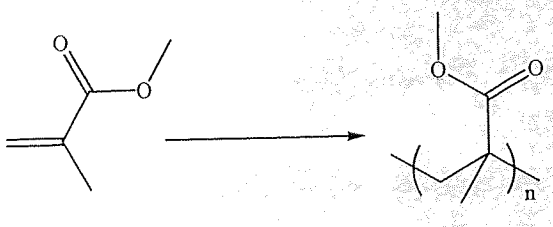
a non-toxic solvent for polymerization, but it is limited by its narrow range of solubility for polymers. Supercritical liquids are also used as reaction media in the synthesis of polymers, but it is not suitable for industrial-scale production, because complex reaction conditions are required such as high temperature and high pressure. In the past few years, ionic liquids have been used as environmentally friendly reaction solvents for polymerization.

The earliest study was reported by Carlin et al. in 1990 (Carlin et al., 1990), in which ethylene polymerization was catalyzed by Cp_2TiCl_2 in $[EMIM]^+ Cl^-/AlCl_3$. This approach achieved a high yield of polyethylene. During 1990s, most studies focused on electrochemical polymerization in chloroaluminate ionic liquids. One of the successful studies was the preparation of poly(para-phenylene) (PPP) in chloroaluminate ionic liquids. The polymerization of phenylene in organic solvents often resulted in PPP with a low mass and a disruption of molecular packing. The resulting PPP was easily contaminated by oxygen, the chlorinated products and the catalysts. When PPP was synthesized in the ionic liquids, PPP was produced with a higher molecular mass which could be altered by changing the benzene concentration. Kobryanslii and Arnautov (1992) successfully synthesized polyphenylene in 1-butylpyridinium chloride/aluminum chloride. Goldenberg and Osteryoung (1994) prepared PPP in 1-ethyl-3-methyl-imidazolium chloride/aluminum chloride. This electronically conducting polymer can be used as coating for semiconductors and charge-storage material.

Although polymerization reactions have been successfully carried out in chloroaluminate ionic liquids, one drawback is that these types of ionic liquids are water sensitive. High degree isomerization is often found when olefins with high molecular weight are prepared. To overcome this problem researchers have made efforts to find alternative ionic liquids in which the polymerization is more controllable and with lower isomerization than in chloroaluminate salts. Different types of polymerization in non-chloroaluminate ionic liquids are discussed below.

1.4.3.1 Free radical polymerization

Free radical polymerization is a common method in polymer synthesis. It has been studied for many years. It has been reported that free radical polymerization can proceed faster in ionic liquids than in conventional solvents with higher molecular weights of polymers (Hong et al., 2002). The early use of free radical polymerization in ionic liquids was related to electrochemistry with the aim of producing highly conductive polymer electrolytes. Noda and Watanabe (2000) described the free radical polymerization of vinyl monomers to achieve highly conductive polymer films in 1-ethyl-3-methylimidazolium tetrafluoroborate $[EMIM]^+[BF_4]^-$ and 1-butylpyridinium tetrafluoroborate $[Bpy]^+[BF_4]^-$. They found that $[EMIM]^+[BF_4]^-$ and $[Bpy]^+[BF_4]^-$ exhibited conductivities of 2×10^{-2} and 3×10^{-3} S cm^{-1} respectively at 30 °C. Several vinyl monomers, such as methyl methacrylate (Scheme 1.12) and 2-hydroxyethyl methacrylate, were polymerized via radical polymerization to provide transparent, highly conductive and mechanically strong polymer electrolyte films. 2-Hydroxyethyl methacrylate network polymers in which $[Bpy]^+[BF_4]^-$ was dissolved exhibited an ionic conductivity of 10^{-3} S cm^{-1} at 30 °C. This polymer network provided a highly conductive polymer electrolyte.



Scheme 1.12 Polymerization of methyl methacrylate in $[EMIM]^+[BF_4]^-$ and $[Bpy]^+[BF_4]^-$

Noda and Watanabe's successful work showed that it was possible to use ionic liquids as low risk and environmentally friendly reaction media to take the place of volatile organic solvents in the process of polymerization. Later, researchers have further investigated the difference between ionic liquids and traditional solvents when they were used as the reaction media.

In 2002, Rogers's group (Hong et al., 2002) synthesized poly(methyl methacrylate) (PMMA) by free radical initiator in $[BMIM]^+[PF_6]^-$. The polymerization of methyl methacrylate was rapid. The resulting PMMA had 10 fold higher molecular weight in $[BMIM]^+[PF_6]^-$ than in conventional organic solvents. It was thought that the enhanced molecular weight of PMMA was mainly due to the high viscosity of ionic liquids that caused the longer termination and the increased propagation rate.

The rate constant of propagation (kp) and termination (kt) for the polymerization of methyl methacrylate (MMA) in $[BMIM]^+[PF_6]^-$ were measured by Harrisson and co-workers (2003). An increase of double kp and an order of magnitude decrease of kt were observed for the polymerization of methyl methacrylate in ionic liquids compared with that in traditional solvents. The increase in propagation rate was attributed to the high polarity of the ionic liquids, while the decrease in the termination rate constant was attributed to the high viscosity of the ionic liquids. The effect on kt would reduce when temperature was increased and viscosity decreased. Free radical polymerization of various monomers could be carried out in ionic liquids with a high molecular weight of polymers (Anon, 2003).

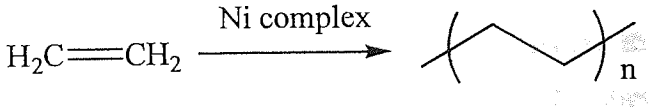
1.4.3.2 Living radical polymerization

Free radical polymerization is a commonly used approach for polymer synthesis, but sometimes it is difficult to obtain a desired polymer. Living radical polymerization is a relatively improved method. In 2002, Carmichael et al. (2002) reported the polymerization of methyl methacrylate (MMA) with the addition of a copper catalyst in an ionic liquid $[BMIM]^+[PF_6]^-$. MMA polymerization grew linearly with the increased time. MMA polymerizaiton proceeded at 30 °C in $[BMIM]^+[PF_6]^-$, while the reaction occurred at 90 °C in toluene. Clean polymers without copper contamination were obtained. This approach avoided the need to remove the catalyst from the resulting polymer compared with the traditional approach. Later, Carmichael explored this polymerization reaction in several ionic liquids such as 1-butyl-, 1-hexyl- and 1-octyl-3-methyl imidazolium hexafluophosphate and also 1-butyl-3-methyl imidazolium tetrafluoroborate. All the reactions proceeded smoothly. They found that mass distribute, when $[BMIM]^+[PF_6]^-$ was use, showed a single peak

that was consistent with living radical polymerization, but in $[BMIM]^+[BF_4]^-$, it showed the same peak as in $[BMIM]^+[PF_6]^-$ and also an additional broad peak with a higher molecular weight, which consist with the result in free radical polymerization. This was detected by SEC (size exclusion chromatography) which is used to separate the polymers according to their sizes. It was possibly due to the contamination of halides as explained by Wasserscheid and Welton (2003). The terminal halide atom on the propagating chain was not separated from the polymer, which created a "caged-radical" that would undergo propagation. Under certain conditions, the halide was separated resulting in irreversible hemolytic fission and production of free radicals. Halide contamination resulted from the synthetic procedures of ionic liquids. The last step of the formation of the above ionic liquids is by the exchange reaction of imidazole halide salts with acids or sodium salts with desired anions. $[BMIM]^+[PF_6]^-$ is immiscible with water, so it is easy to get rid of halide salts by washing with water.

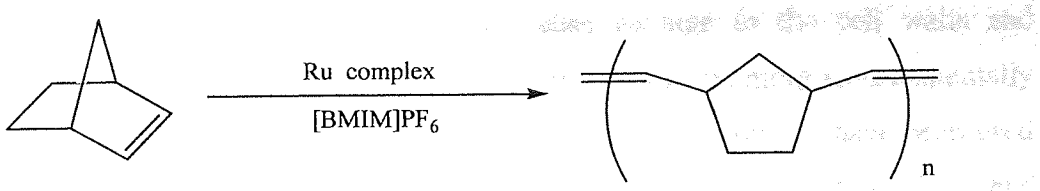
1.4.3.3 Transition metal-catalyzed polymerization

In 2001, Wasserscheid et al. (2001) described a biphasic system of ionic liquids/water for the polymerization of ethylene to produce higher α-olefins (Scheme 1.13). Several ionic liquids based on imidazole cations with different alkyl chains and $[PF_6]^-$ anion were investigated. A Ni complex which had an electrophilic Ni centre was used as a catalyst for the ethylene polymerization. The ionic liquids and Ni catalyst were recycled with no obvious change in selectivity, but a slight loss of ionic liquids was observed. The catalyst activity was lower in ionic liquids with longer alkyl chain on the imidazole cation. The catalyst was more active in ionic liquids than in dichloromethane. This biphasic system of ionic liquids/water overcomes the problem that the formed oligomers inhibit the catalyst activity, which often occur in the monophasic system such as CH_2Cl_2.



Scheme 1.13 Polymerization of ethylene in ionic liquids/water

Csihony and co-workers (Csihony et al., 2002) reported ring opening metathesis polymerization of norbornene (Scheme 1.14) with good yields in a biphasic system consisting of an ionic liquid 1-butyl-2-3-dimethylimidazolium hexafluorophosphate and toluene at 40 °C. The catalyst ruthenium complex remained in ionic liquid phase and the resulting polymer was dissolved in toluene. Both the ionic liquid and the catalyst could be reused for this reaction.



Scheme 1.14 Ring opening metathesis polymerization of norbornene

In conclusion, RTILs provide a potential "green synthetic approach" for industrial polymer synthesis. They can be recovered and reused. Polymers can be produced with a high molecular weight and without catalyst contamination. Biphasic reaction condition improves the efficiency of polymerization.

Although many investigations on polymerization in ionic liquids have been done to date, most studies only focus on the use of chloroaluminate ionic liquids or $[BMIM]^+[PF_6]^-$. There are still many polymers with a poor solubility in these kinds of ionic liquids. There is a need to develop ionic liquids which can satisfy particular polymerization (Anon, 2003). Furthermore, there is lack of understanding of why and how ionic liquids influence polymerization. Efforts are required to identify the roles played by ionic liquids in polymer synthesis.

1.4.4 The use of RTILs in biochemistry

The great success of ionic liquids in synthetic chemistry has led to the application of ionic liquids in biochemistry. The main application has so far focused on the use of ionic liquids as solvents for biocatalysis.

Biocatalysis means that biochemical compounds are converted to the desired products catalyzed by enzymes or cells. The ideal reaction medium for biocatalysis is an aqueous solution with a neutral pH, but an aqueous solution is always associated with some problems such as poor solubility for reagents. Organic solvents are used widely in biochemistry, either in extractions of antibiotics or in biocatalytic reactions in recent years because of their good solubility for reagents. However, organic solvents are usually volatile, flammable and harmful. When whole cells are used to catalyze biocatalytic reactions, organic solvents can cause damage to the cell walls and decrease the catalytic activity (Osborne et al., 1990). Recently, more environmentally friendly reaction media, such as supercritical fluids and ionic liquids have been used to replace organic solvents. $[BMIM]^+[BF_4]^-$, $[BMIM]^+[PF_6]^-$ and $[BMIM]^+[(CF_3SO_2)_2N]^-$ have been widely used as reaction media for biocatalysis.

1.4.4.1 Enzyme-catalyzed biocatalytic reactions

The application of ionic liquids in biocatalysis began in 1984 when Magnuson et al. (1984) found that the activity and stability of alkaline phosphatase increased in an aqueous solution of ethylammonium nitrate.

Since 2000, some successful studies have been carried out. Russell's group (Erbeldinger et al., 2000) described the synthesis of the dipeptide Z-aspartame with carbobenzoxy-L- aspartate and L-phenylalanine methyl ester hydrochloride catalyzed by protease thermolysin in $[BMIM]^+[PF_6]^-$ with 5% water. They found that the enzyme stability was enhanced in $[BMIM]^+[PF_6]^-$, although the enzyme activity and the reaction rate were comparable with those found with common organic solvents.

Sheldon's group (Lau et al., 2000) reported the lipase catalysis in ionic liquids. They tested the activity of Candida antarctica lipase B (CAL-B) in $[BMIM]^+[BF_4]^-$ and $[BMIM]^+[PF_6]^-$ for alcoholysis, aminolysis and perhydrolysis. Again, the experimental results in ionic liquids were similar to those in some common organic solvents.

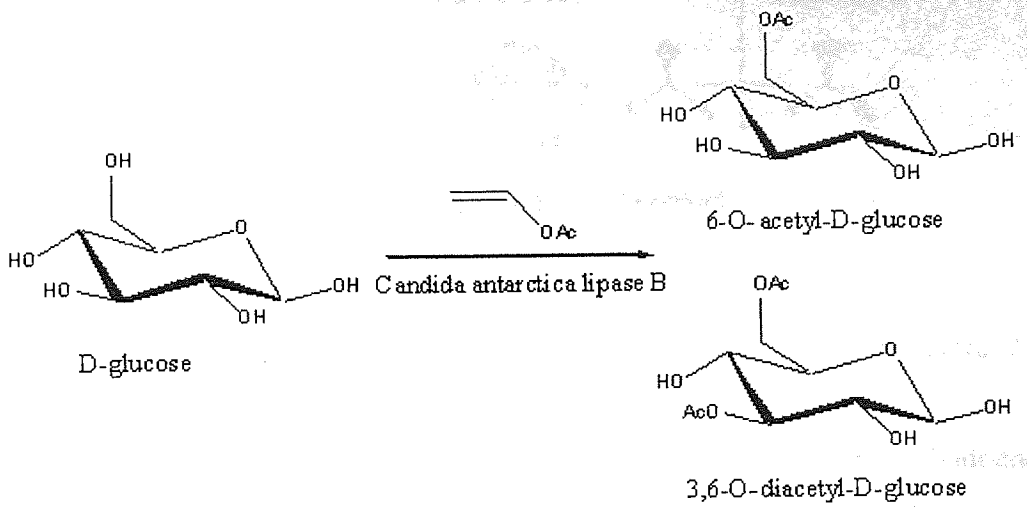
The studies from the Russell's and Sheldon's groups have proved that enzymes have good activity and stability in ionic liquids; hence the latter can replace organic solvents for enzyme catalysis. Following those successful studies, researchers started to investigate more biocatalytic reactions in ionic liquids and some groups tried to identify the correlation between enzyme activity and ionic liquids.

Physical properties of ionic liquids have a significant effect on enzyme activities. Lozano et al. (2001) analyzed α-chymotrypsin in $[EMIM]^+[(CF_3SO_2)_2N]^-$ with a viscosity of 34 cP and $[MTOA]^+[(CF_3SO_2)_2N]^-$ (MTOA=methyl thioctyl ammonium) with a viscosity of 574 cP. A reduced enzyme activity was observed in $[MTOA]^+[(CF_3SO_2)_2N]^-$ compared with that in $[EMIM]^+[(CF_3SO_2)_2N]^-$. Thus, high viscosity led to a relatively low enzyme activity. They also suggested that high polarity of $[EMIM]^+[(CF_3SO_2)_2N]^-$ resulted in the enhanced enzyme activity. Ionic liquids provide reaction media with good substrate solubility and enzyme stability. They have similar polarity with organic solvents such as DMF, but they do not inactivate enzymes (Yang and Pan, 2005).

Moreover, many researchers found that the presence of a small amount of water in ionic liquids would improve the enzyme activity and the reaction rate. Laszlo and Compton (2001) carried out transesterification reactions catalyzed by a protease α-chmotrypsin in $[BMIM]^+[PF_6]^-$ and $[OctMIM]^+[PF_6]^-$. The reaction rates were comparable with those in organic solvents. They also demonstrated that water could affect enzyme activity and therefore influence the reaction rate of transesterification. The presence of a small amount of water was necessary to maintain the enzyme's activity in both ionic liquids and organic solvents. Eckstein et al (2002) observed that the activity of α-chmotrypsin was higher in an ionic liquid $[BMIM]^+[(CF_3SO_2)_2N]^-$ than in the organic solvents when a trace of water was added.

In contrast, impurities in ionic liquids can play an unfavorable role in biocatalysis. Some impurities in ionic liquids may even deactivate enzymes. Park and Kazlauskas (2001) described that, in some lipase catalytic reactions, the slow reaction rate or no reaction was due to the halide impurity produced during the preparation of ionic liquids. After the impurity was removed, these reactions proceeded smoothly. They

also studied an acylation of glucose in several ionic liquids (Scheme 1.15). Glucose was more soluble in ionic liquids than in most organic solvents and a high yield of 6-O-acetyl glucose could be achieved in ionic liquids. However, the acetylation of glucose in organic solvents produced 6-O-acetyl glucose initially and then yielded 3,6-O-diacetyl glucose.



Scheme 1.15 Acylation of glucose in various ionic liquids

In 2008, Mantarosie et al (2008) examined various lipases in water and three ionic liquids: $[BMIM]^+[BF_4]^-$, $[BMIM]^+[PF_6]^-$, $[BMIM]^+[(CF_3SO_2)_2N]^-$. Acylation reactions of various benzenesulfonamides with maleic anhydride catalyzed by lipases proceeded well in both water and ionic liquids. When ionic liquids were used as reaction media, monoacylated products were obtained with 100% selectivity. However, a reduced conversion rate was observed in the ionic liquids compared with that in water. A lower conversion rate was also observed in water miscible ionic liquid $[BMIM]^+[BF_4]^-$ than water immiscible ionic liquid $[BMIM]^+[PF_6]^-$. The highest conversion rate occurred in $[BMIM]^+[(CF_3SO_2)_2N]^-$. This was due to the lower viscosity of $[BMIM]^+[(CF_3SO_2)_2N]^-$ than other two ionic liquids, therefore a higher enzyme activity was generated in $[BMIM]^+[(CF_3SO_2)_2N]^-$.

1.4.4.2 Whole cell-catalyzed biocatalytic reactions

Biphasic biocatalysis of ionic liquid/water has received much attention for the whole cell-catalyzed reactions. The biphasic system of ionic liquid/water overcomes poor

water solubility of reactants. It may also prevent the reactant's effect on the biocatalyst. Ionic liquids do not destroy the cell membrane which organic solvents can often do. The whole cell-biocatalyst also avoids tedious procedures for enzyme purification. A possible mechanism is illustrated below (Figure 1.12).

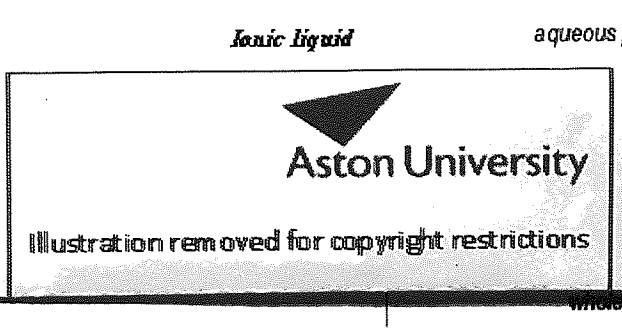


Figure 1.12 A biocatalytic process with a whole cell-biocatalyst (Weuster-Botz, 2007)

In 2000, Seddon's group (Cull et al., 2000) investigated the Rhodococcus R312-catalyzed biotransformation of 1,3-dicyanobenzene (1,3-DCB) in $[BMIM]^+[PF_6]^-$/water and in toluene/water. Both of the two biphasic systems showed similar reaction progress. At the beginning, 3-cyanobenzamide was produced and then 3-cyanobenzoic acid was formed. $[BMIM]^+[PF_6]^-$ was more viscous than toluene, thus 1,3-DCB mass transfer was reduced, which resulted in the lower conversion rate of 3-cyanobenzamide in $[BMIM]^+[PF_6]^-$/water, but the yield of the final product 3-cyanobenzoic acid was higher. Moreover, cells were aggregated together in toluene/water and concentrated at the liquid interface. In contrast, in $[BMIM]^+[PF_6]^-$/water, cells showed little aggregation and most cells remained in water, which was beneficial to phase separation and also the recycle of the ionic liquid and biocatalyst.

In 2001, Howarth et al. (2001) carried out reduction reactions of ketones (Scheme 1.16) catalyzed by baker's yeast in the $[BMIM]^+[PF_6]^-$/water system. Yields of some products in ionic liquid/water were higher than that in traditional solvents. Low vapor property of ionic liquids made it possible to distill the products from $[BMIM]^+[PF_6]^-$ instead of extraction with organic solvents. They also found that the yield and the selectivity were lower when water was not added to the reaction mixture, which was due to the inactivation of the enzyme in the yeast.

Scheme 1.16 Baker's yeast-catalyzed reduction reaction of ketones in $[BMIM]^+[PF_6]^-$/ water

1.4.4.3 Drug delivery

More recently, ionic liquids have been designed to be used in drug delivery. An ionic liquid of anaesthetic (lidocaine) was prepared by Roger's group (Hough et al., 2007). Lidocaine is commonly used as its hydrochloride in pharmaceutical formulations. When the hydrochloride of lidocaine was displaced by docusate (dioctylsulfosuccinate), a room temperature ionic liquid (lidocaine docusate) was formed. The structure of lidocaine docusate is shown in Figure 1.13.

It was found that the ionic liquid form of the drug (lidocaine) delivered longer lasting pain relief than traditional lidocaine hydrochloride. Lidocaine docusate could be slowly released (Hough et al., 2007). Cations or anions of ionic liquids can be designed with particularly biological functions. Ionic liquids as "designer solvents" have a great potential in pharmaceutical areas.

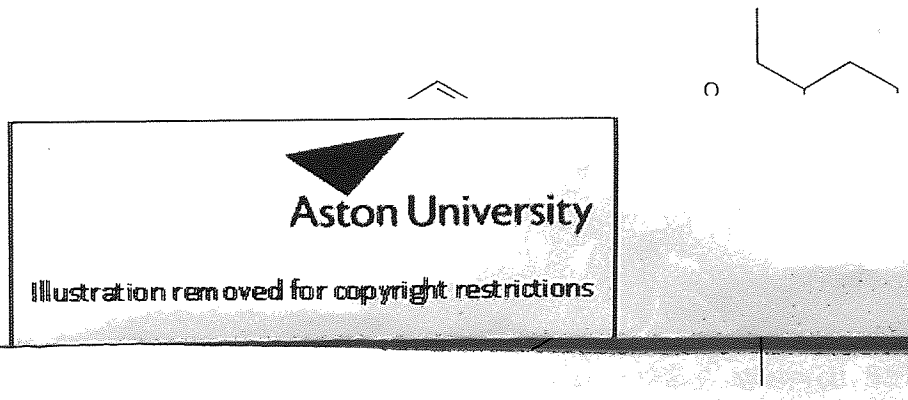


Figure 1.13 Lidocaine docusate (Hough et al., 2007)

1.4.5 Supercritical fluids and ionic liquids

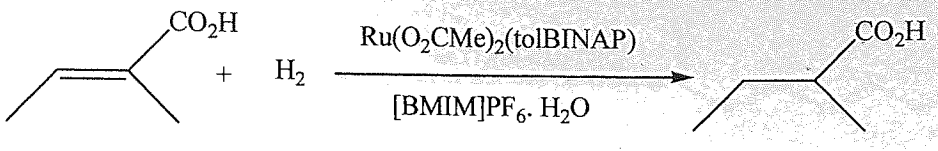
Supercritical fluids as alternative reaction media have been widely investigated. A supercritical fluid can be changed between gas form and liquid form because of its unique critical point. Supercritical CO_2 ($scCO_2$) is commercially available. Researchers have been successful in applying this "green solvent" in a wide range of applications such as polymer synthesis and organic reactions. Recently, $scCO_2$ has been used in combination with ionic liquids. When an ionic liquid is used as a reaction medium for organic synthesis, an organic solvent is often needed to extract the product after the completion of the reaction. Thus volatile organic solvents (VOCs) compromise the "green procedure". In order to avoid VOCs, researchers have tried to use $scCO_2$ as an extractant. Meanwhile, continued interest in biphasic systems for organic reactions has also resulted in the use of $scCO_2$ with ionic liquids. It has been found that a $scCO_2$/ionic liquid system can improve the purity of products and reduce the loss of catalysts when the system is reused.

Supercritical CO_2 is a good extractant for organic solutes from ionic liquids. Blanchard and Brennecke (2001) explored the efficiency of $scCO_2$ extraction of a large range of organic solutes from an ionic liquid $[BMIM]^+[PF_6]^-$ (Figure 1.14). The organic solutes showed over 95% recovery with $scCO_2$ extraction, and some of them were up to 98% in $[BMIM]^+[PF_6]^-$. Benzene and chlorobenzene have poor solubility in $[BMIM]^+[PF_6]^-$, so a small amount of $scCO_2$ was enough to extract them. Phenol, benzoic acid and benzamide were readily soluble in $[BMIM]^+[PF_6]^-$, so a relatively large amount of $scCO_2$ was needed. The organic solutes that have larger dipole moment were more easily dissolved in ionic liquids, so large amount of $scCO_2$ was required. Hexanamide has a large dipole moment, thus twice amount of $scCO_2$ was required for its recovery compared with other hexane organics as shown in Figure 1.14. Blanchard further explored the efficiency of $scCO_2$ extraction for 1,4-butanediol. This compound had a boiling point of 230 °C and it was difficult to be recovered by distillation. $ScCO_2$ extraction of 1,4-butanediol achieved 95% of recovery. This demonstrates that for organic solutes with high boiling points, $scCO_2$ can be used as extractant to replace distillation.

Figure 1.14 $ScCO_2$ extraction of aromatic solutes and aliphatic solutes from $[BMIM]^+[PF_6]^-$ at 40 °C and 138 bar (Blanchard and Brennecke, 2001). Solute dipole moments are shown above.

Following Blanchard's work, Brown et al (2001) tested $scCO_2$ as an extractant for hydrogenation products. They carried out the hydrogenation reaction of tiglic acid catalyzed by $Ru(O_2CMe)_2$((*R*)-tolBINAP) in an ionic liquid $[BMIM]^+[PF_6]^-$ with the addition of a small amount of water (Scheme 1.17). This method gave the product with high conversion and high enantioselectivity. The catalyst complex was more soluble in $[BMIM]^+[PF_6]^-$ than $scCO_2$, thus the product was extracted by $scCO_2$ with

no catalyst contamination. $[BMIM]^+[PF_6]^-$ with the catalyst was reused with no considerable loss of the reactivity and selectivity.

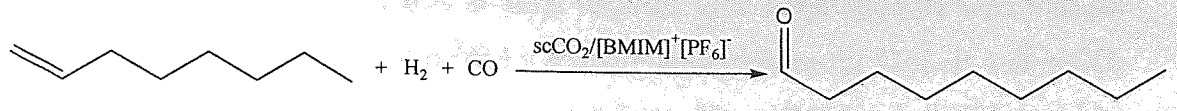


Scheme 1.17 Hydrogenation of tiglic acid in $[BMIM]^+[PF_6]^-$/water

As shown from the studies discussed above, a biphasic system of $scCO_2$ with an ionic liquid has some promising applications for organic chemistry. Generally, under a certain temperature and pressure, supercritical CO_2 and the ionic liquid can form monophasic reaction mixture to achieve the better mixing of reactants including starting materials and catalysts. After the completion of the reactions, conditions are adjusted to give two layers to achieve the easier separation of products and catalysts, the products being extracted into $scCO_2$ layer and the catalysts remaining in the ionic liquid layer.

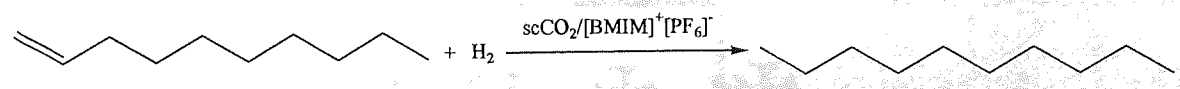
The $scCO_2$/ionic liquid systems have been used in hydroformylation and hydrogenation reactions. Murielle et al. (2001) reported a rhodium complex-catalyzed hydroformylation of 1-octene in a $scCO_2/[BMIM]^+[PF_6]^-$ system (Scheme 1.18). When $[Rh_2(OAc)_4]$/ $P(Oph)_3$ was used as a catalyst, a high yield of product with a low selectivity was obtained in $[BMIM]^+[PF_6]^-$. In contrast, a low yield of product with a high selectivity was obtained in $scCO_2/[BMIM]^+[PF_6]^-$. The catalyst was deactivated after recycling for three times in this biphasic system. Later, they designed two ligands. One was $[BMIM]^+[Ph_2PC_6H_4SO_3]^-$ instead of $P(OPh)_3$. In this case, the catalyst was still active after recycling for 12 times. However, after the ninth recycle, leaching of rhodium into organic phase was observed, but ^{31}P NMR showed no phosphine leaching. They explained the reason for this was because of the ligand oxidation. $[RhH(CO)_4]$ was formed and was soluble in $scCO_2$. The increased isomerisation was also due to $[RhH(CO)_4]$. The other ligand they used was $[PMIM]_2[PhP(C_6H_4SO_3)_2]$ (PMIM=1-propyl-3-methyl imidazolium). In this case, no ligand oxidation was found. This continuous flow $scCO_2/[BMIM]^+[PF_6]^-$ system

provided an effective and efficient approach with easy separation of products without the catalyst and solvent contamination.

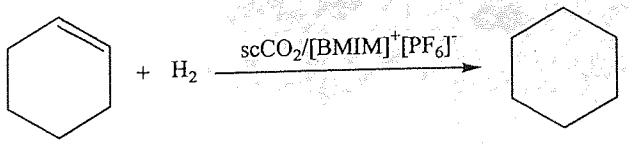


Scheme 1.18 Hydroformylation of 1-octene in $scCO_2/[BMIM]^+[PF_6]^-$

Hydrogenation reaction has also been investigated in the $scCO_2/[BMIM]^+[PF_6]^-$ system. Liu et al. (2001) examined the hydrogenation of 1-decene (Scheme 1.19) and cyclohexene (Scheme 1.20) using Wilkinson's catalyst $RhCl(PPh_3)_3$. This catalyst was soluble in $[BMIM]^+[PF_6]^-$, but not soluble in $scCO_2$. The conversion rate of hydrogenation of 1-decene to decane was 98% after 1 hour in $scCO_2/[BMIM]^+[PF_6]^-$. After recycling for four times, the catalyst activity was still high, and the conversion rate was up to 98% conversion. Under the same reaction conditions, conversions of hydrogenation of 1-decene and cyclohexene in n-hexane/$[BMIM]^+[PF_6]^-$ were similar to that in $scCO_2/[BMIM]^+[PF_6]^-$. For these two hydrogenation reactions, the $scCO_2/[BMIM]^+[PF_6]^-$ system had no significant advantage over the organic solvent/ionic liquid system.

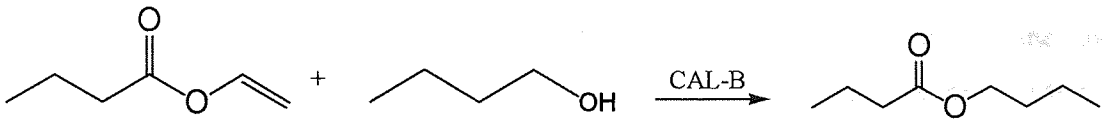


Scheme 1.19 Hydrogenation of 1-decene in $scCO_2/[BMIM]^+[PF_6]^-$



Scheme 1.20 Hydrogenation of 1-cyclohexene in $scCO_2/[BMIM]^+[PF_6]^-$

Recently, the $scCO_2$/ionic liquid system has been used in the biochemistry field. Lozano et al. (2002) investigated Candida antarctica lipase B (CAL-B) in $scCO_2$/ $[EMIM]^+[(CF_3SO_2)_2N]^-$ and $scCO_2/[BMIM]^+[(CF_3SO_2)_2N]^-$. It showed a good reaction activity for the synthesis of butyl butyrate from vinyl butyrate with butanol (Scheme 1.21). Ionic liquids provided a friendly environment for CAL-B and $scCO_2$ acted as an effective agent to extract the products. The $scCO_2$/ionic liquid could be recovered and reused. This study demonstrated that the combination of $scCO_2$ and ionic liquids is a promising approach for biocatalysis.



Scheme 1.21 Synthesis of butyl butyrate in $scCO_2$/ionic liquid

The experimental apparatus is shown in Figure 1.15. It is a continuous biphasic biocatalysis reactor, where an aqueous solution of CAL-B was dissolved in an ionic liquid as the biocatalyst and substrates resided in a $scCO_2$ phase. The products were continuously extracted by $scCO_2$.

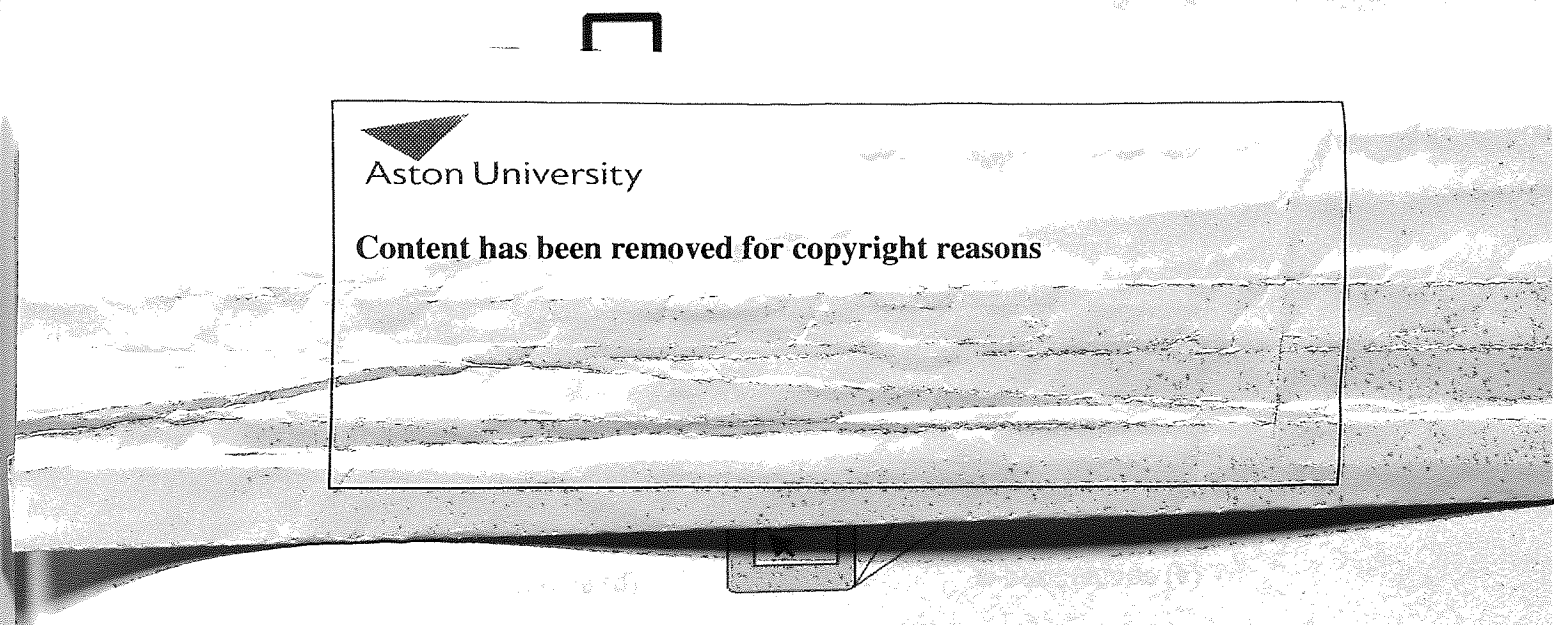
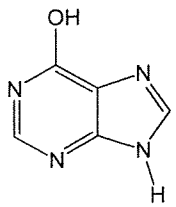


Figure 1.15 A continuous biphasic biocatalysis reactor (Lozano et al., 2001)

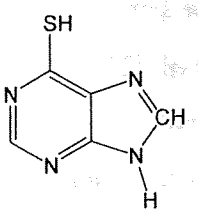
1.5 Anti-cancer activity of 6-mercaptopurine and 6-thioguanine

Nucleoside chemistry is an important research area for drug discovery. For example, AZT, ddC, d4T, etc. are used as anti-HIV agents. Anti-sense and anti-gene oligonucleotides are used as potential and selective inhibitors of gene expression. Protected nucleosides are used as building blocks for the synthetic oligonucleotides used as probes for diagnostic purposes. Nucleobase and nucleoside derivatives are also used as anti-viral and anti-cancer agents. 6-Mercaptopurine, 6-thioguanine and 6-azathioprine are used clinically as anti-cancer and anti-inflammatory drugs for the treatment of actual leukemia, inflammatory bowel disease, rheumatic disease and organ transplantation recipient.

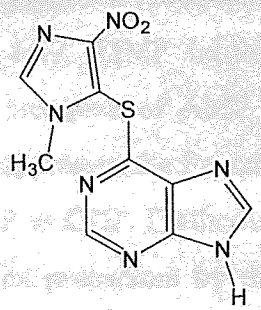
6-Mercaptopurine (Figure 1.16-b) is a sulfur derivative of hypoxanthine (Figure 1.16-a). Azathioprine (Figure 1.16-c) is a nitroimidazole derivative of 6-mercaptopurine. 6-Thioguanine (Figure 1.16-e) is a sulfur derivative of guanine (Figure 1.16-d).



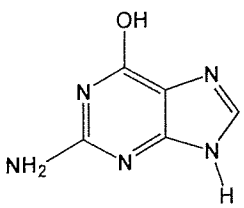
Hypoxanthine (a)



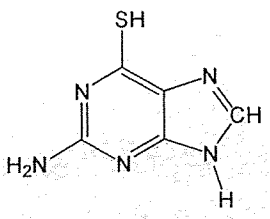
6-mercaptopurine (b)



Azathioprine (c)



Guanine (d)



6-thioguanine (e)

Figure 1.16 Structures of purine and guanine and their derivatives

6-Mercaptopurine, 6-thioguanine and their metabolic derivatives such as thioinosine monophosphate have multiple effects against tumors. Generally, they can cause several inhibitions in the synthesis and utilization of purine nucleotides by cancerous cells. For example, they can prevent purine nucleotide interconversions; they may incorporate into DNA or RNA to induce cytotoxicity; and they are also able to inhibit the de novo purine synthesis, presumably by pseudofeedback inhibition of phosphoribosylpyrophosphate amidotransferase (RxMed).

6-Mercaptopurine (6-MP), 6-thioguanine (6-TG) and azathioprine (AZA) are inactive prodrugs. They need intracellular activation and this process is catalyzed by various enzymes. First, azathioprine is converted to 6-mercaptopurine quickly without enzyme catalysis. 6-MP is converted to thioinosine monophosphate (TIMP) with 5-phospho-D-ribose-1- pyrophosphate (PRPP) as the phosphoribosyl donor under hypoxanthine guanine phosphoribosyl transferase (HPRT1). 6-TG is converted to thioguanosine monophosphate (TGMP) with PRPP as the phosphoribosyl donor under HPRT1 (Zaza et al., 2008).

After 6-MP is converted to TIMP, TIMP can block some important reactions in the synthesis of purine nucleotides as illustrated in Figure 1.17. TIMP inhibits the formation of adenylosuccinic acid (S-AMP) which is the precursor of AMP. TIMP also blocks the conversion of AMP to ADP. In addition, it suppresses the formation of xanthylic acid (XMP) and it blocks the conversion of GMP to GDP. Furthermore, it inhibits additional synthesis of inosinic acid (IMP) from its precursors by exerting pseudo-feedback function (Winkelstein, 1979).

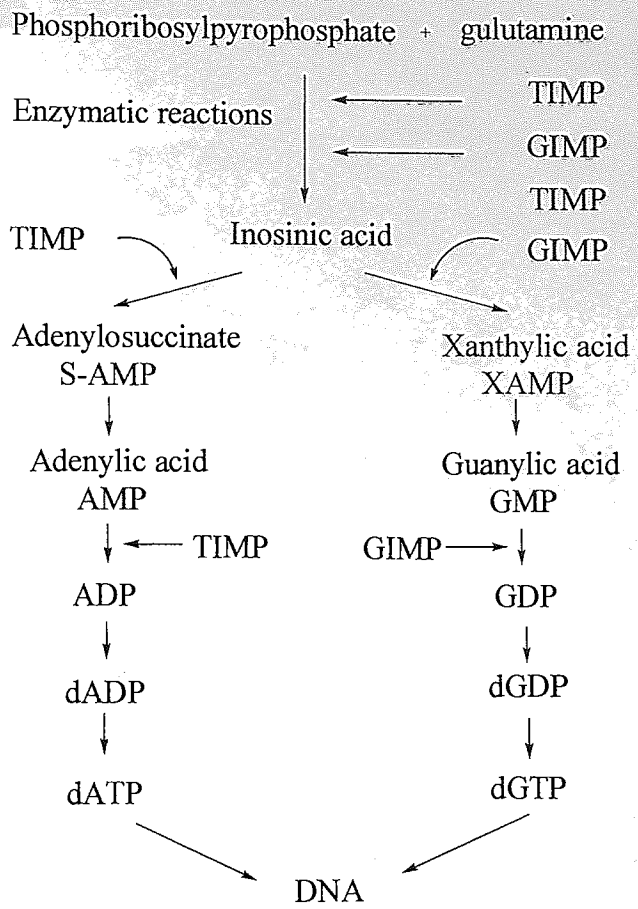
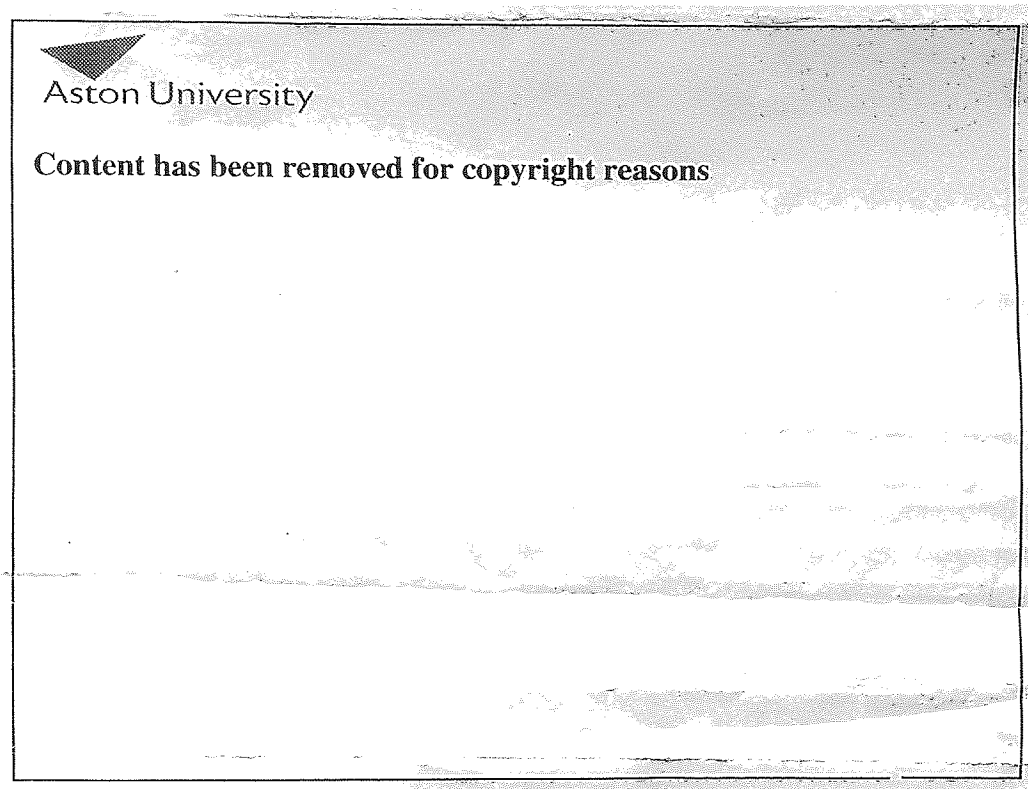


Figure 1.17 The biosynthesis of purine nucleotides

Meantime, the formed TIMP will be converted to thioxanthosine monophosphate (TXMP) by inositol monophosphate dehydrogenase (IMPDH). TXMP is then converted to TGMP by guanosine monophosphate synthetase (GMPS). Following this, TGMP is converted to thioguanine nucleotides diphosphate (TGDP). TGDP is converted to its corresponding triphosphates (TGTP).

Cytotoxic effects of thiopurine drugs are induced by the incorporation of thioguanosine triphosphate (TGTP) into RNA and thio-deoxyguanosine triphosphate (TdGTP) into DNA. The incorporation of TdGTP causes inhibition of several enzymes that are involved in DNA replication and repair. The TdGTP incorporation also induces DNA damage such as single strand-breaks, DNA-protein cross-links and chromatid exchanges (Zaza et al., 2008). The thiopurine metabolic pathway is given below (Figure 1.18).



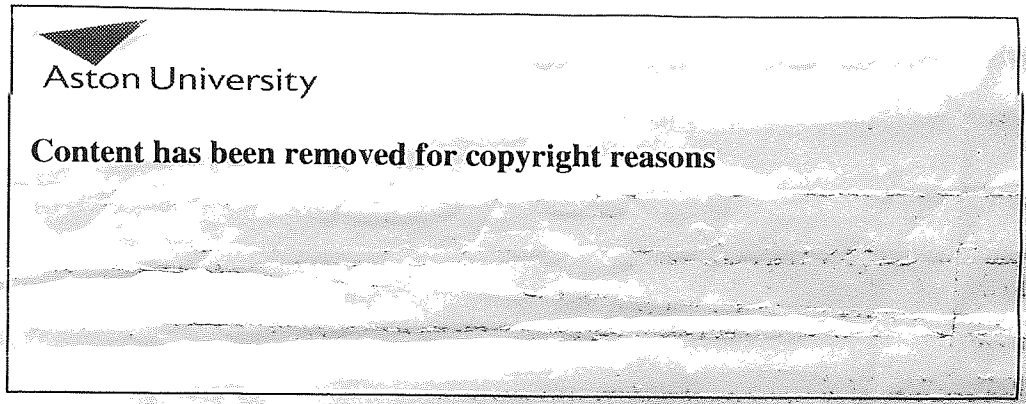


Figure 1.18 The thiopurine metabolic pathway (take from Zaza et al., 2008)

HPRT1: Hypoxanthine guanine phosphoribosyltransferase 1, TIMP: Thioinosine monophosphate, IMPDH1: Inosine monophosphate dehydrogenase type 1, TXMP: Thioxanthosine monophosphate, GMPS: Guanosine monophosphate synthetase, TGMP: Thioguanosine monophosphate, ABCC4: Multidrug resistance-associated protein 4, ABCC5: Multidrug resistance-associated protein 5, TPMT: Thiopurine S-methyltransferase, meTGMP: Methyl-thioguanosine monophosphate, XDH: Xanthine dehydrogenase, AOX1: Aldehyde oxidase 1, 8-OHTG: 8-hydroxythioguanine, meMP: methyl-mercaptopurine, 6-meMPR: 6-methyl-mercaptopurine riboside, MPR: 6-mercaptopurine riboside, meTIMP: Methy-thioinosine monophosphate, ADK: Adenosine kinase, AdoMet: S-adenosyl-methionine, AdoHcy: S-adenosylhomocysteine, AHCY: S-adenosylhomocysteine hydrolase, ADA: Adenosine deaminase, NT5E: Nucleotidase, ecto-5-prime, GAR: Glycinamide ribotide , GART: Phosphoribosylglycinamide formyltransferase, PRA: 5-phosphoribosylamine, PRPP: 5-phospho-D-ribose-1-pyrophosphate, PRPS1: Phosphoribosyl pyrophosphate synthetase 1, TGDP: 6-thio-guanosine diphosphate, TGTP: 6-thio-guanosine triphosphate, TdGDP: 6-thio-deoxy-guanosine diphosphate, PPAT: Phosphoribosyl pyrophosphate amidotransferase, TdGTP: 6-thio-deoxy-guanosine triphosphate.

It is worth to mention that thiopurine methyltransterase (TPMT) plays a crucial role on the thiopurine metabolic pathway. Human TPMT has a molecular mass of 28 kDa, including 245 amino acids. TPMT is genetic polymorphism (Krynetski and Evans, 2003). TPMT can convert TIMP into methyl-mercaptopurine riboside (MMPRP) which can inhibit phosphoribosyl pyrophosphate (PRPP) amidotransferase. This enzyme plays a crucial role in the de novo purine synthesis pathway (Dollery, 1991).

Furthermore, TPMT catalyzes methylation of mercaptopurine, thioguanine, and their corresponding nucleosides and nucleotides (Deininger et al., 1994; Krynetskiet al., 1995). TPMT transfers a methyl group from S-adenosyl-methionine to convert 6-mercaptopurine into methylmecaptopurine (Krynetski and Evans, 2003). S-adenosyl-methionine is the cellular donor of methyl groups in enzymatic reactions.

Recently, it is suggested that 6-methylthioguanine has a certain function to trigger cell death (Karran, 2007). The treatment of 6-mercaptopurine or 6-thioguanine causes the accumulation of these thionucleobase in DNA. Some incorporated 6-thioguanine is methylated with S-adenosyl-methionine. The general process is explained in Figure 1.19.

Figure 1.19 DNA mismatch repair and lethal processing of aberrant base pairs (Karran, 2007)

DNA 6-methyl thioguanine prefers to base pair with thymine in the replication process. The base pair of 6-methyl thioguanine : thymine is a mismatch and this causes the replication error. Normally, this mismatch is processed via mismatch repair

(MMR), which generally corrects errors caused by DNA polymerases during replication. Some mismatch base pairs that escaped proof read can also be recognized and bonded by the MutSa mismatch binding complex. This complex consists of proteins MSH2 and MSH6. Following that, the mismatched pairs complex interacts with MutLa consisting of proteins MLH1 and PMS2. Consequently, the mismatch segment is removed and the corrected sequence is synthesized. However, any error in the mismatch repair process or any defect in these four proteins (MSH2, MSH6, MLH1, PMS2) will result in an inactive mismatch repair. This will block the aberrant base pairs recognition and cause the replication errors to trigger cell death.

Under the methylation reaction, 6-thioguanine is converted to 6-methylthioguanine. Replication error occurs when 6-methylthioguanine : T base pairs are generated. Subsequent processing is lethal. In a similar way, O^6-methylguanine is produced by methylating agents MNU (N-methy-N-nitrosourea) or MNNG (N-methyl-N_0-nitro-N-nitrosoguanidine). DNA O^6-methylguanine : T base pairs are generated and this process is lethal as well (Figure 1.20) (Karran, 2007).

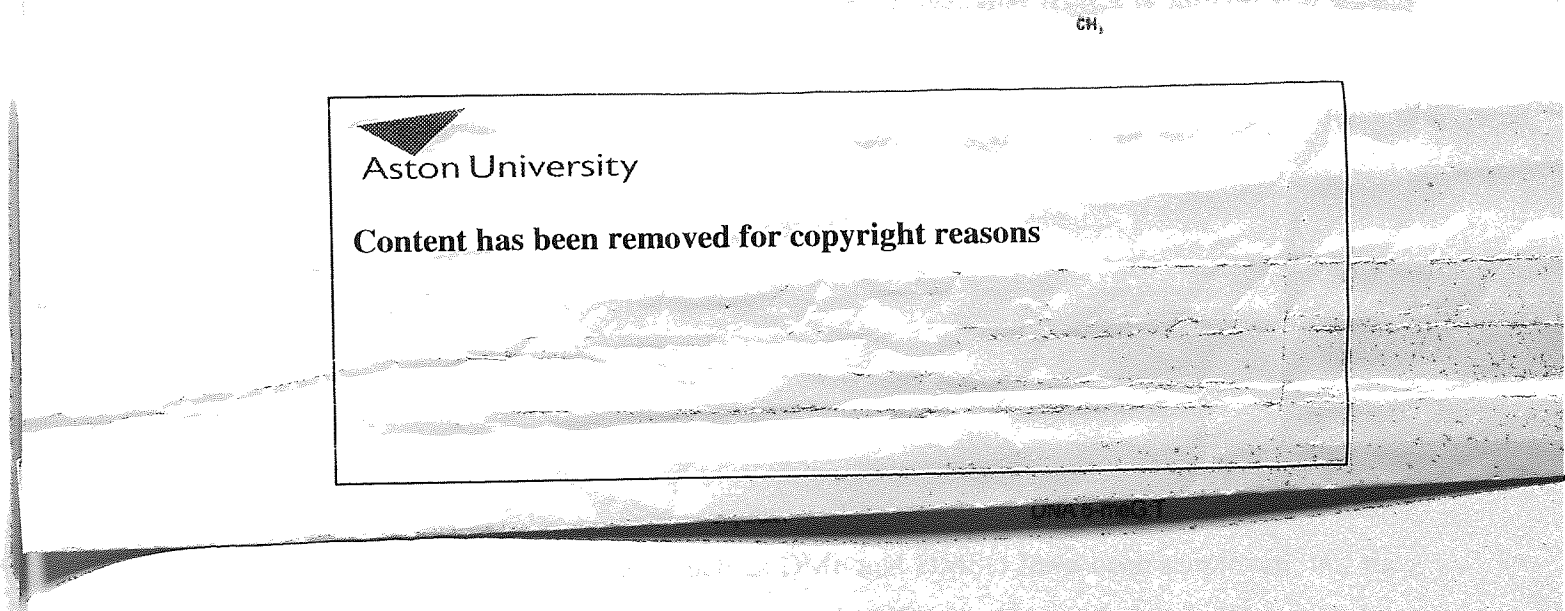


Figure 1.20 6-Methylthioguanine and O^6-methylguanine mismatch process (Karran, 2007)

1.6 Aims and objectives

The use of large amounts of organic solvents causes environmental pollution due to their inherent volatility, flammability or toxicity. There is an urgent need to develop alternative solvents and technologies for synthetic chemistry due to the increasing need for protecting the environment. Room temperature ionic liquids have received a great deal of interest because of their favorable properties such as non-flammability, low vapor pressure and high thermal stability. RTILs usually exhibit good solvent properties and they can facilitate and influence organic reactions. RTILs seem a good choice to be used as solvents for organic synthesis.

My research project is concerned with the development and use of RTILs for a variety of organic transformation for the preparation of organic chemicals with potentially pharmaceutical applications.

Currently, RTILs are commercially available from several chemical suppliers such as Fisher, Sigma-Aldrich. However, the range of available RTILs is limited and RTILs are supplied in limited amounts at relatively high prices. Our aim is to prepare RTILs and to use these RTILs to carry out a range of organic reactions. Therefore, for the first part of the project, a series of RTILs has been synthesized. Some novel ionic liquids have been prepared with the aim of developing more suitable RTILs to be used as reaction media for organic synthesis.

It has been one of our interests to develop synthetic methods for modified thionucleobases and thionucleosides as potential anti-cancer agents. However, thio-substituted nucleobases and nucleosides have poor solubility in organic solvents. Conventional polar solvents such as DMF and DMSO have been employed, but they are hazardous to the environment and difficult to recycle. Some reports have demonstrated that RTILs have a good solubility for nucleobases and nucleosides (Uzagare et al., 2003). In the second part of this project, we want to develop synthetic methods for modified thionucleobases and thionucleosides using RTILs as reaction media.

Furthermore, Knoevenagel condensation reaction has been widely used in organic synthesis to prepare coumarins. It is one of the most useful methods for carbon-carbon bond formation in organic synthesis and is generally carried out in the presence of a weak base such as ethylenediamine and piperidine. However, in many reported approaches, the reactions usually take a long time and high reaction temperatures may be required in some cases. Organic solvents are always used as the reaction medium. For example, a condensation reaction of benzaldehyde with ethyl cyanoacetate in the presence of (L)-proline took 16 hours to complete at room temperature in DMSO (Cardillo et al., 2003). Recently, Knoevenagel reactions have also been investigated in RTILs. In most cases, the addition of a catalyst is required. Moreover, limited work has been done on Knoevenagel condensations involving ketones, as sterically hindered ketones are not very reactive regents for these reactions. Thus there is a need to develop the synthetic approach for Knoevenagel reactions, especially the reactions involving ketones. In the third part of this project, efforts are made to identify some RTILs, in which Knoevenagel reactions proceeds smoothly with a short reaction time and at room temperature.

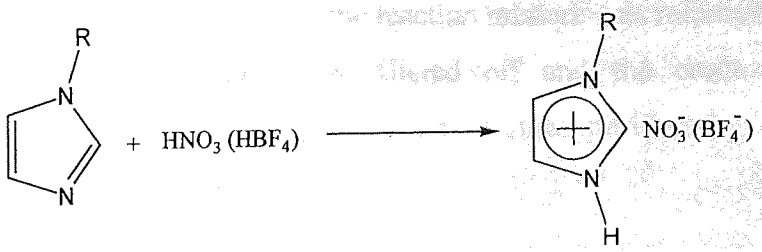
Chapter 2

Synthesis of Ionic Liquids

2.1 Introduction

2.1.1 Synthesis of RTILs using protonation method

The history of ionic liquids started in 1914. Walden (1914) reported the preparation of ethylammonium nitrate. This compound was formed by the treatment of nitric acid with ethylamine. The protonation reaction is employed for the preparation of ionic liquids such as ethylammonium nitrate. Amines are reacted with acids to afford the desired ionic liquids. A series of nitrate and tetrafluoroborate salts (Scheme 2.1) using the protonation approach was prepared by Lee et al. (2000). A problem associated with these types of ionic liquids is that the residue amines may contaminate the ionic liquids and these ionic liquids are easily decomposed by deprotonation (Wasserscheid and Welton, 2003).



Scheme 2.1 Synthesis of 1-alkylimidazolium nitrate salts

2.1.2 Synthesis of RTILs using quaternization reactions and anion exchange reactions

Most ionic liquids are formed without the direct treatment of the free acids. Several synthetic approaches are employed. First of all, a direct synthetic method can be used. Some ionic liquids are often prepared in this manner, for example, an ionic liquid

1,3-dialkylimidazole triflate has been produced by the direct treatment of 1-alkylimidazole and methyl triflate (Bonhote et al., 1996). However, this approach has been used on a limited scale. One reason is that the numbers of appropriate reagents with suitable anions are limited and many of them are not commercially available.

In recent years, the most commonly used synthetic method for ionic liquids is a two step approach as illustrated in Scheme 1.1 (page 21). The first step is called a quaternization reaction, in which a halide salt with a desired cation is formed. The second step is called an anion exchange reaction, in which the halide ion of the prepared halide salt is exchanged with a suitable anion to form a desired ionic liquid.

The common starting materials are 1-alkylimidazoles and pyridine. The use of 1-methylimidazole is preferred, because it is commercially available in high quality and at a resonable price. However, there are not many other 1-alkylimidazoles commercially available.Various 1-alkylimidazoles can be synthesized using imidazole with a haloalkane to provide a range of possible starting materials for the synthesis of ionic liquids. Bonhote (1996) reported one approach for the preparation of 1-ethylimidazole. After treating imidazole with sodium ethoxide in ethanol, bromoethane was added dropwise and the reaction mixture was refluxed with stirring. The resulting precipitate, NaBr, was filtered off and the crude product was concentrated under vacuum. The product was further purified by distillation at 79-81°C at 12mbar of pressure.

After the 1-alkylimidazole has been prepared, it is reacted with a further equivalent of haloalkane to form the imidazole halide salt. The process involves mixing 1-alkylimidazole with a selected haloalkane and heating the reaction mixture with stirring. Various solvents can be used in quaternization reactions such as toluene and ethyl acetate, and the reaction is carried out free of moisture. The reaction rate increases in the order Cl<Br<I, iodoalkanes being the most reactive alkyl halides. However, since iodoalkanes are light sensitive, the reaction needs shielding from light. In order to get the pure product, it is necessary to remove all the unreacted starting materials by distillation under vacuum.

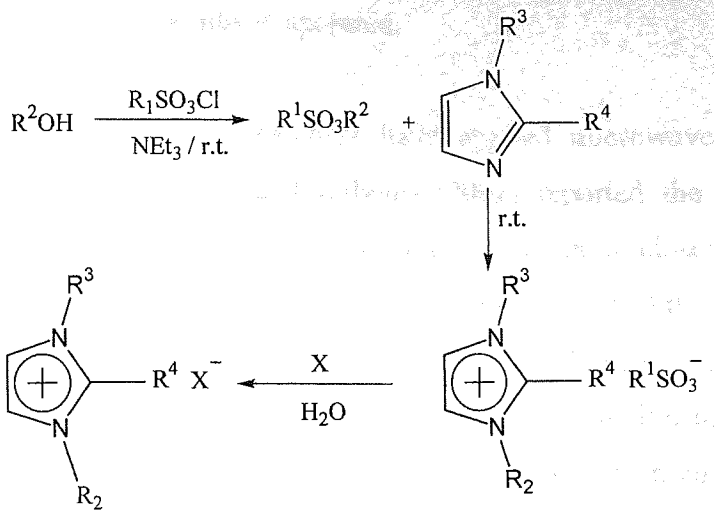
After the imidazole halide salt is formed, the halide ion can be displaced with a desired anion via the exchange reaction. The anion exchange reaction of ionic liquids includes two categories, anion formation for Lewis acid-based ionic liquids and anion metathesis.

The details for the synthesis of Lewis acid-based ionic liquids have already been discussed in Chapter 1. They are produced from direct treatment of halide salts with Lewis acids such as $AlCl_3$ and $SnCl_2$. Acidity and basicity can be controlled by changing the ratio of the Lewis acid. These Lewis acid-based ionic liquids were widely used in the early applications of ionic liquids in electrochemistry. They were also used as solvents and catalysts in organic chemistry (Oye, 1991). In this chapter, synthetic methods for moisture stable ionic liquids will be the main focus.

Anion metathesis is commonly used for the preparation of moisture stable ionic liquids. The general approach is to prepare an aqueous solution of a halide salt and then mix this with an acid or a metal salt with an appropriate anion. When water-immiscible ionic liquid is produced, the ionic liquid is readily separated from the aqueous phase and any excess acid or metal salt can be removed by further washing with water. While for water-miscible ionic liquid, it is extracted with dichloromethane after the completion of the reaction. The extract is then washed with water until the pH is neutral, if an acid is used as a reagent, and is free of halide by checking with $AgNO_3$ solution.

This two step synthetic approach is widely used for the preparation of ionic liquids. However, a high level of halide ions can contaminate the ionic liquids prepared using the above method. Recently, chemists have developed an alternative way to overcome this problem. Cassol et al. (2006) developed a rapid methodology for the preparation of halide-free ionic liquids (Scheme 2.2). In their method, initially an alcohol was reacted with an alkanesulfonyl chloride to afford the alkylsulfonate ester. The alkylsulfonate ester was then reacted with an 1-alkylimidazole for 2 to 3 days to give 1,3-dialkylimidazolium alkanesulfonate. This product is often a crystalline solid and can be recrystallized from acetone. Compared with the classical method, this approach was performed at room temperature instead of at reflux temperature.

A range of alkylsulfonate salts were prepared. Cassol et al. (2006) found that the alkylsulfonate anion could be dispalced with other desired anions using metal salts or acids in water. When the reactions were completed, the products were extracted using dichloromethane. Yields of ionic liquids were 80-95% and their purity was confirmed by ^{1}H NMR analysis.



R^1, R^2, R^3 = CH_3, $CH_2CH_2CH_2CH_3$, R_4= H, CH_3
X = $NaBF_4$, KPF_6, $HPF_3(CF_2CF_3)_3$, HCF_3SO_3, $LiN(CF_3SO_2)_2$

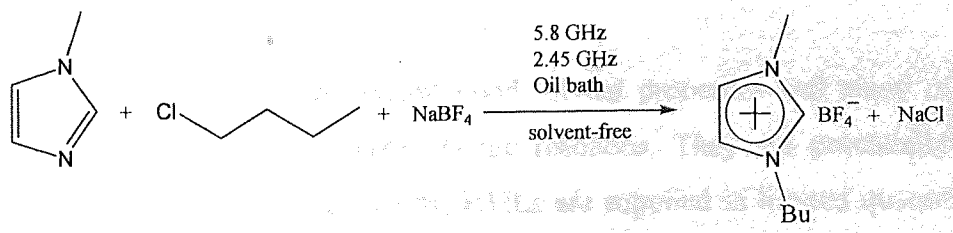
Scheme 2.2 Synthesis of ionic liquids using alkylsulfonate salts

2.1.3 Synthesis of RTILs using microwave irradiation

The standard equipment for the above approach is a round bottom flask, fitted with a reflux condenser if required. This is straightforward and can be readily employed in most laboratories. Recently, microwave irradiation has been used as an alternative way for the preparation of ionic liquids. This approach can be applied for limited quantities of materials. A high microwave power is usually required. The first publication of using microwave irradiation was in 2001 by Varma and Namboodiri (2001). They developed a solvent-free microwave approach to synthesize 1,3-dialkylimidazolium halide salts using a household microwave oven at a power of 240 W. They put the starting materials in an open container in the oven and irradiated them with microwaves. After some seconds, they took the mixture out of oven and stirred it and then reheated it at the same power. This procedure was repeated until a clear ionic liquid was formed. The crude product was washed with ether and dried

under high vacuum. Higher yields were obtained within minutes using microwaves compared with using a conventional approach which required some hours. The author pointed out that alkyl halides with high boiling points were quickly converted to the corresponding halide salts, however, the loss of reactivity was observed for alkyl halides with low boiling points such as 1-chlorobutane and 2-bromobutane. This was due to these reagents being rapidly evaporated.

Following this work, several researchers have applied microwave irradiation to prepare ionic liquids. Khadilkar and Rebeiro (2002) reported the preparation of alkylpyridinium and 1-alkyl-3-methylimidazolium salts in a closed vessel under 2.45-GHz microwave irradiation. Horikoshi et al. (2008) reported the synthesis of an ionic liquid $[BMIM]^+[BF_4]^-$ under solvent-free conditions (Scheme 2.3). The yield of the product was up to 87% under 5.8-GHz microwave irradiation in a batch mode reactor. A microwave power of 30 W was used in this reaction. In contrast, the yield was 28% under 2.45-GHz microwave irradiation and only 21% using a heating bath. In those cases, microwave irradiation was more effective than the traditional heating bath. 5.8-GHz microwave was more efficient than 2.45-GHz microwave for the preparation of $[BMIM]^+[BF_4]^-$ in the batch-mode reactor. The yield of $[BMIM]^+[BF_4]^-$ was reduced to less than 10% in the reflux mode compared with batch mode reactor. An advantage of Horikoshi's work is that this direct synthetic process avoids the requirement of preparing the halide salts.



Scheme 2.3 One step reaction for the synthesis of ionic liquids using microwave irradiation

The microwave irradiation reactor for the above synthesis is shown in Figure 2.1. A high pressure Pyrex glass cylindrical reactor was installed in the 5.8-GHz microwave apparatus. The 5.8-GHz microwave generator had a maximum power of 700 W. A pressure gauge and a release bulb were connected to the cover of the reactor. A thermometer was used to monitor reaction temperature. In a batch mode, the reactor

was sealed with a stainless steel cap. In a reflux mode, the reactor was connected to a reflux condenser. The reagents were added to the reactor and the mixture was stirred continuously.

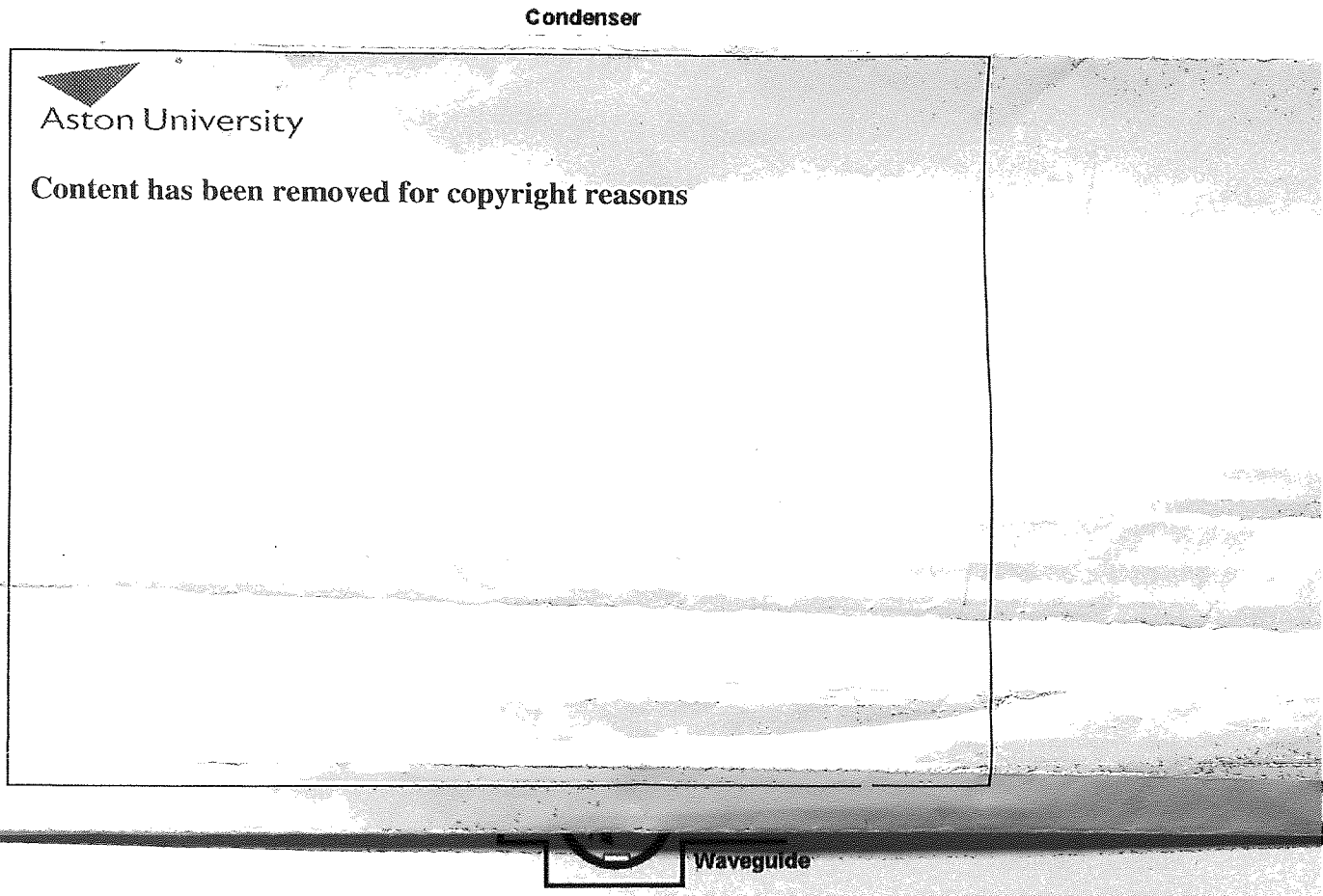


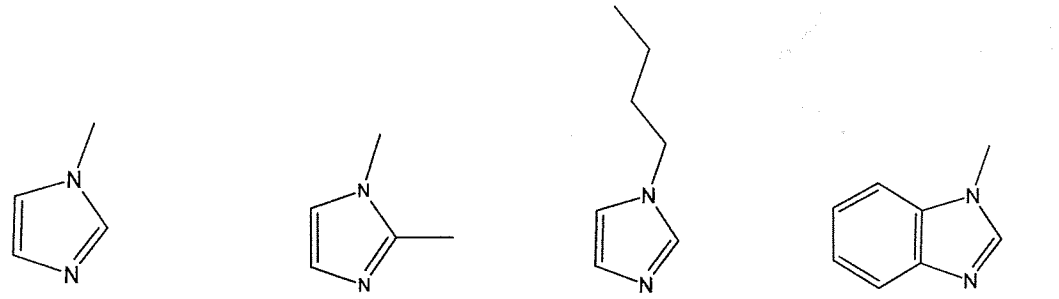
Figure 2.1 A microwave irradiation reactor (Horikoshi et al., 2008)

Room temperature ionic liquids exhibit good solvent properties and many of them have been demonstrated to promote organic reactions. They are potentially good solvents for organic reactions. Currently, RTILs are supplied in limited quantities by several chemical companies. However, the range of commercially available RTILs is limited and the price of RTILs is high. My research project was concerned with the use of RTILs for the preparation of organic chemicals. Therefore, a series of RTILs have been prepared. RTILs that have been widely used for organic synthesis were prepared and some new ionic liquids were synthesized with aim of developing and exploring more suitable RTILs as the reaction media for the organic reactions that were investigated in this project.

2.2 Results and discussion

2.2.1 Synthesis of ionic liquids

In this project, four commercially available alkylimidazoles were used: 1-methyl imidazole, 1,2-dimethylimidazole, 1-butylimidazole and 1-methyl benzimidazole. Their structures are shown below.



1-methylimidazole 1,2-dimethylimidazole 1-butylimidazole 1-methyl benzimidazole

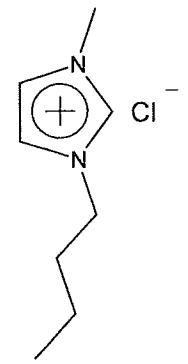
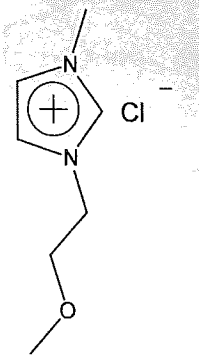
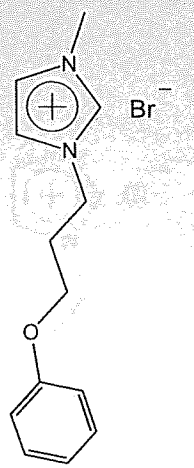
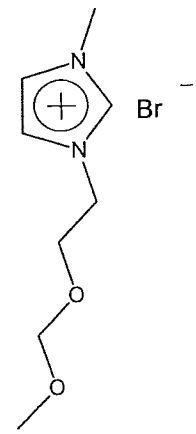
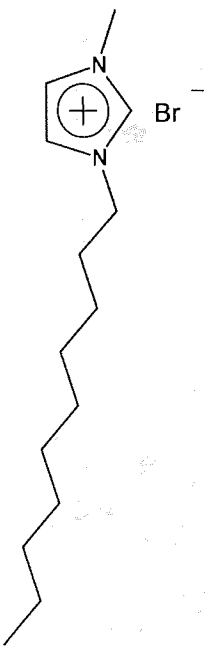
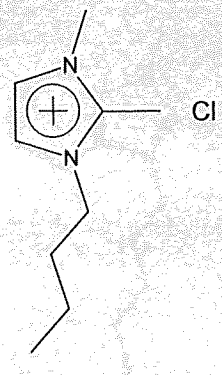
Figure 2.2 Structures of imidazole derivatives used in the project

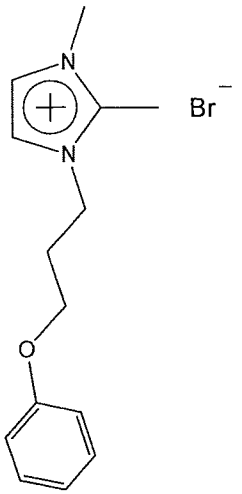
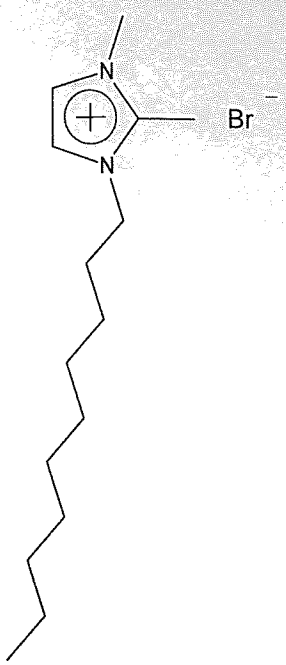
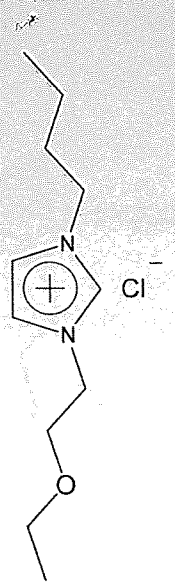
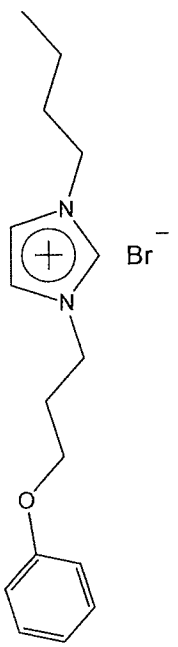
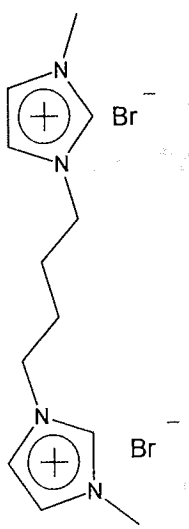
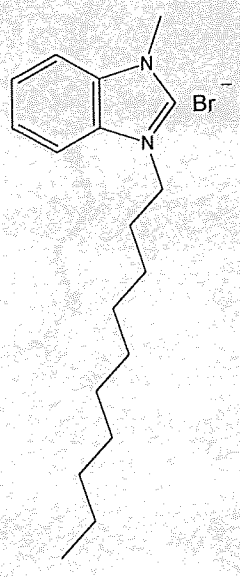
The synthesis of ionic liquids involves two steps, the formation of an imidazole halide salt followed by an anion exchange reaction as described previously. Imidazole halide salt with a desired cation was formed via a quaternization reaction. In general, an alkylimidazole was reacted with an alkyl halide with stirring to afford the halide salt. The reaction was carried out under anhydrous condition.

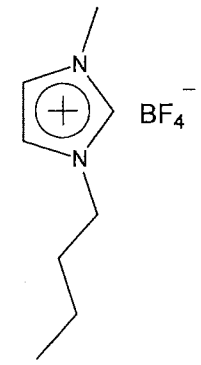
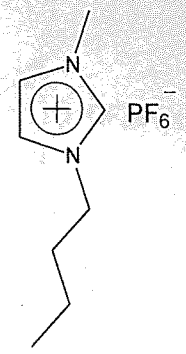
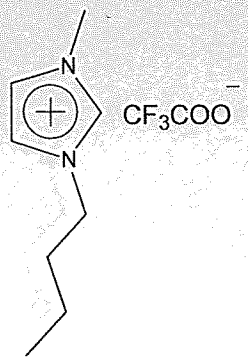
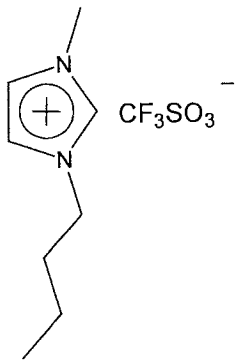
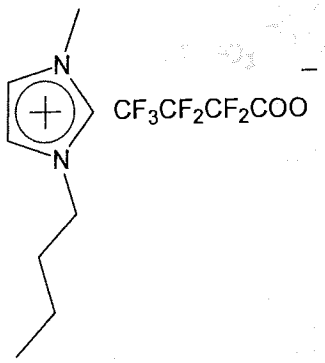
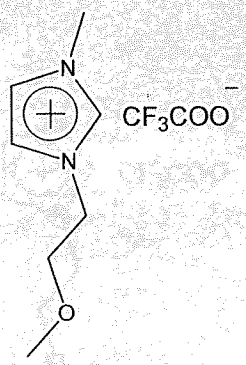
After the imidazole halide salt was prepared, the halide ion could be displaced by a suitable anion to form the desired ionic liquid. Various reagents were used for the displacement of the halide ions, such as acids, silver salts and sodium salts. The reaction with a silver salt was rapid. A longer reaction time was required when an acid was used as the anion exchange reagent.

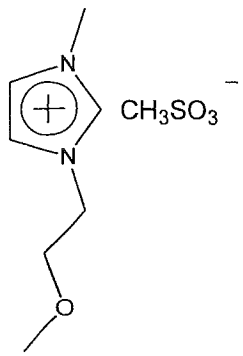
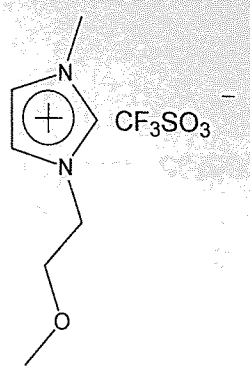
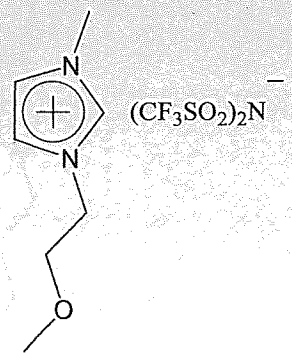
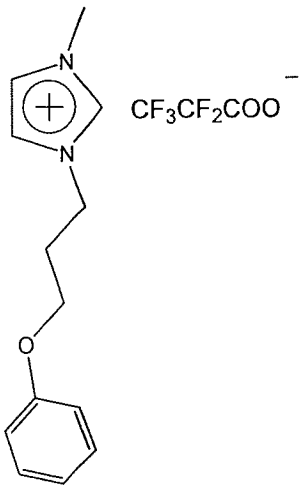
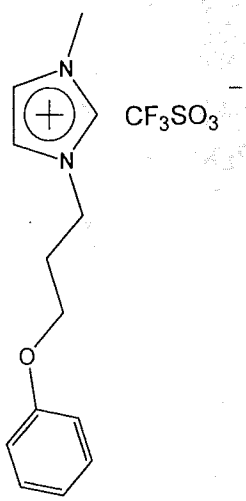
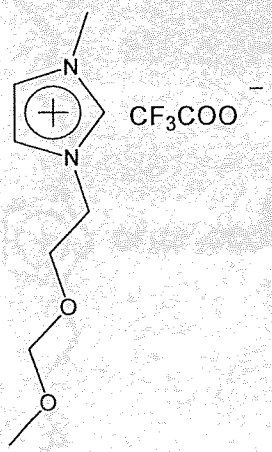
The structures of the ionic liquids prepared in this project are summarized in Figure 2.3. The compounds with bold headings are novel RTILs and have not been reported in the literature.

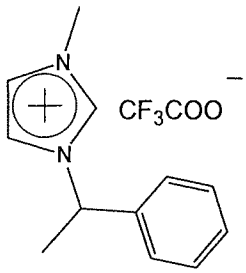
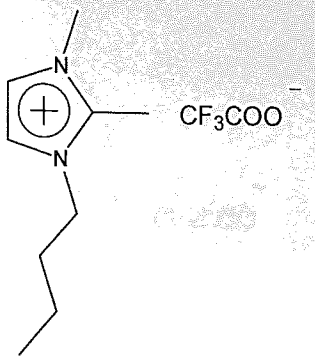
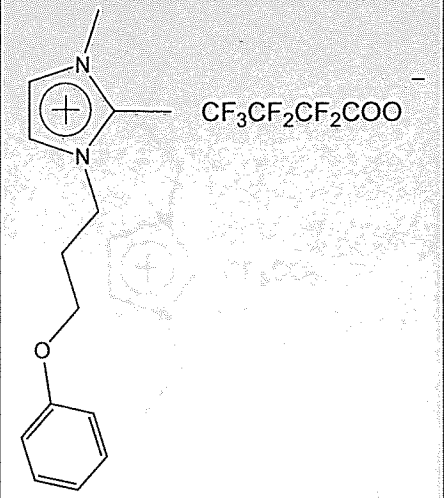
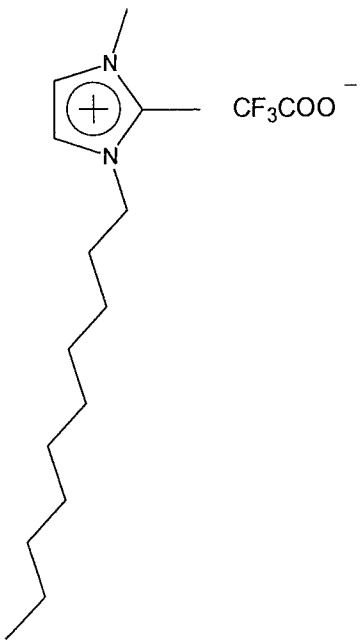
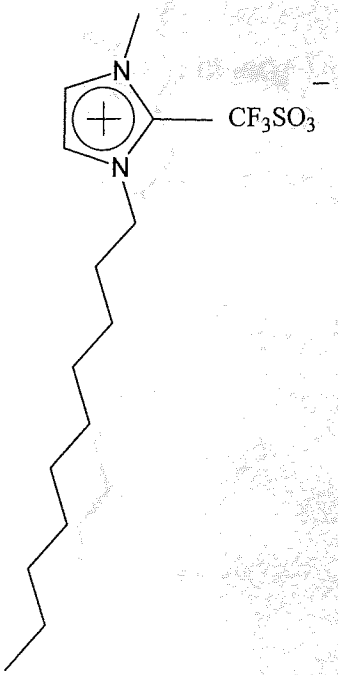
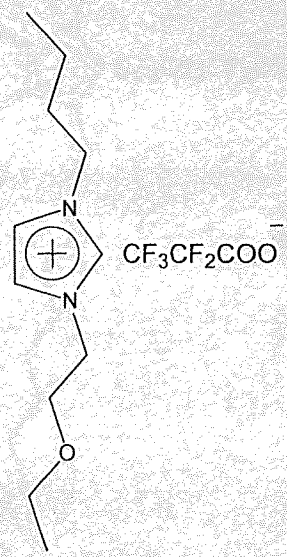
Figure 2.3 Ionic liquids synthesized in this project

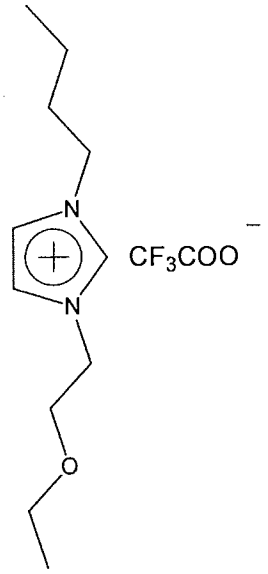
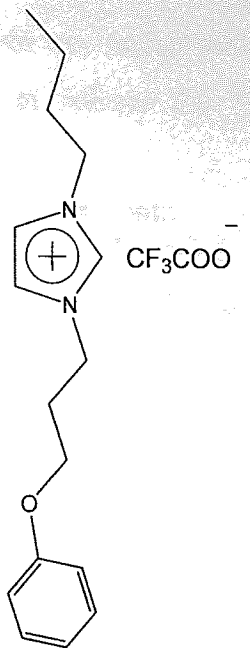
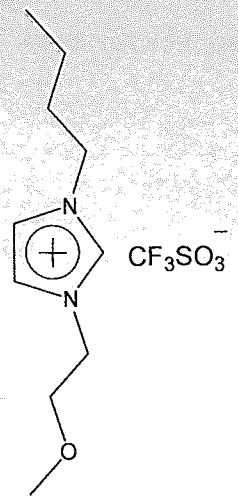
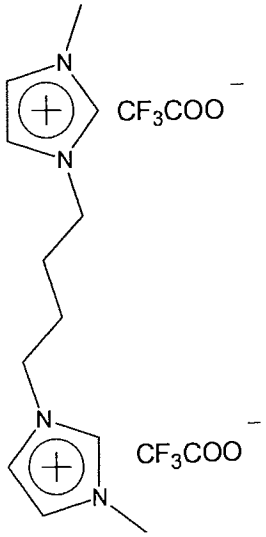
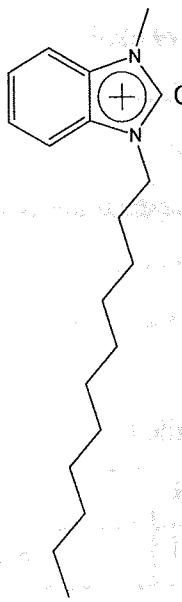
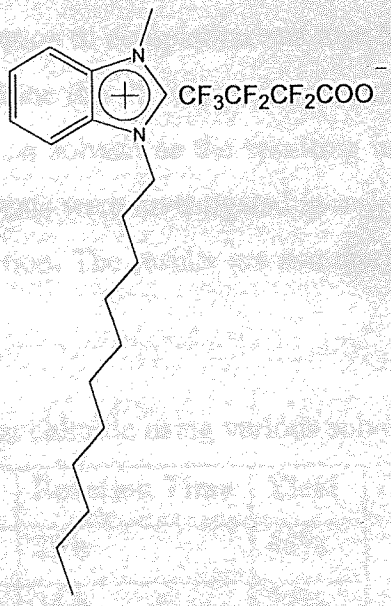
$[BMIM]^+Cl^-$  (2.3.1)	$[MeOEtMIM]^+Cl^-$  (2.3.2)	**$[PhOPMIM]^+Br^-$**  (2.3.3)
$[MeOMeOEtMIM]^+Br^-$  (2.3.4)	$[DecMIM]^+Br^-$  (2.3.5)	$[BMMIM]^+Cl^-$  (2.3.6)

[PhOPMMIM]$^{+}$Br^{-}	[DecMMIM]$^{+}$Br^{-}	**[EtOEtBuIM]$^{+}$Cl^{-}**
		
(2.3.7)	(2.3.8)	(2.3.9)
[PhOPBuIM]$^{+}$Br^{-}	Bis(MIM)butane Br_2	**[DecMBzIM]$^{+}$Br^{-}**
		
(2.3.10)	(2.3.11)	(2.3.12)

$[BMIM]^+[BF_4]^-$  (2.3.13)	$[BMIM]^+[PF_6]^-$  (2.3.14)	$[BMIM]^+[CF_3COO]^-$  (2.3.15)
$[BMIM]^+[CF_3SO_3]^-$  (2.3.16)	**$[BMIM]^+$ $[CF_3CF_2CF_2COO]^-$**  (2.3.17)	$[MeOEtMIM]^+[CF_3COO]^-$  (2.3.18)

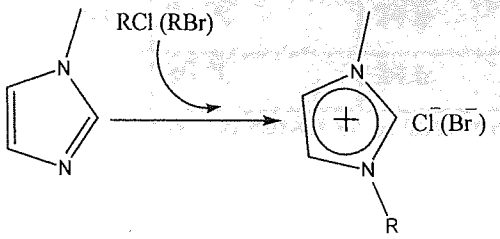
$[MeOEtMIM]^+[CH_3SO_3]^-$  (2.3.19)	**$[MeOEtMIM]^+[CF_3SO_3]^-$**  (2.3.20)	**$[MeOEtMIM]^+$ $[(CF_3SO_2)_2N]^-$**  (2.3.21)
$[PhOPMIM]^+$ $[CF_3CF_2COO]^-$  (2.3.22)	**$[PhOPMIM]^+[CF_3SO_3]^-$**  (2.3.23)	**$[MeOMeOEtMIM]^+$ $[CF_3COO]^-$**  (2.3.24)

[MPhMIM]$^+$[CF_3COO]$^-$  (2.3.25)	**[BMMIM]$^+$[CF_3COO]$^-$**  (2.3.26)	**[PhOPMMIM]$^+$ [$CF_3CF_2CF_2COO$]$^-$**  (2.3.27)
[DecMMIM]$^+$ [CF_3COO]$^-$  (2.3.28)	**[DecMMIM]$^+$[CF_3SO_3]$^-$**  (2.3.29)	**[EtOEtBuIM]$^+$ [CF_3CF_2COO]$^-$**  (2.3.30)

[EtOEtBuIM]$^+$ [CF_3COO]$^-$  (2.3.31)	**[PhOPBuIM]$^+$[CF_3COO]$^-$**  (2.3.32)	**[MeOEtBuMIM]$^+$ [CF_3SO_3]$^-$**  (2.3.33)
Bis(MIM)butane [CF_3COO]$_2$  (2.3.34)	**[DecMBzIM]$^+$[CF_3SO_3]$^-$**  (2.3.35)	**[DecMBzIM]$^+$ [$CF_3CF_2CF_2COO$]$^-$**  (2.3.36)

2.2.1.1 Quaternization reactions

In general, an alkylimidazole was reacted with an alkyl halide with stirring to afford the halide salt as shown in Scheme 2.4. The reactions were carried out under anhydrous conditions.



Scheme 2.4 Quaternization reactions

Solvents for Quaternization reactions

A number of solvents have been used for the quaternization reactions, such as 1,1,1-trichloroethane (Bonhote et al., 1996) and toluene (Lucas et al., 2000). In general, the solvent should be chemically stable under the reaction conditions and have a boiling point above the reaction temperature. If the solvent is immiscible with the resulting ionic liquid, it will help to drive the reaction to completion and also help product isolation. The starting materials, 1-chlorobutane (bp 78 °C) or 2-chloroethyl methyl ether (bp 90 °C) could be used as the reaction solvent as the resulting ionic liquid was insoluble in these halokanes. Various solvents were investigated in order to identify the suitable ones for the quaternization reaction. The results are summarized in Table 2.1, Table 2.2 and in Figure 2.4.

Table 2.1 Preparation of 1-butyl-3-methylimidazolium chloride using various solvents

Solvent	**Temperature**	**Reaction Time**	**Yield**
1,1,1-trichloroethane	100 °C	29 h	46%
Ethyl acetate	75-80 °C	24 h	22%
Chlorobutane	75-80 °C	24 h	87%
No solvent	80 °C	24 h	93%

No solvent: equal molar of starting materials without the addition of other organic solvent

Table 2.2 Preparation of 1-methoxyethyl-3-methylimidazolium chloride using various solvents

Solvent	Temperature	Reaction Time	Yield
Toluene	80 °C	24 h	14%
Ethyl acetate	80 °C	24 h	12%
1,1,1-trichloroethane	80 °C	24 h	16%
2-chloroethyl methyl ether	80 °C	24 h	70%
No solvent	80 °C	24 h	90%

No solvent: equal molar of starting materials without the addition of other organic solvent

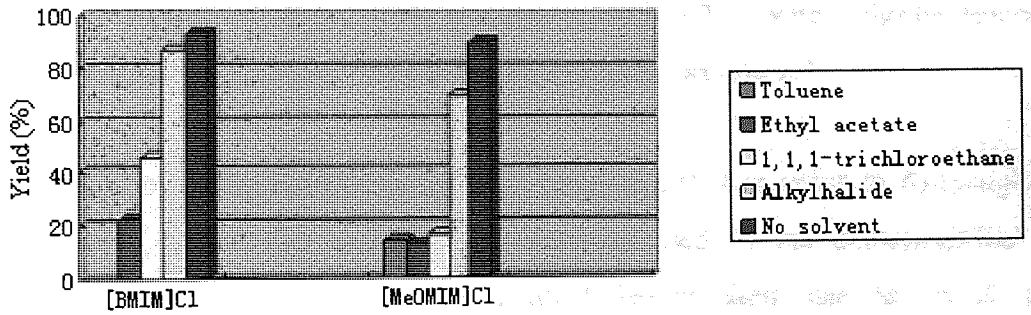


Figure 2.4 Comparision of various solvents for the preparation of $[BMIM]^+Cl^-$ and $[MeOEtMIM]^+Cl^-$

The above data showed that when 1-chlorobutane was used as a solvent for the preparation of $[BMIM]^+Cl^-$ or 2-chloroethyl methyl ether was used for the synthesis of $[MeOEtMIM]^+Cl^-$, the reaction proceeded at a lower temperature with a shorter reaction time, and the yields of the products were higher than that in other solvents. In addition, 1,1,1-trichloroethane seems to be better than ethyl acetate or toluene. However, this kind of chemical is toxic to the environment, thus after the reaction, it is necessary to dispose 1,1,1-trichloroethane in a separate container. Compared with 1,1,1-trichloroethane, monohaloalkanes are cheaper and less toxic to the environment. Considering these factors it would be better to use the starting material monohaloalkane as the solvent for the preparation of imidazole halide salts. Moreover, it was found that quaternization reactions with no solvent (equal molar of starting materials without the addition of other organic solvents) also proceeded well with excellent product yields.

Caution in the process of quaternization reactions

In the process of the synthesis of imidazolium halide salts, some caution needs to be taken. The quaternization reactions need to be carried out free of moisture, because starting materials and products are both very hygroscopic. Moisture can alter some of physical or chemical properties of ionic liquids. Thus all glassware was dried in the oven overnight before their use and the reaction was carried out under dry conditions. Overheating can lead to the reversal of the quaternization reaction (Wasserscheid and Welton, 2003). So the reaction temperature was set at 75-80 °C for the synthesis of imidazole chloride salts with the reaction time of 1-2 days. Imidazole bromide salts being more reactive required a lower temperature of 50-60 °C with a shorter reaction time of a few hours as demonstrated in the experimental section 2.3.

It is difficult to prepare completely colorless ionic liquids. According to Armarego & Perrin (1997), all starting materials and solvents used in the quaternization or anion-exchange reactions should be distilled before their use to avoid the discoloration of ionic liquids. From the experience of this work, the color was very dependant on the reaction temperature of the quaternization reaction. High temperatures resulted in discolored ionic liquids. If colorless imidazolium halide salts are required, the reaction needs to be carried out at relatively low temperature. Some researchers have indicated that activated charcoal can be used to purify ionic liquids and remove or reduce the color. However, no improvements were observed after the treatment of $[BMIM]^+[BF_4]^-$ and $[BMIM]^+[PF_6]^-$ with activated charcoal. The impurities that cause the color are unknown and they could not be detected by the analytical techniques used in this work. In most cases, color was not an important issue and did not affect the application of the ionic liquids.

Furthermore, after the completion of the reactions, all the unreacted starting materials should be removed. 1-Methylimidazole in the final products plays an unfavourable role in some applications of ionic liquids. Many electrophilic catalysts will coordinate to the base in an irreversible manner and the catalysts will be deactivated. A halide impurity will cause the increased viscosity and it will also deactivate some transition metal catalysts. 1-Methylimidazole is particularly difficult to remove due to its high

boiling point (198 °C). The crude product was kept under high vacuum at 80 °C for 4 hours. Most unreacted 1-methylimidazole was removed by this approach, but ^{1}H NMR analysis indicated that there was still up to 5% of residual 1-methylimidazole remaining in the crude product (Figure 2.5).

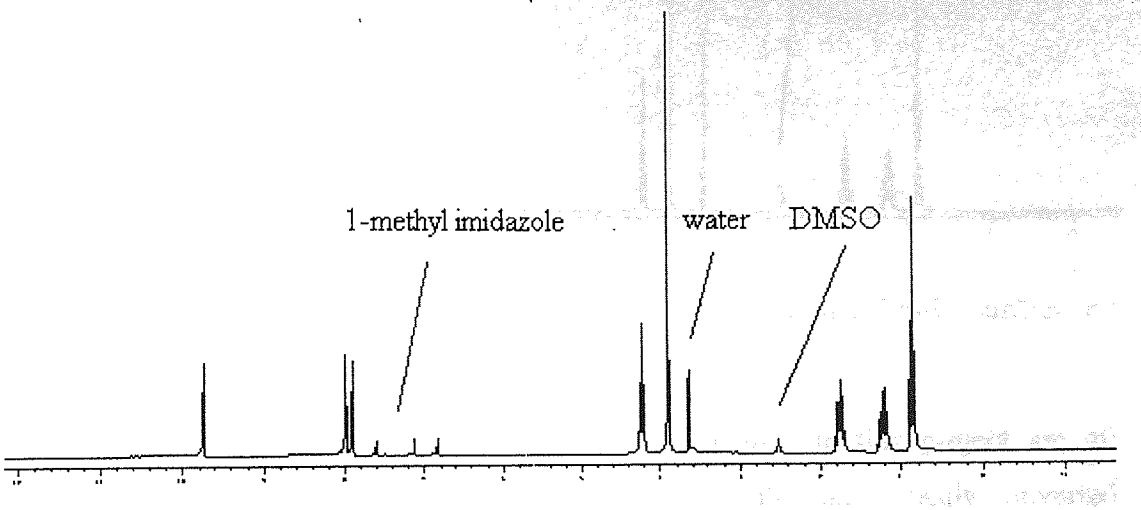


Figure 2.5 ^{1}H NMR spectrum of 1-butyl-3-methylimidazolium chloride purified by high vacuum

In order to obtain the product with a higher purity, an alternative approach was used instead of high vacuum. This was to dissolve the halide salt in dry acetonitrile at 50 °C and add it to a mixture of dry acetonitrile/diethyl ether cooled in an ice bath. The recrystallization was carried out with vigorous stirring to prevent the imidazole halides forming a hard crystalline mass which was difficult to be removed from the flask. ^{1}H NMR spectrum (Figure 2.6) of $[BMIM]^+Cl^-$ obtained using this method confirmed that there was no residual 1-methylimidazole.

Sometimes, the halide salt $[BMIM]^+Cl^-$ did not crystallize and it separated as a liquid in acetonitrile/diethyl ether. To overcome this problem a small amount of crystals of $[BMIM]^+Cl^-$ were used as "seeds" to induce the crystallization. This approach greatly improved the efficiency and effectiveness of the recrystallization.

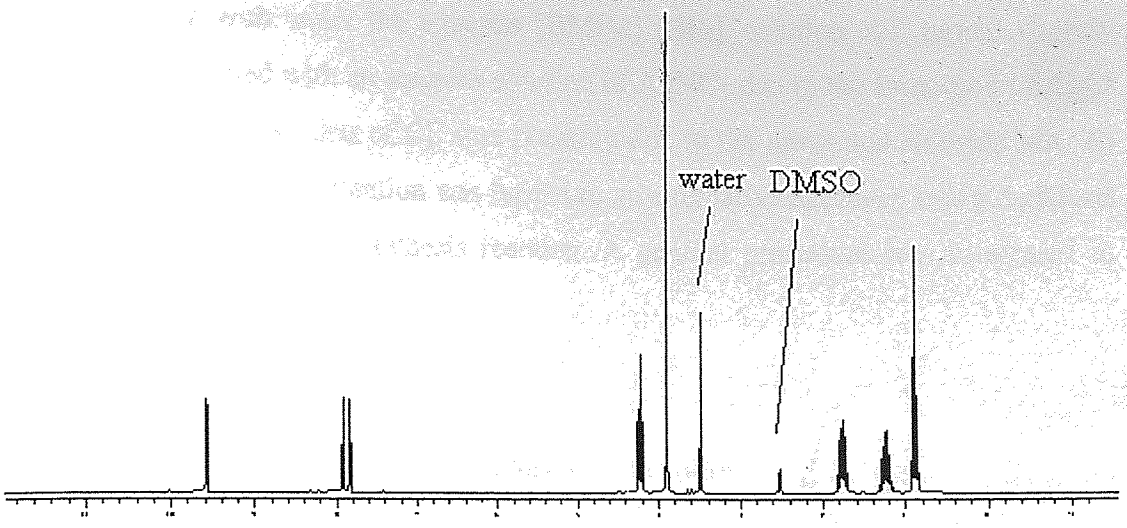


Figure 2.6 ^{1}H NMR spectrum of 1-butyl-3-methylimidazolium chloride purified by recrystallization

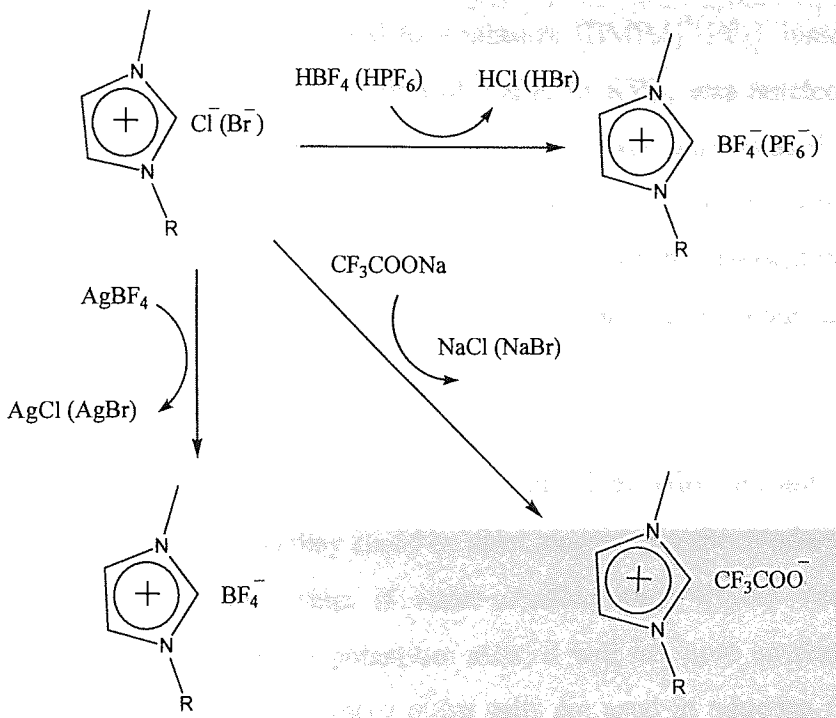
Haloalkanes used as solvents for quaternization reactions in this project are all commercially available. The resulting imidazole halide salts can be easily converted to the desired ionic liquids in the next step of the synthesis.

2.2.1.2 Anion metathesis reactions

The following anions were used in the anion metathesis reaction, $[BF_4]^-$, $[PF_6]^-$, $[CF_3SO_3]^-$, $[CH_3SO_3]^-$, $[CF_3COO]^-$, $[CF_3CF_2COO]^-$, $[CF_3CF_2CF_2COO]^-$, $[(CF_3SO_2)_2N]^-$. Different methods were applied to different types of ionic liquids. At the beginning of this project, two commonly used ionic liquids $[BMIM]^+[BF_4]^-$ and $[BMIM]^+[PF_6]^-$ were synthesized.

Over the last decade, HBF_4 and HPF_6 have been widely used for the formation of $[BMIM]^+[BF_4]^-$ and $[BMIM]^+[PF_6]^-$, because of the reasonable price and availability of the acids HBF_4 and HPF_6. HBF_4 seems to be a good choice for the preparation of $[BMIM]^+[BF_4]^-$, which is cheap and easy to handle. However, during this research, it was found that, the water miscible ionic liquid $[BMIM]^+[BF_4]^-$ was difficult to be extracted completely from water with dichloromethane even after repeated extractions. There was a significant loss of the product in the aqueous phase. Furthermore, it was difficult to obtain a halide-free $[BMIM]^+[BF_4]^-$ when HBF_4 was used as the reagent.

After washing with water the aqueous $[BMIM]^+[BF_4]^-$ solution still turned slightly cloudy when treated with an aqueous solution of $AgNO_3$ due to the formation of AgCl. The residual concentration of Cl^- was possibly due to the unreacted chloride salt. To overcome this problem attention was turned to an alternative approach using $AgBF_4$ as a reagent for the anion metathesis reaction. A general procedure was illustrated in Scheme 2.5.



Scheme 2.5 Anion metathesis reactions

A more efficient method for the synthesis of ionic liquids, especially water-miscible ones such as $[BMIM]^+[BF_4]^-$, is to use silver salts instead of acids. A solution of the halide salts and silver salts in methanol or water were mixed together with stirring for 1 hour. The precipitated AgCl could be filtered off directly. This approach led to a complete reaction with very high yields. However, silver salts are expensive, so they are not appropriate for large-scale production, especially for industrial ionic liquid synthesis.

For the synthesis of $[BMIM]^+[PF_6]^-$, a representative of water-immiscible ionic liquids, HPF_6 was used initially as the reagent for the metathesis reaction. As the

resulting $[BMIM]^+[PF_6]^-$ is insoluble in water, this approach produced halide-free ionic liquids. However, HPF_6 is a strong acid which can cause severe burns and it is very toxic when in contact with skin, so special attention should be given when handling it. When the reaction is carried out in an aqueous solution or using water to wash out the remaining acid, some HF was formed in either the reaction process or the purification process, which may cause a hazardous situation.

Consequently, $NaPF_6$ or KPF_6 was used to synthesize $[BMIM]^+[PF_6]^-$ instead of the acid or the silver salt. An aqueous solution of $NaPF_6$ or KPF_6 was reacted with the imidazole halide salt at room temperature. A biphasic layer was formed when the reaction was completed. The aqueous layer was separated off and the organic layer was washed with water to give a pure product. The above results demonstrate that the sodium or potassium salt is a better reagent for the preparation of water-immiscible ionic liquids.

Sodium and potassium salts are not as expensive as silver salts and are easier and safer to handle than the acids, so they could be ideal reagents for the synthesis of ionic liquids in the anion exchange step. If water-miscible ionic liquids can also be synthesized using these sodium or potassium salts, it will be more economical than the use of silver salts. However, if these metal salts are used in aqueous conditions, the reactions are difficult to complete, which is a similar situation to that when acids are used as described above. To overcome this problem an effective solvent is needed that can dissolve the sodium salts or potassium salts with the desired anions, but will precipitate the resulting sodium or potassium halide. Acetonitrile and acetone were found to be able to dissolve some of these metal salts, thus they were used as the solvents for the synthesis of water-miscible ionic liquids using these reagents. For example, $[MeOEtMIM]^+[CF_3COO]^-$ and $[MeOEtMIM]^+[CF_3SO_3]^-$ were successfully prepared by this approach as CF_3COONa or CF_3SO_3Na were soluble in acetonitrile and acetone. CF_3COONa and $[MeOEtMIM]^+Cl^-$ was dissolved in acetonitrile or acetone and the two solutions was mixed with efficient stirring. The reaction was completed with NaCl precipitating out spontaneously. Unfortunately, KBF_4 was not soluble in acetonitrile/acetone, so $[BMIM]^+[BF_4]^-$ could not be prepared using this method.

Further problems were encountered in the synthesis of 1-methoxyethyl-3-methyl-imidazolium methanesulfonate $[MeOEtMIM]^+[CH_3SO_3]^-$. CH_3SO_3Na is not soluble in acetonitrile or acetone and CH_3SO_3Ag is not soluble in water, which means both silver salt and sodium salt methods described above are inappropriate for the preparation of $[MeOEtMIM]^+[CH_3SO_3]^-$. Initially, the preparation of $[BMIM]^+[CH_3SO_3]^-$ from CH_3SO_3H and $[BMIM]^+Cl^-$ was studied and the anion exchange reaction was found to be incomplete similarly to when HBF_4 was used to prepare $[BMIM]^+[BF_4]^-$. This incomplete reaction was confirmed by ^1H NMR (Figure 2.7).

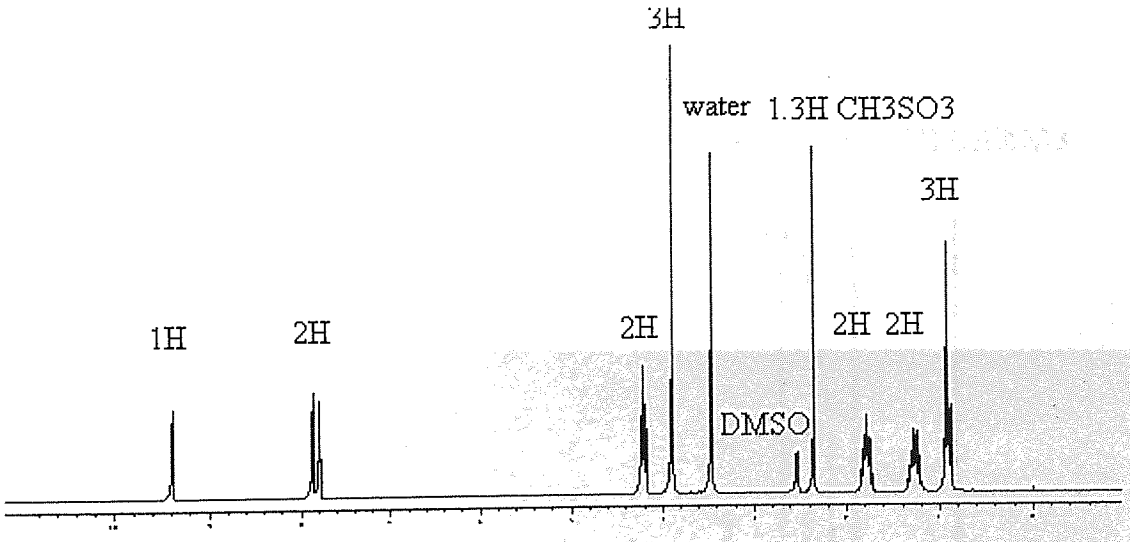
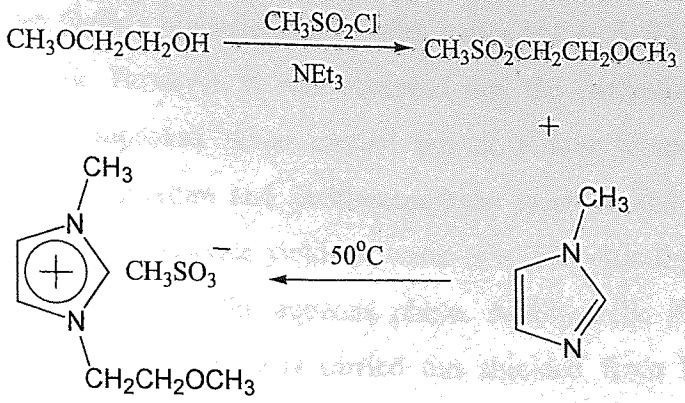


Figure 2.7 ^1H NMR spectrum of $[BMIM]^+[CH_3SO_3]^-$ synthesized by the reaction of $[BMIM]^+Cl^-$ with CH_3SO_3H

A new approach was applied as illustrated in Scheme 2.5. 2-Methoxy ethyl methanesulfonate was formed by the reaction of 2-methoxyethanol with methanesulfonyl chloride. The product 2-methoxy ethyl methanesulfonate was distilled before being use for the next step of the reaction. 1-Methylimidazole was then reacted with the 2-methoxy ethyl methanesulfonate to give the desired ionic liquid. ^1H NMR analysis of $[BMIM]^+[CH_3SO_3]^-$ (Figure 2.8) confirmed that the reaction was completed.



Scheme 2.5 Synthesis of 1-methoxyethyl-3-methylimidazolium methanesulfonate

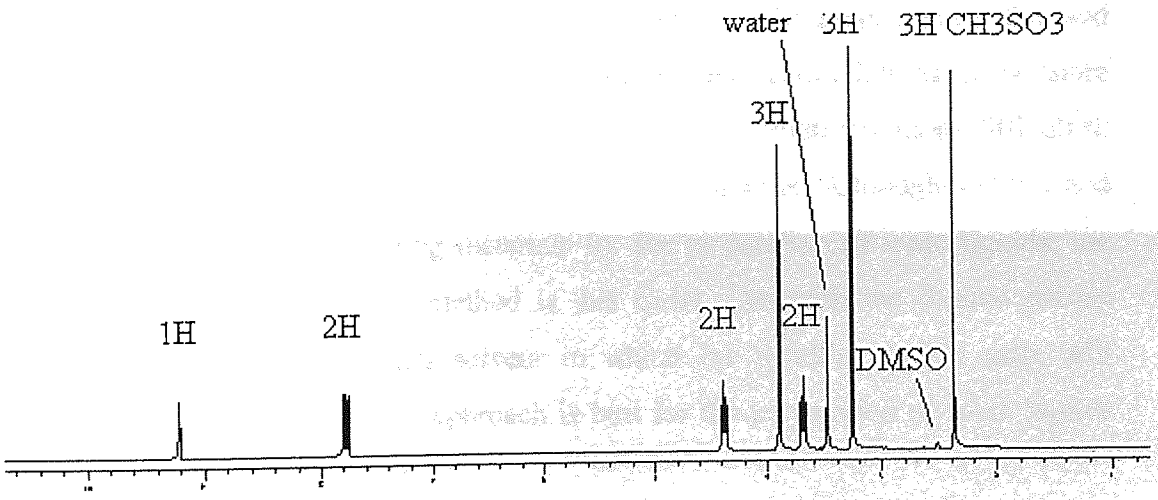


Figure 2.8 ^{1}H NMR spectrum of $[MeOEtMIM]^{+}[CH_3SO_3]^{-}$ synthesized by the reaction of $CH_3OCH_2CH_2OH$, CH_3SO_3Cl and 1-methylimidazole

Caution in the process of anion metathesis reactions

The anion metathesis reaction is exothermic, so it needs to be carried out in an ice bath. When the acid approach is used, the acid needs to be added slowly to the halide salt in order to avoid the excess heat that can cause the decomposition of ionic liquids. Moreover, it is difficult to extract the water-miscible ionic liquids such as $[BMIM]^{+}[BF_4]^{-}$ from water with dichloromethane. It has been reported that

$[BMIM]^+[BF_4]^-$ can form a biphasic system with water below 5 °C, which was not observed in this work. However, it was observed that the extraction efficiency of $[BMIM]^+[BF_4]^-$ was improved when carried out at a low temperature. In this procedure, the reaction mixture and dichloromethane were cooled in an ice bath before the extraction. The moderate yields of water-miscible ionic liquids are mainly due to the loss of RTILs into the aqueous phase. Additionally, if the silver salt approach was used, the reaction was carried out shielded from light conditions because the silver salts are light sensitive.

In summary, four methods were used for the anion exchange step in the preparation of both water-immiscible and water-miscible ionic liquids as discussed above. If highly pure ionic liquids are required, the silver salt approach is more appropriate. If it is not significant that residual imidazole halides salts remain in the ionic liquids, the acid approach can be used, especially for industrial-scale production as it is more economical than the other approaches. However, acids are relatively more difficult to handle, so more care is needed during the synthetic process. Although sodium and potassium salts are good starting materials for the preparation of ionic liquids, the limitation associated with this method is that metal salts with the desired anions should be soluble in a certain solvent in which the resulting halide salts will precipitate out. A sulfonate salt approach is best for the preparation of ionic liquids based on the anion of alkylsulfonate.

2.2.2 Properties of ionic liquids

2.2.2.1 Physical properties of ionic liquids at room temperature

Most of the prepared ionic liquids have low melting points. As the size of the alkyl chain increases, the melting point of the ionic liquid decreases. With the size of the cation or anion increases, the melting point of the ionic liquid also decreases. For example, $[MeOEtMIM]^+Cl^-$ is a solid at room temperature, but $[EtOEtBuIM]^+Cl^-$ is a liquid.

Generally, 1,3-dialkyl imidazole halide salts are solids or very viscous liquids at room temperature. After the exchange reaction with the desired anions such as $[PF_6]^-$ and $[CF_3COO]^-$, the melting points of the ionic liquids dramatically decrease. For example, $[BMIM]^+[PF_6]^-$ has a melting point of -8 °C, which is a significant reduction compared with the melting point of $[BMIM]^+Cl^-$ (65 °C). However, ionic liquids based on 1-alkyl-2,3-dimethyl imidazole usually exist as solids at room temperature and have higher melting points.

Table 2.3 The physical properties of ionic liquids at room temperature

Ionic liquid	**Status**	**Ionic liquid**	**Status**
$[BMIM]^+Cl^-$	solid	$[MeOEtMIM]^+[CH_3SO_3]^-$	liquid
$[MeOEtMIM]^+Cl^-$	solid	$[MeOEtMIM]^+[CF_3SO_3]^-$	liquid
$[PhOPMIM]^+Br^-$	liquid	$[MeOEtMIM]^+[(CF_3SO_2)_2N]^-$	liquid
$[MeOMeOEtMIM]^+Br^-$	liquid	$[PhOPMIM]^+[CF_3CF_2COO]^-$	liquid
$[DecMIM]^+Br^-$	liquid	$[PhOPMIM]^+[CF_3SO_3]^-$	liquid
$[BMMIM]^+Cl^-$	solid	$[MeOMeOEtMIM]^+[CF_3COO]^-$	solid
$[PhOPMMIM]^+Br^-$	solid	$[MPhMIM]^+[CF_3COO]^-$	liquid
$[DecMMIM]^+Br^-$	solid	$[BMMIM]^+[CF_3COO]^-$	solid
$[EtOEtBuIM]^+Cl^-$	liquid	$[PhOPMMIM]^+[CF_3CF_2CF_2COO]^-$	solid
$[PhOPBuIM]^+Br^-$	liquid	$[DecMMIM]^+[CF_3COO]^-$	solid
Bis(MIM)butane Br_2	solid	$[DecMMIM]^+[CF_3SO_3]^-$	solid
$[DecMBzIM]^+Br^-$	solid	$[EtOEtBuIM]^+[CF_3CF_2COO]^-$	liquid
$[BMIM]^+[BF_4]^-$	liquid	$[EtOEtBuMIM]^+[CF_3COO]^-$	liquid
$[BMIM]^+[PF_6]^-$	liquid	$[PhOPBuMIM]^+[CF_3COO]^-$	liquid
$[BMIM]^+[CF_3SO_3]^-$	liquid	$[MeOEtBuMIM]^+[CF_3SO_3]^-$	liquid
$[BMIM]^+[CF_3CF_2CF_2COO]^-$	liquid	Bis(MIM)butane $[CF_3COO]_2$	solid
$[BMIM]^+[CF_3COO]^-$	liquid	$[DecMBzIM]^+[CF_3SO_3]^-$	solid
$[MeOEtMIM]^+[CF_3COO]^-$	liquid	$[DecMBzIM]^+[CF_3CF_2CF_2COO]^-$	solid

2.2.2.2 Density, viscosity and conductivity

The following data (Table 2.4) for the ionic liquids synthesized in this project are taken from literature (Bonhote et al., 1996; Galinski et al., 2006).

Table 2.4 Physical properties of ionic liquids: density, conductivity, viscosity (293K)

Ionic liquids	Density (ρ), g cm-3	Viscosity (ν), cp	Conductivity (κ), mS cm^{-1}
$[BMIM]^+[BF_4]^-$	1.17	233	1.73
$[BMIM]^+[PF_6]^-$	1.36	312	1.4
$[BMIM]^+[CF_3COO]^-$	1.21	73	3.2
$[BMIM]^+[CF_3CF_2CF_2COO]^-$	1.33	182	1.0
$[BMIM]^+[CF_3SO_3]^-$	1.29	90	3.7
$[MeOEtMIM]^+[CF_3SO_3]^-$	1.36	74	3.6
$[MeOEtMIM]^+[(CF_3SO_2)_2N]^-$	1.50	54	4.2

2.2.2.3 Solubility of the ionic liquids in other solvents

All of the prepared ionic liquids in this project were found to be soluble in methanol, acetone and acetonitrile. Most of the prepared ionic liquids were soluble in water except $[BMIM]^+[PF_6]^-$ and $[MeOEtMIM]^+[(CF_3SO_2)_2N]^-$ which were insoluble in water. All of the synthesized ionic liquids were immiscible with diethyl ether and only a few of them were slightly miscible with ethyl acetate. These immiscible organic solvents could be used to extract reaction products from reaction mixtures where an ionic liquid is used as the reaction medium. Water could be added to water-miscible ionic liquids to improve the extraction efficiency of the organic products.

Table 2.5 Solubility of the ionic liquids with other solvents

Solvents / Ionic liquids	Methanol	Acetone	Acetonitrile	Ethyl acetate	Ether	Petroleum ether	Water
$[BMIM]^+Cl^-$	s	s	s	i	i	i	s
$[MeOEtMIM]^+Cl^-$	s	s	s	i	i	i	s
$[PhOPMIM]^+Br^-$	s	s	s	i	i	i	s
$[MeOMeOEtMIM]^+Br^-$	s	s	s	i	i	i	s
$[DecMIM]^+Br^-$	s	s	s	i	i	i	s
$[BMMIM]^+Cl^-$	s	s	s	i	i	i	s
$[PhOPMMIM]^+Br^-$	s	s	s	i	i	i	s
$[DecMMIM]^+Br^-$	s	s	s	i	i	i	s
$[EtOEtBuIM]^+Cl^-$	s	s	s	i	i	i	s
$[PhOPBuIM]^+Br^-$	s	s	s	i	i	i	s
Bis(MIM)butane Br_2	s	s	sl	i	i	i	s
$[DecMBzIM]^+Br^-$	s	s	s	i	i	i	s
$[BMIM]^+[BF_4]^-$	s	s	s	i	i	i	s
$[BMIM]^+[PF_6]^-$	s	s	s	i	i	i	i
$[BMIM]^+[CF_3SO_3]^-$	s	s	s	i	i	i	s
$[BMIM]^+[CF_3CF_2CF_2COO]^-$	s	s	s	i	i	i	s
$[BMIM]^+[CF_3COO]^-$	s	s	s	i	i	i	s
$[MeOEtMIM]^+[CF_3COO]^-$	s	s	s	i	i	i	s
$[MeOEtMIM]^+[CH_3SO_3]^-$	s	s	s	i	i	i	s
$[MeOEtMIM]^+[CF_3SO_3]^-$	s	s	s	i	i	i	s
$[MeOEtMIM]^+[(CF_3SO_2)_2N]^-$	s	s	s	s	i	i	i
$[PhOPMIM]^+[CF_3CF_2COO]^-$	s	s	s	i	i	i	s
$[PhOPMIM]^+[CF_3SO_3]^-$	s	s	s	i	i	i	s
$[MeOMeOEtMIM]^+[CF_3COO]^-$	s	s	s	i	i	i	s
$[MPhMIM]^+[CF_3COO]^-$	s	s	s	i	i	i	s
$[BMMIM]^+[CF_3COO]^-$	s	s	s	i	i	i	s
$[PhOPMMIM]^+[CF_3CF_2CF_2COO]^-$	s	s	s	i	i	i	s
$[DecMMIM]^+[CF_3COO]^-$	s	s	s	i	i	i	s
$[DecMMIM]^+[CF_3SO_3]^-$	s	s	s	i	i	i	s
$[EtOEtBuIM]^+[CF_3CF_2COO]^-$	s	s	s	i	i	i	s
$[EtOEtBuMIM]^+[CF_3COO]^-$	s	s	s	i	i	i	s
$[PhOPBuIM]^+[CF_3COO]^-$	s	s	s	s	i	i	s
$[MeOEtBuMIM]^+[CF_3SO_3]^-$	s	s	s	i	i	i	s
Bis(MIM)butane $[CF_3COO]_2$	s	s	s	i	i	i	s
$[DecMBzIM]^+[CF_3SO_3]^-$	s	s	s	i	i	i	s
$[DecMBzIM]^+[CF_3CF_2CF_2COO]^-$	s	s	s	i	i	i	s

s: soluble; i: insoluble; sl:slightly soluble

In this project, most of the bromide and chloride imidazole salts prepared were solids or very viscous liquids at room temperature. Ionic liquids based on the cations of 1,2-dimethyl imidazole and 1-methyl benzimidazole are solids at room temperature. As the aim of this project is to investigate some organic reactions in RTILs, these types of ionic liquids are not suitable to be used as reaction solvents. Therefore, only the ionic liquids that are liquid at room temperature were used in the work as described in the following chapters.

2.3. Experimental section

Chemicals were purchased from Aldrich Company or Fisher Company and were used as received. Melting points were determined on a Reichert-Jung Thermo Galen hot stage microscope and were uncorrected. Infrared spectra were recorded on a Mattson 3000 FT-IR spectrophotometer using KBr discs for solids and thin films for liquids. Atmospheric pressure chemical ionization mass spectrometry (APCI-MS) was carried out on a Hewlett-Packard 5989B quadrupole instrument connected to an electrospray 59987A unit with an APCI accessory and automatic injection using a Hewlett-Packard 1100 series autosampler and was uncorrected. TLC was carried out on pre-coated Merck 60 F254 aluminium-backed plates and visualized using UV (254 and 360 nm). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-250 instrument operating at ^{1}H (250.1 MHz) and at ^{13}C (62.9 MHz) running at 18 °C when $CDCl_3$ was used to prepare the sample and 25 °C when DMSO was used. ^{13}C NMR spectra were APT (Attached Proton Test) spectra. CH_0 and CH_2 are positive. CH and CH_3 are negative.

2.3.1 1-Butyl-3-methylimidazolium chloride {[BMIM]$^{+}$Cl^{-}}

1-Methylimidazole (80 ml, 1 mol) was added dropwise to 1-chlorobutane (200 ml, 1.9 mol). The mixture was stirred vigorously and refluxed at 75-80 °C for 24 h. The reaction course was followed by TLC and the TLC developing solvent was ethyl acetate/methanol (2/3). When the reaction was completed, the excess 1-chlorobutane was decanted and the crude ionic liquid was washed with cholrobutane (2 × 20 ml). The trace of remaining 1-chlorobutane was removed with rotary evaporation at 60 °C for 30 min, followed by at 80 °C for 4 h under high vacuum (5 mm Hg) in order to remove the starting materials completely, especially 1-methyl-imidazole (Bonhte et al., 1996). The crude product was further puried by recrystallization (acetonitrile/ether) and dried under vacuum. The product [BMIM]$^{+}$Cl^{-} was a white solid. The yield was 151.97 g (87%). ^{1}H NMR (DMSO-d_6): δ = 9.57 (s, 1H, N-CH=N), 7.91 (m, 1H, N-CH=C), 7.83 (m, 1H, C=CH-N), 4.21 (t, J = 6.95Hz, 2H, N-CH_2-), 3.88 (s, 3H, N-CH_3), 1.76 (quint, J = 7.58Hz, 2H, N-CH_2-C**H_2**-), 1.23 (sext, J=7.58Hz, 2H,

N-CH_2CH_2-CH_2-), 0.88 (t, J=7.58Hz, 3H, N-$CH_2CH_2CH_2$-CH_3). MS ES^+ (m/z) = 139{$[BMIM]^+$}. IR (cm^{-1}) = 3404, 3096, 2954, 1570, 1463, 1170, 756, 623. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 136.66 (N-CH=N), 48.27 (N-CH_2-), 31.31(N-CH_2-CH_2-), 18.67(N-CH_2CH_2-CH_2-). Negative peaks: δ = 123.47 (N-CH=C), 122.19 (C=CH-N), 35.60 (N-CH_3), 13.21(N-$CH_2CH_2CH_2$-CH_3).

2.3.2 1-Methoxyethyl-3-methylimidazolium chloride {$[MeOEtMIM]^+Cl^-$}

Under vigorous stirring, 1-methylimidazole (8 ml, 0.1 mol) was added dropwise to 2-chloro ethyl methyl ether (25 ml, 0.27 mol). The mixture was stirred and refluxed at 80 °C for 50 h. The upper solvent layer, 2-chloroethyl methyl ether, was decanted. The resulting ionic liquid was in the second layer which was washed with 2-chloroethyl methyl ether (2 × 5 ml) and evaporated for 30 min. The crude product was dissolved in acetonitrile and recrystallized in acetonitrile/ether. The pure product was dried under vacuum overnight. The yield was 17.59 g (99%). ^1H NMR (DMSO-d_6): δ = 9.57 (s, 1H, N-CH=N), 7.91 (t, J = 1.90Hz, 1H, N-CH=C), 7.85 (t, J = 1.90Hz, 1H, C=CH-N), 4.42 (t, J = 5.05Hz, 2H, N-CH_2-), 3.90 (s, 3H, N-CH_3), 3.71 (t, J = 5.05Hz, 2H, -CH_2-O), 3.24 (s, 3H, O-CH_3). MS ES^+ (m/z) = 141{$[MeOEtMIM]^+$}. IR (cm^{-1}) = 3391, 3072, 1570, 1449, 1177, 1117, 1013, 832. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 136.93(N-CH=N), 69.52(N-CH_2-), 48.36(-CH_2-O). Negative peaks: δ = 123.33(N-CH=C), 122.51(C=CH-N), 57.93(N-CH_3), 35.61(O-CH_3).

2.3.3 1-Phenoxypropyl-3-methylimidazolium bromide {$[PhOPMIM]^+Br^-$}

1-Methylimidazole (4 ml, 0.05 mol) was mixed with 3-phenoxypropyl bromide (8 ml, 0.05 mol). The mixture was stirred at 50 °C for 20 h. The resulting product was washed with ethyl acetate (2 × 5 ml) and then kept in a high vacuum for 2 h at 80 °C. The product was yellowish liquid and the yield was 14.91 g (98%). ^1H NMR (DMSO-d_6): δ = 9.24 (s, 1H, N-CH=N), 7.85 (m, 1H, N-CH=C), 7.74 (m, 1H,

C=CH-N), 7.29 (t, J = 7.58Hz, 2H, Ph), 6.98-6.86 (m, 3H, Ph), 4.36 (t, J = 6.95Hz, 2H, N-CH_2-), 4.02 (t, J = 6.32Hz, 2H, -CH_2-O), 3.85 (s, 3H, N-CH_3), 2.27 (quint, J = 6.32Hz, 2H, -CH_2-). MS ES^+ (m/z) = 217{$[PhOPMIM]^+$}. IR (cm^{-1}) = 3434, 3070, 1600, 1492, 1240, 1168, 1043, 760, 692, 620. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 158.05(Ph), 64.28 (-CH_2-O), 46.34(N-CH_2-), 28.99(-CH_2-). Negative peaks: δ = 129.44(Ph), 123.49(N-CH=C), 122.38(C=CH-N), 120.68(Ph), 114.30(Ph), 35.68(N-CH_3).

2.3.4 1-Methoxymethoxyethyl-3-methylimidazolium bromide {$[MeOMeOEtMIM]^+Br^-$}

A similar method was used to the synthesis of $[PhOPMIM]^+Br^-$ (2.3.3). 1-Methylimidazole (2.4 g, 0.03 mol) was treated with 1-methoxy methoxyethyl bromide (5 g, 0.03 mol) and stirred for 20 h at 50 °C to give the product (7.2 g, 97%).^1H NMR (DMSO-d_6): δ = 9.31 (s, 1H, N-CH=N), 7.88 (t, J = 1.90Hz, 1H, N-CH=C), 7.85 (t, J = 1.90Hz, 1H, C=CH-N), 4.60-4.57 (m, 2H, O-CH_2-OCH_3), 4.42 (t, J = 5.05Hz, 2H, N-CH_2-), 3.89 (s, 3H, N-CH_3), 3.82 (t, J = 5.05Hz, 2H, -CH_2-O), 3.17-3.15 (m, 3H, O-CH_3). MS ES^+ (m/z) = 171{$[MeOMeOEtMIM]^+$}. IR (cm^{-1}) = 3433, 2961, 1562, 1466, 1159, 1115, 1040, 909, 760. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 136.93(N-CH=N), 69.61(CH_2-CH_2-O), 48.59 (N-CH_2). Negative peaks: δ = 123.49(N-CH=C), 122.66(C=CH-N), 57.95(O-CH_3), 35.62(N-CH_3).

2.3.5 1-Undecyl-3-methylimidazolium bromide {$[DecMIM]^+Br^-$}

1-Methylimidazole (15 ml, 0.19 mol) was added to decyl bromide (39.05 ml, 0.19 mol). The reaction was carried out for 20 h at 50 °C to give the product (55.03 g, 97%). ^1H NMR (DMSO-d_6): δ = 9.24 (s, 1H, N-CH=N), 7.82 (t, J = 1.90Hz, 1H, N-CH=C), 7.75 (t, J = 1.90Hz, 1H, C=CH-N), 4.16 (t, J = 6.95Hz, 2H, N-CH_2-), 3.86 (s, 3H, N-CH_3), 1.76 (quint, J = 6.95Hz, 2H, -CH_2-), 1.23 (s, 14H, (-CH_2-)$_7$), 0.84 (t, J = 6.95Hz, 3H, -CH_3). MS ES^+ (m/z) = 223{$[DecMIM]^+$}. IR (cm^{-1}) = 3420, 3077, 2932, 1578, 1464, 1169, 756, 620. ^{13}C NMR (DMSO-d_6): Positive peaks: δ =

48.66(N-CH_2-), 31.22(-CH_2-), 29.33(-CH_2-), 28.84(-CH_2-), 28.77(-CH_2-), 28.61(-CH_2-), 28.32(-CH_2-), 25.42(-CH_2-), 22.04(-CH_2-). Negative peaks: δ = 123.52(N-CH=C), 122.19(C=CH-N), 35.70(N-CH_3), 13.91(-CH_3).

2.3.6 1-Butyl-2,3-dimethylimidazolium chloride {$[BMMIM]^+Cl^-$}

1,2-Dimethylimidazole (10 g, 0.1 mol) was mixed with 2-chlorobutane (12 ml, 0.11 mol). The mixture was stirred at 80 °C for 24 h. The crude product was further recrystallized in acetonitrile/ether. The product was dried under vacuum overnight. The yield was 12.65 g (65%). Mp: 78-81 °C. ^{1}H NMR (DMSO-d_6): δ = 7.71 (d, J=1.90Hz, 1H, N-CH=C), 7.69 (d, J = 1.90Hz, 1H, C=CH-N), 4.12 (t, J = 7.58Hz, 2H, N-CH_2-), 3.76 (s, 3H, N-CH_3), 2.59 (s, 3H, C-CH_3), 1.69 (quint, J = 7.58Hz, 2H, N-CH_2-C**H_2**-), 1.28 (sext, J = 7.58Hz, 2H, N-CH_2CH_2-C**H_2**-), 0.91 (t, J = 7.58Hz, 3H, N-$CH_2CH_2CH_2$-C**H_3**). MS ES^+ (m/z) = 153{$[BMMIM]^+$}. IR (cm^{-1}) = 3402, 3068, 2967, 1591, 1543, 1472, 1253, 1138, 752. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 144.15(N-C=N), 47.18(N-CH_2-), 31.16(N-CH_2-**CH_2**-), 18.81(N-CH_2CH_2-**CH_2**-). Negative peaks: δ = 122.25(N-CH=C), 120.83(C=CH-N), 34.61(N-CH_3), 13.36(C-CH_3), 9.13(N-$CH_2CH_2CH_2$-**CH_3**).

2.3.7 1-Phenoxypropyl -2,3-dimethylimidazolium bromide {$[PhOPMMIM]^+Br^-$}

1,2-Dimethylimidazole (2.87 g, 0.03 mol) was added to 3-phenoxypropyl bromide (5 ml, 0.03 mol). The mixture was stirred at 60 °C for 1 h. Acetonitrile (10 ml) was then added to the reaction mixture and the mixture was stirred for 6 h at 60 °C. After that, the mixture was poured into cold diethyl ether (30 ml) in an ice bath. The product precipitated out as a white solid, which was dried overnight. The yield was 8.21 g (89%). Mp: 120-122 °C. ^{1}H NMR (DMSO-d_6): δ = 7.70 (m, 1H, N-CH=C), 7.65 (m, 1H, C=CH-N), 7.30 (t, J = 7.58Hz, 2H, Ph), 7.02-6.88 (m, 3H, Ph), 4.31 (t, J = 6.95Hz, 2H, N-CH_2-), 4.00 (t, J = 6.32Hz, 2H, -CH_2-O), 3.75 (s, 3H, N-CH_3), 2.57 (s, 3H, C-CH_3), 2.20 (quint, J = 6.32Hz, 2H, -CH_2-). MS ES^+ (m/z) = 231{$[PhOPMMIM]^+$}.

IR (cm^{-1}) = 3423, 3047, 2945, 1593, 1539, 1473, 1247, 1176, 1047, 945, 755, 688. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 157.99(Ph), 144.42(N-C=N), 63.90(-CH_2-O), 44.77(N-CH_2-), 28.65(-CH_2-). Negative peaks: δ = 129.49(Ph), 122.33(N-CH=C), 120.92(C=CH-N), 120.73(Ph), 114.31(Ph), 34.66(N-CH_3), 9.13(C-CH_3).

2.3.8 1-Undecyl -2,3-dimethylimidazolium bromide {[DecMMIM]$^+$Br$^-$}

1,2-Dimethylimidazole (14.19 g, 0.15 mol) and decyl bromide (50 ml, 0.24 mol) were mixed. The mixture was stirred at 60 °C for 3-5 h. The resulting product was further recrystallized in acetonitrile/ether and dried under vacuum overnight. The yield was 23.49g (51%). Mp: 78-80 °C. ^1H NMR (DMSO-d_6): δ = 7.76 (dd, J = 2.05Hz, J = 2.37, 2H, N-CH=CH-N), 4.16 (t, J = 7.27Hz, 2H, N-CH_2-), 3.80 (s, 3H, N-CH_3), 2.63 (s, 3H, C-CH_3), 1.81-1.59 (m, 2H, -CH_2-), 1.23 (s, 14H, (-CH_2-)$_7$), 0.83 (t, J = 6.95Hz, 3H, -CH_3). MS ES$^+$ (m/z) = 237{[DecMMIM]$^+$}. IR (cm^{-1}) = 3425, 3051, 2923, 1546, 1468, 812. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 144.06(N-C=N), 47.33(N-CH_2-), 31.16(-CH_2-), 29.16(-CH_2-), 28.82(-CH_2-), 28.78(-CH_2-), 28.57(-CH_2-), 28.42(-CH_2-), 25.45(-CH_2-), 21.97(-CH_2-). Negative peaks: δ = 122.13(N-CH=CH-N), 120.73(N-CH=CH-N), 34.67(N-CH_3), 13.80(-CH_3), 9.36(C-CH_3).

2.3.9 1-Ethoxy-ethyl-3-butyl-imidazolium chloride {[EtOEtBuIM]$^+$Cl$^-$}

1-Butylimidazole (7 ml, 0.05 mol) was added to 2-chloroethyl ethyl ether (11 ml, 0.1 mol). The reaction was carried out at 80 °C for 48 h. The resulting viscous liquid was washed with ethyl acetate (2 × 7 ml) and dried in a high vacuum for 4 h at 60 °C to give a yellowish and viscous ionic liquid. The yield was 11.52 g (95%). ^1H NMR (DMSO-d_6): δ =9.55 (s, 1H, N-CH=N), 7.92 (m, 1H, N-CH=C), 7.88 (m, 1H, C=CH-N), 4.39 (t, J = 5.05Hz, 2H, N-CH_2-CH_2O), 4.24 (t, J = 6.95Hz, 2H N-C**H$_2$**-CH_2CH_2), 3.72 (t, J = 5.05Hz, 2H, -CH_2O), 3.43 (q, J = 6.95Hz, 3H, O-CH_2), 1.77 (quint, J = 7.58Hz, 2H, N-CH_2-C**H$_2$**-CH_2), 1.22 (sext, J = 7.58Hz, 2H, N-CH_2CH_2-C**H$_2$**-), 1.04 (t, J = 6.95Hz, 3H, OCH_2-CH_3), 0.88 (t, J = 7.58Hz, 3H,

N-$CH_2CH_2CH_2$-CH_3). MS ES^+ (m/z) = 197{$[EtOEtBuIM]^+$}. IR (cm^{-1}) = 3393, 2964, 1565, 1461, 1375, 1171, 1119, 755, 660. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 136.50(N-CH=N), 67.39(N-CH_2-CH_2-O), 65.37(O-CH_2-CH_3), 48.70(N-CH_2-CH_2-O), 48.33(N-CH_2-CH_2CH_2), 31.29(N-CH_2-CH_2-CH_2), 18.61(N-CH_2CH_2-CH_2-). Negative peaks: δ = 122.65(N-CH=C), 122.19(C=CH-N), 14.77(O-CH_2-CH_3), 13.17(N-$CH_2CH_2CH_2$-CH_3).

2.3.10 1-Phenoxypropyl-3-butylimidazolium bromide {$[PhOPBuIM]^+Br^-$}

A similar method was followed as described for the synthesis of $[EtOEtBuIM]^+Cl^-$ (2.3.9). 1-butylimidazole (4 ml, 0.03 mol) was reacted with 1-phenoxypropyl bromide (4.75 ml, 0.03 mol) at 50 °C for 15 h to afford the product (10.02 g, 97%). ^1H NMR (DMSO-d_6): δ =9.37 (s, 1H, N-CH=N), 7.89 (m, 1H, N-CH=C), 7.86 (m, 1H, C=CH-N), 7.28 (t, J = 7.58Hz, 2H, Ph), 7.01-6.84 (m, 3H, Ph), 4.38 (t, J = 6.95Hz, 2H, N-CH_2-CH_2CH_2-O), 4.17 (t, J = 6.95Hz, 2H, N-CH_2-CH_2CH_2), 4.00 (t, J = 6.32Hz, 2H, CH_2CH_2-CH_2-O), 2.29 (quint, J = 6.32Hz, 2H, CH_2-CH_2-CH_2O), 1.74 (quint, J = 7.58Hz, 2H, CH_2-CH_2-CH_2CH_3), 1.21 (sext, J = 7.58Hz, 2H, CH_2CH_2-CH_2-CH_3), 0.86 (t, J = 6.95Hz, 3H, $CH_2CH_2CH_2$-CH_3). MS ES^+ (m/z) = 259{$[PhOPBuIM]^+$}. IR (cm^{-1}) = 3436, 3067, 2958, 1601, 1565, 1492, 1242, 1169, 755. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 158.05(Ph), 64.34(N-CH_2CH_2-CH_2-O), 48.47(N-CH_2-CH_2CH_2-O), 46.45(N-CH_2-CH_2-CH_2-O), 31.21(N-CH_2-CH_2CH_2), 28.86(N-CH_2-CH_2-CH_2), 18.70(N-CH_2CH_2-CH_2-). Negative peaks: δ = 129.41(Ph), 122.54(N-CH=C), 122.36(C=CH-N), 120.68(Ph), 114.29(Ph), 13.21(N-$CH_2CH_2CH_2$-CH_3).

2.3.11 1,4-Bis(3-methylimidazolium)butane bromide {[Bis(MIM)butane] Br_2}

1-Methylimidazole (7 ml, 0.09 mol) and 1,4-dibromobutane (5.2 ml, 0.05 mol) were mixed together at a molar ratio of 2:1. The mixture was stirred at 60 °C for 20 h. The resulting product was recrystallized in acetonitrile/ether and dried under vacuum overnight to give a white solid. The yield was 14.34 g (85%). Mp: 55-60 °C. ^1H NMR

(DMSO-d_6): δ =9.30 (s, 2H, N-CH=N), 7.84 (m, 2H, N-CH=C), 7.75 (m, 2H, C=CH-N), 4.32-4.20 (m, 4H, N-CH_2), 3.87 (s, 6 H, -CH_3), 1.86-1.72 (m, 4H, -CH_2-CH_2-). MS ES^+ (m/z) = 299{[Bis(MIM)butane] Br}. IR (cm^{-1}) = 3459, 3068, 2045, 1632, 1577, 1559, 1454, 1372, 1232, 1168, 1150, 854, 786, 559. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 136.53(N-CH=N), 47.79(N-CH_2), 25.93(-CH_2-CH_2-). Negative peaks: δ = 123.54(N-CH=C), 122.15(C=CH-N), 35.74(-CH_3).

2.3.12 1-Undecyl-3-methylbenzimidazole bromide {[DecMBzIM]$^+$Br$^-$}

1-Methylbenzimidazole (5 g, 0.04 mol) and decyl bromide (20 ml, 0.09 mol) was mixed together and stirred at 50 °C for 20 h. The resulting crude product was recrystallized in acetonitrile/ether and then dried under vacuum overnight. The yield was 6.96 g (53%). Mp: 68-69 °C. ^1H NMR (DMSO-d_6): δ =9.82 (s, 1H, N-CH=N), 8.16-7.99 (m, 2H, Ph), 7.76-7.67 (m, 2H, Ph), 4.50 (t, J = 7.27Hz, 2H, N-CH_2-), 4.09 (s, 3 H, N-CH_3), 1.97-1.81 (m, 2H, -CH_2-), 1.40-1.14 (m, 14H, (-CH_2-)$_7$), 0.84 (t, J = 6.79Hz, 3H, -CH_3). MS ES^+ (m/z) = 273{[DecMBzIM]$^+$}. IR (cm^{-1}) = 3427, 3368, 2966, 1627, 1595, 1524, 1376, 1161, 1130, 821, 767, 593, 463. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 131.73(Ph), 130.88(Ph), 46.45(-CH_2-), 31.18(-CH_2-), 28.81(-CH_2-), 28.75(-CH_2-), 28.58(-CH_2-), 28.55(-CH_2-), 28.39(-CH_2-), 25.64(-CH_2-), 22.00(-CH_2-). Negative peaks: δ = 126.36(Ph), 113.53(Ph), 113.45(Ph), 33.18(N-CH_3), 13.88(-CH_3).

2.3.13 1-Butyl-3-methylimidazolium tetrafluoroborate {[BMIM]$^+$[BF_4]$^-$}

Method 1

Reaction of 1-butyl-3-methylimidazolium chloride with HBF_4

1-Butyl-3-methylimidazolium chloride [BMIM]$^+$Cl$^-$ (2.3.1) (151.97 g, 0.9 mol) produced in the previous step was dissolved in water (20 ml). Tetrafluoroboric acid (126 ml, 1 mol) was added dropwise to the solution of [BMIM]$^+$Cl$^-$ with stirring in an

ice bath. The mixture was stirred at room temperature for 24 h. The resulting $[BMIM]^+[BF_4]^-$ was extracted with chilled dichloromethane (6 × 20 ml), and then the dichloromethane fraction was washed with water (6 × 10 ml) until the aqueous fraction pH became neutral. The dichloromethane was removed by rotary evaporation. After that, the crude ionic liquid was mixed with charcoal (2g) and the mixture was stirred for 24 h at room temperature. The charcoal was filtered off. The product $[BMIM]^+[BF_4]^-$ was kept in the high vacuum for 3 h. $[BMIM]^+[BF_4]^-$ was a colorless viscous liquid (Lancaster etc al., 2001). The yield was 135.88 g (69%). ^1H NMR (DMSO-d_6): δ =9.07 (s, 1H, N-CH=N), 7.75 (m, 1H, N-CH=C), 7.68 (m, 1H, C=CH-N), 4.17 (t, J = 6.96, 2H, N-CH_2-), 3.86 (s, 3H, N-CH_3), 1.78 (quint, J = 7.74, 2H, N-CH_2-C**H**$_2$-), 1.27 (sext, J = 7.60, 2H, N-CH_2CH_2-C**H**$_2$-), 0.91 (t, J = 7.74, 3H, -CH_3). MS ES^+ (m/z) = 139{$[BMIM]^+$}. IR (cm^{-1}) = 3636, 3159, 2962, 1573, 1465, 1079, 1043, 849, 751, 625. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 136.34(N-CH=N), 48.47(N-CH_2-), 31.29(N-CH_2-**C**H_2-), 18.79(N-CH_2CH_2-**C**H_2-). Negative peaks: δ = 123.52(N-CH=C), 122.18(C=CH-N), 35.62(N-CH_3), 13.16(N-$CH_2CH_2CH_2$-**C**H_3).

Method 2

Reaction of 1-butyl-3-methylimidazolium chloride with $AgBF_4$

A solution of $AgBF_4$ (9 g, 0.05 mol) in methanol (15 ml) was added dropwise to a solution of $[BMIM]^+Cl^-$ (2.3.1) (8 g, 0.05 mol) in methanol (10 ml) with stirring in an ice bath. The mixture was stirred for 1 h at room temperature. AgCl was filtered off and methanol was removed by rotary evaporation at 50 °C. The product $[BMIM]^+[BF_4]^-$ was kept in the high vacuum at 60 °C for 3 h to give a colorless viscous liquid (Wikes and Zaworotko, 1992). The yield was 9.94 g (96%). ^1H NMR (DMSO-d_6): δ = 9.09 (s, 1H, N-CH=N), 7.76 (t, J = 1.90Hz, 1H, N-CH=C), 7.69 (t, J = 1.90Hz, 1H, C=CH-N), 4.16 (t, J = 6.95Hz, 2H, N-CH_2-), 3.84 (s, 3H, N-CH_3), 1.76 (quint, J = 7.58Hz, 2H, N-CH_2-C**H**$_2$-), 1.25 (sext, J = 7.58Hz, 2H, N-CH_2CH_2-C**H**$_2$-), 0.90 (t, J = 6.95Hz, 3H, -CH_3). MS ES^+ (m/z) = 139{$[BMIM]^+$}. IR (cm^{-1}) = 3640, 3164, 2962, 1573, 1465, 1079, 1052, 854, 755, 625. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 136.35(N-CH=N), 48.47(N-CH_2-), 31.28(N-CH_2-**C**H_2-),

18.79(N-CH_2CH_2-CH_2-). Negative peaks: δ = 123.54(N-CH=C), 122.19(C=CH-N), 35.62(N-CH_3), 13.16(N-$CH_2CH_2CH_2$-CH_3).

2.3.14 1-Butyl-3-methylimidazolium Hexafluorophosphate {$[BMIM]^+[PF_6]^-$}

$[BMIM]^+Cl^-$ (2.3.1) (17.6 g, 0.1 mol) was dissolved in H_2O (20 ml). KPF_6 (18.6 g, 0.1 mol) was dissolved in H_2O (50 ml). The solution of KPF_6 was added dropwise to $[BMIM]^+Cl^-$ under vigorous stirring. The mixture was stirred at room temperature for 2 h. After that, a two-phase system was formed and $[BMIM]^+[PF_6]^-$ in lower layer was washed with water (3 × 10 ml). The product $[BMIM]^+[PF_6]^-$ was kept in the high vacuum at 60 °C for 3 h. The yield was 21.45 g (75%). ^1H NMR (DMSO-d_6): δ = 9.07 (s, 1H, N-CH=N), 7.73 (m, 1H, N-CH=C), 7.66 (m, 1H, C=CH-N), 4.17 (t, J = 7.15, 2H, N-CH_2-), 3.86 (s, 3H, N-CH_3), 1.79 (quint, J = 7.71, 2H, N-CH_2-CH_2-), 1.28 (sext, J = 7.40, 2H, N-CH_2CH_2-CH_2-), 0.91 (t, J = 7.22, 3H, -CH_3). MS ES^+ (m/z) = 139{$[BMIM]^+$}. IR (cm^{-1}) = 3673, 3173, 2964, 1573, 1464, 1168, 882, 832, 745, 627. IR (cm^{-1}) = 3640, 3164, 2962, 1573, 1465, 1079, 1052, 854, 755, 625. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 136.40(N-CH=N), 48.49(N-CH_2-), 31.26(N-CH_2-CH_2-), 18.69(N-CH_2CH_2-CH_2-). Negative peaks: δ = 123.48(N-CH=C), 122.12(C=CH-N), 35.57(N-CH_3), 13.09(N-$CH_2CH_2CH_2$-CH_3).

2.3.15 1-Butyl-3-methylimidazolium trifluoroacetate {$[BMIM]^+[CF_3COO]^-$}

A solution of $[BMIM]^+Cl^-$ (2.3.1) (20.32 g, 0.12 mol) in acetonitrile was mixed with a solution of sodium trifluoroacetate (15.82 g, 0.12 mol) in acetonitrile/acetone (1:1). The mixture was stirred for 4 h. The precipitate (NaCl) was filtered off through celite and the solvent was removed. Dichloromethane (20 ml) was added into the product and the solution was filtered off again. Dichloromethane was removed and the product was kept in high vacuum at 60 °C for 3 h (Kumar et al., 2007). The yield was 23.18 g (79%). ^1H NMR (DMSO-d_6): δ = 9.35 (s, 1H, N-CH=N), 7.85 (t, J = 1.90Hz, 1H, N-CH=C), 7.77 (t, 1H, J = 1.90Hz,C=CH-N), 4.18 (t, J = 7.58Hz, 2H, N-CH_2-), 3.87

(s, 3H, N-CH_3), 1.76 (quint, J = 7.58Hz, 2H, N-CH_2-C**H**$_2$-), 1.24 (sext, J = 7.58Hz, 2H, N-CH_2CH_2-C**H**$_2$-), 0.88 (t, J = 7.58Hz, 3H, -CH_3). MS ES^+ (m/z) = 139{$[BMIM]^+$}. IR (cm^{-1}) = 3434, 3092, 2961, 1698, 1571, 1466, 1409, 1202, 1163, 1119, 825, 795, 716, 624. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 48.42(N-CH_2-), 31.38(N-CH_2-**C**H_2-), 18.72(N-CH_2CH_2-**C**H_2-). Negative peaks: δ = 123.59(N-CH=C), 122.29(C=CH-N), 35.58(N-CH_3), 13.13(N-$CH_2CH_2CH_2$-**C**H_3).

2.3.16 1-Butyl-3-methylimidazolium trifluoromethanesulfonate {$[BMIM]^+[CF_3SO_3]^-$}

A solution of $[BMIM]^+Cl^-$ (2.3.1) (10.1 g, 0.06 mol) in acetonitrile was added a solution of sodium trifluoromethanesulfate (9.95 g, 0.06 mol) in acetone. The reaction was continued for 4 h. After that, the white precipitate (NaCl) was filtered off through celite and the solvent was removed to afford the product as a viscous liquid (11.62g, 71%). ^1H NMR (DMSO-d_6): δ = 9.09 (s, 1H, N-CH=N), 7.76 (t, J = 1.90Hz, 1H, N-CH=C), 7.69 (t, 1H, J = 1.90Hz,C=CH-N), 4.16 (t, J = 6.95Hz, 2H, N-CH_2-), 3.85 (s, 3H, N-CH_3), 1.76 (quint, J = 7.58Hz, 2H, N-CH_2-C**H**$_2$-), 1.25 (sext, J = 7.58Hz, 2H, N-CH_2CH_2-C**H**$_2$-), 0.89 (t, J = 7.58Hz, 3H, -CH_3). MS ES^+ (m/z) = 139{$[BMIM]^+$}. IR (cm^{-1}) = 3551, 3116, 2966, 1576, 1465, 1266, 1163, 1030, 760, 640. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 136.63(N-CH=N), 48.32(N-CH_2-), 31.32(N-CH_2-**C**H_2-), 18.68(N-CH_2CH_2-**C**H_2-). Negative peaks: δ = 123.51(N-CH=C), 122.20(C=CH-N), 35.59(N-CH_3), 13.62(N-$CH_2CH_2CH_2$-**C**H_3).

2.3.17 1-Butyl-3-methylimidazolium heptafluorobutyrate {$[BMIM]^+[CF_3CF_2CF_2COO]^-$}

Silver heptafluorobutyrate (5 g, 0.16 mol) and $[BMIM]^+Cl^-$ (2.3.1) (2.72 g, 0.16 mol) was dissolved in water respectively. The two solutions were mixed together and stirred for 4 h. The resulting white precipitate (AgCl) was filtered off and the filtrate was consentrated to give a viscous liquid (4.53 g, 83%). ^1H NMR (DMSO-d_6): δ = 9.44 (s, 1H, N-CH=N), 7.87 (t, J = 1.90Hz, 1H, N-CH=C), 7.79 (t, 1H, J = 1.90Hz,C=CH-N), 4.19 (t, J = 6.95Hz, 2H, N-CH_2-), 3.87 (s, 3H, N-CH_3), 1.76 (quint,

J = 7.58Hz, 2H, N-CH_2-CH_2-), 1.23 (sext, J = 7.58Hz, 2H, N-CH_2CH_2-CH_2-), 0.88 (t, J = 7.58Hz, 3H, -CH_3). MS ES^+ (m/z) = 139{$[BMIM]^+$}. IR (cm^{-1}) = 3411, 3101, 2971, 1690, 1465, 1330, 1222, 1168, 957, 746. ^{13}C NMR (DMSO-d_6): Positive peaks: 136.63(N-CH=N), 48.32(N-CH_2-), 31.32(N-CH_2-CH_2-), 18.68(N-CH_2CH_2-CH_2-). δ = Negative peaks: δ = 123.51(N-CH=C), 122.20(C=CH-N), 35.59(N-CH_3), 13.62(N-$CH_2CH_2CH_2$-CH_3).

2.3.18 1-Methoxyethyl-3-methylimidazolium trifluoroacetate {$[MeOEtMIM]^+[CF_3COO]^-$}

A solution of $[MeOEtMIM]^+Cl^-$ (2.3.2) (36.06 g, 0.2 mol) in acetonitrile was added to a solution of sodium trifluoroacetate (27.76 g, 0.2 mol) in acetone. The reaction was continued for 4 h. After that, the white solid NaCl was filtered off and the solvent was removed by rotary evaporation. The product was dissolved in dichloromethane (30 ml) and filtered through celite again. Dichloromethane was removed by rotary evaporation and the product was kept in high vacuum for 3 h at 60 °C (Kumar et al., 2007). The yield was 43.07 g (83%). 1-methoxyethyl-3-methylimidazolium trifluoroacetate was a yellowish and viscous liquid. ^1H NMR (DMSO-d_6): δ = 9.22 (s, 1H, N-CH=N), 7.78 (t, J = 1.90Hz, 1H, N-CH=C), 7.74 (t, J = 1.90Hz, 1H, C=CH-N), 4.37 (t, J = 5.05Hz, 2H, N-CH_2-), 3.88 (s, 3H, N-CH_3), 3.69 (t, J = 5.05Hz, 2H, -CH_2-O), 3.26 (s, 3H, O-CH_3). MS ES^+ (m/z) = 141{$[MeOEtMIM]^+$}. IR (cm^{-1}) = 3436, 3086, 1695, 1682, 1573, 1454, 1404, 1191, 1123, 823, 800, 718, 623. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 136.87(N-CH=N), 69.54(N-CH_2-), 48.54(-CH_2-O). Negative peaks: δ = 123.42(N-CH=C), 122.58(C=CH-N), 57.96(O-CH_3), 35.65(N-CH_3).

2.3.19 1-Methoxyethyl-3-methylimidazolium methanesulfonate {$[MeOEtMIM]^+[CH_3SO_3]^-$}

2-methoxy methanesulfonate

Methanesulfonyl chloride (32 ml, 0.41 mol) was added dropwise (over 1 h) to a solution of 1-methoxy ethanol (32 ml, 0.41 mol) and triethylamine (57 ml, 0.41 mol) in dichloromethane (100 ml). The mixture was stirred for further 4 h in an ice bath at

room temperature. The white solid triethylammonium chloride was filtered off, and the filtrate was washed with water and dried with $MgSO_4$. Dichloromethane was removed by rotary evaporation to give the desired product as a colorless liquid. 2-Methoxy methanesulfonate was further purified by distillation (Cassol et al., 2006). The yield was 49.95 g (80%). ^{1}H NMR (DMSO-d_6): δ = 4.35-4.29 (m, 2H, CH_2), 3.63-3.57 (m, 2H, CH_2), 3.30 (s, 3H, CH_3), 3.19 (s, 3H, CH_3). IR (cm^{-1}) = 2947, 1354, 1174, 1130, 1021, 977, 923, 809. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 69.50(O-CH_2-), 69.32(-CH_2-S). Negative peaks: δ = 58.00(O-CH_3), 36.64(-CH_3-S).

1-methoxy-3-methylimidazolium methanesulfonate

2-Methoxy methanesulfonate (12.73 g, 0.08 mol) was mixed with 1-methylimidazole (6.57 ml, 0.08 mol). Then the reaction mixture was stirred for 2 days at 60 °C. The resulting liquid was washed twice with ethyl acetate and kept in the high vacuum at 60 °C for 3 h. 1-methoxy-3methylimidazolium methanesulfonate was obtained as colorless and very hygroscopic liquid (Cassol et al., 2006). The yield was 17.72g (91%) ^{1}H NMR (DMSO-d_6): δ = 9.21 (s, 1H, N-CH=N), 7.79 (t, J = 1.90Hz, 1H, N-CH=C), 7.57 (t, J = 1.90Hz, 1H, C=CH-N), 4.37 (t, J = 5.05Hz, 2H, N-CH_2-), 3.88 (s, 3H, N-CH_3), 3.68 (t, J = 5.05Hz, 2H, -CH_2-O), 3.25 (s, 3H, O-CH_3), 2.36 (s, 3H, CH_3SO_3). MS ES^+ (m/z) = 141{$[MeOEtMIM]^+$}. IR (cm^{-1}) = 3452, 3100, 1648, 1574, 1457, 1339, 1217, 1174, 1122, 1044, 835, 774. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 136.98(N-CH=N), 69.60(N-CH_2-), 48.50(-CH_2-O). Negative peaks: δ = 123.46(N-CH=C), 122.61(C=CH-N), 57.98(O-CH_3), 39.76(S-CH_3), 35.66(N-CH_3).

2.3.20 1-Methoxyethyl-3-methylimidazolium trifluomethanesulfonate {$[MeOEtMIM]^+[CF_3SO_3]^-$}

A similar method was followed as described for the synthesis of $[MeOEtMIM]^+[CF_3COO]^-$ (2.3.18). $[MeOEtMIM]^+Cl^-$ (2.3.2) (6.93 g, 0.04 mol) was reacted with CF_3SO_3Na (6.75 g, 0.04 mol) to give the product (8.92 g, 79%). ^{1}H NMR (DMSO-d_6): δ = 9.10 (s, 1H, N-CH=N), 7.75 (t, J = 1.90Hz, 1H, N-CH=C), 7.70 (t, J = 1.90Hz, 1H, C=CH-N), 4.35 (t, J = 5.21Hz, 2H, N-CH_2-), 3.86 (s, 3H, N-CH_3), 3.67 (t, J = 5.05Hz, 2H, -CH_2-O), 3.26 (s, 3H, O-CH_3). MS ES^+ (m/z) =

141{[MeOEtMIM]$^+$}. IR (cm^{-1}) = 3565, 3112, 2943, 2899, 1572, 1452, 1266, 1163, 1030, 835, 755. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 136.76(N-CH=N), 69.52(N-CH_2-), 48.59(-CH_2-O). Negative peaks: δ = 123.41(N-CH=C), 122.56(C=CH-N), 57.98(N-CH_3), 35.68(O-CH_3).

2.3.21 1-Methoxyethyl-3-butylimidazolium bis((trifluoromethyl)sulfonyl)amide {[MeOEtMIM]$^+$[$(CF_3SO_2)_2N$]$^-$}

A similar method was used for the synthesis of [MeOEtMIM]$^+$[CF_3COO]$^-$ (2.3.18). [MeOEtMIM]$^+Cl^-$ (2.3.2) (6.15 g, 0.04 mol) was reacted with Li$(CF_3SO_2)_2N$ (10 g, 0.04 mol) to give the product (11.3 g, 77%). The product was washed with water. ^1H NMR (DMSO-d_6): δ =9.09 (s, 1H, N-CH=N), 7.72 (t, J = 1.90Hz, 1H, N-CH=C), 7.69 (t, J = 1.90Hz, 1H, C=CH-N), 4.35 (t, J = 5.05Hz, 2H, N-CH_2-), 3.86 (s, 3H, N-CH_3), 3.68 (t, J = 5.05Hz, 2H, -CH_2-O), 3.27 (s, 3H, O-CH_3). MS ES^+ (m/z) = 141{[MeOEtMIM]$^+$}. IR (cm^{-1}) = 3162, 2943, 2904, 1571, 1343, 1189, 1058, 742, 615. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 136.75(N-CH=N), 69.52(N-CH_2-), 48.59(-CH_2-O). Negative peaks: δ = 123.40(N-CH=C), 122.56(C=CH-N), 57.97(O-CH_3), 35.67(N-CH_3).

2.3.22 1-Phenoxypropyl-3-methylimidazolium pentafluoropropionate {[PhOPMIM]$^+$[CF_3CF_2COO]$^-$}

Silver pentafluoropropionate (13 g, 0.05 mol) was dissolved in water (15 ml) and 1-(phenoxy propyl)-3-methyl bromide (2.3.3) (14 g, 0.05 mol) in acetonitrile (20 ml). Two solutions were mixed together and stirred for 4 h. After that, the precipitate (AgBr) was filtered off and all the solvent was evaporated in high vacuum to give yellowish liquid (16.06 g, 90%). ^1H NMR (DMSO-d_6): δ = 9.22 (s, 1H, N-CH=N), 7.83 (t, J = 1.90Hz 1H, N-CH=C), 7.73 (t, J = 1.20Hz,1H, C=CH-N), 7.29 (t, J = 7.58Hz, 2H, Ph), 7.02-6.86 (m, 3H, Ph), 4.36 (t, J = 6.95Hz, 2H, N-CH_2-), 4.01 (t, J = 6.32Hz, 2H, -CH_2-O), 3.84 (s, 3H, N-CH_3), 2.27 (quint, J = 6.32Hz, 2H, -CH_2-). MS ES^+ (m/z) = 217{[PhOPMIM]$^+$}. IR (cm^{-1}) = 3430, 3097, 1689, 1601, 1496, 1321, 1211, 1159, 1023, 808, 760, 729. ^{13}C NMR (DMSO-d_6): Positive peaks: δ =

158.10(Ph), 64.28(-CH_2-O), 46.37(N-CH_2-), 29.01(-CH_2-). Negative peaks: δ = 129.46(Ph), 123.55(N-CH=C), 122.42(C=CH-N), 120.71(Ph), 114.32(Ph), 35.64(N-CH_3).

2.3.23 1-Phenoxypropyl-3-methylimidazolium trifluoromethanesulfonate {$[PhOPMIM]^+[CF_3SO_3]^-$}

A similar method was used for the synthesis of $[MeOEtMIM]^+[CF_3COO]^-$ (2.3.18). $[PhOPMIM]^+Br^-$ (2.3.3) (17.05 g, 0.06 mol) was reacted with $NaCF_3SO_3$ (9.87 g, 0.06 mol) to give the product (15.75 g, 75%). Mp: 60-62°C. ^{1}H NMR (DMSO-d_6): δ = 9.13 (s, 1H, N-CH=N), 7.79 (t, J = 1.58Hz, 1H, N-CH=C), 7.69 (t, J = 1.58Hz,1H, C=CH-N), 7.29 (t, J = 7.11Hz, 2H, Ph), 7.00-6.87 (m, 3H, Ph), 4.36 (t, J = 6.95Hz, 2H, N-CH_2-), 4.02 (t, J = 6.00Hz, 2H, -CH_2-O), 3.85 (s, 3H, N-CH_3), 2.27 (quint, J = 6.48Hz, 2H, -CH_2-). MS ES^+ (m/z) = 217{$[PhOPMIM]^+$}. IR (cm^{-1}) = 3593, 3152, 3126, 3087, 2961, 1603, 1581, 1495, 1473, 1265, 1162, 1032, 945, 751, 638. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 158.13(Ph), 64.28(-CH_2-O), 46.43(N-CH_2-), 28.98(-CH_2-). Negative peaks: δ = 129.47(Ph), 123.52(N-CH=C), 122.39(C=CH-N), 120.73(Ph), 114.33(Ph), 35.64(N-CH_3).

2.3.24 1-Methoxymethoxyethyl-3-methylimidazolium trifluoroacetate {$[MeOMeOEtMIM]^+[CF_3COO]^-$}

A similar method was followed as described for the synthesis of $[MeOEtMIM]^+[CF_3COO]^-$ (2.3.18). $[MeOMeOEtMIM]^+Br^-$ (7 g, 0.03 mol) (2.3.4) was reacted with CF_3COONa (4.80 g, 0.03 mol) to give the product (7.23 g, 81%). ^{1}H NMR (DMSO-d_6): δ = 9.25 (s, 1H, N-CH=N), 7.82 (t, J = 1.90Hz, 1H, N-CH=C), 7.76 (t, J = 1.90Hz, 1H, C=CH-N), 4.56-4.54 (m, 2H, O-CH_2-OCH_3), 4.40 (t, J = 5.05Hz, 2H, N-CH_2-), 3.88 (s, 3H, N-CH_3), 3.81 (t, J = 5.05Hz, 2H, -CH_2-O), 3.16-3.15 (m, 3H, O-CH_3). MS ES^+ (m/z) = 171{$[MeOMeOEtMIM]^+$}. IR (cm^{-1}) = 3429, 3087, 2953, 1694, 1429, 1173, 1047, 831, 724. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 95.50(O-CH_2-O), 64.93(CH_2-CH_2-O), 48.87(N-CH_2). Negative peaks: δ = 123.47(N-CH=C), 122.55(C=CH-N), 54.72(O-CH_3), 35.68(N-CH_3).

2.3.25 1-(1-Methylbenzyl)-3-methylimidazolium bromide {$[MPhMIM]^+[CF_3COO]^-$}

1-Methyl imidazole (3 ml, 0.04 mol) was reacted with α-methylbenzyl bromide (6 ml, 0.04 mol) at 50 °C for 2-3 h. The yield of $[MPhMIM]^+Br^-$ was 9 g (92%). Following that, a similar method was used as for $[MeOEtMIM]^+[CF_3COO]^-$ (2.3.18). $[MPhMIM]^+Br^-$ (8.32 g, 0.03 mol) was reacted with CF_3COONa (4.24 g, 0.03 mol) to afford the ionic liquid $[MPhMIM]^+[CF_3COO]^-$ (7.14 g, 77%). ^1H NMR (DMSO-d_6): δ = 9.41 (s, 1H, N-CH=N), 7.89 (t, J = 1.58Hz, 1H, N-CH=C), 7.75 (t, J = 1.58Hz, 1H, C=CH-N), 7.48-7.36 (m, 5H, Ph), 5.80 (q, J = 7 .11Hz, 1H, -CH-), 3.85 (s, 3H, $-CH_3$), 1.86 (d, J = 7.11Hz, 3H, $-CH_3$). MS ES^+ (m/z) = 187{$[MPhMIM]^+$}. IR (cm^{-1}) = 3430, 3071, 1688, 1457, 1423, 1213, 1171, 1124, 807, 717. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 139.51(Ph). Negative peaks: δ = 128.92(Ph), 128.62(Ph), 126.51(Ph), 123.94(N-CH=C), 120.08(C=CH-N), 58.43(N-**C**H-CH_3), 38.42(N-CH_3), 20.41(CH-**C**H_3).

2.3.26 1-Butyl-2,3-dimethylimidazolium trifluoroacetate {$[BMMIM]^+[CF_3COO]^-$}

A similar method was followed as described for the synthesis of $[MeOEtMIM]^+[CF_3COO]^-$ (2.3.18). $[BMMIM]^+Cl^-$ (2.3.6) (5.37 g, 0.03 mol) was reacted with CF_3COONa (3.87 g, 0.03 mol) to afford the product (7.12 g, 94%). ^1H NMR (DMSO-d_6): δ = 7.68 (m, 1H, N-CH=C), 7.66 (m, 1H, 1H, C=CH-N), 4.11 (t, J = 6.95Hz, 2H, N-CH_2-), 3.75 (s, 3H, N-CH_3), 2.58 (s, 3H, , C-CH_3), 1.68 (quint, J = 7.58Hz, 2H, N-CH_2-C**H**$_2$-), 1.28 (sext, J = 7.58Hz, 2H, N-CH_2CH_2-C**H**$_2$-), 0.90 (t, J = 6.95Hz, 3H, $-CH_3$). MS ES^+ (m/z) = 153{$[BMMIM]^+$}. IR (KBr, cm^{-1}) = 3443, 2967, 1697, 1540, 1464, 1423, 1203, 1172, 1123, 826, 799, 719. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 47.21(N-CH_2-), 31.16(N-CH_2-**C**H_2-), 18.83(N-CH_2CH_2-**C**H_2-). Negative peaks: δ = 34.58(N-CH_3), 13.35(C-CH_3), 9.05(N-$CH_2CH_2CH_2$-**C**H_3).

2.3.27 1-Phenoxypropyl -2,3-dimethylimidazolium heptafluorobutyrate {$[PhOPMMIM]^+[CF_3CF_2CF_2COO]^-$}

1-Phenoxypropyl-2,3-dimethylimidazolium bromide (2.3.7) (4.7 g, 0.02 mol) dissolved in acetonitrile (10 ml) was mixed with silver heptafluorobutyrate (5 g, 0.02 mol) dissolved in acetone (20 ml). After the 3 h, a little water was added to the mixture. The resulting precipitate (AgBr) was filtered off and the solvent was removed. The neat ionic liquid was filtered off again to give the product (5.23 g, 78%). ^{1}H NMR (DMSO-d_6): δ = 7.70 (m, 1H, N-CH=C), 7.65 (m, 1H, C=CH-N), 7.30 (t, J = 7.58Hz, 2H, Ph), 7.02-6.88 (m, 3H, Ph), 4.31 (t, J = 6.95Hz, 2H, N-CH_2-), 4.00 (t, J = 6.32Hz, 2H, -CH_2-O), 3.75 (s, 3H, N-CH_3), 2.57 (s, 3H, C-CH_3), 2.20 (quint, J = 6.32Hz, 2H, -CH_2-). MS ES$^+$ (m/z) = 231{$[PhOPMMIM]^+$}. IR (cm^{-1}) = 3449, 3130, 3094, 1696, 1496, 1328, 1199, 968, 755. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 158.03(Ph), 144.45(N-C=N), 63.90(-CH_2-O), 44.77(N-CH_2-), 28.66(-CH_2-). Negative peaks: δ = 129.46(Ph), 122.36(N-CH=C), 120.93(C=CH-N), 120.71(Ph), 114.30(Ph), 34.58(N-CH_3), 9.01(C-CH_3).

2.3.28 1-Undecyl -2, 3-dimethylimidazolium trifluoroacetate {$[DecMMIM]^+[CF_3COO]^-$}

A similar method was followed as described for the synthesis of $[MeOEtMIM]^+[CF_3COO]^-$ (2.3.18). $[DecMMIM]^+Cl^-$ (2.3.8) (15.76 g, 0.05 mol) was reacted with CF_3COONa (6.76 g, 0.05 mol) to give the product (10.97 g, 64%). ^{1}H NMR (DMSO-d_6): δ = 7.71 (d, J = 1.90Hz, 2H, N-CH=CH-N), 7.69 (d, J = 1.90Hz, 2H, N-CH=CH-N), 4.11 (t, J = 7.27Hz, 2H, N-CH_2-), 3.76 (s, 3H, N-CH_3), 2.59 (s, 3H, C-CH_3), 1.77-1.60 (m, 2H, -CH_2-), 1.39-1.10 (m, 14H, (-CH_2-)$_7$), 0.84 (t, J = 6.95Hz, 3H, -CH_3). MS ES$^+$ (m/z) = 237{$[DecMMIM]^+$}. IR (KBr, cm^{-1}) = 3414, 3046, 2927, 1691, 1542, 1469, 1204, 1174, 1127, 802, 725, 665. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 144.14(N-C=N), 47.40(N-CH_2-), 31.22(-CH_2-), 29.17(-CH_2-), 28.86(-CH_2-), 28.83(-CH_2-), 28.62(-CH_2-), 28.45(-CH_2-), 25.51(-CH_2-), 22.05(-CH_2-). Negative peaks: δ = 122.23(N-CH=CH-N), 120.81(N-CH=CH-N), 34.60(N-CH_3), 13.86(-CH_3), 9.13(C-CH_3).

2.3.29 1-Undecyl-2,3-dimethylimidazolium trifluoromethanesulfonate {[DecMMIM]$^+$[CF_3SO_3]$^-$}

A similar method was used for the synthesis of [MeOEtMIM]$^+$[CF_3COO]$^-$ (2.3.18). [DecMMIM]$^+$$Cl^-$ (2.3.8) (7.73 g, 0.02 mol) was reacted with CF_3SO_3Na (4.2 g, 0.02 mol) to give the product (6.49 g, 69%). ^{1}H NMR (DMSO-d_6): δ = 7.65 (d, J = 2.21Hz, 1H, N-CH=CH-N), 7.61 (d, J = 2.05Hz, 1H, N-CH=CH-N), 4.09 (t, J = 7.27Hz, 2H, N-CH_2-), 3.74 (s, 3H, N-CH_3), 2.57 (s, 3H, C-CH_3), 1.76-1.62 (m, 2H, -CH_2-), 0.90 (s, 14H, (-CH_2-)$_7$), 0.81 (t, J = 6.95Hz, 3H, -CH_3). MS ES$^+$ (m/z) = 237{[DecMMIM]$^+$}. IR (cm^{-1}) = 3426, 2966, 1539, 1464, 1197, 1048. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 144.16(N-C=N), 47.41(N-CH_2-), 31.22(-CH_2-), 29.13(-CH_2-), 28.85(-CH_2-), 28.83(-CH_2-), 28.62(-CH_2-), 28.43(-CH_2-), 25.53(-CH_2-), 22.05(-CH_2-). Negative peaks: δ = 122.22(N-CH=CH-N), 120.78(N-CH=CH-N), 34.59(N-CH_3), 13.91(-CH_3), 9.05(C-CH_3).

2.3.30 1-Ethoxy-ethyl-3-butylimidazolium pentafluoropropionate {[EtOEtBuIM]$^+$[CF_3CF_2COO]$^-$}

A solution of 1-ethoxy-ethyl-3-butyl-imidazolium chloride (2.3.9) (11.30 g, 0.05 mol) in acetonitrile (20 ml) was mixed with a solution of silver pentafluoropropionate (13.20 g, 0.05 mol) in acetone (30 ml). The mixture was stirred for 3 h. After that, AgCl was filtered off. The product was yellowish and viscous liquid. The yield was 8.75 g (52%). ^{1}H NMR (DMSO-d_6): δ = 9.27 (s, 1H, N-CH=N), 7.84 (t, J = 1.90Hz,1H, N-CH=C), 7.80 (t, J = 1.90Hz, 1H, C=CH-N), 4.36 (t, J = 5.05Hz, 2H, N-C**H$_2$**-CH_2O), 4.21 (t, J = 6.95Hz, 2H N-C**H$_2$**-CH_2CH_2), 3.72 (t, J = 5.05Hz, 2H, -CH_2O), 3.44 (q, J = 6.95Hz, 3H, O-CH_2), 1.77 (quint, J = 7.58Hz, 2H, CH_2-C**H$_2$**-CH_2), 1.23 (sext, J = 7.58Hz, 2H, CH_2-C**H$_2$**-CH_3), 1.06 (t, J = 6.95Hz, 3H, OCH_2-C**H$_3$**), 0.89 (t, J = 7.58Hz, 3H, CH_2CH_2-C**H$_3$**). MS ES$^+$ (m/z) = 197{[EtOEtBuIM]$^+$}. IR (cm^{-1}) = 3469, 3092, 2972, 1684, 1325, 1209, 1162, 1021, 803, 725. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 136.42(N-CH=N), 67.39(N-CH_2-**C**H_2-O), 65.42(O-**C**H_2-CH_3), 48.82(N-**C**H_2-CH_2-O), 46.58(N-**C**H_2-$CH_2CH_2CH_3$), 31.31(N-CH_2-**C**H_2-CH_2CH_3), 18.64(N-CH_2CH_2-**C**H_2

-CH_3). Negative peaks: δ = 122.71(N-CH=C), 122.24(C=CH-N), 14.72(O-CH_2-**C**H_3), 13.11(N-$CH_2CH_2CH_2$-**C**H_3).

2.3.31 1-Ethoxy-ethyl-3-butylimidazolium trifluoroacetate {$[EtOEtBuIM]^+[CF_3COO]^-$}

A similar method was followed as described for the synthesis of $[MeOEtMIM]^+[CF_3COO]^-$ (2.3.17). $[EtOEtBuIM]^+Cl^-$ (2.3.9) (4.46 g, 0.02 mol) was reacted with CF_3COONa (2.61 g, 0.02 mol). The product was yellow viscous liquid and the yield was 3.86 g (65%). ^1H NMR (DMSO-d_6): δ = 9.55 (s, 1 H, N-CH=N), 7.96 (m, 1H, N-CH=C), 7.89 (m, 1H, C=CH-N), 4.42 (t, J = 4.90Hz, 2H, N-C**H**$_2$-CH_2O), 4.26 (t, J = 7.11Hz, 2H N-C**H**$_2$-CH_2CH_2), 3.72 (t, J = 4.90Hz, 2H, -CH_2O), 3.41 (q, J = 6.95Hz, 3H, O-CH_2), 1.76 (quint, J = 7.11Hz, 2H, CH_2-C**H**$_2$-CH_2), 1.21 (sext, J = 7.27Hz, 2H, CH_2-C**H**$_2$-CH_3), 1.01 (t, J = 7.11Hz, 3H, OCH_2-C**H**$_3$), 0.84 (t, J = 7.27Hz, 3H, CH_2CH_2-C**H**$_3$). MS ES^+ (m/z) = 197{$[EtOEtBuMIM]^+$}. IR (cm^{-1}) = 3445, 3089, 2966, 1688, 1380, 1200, 1169, 1125, 822, 800, 712. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 136.86(N-CH=N), 67.54(N-CH_2-**C**H_2-O), 65.50(O-**C**H_2-CH_3), 48.99(N-**C**H_2-CH_2-O), 48.51(N-**C**H_2-$CH_2CH_2CH_3$), 31.56(N-CH_2-**C**H_2-CH_2CH_3), 18.69(N-CH_2CH_2-**C**H_2 -CH_3). Negative peaks: δ = 122.82(N-CH=C), 122.41(C=CH-N), 14.57(O-CH_2-**C**H_3), 12.96(N-$CH_2CH_2CH_2$-**C**H_3).

2.3.32 1-Phenoxypropyl-3-butylimidazolium trifluoroacetate {$[PhOPBuIM]^+[CF_3COO]^-$}

A similar method was followed as described for the synthesis of $[MeOEtMIM]^+[CF_3COO]^-$ (2.3.18) . $[PhOPBuIM]^+Br^-$ (2.3.10) (11.40 g, 0.03 mol) was reacted with CF_3COONa (4.6 g, 0.03 mol) to give the product (8.63 g, 69%). ^1H NMR (DMSO-d_6): δ = 9.34 (m, 1H, N-CH=N), 7.88 (m, 1H, N-CH=C), 7.85 (m, 1H, C=CH-N), 7.28 (t, J = 7.58Hz, 2H, Ph), 6.99-6.86 (m, 3H, Ph), 4.37 (t, J = 6.95Hz, 2H, N-C**H**$_2$-CH_2CH_2O), 4.16 (t, J = 6.95Hz, 2H, N-C**H**$_2$-CH_2CH_2), 4.00 (t, J = 6.32Hz, 2H, CH_2CH_2-C**H**$_2$-O), 2.29 (quint, J = 6.32Hz, 2H, CH_2-C**H**$_2$-CH_2O), 1.74 (quint, J =

7.58Hz, 2H, CH_2-C**H**$_2$-CH_2CH_3), 1.22 (sext, J = 7.58Hz, 2H, CH_2CH_2-C**H**$_2$-CH_3), 0.87 (t, J = 6.95Hz, 3H, $CH_2CH_2CH_2$-C**H**$_3$). MS ES^+ (m/z) = 259{$[PhOPBuIM]^+$}. IR (cm^{-1}) = 3428, 3086, 2960, 1682, 1600, 1496, 1201, 1167, 1124, 825, 799, 755. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 158.09(Ph), 64.34(N-CH_2-**C**H_2-O), 48.50(N-**C**H_2-CH_2O), 46.49(N-**C**H_2-$CH_2CH_2CH_3$), 31.24(N-**C**H_2-$CH_2CH_2CH_3$), 28.87(N-CH_2-**C**H_2-CH_2CH_3), 18.72(N-CH_2CH_2-**C**H_2-CH_3). Negative peaks: δ = 129.43(Ph), 122.58(N-CH=C), 122.41(C=CH-N), 120.71(Ph), 114.30(Ph), 13.19(N-$CH_2CH_2CH_2$-**C**H_3).

2.3.33 1-Methoxy-3-butylimidazolium trifluoromethanesulfonate {$[MeOEtBuMIM]^+[CF_3SO_3]^-$}

1-Butylimidazol (10 ml, 0.08 mol) was added to 2-chloroethyl methyl ether (20 ml, 0.22 mol). The reaction was stirred at 80 °C for 28 h. The resulting viscous liquid was washed with ethyl acetate (2 × 10 ml) and dried in a high vacuum for 4 h at 80 °C to give $[MeOEtBuMIM]^+Cl^-$ 6.73 g (42%). Following that, a similar method was used as for $[MeOEtMIM]^+[CF_3COO]^-$ (2.3.18). $[MeOEtBuMIM]^+$ Cl^- (6.7 g, 0.03 mol) was reacted with CF_3COONa (5.3 g, 0.03 mol) to give the product (6.75 g, 66%). ^1H NMR (DMSO-d_6): δ = 9.14 (t, J = 1.42Hz, 1H, N-CH=N), 7.78 (t, J = 1.74Hz, 1H, N-CH=C), 7.74 (t, J = 1.74Hz, 1H, C=CH-N), 4.37 (t, J = 4.74Hz, 2H, N-C**H**$_2$-CH_2O), 4.20 (t, J = 7.27Hz, 2H, N-C**H**$_2$-CH_2CH_2), 3.70 (t, J = 4.74Hz, 2H, -CH_2O), 3.26 (s, 3H, O-CH_3), 1.78 (quint, J = 7.27Hz, 2H, CH_2-C**H**$_2$-CH_2), 1.25 (sext, J = 7.58Hz, 2H, CH_2-C**H**$_2$-CH_3), 0.89 (t, J = 7.58, 3H, CH_2CH_2-C**H**$_3$). MS ES^+ (m/z) = 183{$[MeOEtBuMIM]^+$}. IR (cm^{-1}) = 3559, 3114, 2971, 1564, 1461, 1263, 1159, 1029, 836, 755, 638. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 69.50(N-CH_2-**C**H_2-O), 48.74(N-**C**H_2-CH_2-O), 48.65(N-**C**H_2-$CH_2CH_2CH_3$), 31.38(N-CH_2-**C**H_2-CH_2CH_3), 18.74(N-CH_2CH_2-**C**H_2-CH_3). Negative peaks: δ = 122.76(N-CH=C), 122.22(C=CH-N), 57.94(O-CH_2-**C**H_3), 13.06(N-$CH_2CH_2CH_2$-**C**H_3).

2.3.34 1,4-Bis(3-methylimidazolium)butane trifluoroacetate {Bis(MIM)butane $[CF_3COO]_2$}

1,4-Bis(3-methylimidazolium)butane bromide (2.3.11) (7.05 g, 0.02 mol) was dissolved in the solution (25 ml) of methanol and acetonitrile (1:5). Sodium trifluoacetate (5.05 g, 0.04 mol) was dissolved in acetone (15 ml). Two solutions were mixed together and stirred for 3 h. The precipitate (NaBr) was filtered off. The filtrate was concentrated under rotary evaporation. The neat ionic liquid was filtered off again to remove the further precipitated NaBr and kept in high vacuum for 2 h. The product was yellowish and very viscous liquid. After 4-5 days, the liquid product was changed to a solid. The yield was 6.04 g (73%). Mp: 66°C-68°C. ^{1}H NMR (DMSO-d_6): δ = 9.26 (s, 2H, N-CH=N), 7.81 (t, J = 1.74Hz, 2H, N-CH=C), 7.74 (t, J = 1.74Hz, 2H, C=CH-N), 4.34-4.15 (m, 4H, N-CH_2), 3.87 (s, 6H, -CH_3), 1.89-1.71 (m, 4H, -CH_2-CH_2-). MS ES^+ (m/z) = 333{Bis(MIM)butane $[CF_3COO]$}. IR (KBr, cm^{-1}) = 3458, 3072, 1688, 1428, 1211, 1172, 1133, 834, 799, 721.^{13}C NMR (DMSO-d_6): Positive peaks: δ = 136.63(N-CH=N), 47.84(N-CH_2), 25.56(-CH_2-CH_2-). Negative peaks: δ = 123.61(N-CH=C), 122.19(C=CH-N), 35.70(-CH_3).

2.3.35 1-decyl-3-methylbenzimidazole trifluoromethanesulfonate $\{[DecMBzIM]^+[CF_3SO_3]^-\}$

A similar method was used for the synthesis of $[MeOEtMIM]^+[CF_3COO]^-$ (2.3.18). $[DecMBzIM]^+Br^-$ (2.3.12) (6.96 g, 0.02 mol) was reacted with CF_3SO_3Na (3.39 g, 0.02 mol) to give the product (6.19 g, 75%). Mp: 66-68 °C. ^{1}H NMR (DMSO-d_6): δ = 9.71 (s, 1H N-CH=N), 8.16-7.99 (m, 2H, Ph), 7.75-7.67 (m, 2H, Ph), 4.48 (t, J = 7.27Hz, 2H, N-CH_2-), 4.07 (s, 3H, N-CH_3), 1.96-1.81 (m, 2H, -CH_2-), 1.39-1.15 (m, 14H, $(-CH_2-)_7$), 0.91-0.79 (m, 3H, -CH_3). MS ES^+ (m/z) = 273{$[DecMBzIM]^+$}. IR (cm^{-1}) = 3457, 3098, 2927, 1578, 1464, 1276, 1258, 1158, 1031, 759, 645. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 131.77(Ph), 130.90(Ph), 46.46(-CH_2-), 31.21(-CH_2-), 28.83(-CH_2-), 28.76(-CH_2-), 28.60(-CH_2-), 28.55(-CH_2-), 28.41(-CH_2-), 25.66(-CH_2-), 22.02(-CH_2-). Negative peaks: δ = 126.39(Ph), 113.52(Ph), 113.44(Ph), 33.16(N-CH_3), 13.89(-CH_3).

2.3.36 1-Undecyl-3-methylbenzimidazole heptafluorobutyrate {$[DecMBzIM]^+[CF_3CF_2CF_2COO]^-$}

$[DecMBzIM]^+[CF_3SO_3]^-$ (2.3.35) (6.19 g, 0.02 mol) was mixed with $CF_3CF_2CF_2COOAg$ (4.71 g, 0.02 mol) in water (20 ml). The reaction mixture was stirred for 3 h. The precipitate (CF_3SO_3Ag) was filtered off. Water was removed under high vacuum to give the product (4.92 g, 69%). ^{1}H-NMR (DMSO-d_6): δ = 9.73 (s, 1H N-CH=N), 8.15-7.99 (m, 2H, Ph), 7.76-7.65 (m, 2H, Ph), 4.48 (t, J = 7.27Hz, 2H, N-CH_2-), 4.07 (s, 3H, N-CH_3), 1.96-1.81 (m, 2H, -CH_2-), 1.38-1.15 (m, 14H, (-CH_2-)$_7$), 0.90-0.80 (m, 3H, -CH_3). MS ES^+ (m/z) = 273{$[DecMBzIM]^+$}. IR (KBr, cm^{-1}) = 3451, 3087, 2928, 1664, 1467, 1240, 1167, 1030, 760. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 131.78(Ph), 130.91(Ph), 46.46(-CH_2-), 31.21(-CH_2-), 28.83(-CH_2-), 28.76(-CH_2-), 28.60(-CH_2-), 28.56(-CH_2-), 28.41(-CH_2-), 25.66(-CH_2-), 22.03(-CH_2-). Negative peaks: δ = 126.39(Ph), 113.53(Ph), 113.45(Ph), 33.16(N-CH_3), 13.98(-CH_3).

Chapter 3

Preparation of Modified Thionucleobases and Thionucleosides using Room Temperature Ionic Liquids as Solvents and Catalysts

3.1 Introduction

3.1.1 Thionucleobases, thionucleosides and their derivatives

In 1951, Elion and co-workers (Elion et al., 1951) made a great effort in the synthesis of purine analogues and investigated these analogues for anti-tumor activities. One of these analogues was 6-mercaptopurine which was derived from hypoxanthine. Later, this compound was found to inhibit mouse tumour Sarcoma 180 by Clarke et al. (1953). 6-Thioguanine was prepared by Elion in 1954 which was found to exhibit similar activity against animal tumours as 6-mercaptopurine (Elion and Hitching, 1955). Burchena (1954) demonstrated that 6-mercaptopurine could cause good remissions in a very high percentage of patients with acute lymblastic leukaemia (ALL) with a dose of 2.5 mg/Kg of the body weight and 6-thioguanine and 6-chloropurine could also cause remissions in chronic myelocytic leukemia at non-toxic doses.

The successful work on the anti-tumor activity of 6-thiopurines has led to more intensive studies. Here, the studies related to the synthesis and investigation of modified thionucleobases and thionucleosides are the main focus as those studies are related to our work presented in this chapter. Clarke et al. (1958) examined a wide range of analogues of 6-mercaptopurine (6-MP) against Sarcoma 180 in 1958. Some 6-substituted mercaptopurines such as 6-methyl-mercaptopurine and 6-benzyl-mercaptopurine showed significant tumor inhibitory effects. The substitution on the mercapto group using halogen, cyano and carboxy were found to have some anti-tumor activity, but less active than 6-MP. Alkylation of 9-nitrogen of 6-MP

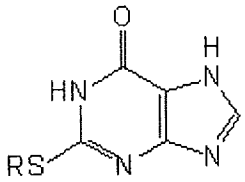
resulted in lower activity as well. In addition, 6-thioguanine was found to inhibit Sarcoma 180. 6-Methyl- and 6-benzyl thioguanine were also active against Sarcoma 180. However, the replacement of the 2-amino group of 6-thioguaine by alkylamino, arylamino, or heterocyclic amino groups lowered the inhibitory activity.

Skipper et al. (1959) investigated a series of derivatives of 6-mercaptopurine. It was found that 6-mercaptopurine, 6-benzyl-thiopurine and 6-methyl-thiopurine generated high activity against the growth of Adenocarcinoma 755. 6-Mercaptopurine riboside had higher therapeutic activity than 6-mercaptopurine. In contrast, 6-methyl-thiopurine riboside had lower therapeutic activity than 6-methyl-thiopurine. Moreover, 2,6-dimercaptopurine and 2-hydroxy-6-mercaptopurine showed some therapeutic effect, whereas 2-ethyl-6-mercaptopurine and 2-fluoro-6-mercaptopurine ribonucleoside were inactive even at a high tolerant dose. Long alkyl chain of S-substituted thiopurines generated a low inhibitory activity. However, two of the thio-substituted compounds, 6-naphthyl-thiopurine and 6-methoxycarbonyl-methyl-thiopurine showed no inhibitory activity and no toxicity at the highest possible level of the dose tested.

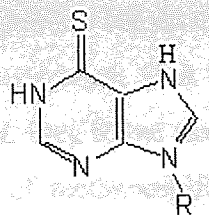
Furthermore, some 9-alkyl-6-thionucleobases were studied by several researchers. 9-Ethyl-mercaptopurine was found to inhibit adult chronic granulocytic leukemia (Johnson et al., 1962). This compound was also found to be as effective as 6-mercaptopurine in maintaining prednisone-induced remissions in childhood leukemia (Pierce et al., 1968). However, Nelson and Vidale (1986) studied the metabolism of 9-butyl-6-thioguanine (BTG), 9-butyl-6-mercaptopurine (BMP) and 9-ethyl-6-mercaptopurine (EMP) in mice. They suggested that the anti-tumor activity of these compounds was due to the dealkylation of BTG, BMP and EMP into TG or MP.

Recently, a significant work was reported by Elgemeie (2003). He synthesized a series of mercaptopurine and thioguanine analogues and their thionucleosides. 2-Thioalkylsubstituted purines (Figure 3.1) showed good inhibitory activity against xanthine enzyme. This enzyme could induce an inactive thiopurine metabolic pathway. 6-Mercapto-9-substituted purines showed active anti-L1210 leukaemia in BD2F1

mice (Figure 3.1). A range of derivatives of 6-alkyl-thiopurines and 9-alkyl-substituted-6-thiopurines was found to be active against adeno-carcinoma 755 or L1210 leukemia and some of derivatives against solid tumors (Kelley et al., 1989; Rao and Revankar, 1995).



R = $(CH_2)_3CH_3$, $(CH_2)_4CH_3$ or $(CH_2)_5CH_3$



R = $(CH_2)_3CH_3$, $(CH_2)_4CH_3$ or $(CH_2)_5CH_3$

Figure 3.1 2-Thioalkylsubstituted purines and 6-mercapto-9-substituted purines

Elgemeie (2003) also described that 6-mercaptopurine riboside and 6-methyl-thio-guanine riboside were effective initiators of maturation, which caused 50% of the cell population to undergo a differentiated phenotype. Angiogenesis was identified as a crucial target for anti-neoplastic therapy. 6-Mercaptopurine riboside and 6-methyl-mercaptopurine riboside were studied for the capability to inhibit angiogenesis *in vitro* and *in vivo*. 6-Methyl-mercaptopurine riboside inhibited the fibroblast growth factor-2 induced proliferation.

3.1.2 Nucleoside chemistry and ionic liquids

Nucleoside chemistry is an important research area in drug development. However, one of the big problems associated with the nucleoside chemistry is the poor solubility of these nucleoside compounds in the commonly used organic solvents. Thio-substituted nucleobase and nucleoside have the poor solubility in organic solvents as well. The conventional polar solvents such as DMF, DMSO and *N*-methylpyrrolidone (NMP) have been employed, but they are hazardous to the environment. Thus there is a need to develop alternative solvents and technologies for nucleoside chemistry due to the increasing need for protecting the environment. Good solubility of ionic liquids provides an opportunity to solve this problem.

In 2003, Uzagare et al. (2003) reported a successful work on the use of ionic liquids in nucleoside chemistry. They described an ionic liquid $[MeOEtMIM]^+[CH_3SO_3]^-$ which had a good solubility for nucleobases and nucleosides. In their study, they first explored the solubility of thymine in various ionic liquids (Figure 3.2). Unfortunately, thymine was not soluble in ionic liquids containing tetrafluoroborate and hexafluorophosphate anions. $[BMIM]^+Cl^-$ had a good solubility for thymine. However, this ionic liquid often exists as a hard solid at room temperature, so it is not suitable for nucleoside reactions at room temperature. Eventually, they found that thymine had a high solubility in the ionic liquids with the anion of methanesulfonate such as *N*-butyl pyridinium methanesulfonate $[Bpy]^+[CH_3SO_3]^-$, 1-ethyl-3-methyl imidazolium methanesulfonate $[EMIM]^+[CH_3SO_3]^-$ and *N*-ethyl pyridinium methanesulfonate $[Epy]^+[CH_3SO_3]^-$.

Figure 3.2 Comparison of the solubility of thymine in various ionic liquids (Uzagare et al., 2003)

Uzagare and co-workers (2003) further compared the solubility of 2'-deoxynucleosides in pyridine, DMF and $[MeOEtMIM]^+[CH_3SO_3]^-$. As shown in Figure 3.3, $[MeOEtMIM]^+[CH_3SO_3]^-$ exerted excellent solubility for 2'-deoxynucleosides compared with the classical organic solvents. They also carried out the acylation of 2'-deoxynucleosides with several acylating agents, such as acetic anhydride, benzoyl chloride or isobutyryl chloride, in the presence of 1-methylimidazole as a base and 4-dimethylaminopyridine (DMAP) as a catalyst in $[MeOEtMIM]^+[CH_3SO_3]^-$. High yields (over 90%) of the products were obtained.

Their results demonstrated that $[MeOEtMIM]^+[CH_3SO_3]^-$ could be a suitable solvent for nucleoside reactions.

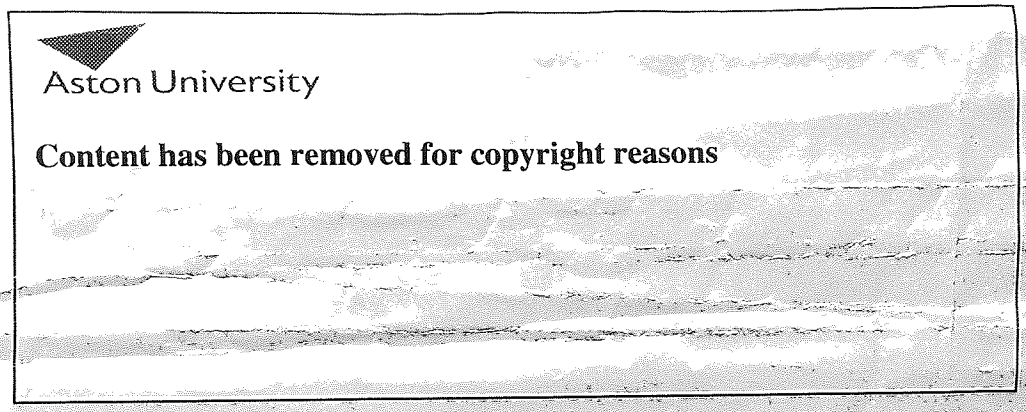
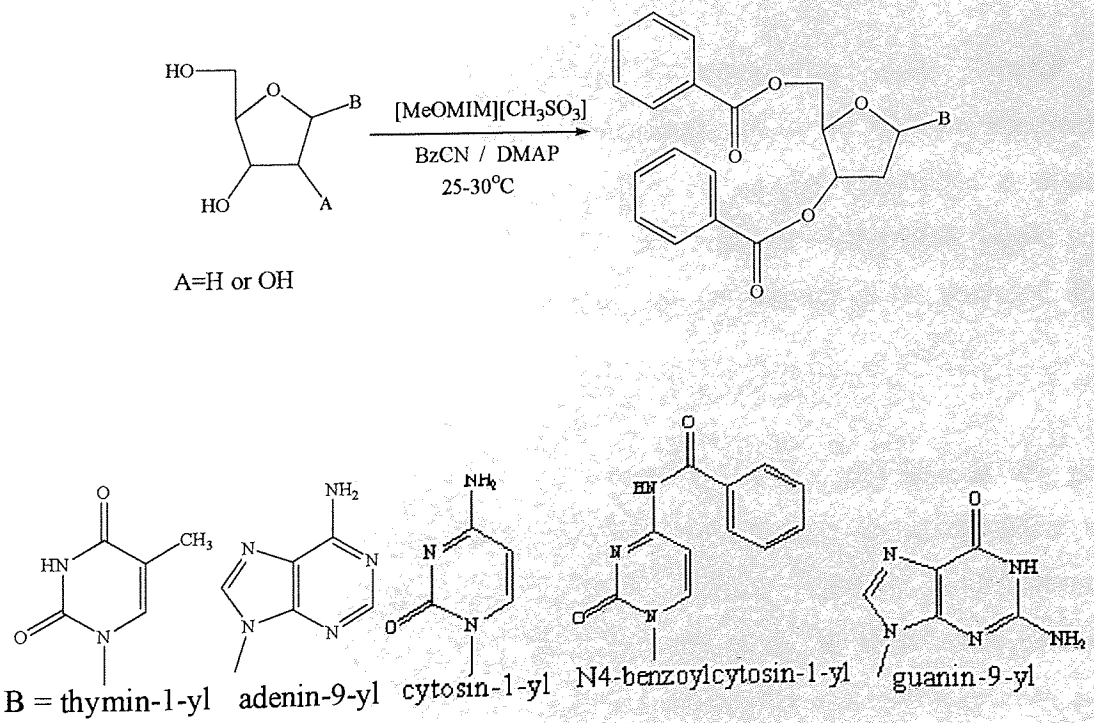


Figure 3.3 Comparison of the solubility of 2'-deoxynucleosides in pyridine, DMF and $[MeOEtMIM]^+[CH_3SO_3]^-$ (Uzagare et al., 2003)

Following Uzagare's work, Prasad et al. (2005) expanded the acylating reactions (Scheme 3.1) in $[MeOEtMIM]^+[CH_3SO_3]^-$.



Scheme 3.1 Benzoylation of nucleosides in $[MeOEtMIM]^+[CH_3SO_3]^-$

Good yields of products were achieved from benzoylation of adenosine, thymine and their corresponding deoxy formations in the presence of DMAP at 25-30 °C. Moderate yields were obtained from the reaction of guanosine and 2'-deoxyguanosine. For the benzoylation of cytidine or 2'-deoxycytidine, a small amount of perbenzoylated product (N_4-benzoylcytosin-1-yl) was produced, which indicated that benzoyl cyanide in the ionic liquids had the selectivity towards hydroxyl group. Moreover, they carried out benzoylation of 2'-deoxyadenosine under the same reaction conditions, but the reaction was not completed without DMAP even after 24 hours. They demonstrated that benzoyl cyanide was a good benzoylating agent and the reactions proceeded effectively in the ionic liquid $[MeOEtMIM]^+[CH_3SO_3]^-$.

In 2006, Kumar et al (2007) investigated the solubility of nucleosides in various ionic liquids mainly based on the cation of 1-methoxy-3-methyl-imidazole. In their research, ionic liquids showed good solubility for all the test nucleosides compared with common organic solvents such as pyridine and DMF. $[MeOEtMIM]^+[CH_3SO_3]^-$ achieved the best solubility, followed by $[Epy]^+[CF_3COO]^-$ and $[MeOEtMIM]^+[CF_3COO]^-$. However, $[MeOMIM]^+[BF_4]^-$ and $[MeOMIM]^+[PF_6]^-$ showed poor dissolving ability.

They further carried out benzoylation of nucleosides with DMAP in $[MeOEtMIM]^+[CH_3SO_3]^-$. The reactions were carried out at 50 °C for a reasonable time. The products were produced in good yields with a high selectivity. A slightly decreased yield of the product and loss of a small amount of the ionic liquid were observed when the benzoylation of adenosine was carried out in the recycled ionic liquid $[MeOEtMIM]^+[CH_3SO_3]^-$.

The successful studies described above demonstrate that ionic liquids are good reaction solvents for nucleoside chemistry. Benzoylation of nucleosides was successfully carried out in the ionic liquids. In addition, chemical modification of nucleobases and nucleosides could afford a wide range of their analogues and derivatives for therapeutic purposes. As 6-mercaptopurine and 6-thioguanine have been used as effective anti-cancer and anti-inflammatory drugs and the potential

therapeutic effects of thio-substituted nucleobase and nucleoside analogues have been investigated by other researchers (Elgemeie, 2003), it is worthwhile to explore a large range of modified thionucleobases and thionucleosides. Considering the advantages of using ionic liquids for nucleoside chemistry, we have, for the first time, synthesized modified thionucleobases and thionucleosides using various RTILs with the aim of developing anti-viral and anti-cancer agents.

3.2 Results and discussion

3.2.1 Solubility of thionucleobases in various RTILs

All the tested thionucleobases had a good solubility in DMSO, but they were not soluble in methanol, except 6-aza-2-thiothymine. Most thionucleobases were soluble in DMF, but 6-thioguanine and 2-mercaptopyrimidine had a poor solubility in DMF. 6-Thioguanine was not soluble in DMF even at a temperature of 70 °C (1mmol 6-thioguanine in 10-15 ml DMF).

Initially, 6-mercaptopurine, 6-thioguanine and 2-mercaptopyrimidine were chosen to test their solubility in a series of ionic liquids as they are more difficult to dissolve in traditional organic solvents than other thionucleobases or thionucleosides. The results are shown in Table 3.1(a), Table 3.1(b) and Table 3.2. Ionic liquids such as $[MeOEtMIM]^+[CF_3COO]^-$, $[MeOEtMIM]^+[CH_3SO_3]^-$ and $[BMIM]^+[CF_3COO]^-$ showed a good solubility for all the tested thionucleobases. Unfortunately, their solubility was poor in $[BMIM]^+[BF_4]^-$ and $[BMIM]^+[PF_6]^-$. $[PhOPMIM]^+[CF_3CF_2COO]^-$ had a poor solubility for 6-thioguanine, but this ionic liquid could dissolve 6-mercaptopurine and 2-mercaptopyrimidine. Therefore, the ionic liquids (Table 3.2), in which 6-thioguanine was insoluble, still could be used for other thionucleobases or thionucleosides.

Table 3.1(a) Solubility of 6-mercaptopurine in RTILs at room temperature

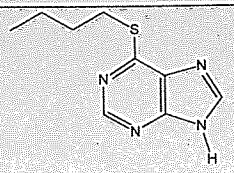
Thionucleobases / Reaction Solvent	 (1 mmol)
$[MeOEtMIM]^+[CF_3COO]^-$ (3 ml)	Soluble
$[BMIM]^+[CF_3COO]^-$ (3 ml)	Soluble
$[PhOPMIM]^+[CF_3CF_2COO]^-$ (3 ml)	Soluble
$[MeOEtMIM]^+[CH_3SO_3]^-$ (2 ml)	Soluble
$[BMIM]^+[BF_4]^-$ (5 ml)	Insoluble
$[BMIM]^+[PF_6]^-$ (5 ml)	Insoluble

Table 3.1(b) Solubility of 2-thiopyrimidine in RTILs

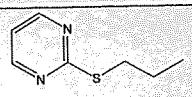
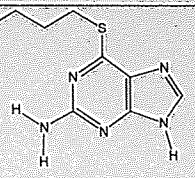
Thionucleobases / Reaction Solvent	 (1 mmol)	Temperature
$[MeOEtMIM]^+[CF_3COO]^-$ (7 ml)	Soluble	25 °C
$[MeOEtMIM]^+[CH_3SO_3]^-$ (7 ml)	Soluble	25 °C
$[BMIM]^+[CF_3COO]^-$ (5 ml)	Soluble	50 °C
$[PhOPMIM]^+[CF_3CF_2COO]^-$ (7 ml)	Soluble	50 °C
$[BMIM]^+[BF_4]^-$ (7 ml)	Insoluble	50 °C
$[BMIM]^+[PF_6]^-$ (7 ml)	Insoluble	50 °C

Table 3.2 Solubility of 6-thioguanine in RTILs

6-Thioguanine / Reaction Solvent	 (1 mmol)	Temperature
$[MeOEtMIM]^+[CF_3COO]^-$ (5 ml)	Soluble	50 °C
$[MeOMeOEtMIM]^+[CF_3COO]^-$ (5 ml)	Soluble	50 °C
$[BMIM]^+[CF_3COO]^-$ (5 ml)	Soluble	50 °C
$[EtOEtBuMIM]^+[CF_3COO]^-$ (7 ml)	Soluble	50 °C
$[MeOEtMIM]^+[CH_3SO_3]^-$ (5 ml)	Soluble	50 °C
$[PhOPMIM]^+[CF_3COO]^-$ (7 ml)	Soluble	70 °C
$[PhOPMIM]^+[CF_3CF_2COO]^-$ (7 ml)	Insoluble	70 °C
$[MeOEtMIM]^+[CF_3SO_3]^-$ (7 ml)	Insoluble	70 °C
$[MeOEtBuMIM]^+[CF_3SO_3]^-$ (7 ml)	Insoluble	70 °C
$[MeOEtMIM]^+[(CF_3SO_2)_2N]^-$ (7 ml)	Insoluble	70 °C
$[BMIM]^+[BF_4]^-$ (10 ml)	Insoluble	70 °C
$[BMIM]^+[PF_6]^-$ (10 ml)	Insoluble	70 °C

From the results, it also can be seen that the solubility of ionic liquids for the tested thionucleobases mainly depends on the type of anions, while cations have no significant effect. For example, with the same cation of $[MeOEtMIM]^+$, the ionic liquid $[MeOEtMIM]^+[CF_3COO]^-$ could dissolve 6-thioguanine, but $[MeOEtMIM]^+[CF_3SO_3]^-$ could not. Ionic liquids based on the anion of $[CF_3COO]^-$ or $[CH_3SO_3]^-$ have a good solubility. Therefore, two ionic liquids $[MeOEtMIM]^+[CH_3SO_3]^-$ and $[MeOEtMIM]^+[CF_3COO]^-$ were chosen as solvents for the following reactions involving thionucleobases and thionucleosides. All these thio-reagents were soluble in both of the two RTILs. Generally 1 mmol thionucleoside or base could be dissolved in 2-3 mL in either of the two ionic liquids. However, to dissolve 1 mmol 2-mercaptopyrimidine, 7 ml ionic liquid was required at room temperature. 6-Thioguanine was not soluble in both of the two RTILs at room temperature, but it was dissolved in 5 ml ionic liquid at 50 °C.

3.2.2 Preparation of modified thionucleobases and thionucleosides

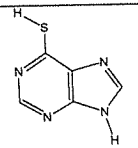
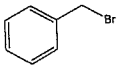
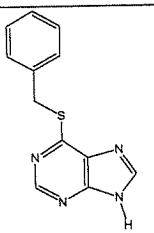
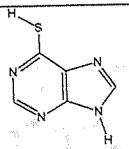
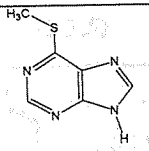
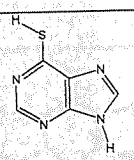
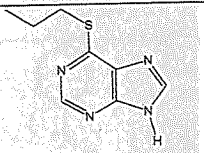
The synthetic approach was straightforward. Thiopurines or thiopyrimidines and haloalkanes were mixed in one of the chosen ionic liquids and stirred for an appropriate time. These reactions occurred easily in the ionic liquids at room temperature. The reaction schemes (Scheme 3.2) and results (Table 3.3) are summarized below.

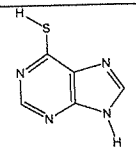
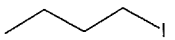
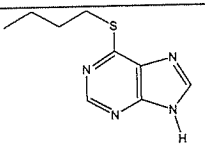
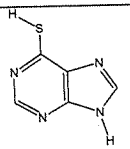
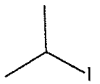
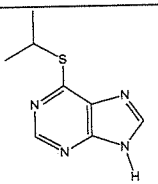
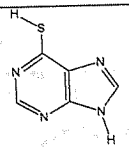
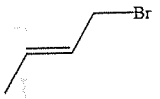
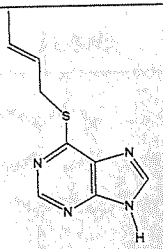
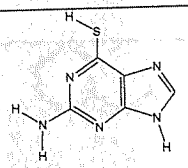
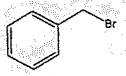
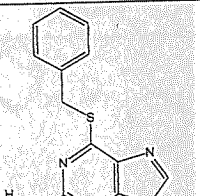
$$Y + RX \xrightarrow{\text{r.t.}} RY + X \ (X = Br, I)$$

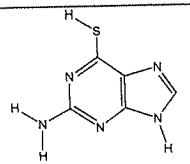
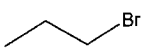
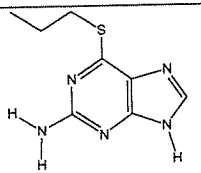
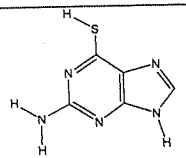
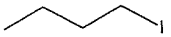
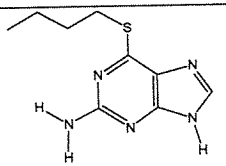
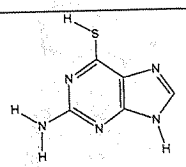
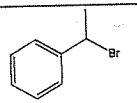
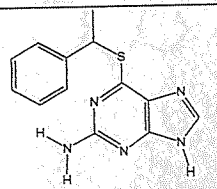
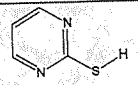
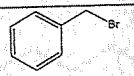
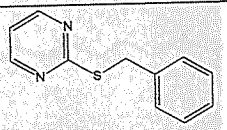
Scheme 3.2 Alkylation of thionucleobases and thionucleosides in $[MeOEtMIM]^+[CH_3SO_3]^-$ and $[MeOEtMIM]^+[CF_3COO]^-$

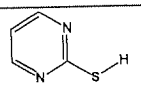
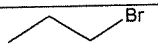
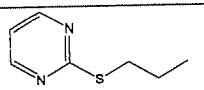
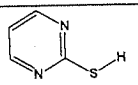
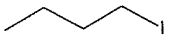
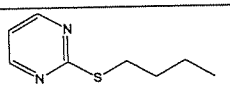
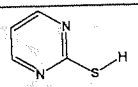
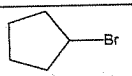
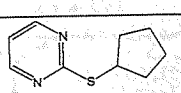
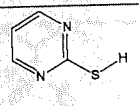
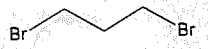
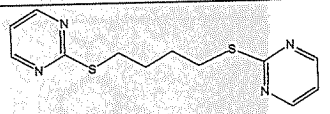
The results in Table 3.3 demonstrated that the reactions of thionucleobase or thionucleoside proceeded smoothly in the ionic liquids $[MeOEtMIM]^+[CF_3COO]^-$ and $[MeOEtMIM]^+[CH_3SO_3]^-$. High yields of the products were obtained. As expected, when the alkyl chain of haloalkanes increased, the longer reaction time was needed. The higher symmetry of alkyl halide (e.g. isopropyl iodide), the longer reaction time was required. Alkyl iodide was more reactive than alkyl bromide due to the nucleophilic order of halide ions. However, no products were obtained from the reaction of 2-methyl-2-iodo propane with thionucleobase, such as 6-mercaptopurine and 2-mercaptopyrimidine, after a relatively long reaction time of 2-3 days at an elevated temperature (50-60 °C).

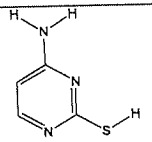
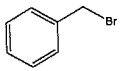
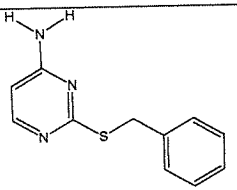
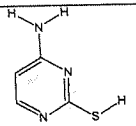
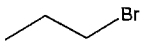
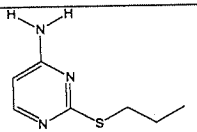
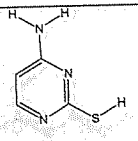
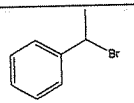
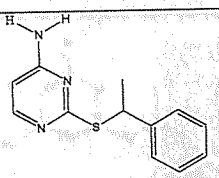
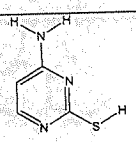
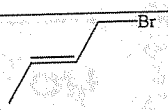
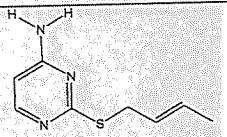
Table 3.3 Modification of thionucleobases and thionucleosides in $[MeOEtMIM]^+[CH_3SO_3]^-$ or $[MeOEtMIM]^+[CF_3COO]^-$

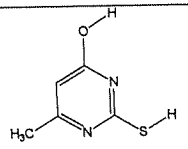
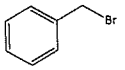
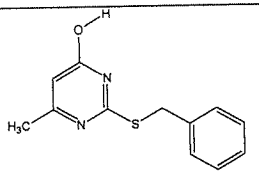
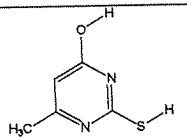
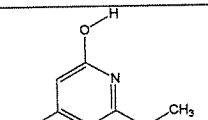
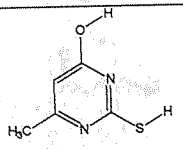
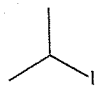
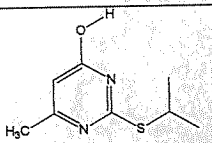
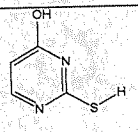
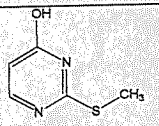
Entry	Y	RX	RY	NEt_3	Temperature	Time	Yield (%)	Solvent
1	 6-Mercaptopurine		 (3.3.1)	No	25 °C	30 min	94	$[MeOEtMIM]^+[CH_3SO_3]^-$
2		CH_3I	 (3.3.2)	Yes	25 °C	30 min	55	$[MeOEtMIM]^+[CH_3SO_3]^-$
3			 (3.3.3)	Yes	25 °C	3 h	83	$[MeOEtMIM]^+[CF_3COO]^-$

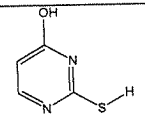
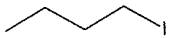
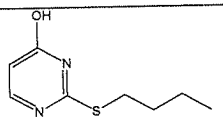
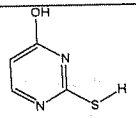
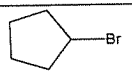
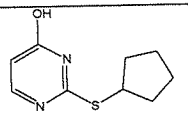
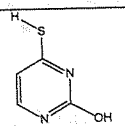
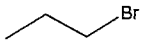
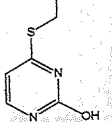
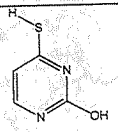
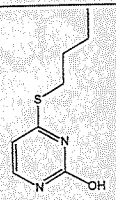
4			 (3.3.4)	Yes	25 °C	2 h	96	$[MeOEtMIM]^+[CF_3COO]^-$
5			 (3.3.5)	Yes	25 °C	3 h	76	$[MeOEtMIM]^+[CF_3COO]^-$
6			 (3.3.6)	Yes	25 °C	2.5 h	92	$[MeOEtMIM]^+[CF_3COO]^-$
7	 6-Thioguanine		 (3.3.7)	No	3 °C	30 min	88	$[MeOEtMIM]^+[CF_3COO]^-$

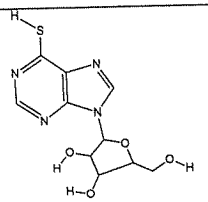
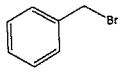
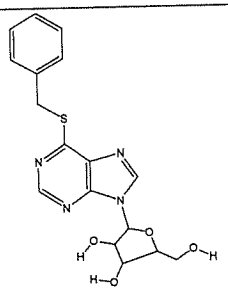
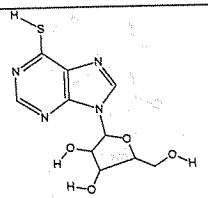
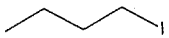
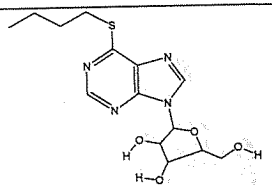
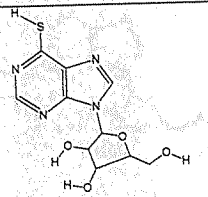
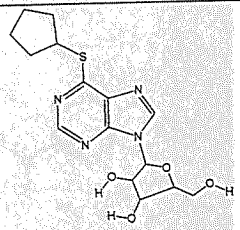
8			 (3.3.8)	Yes	25 °C	4 h	88	$[MeOEtMIM]^+[CF_3COO]^-$
9			 (3.3.9)	No	25 °C	6 h	93	$[MeOEtMIM]^+[CF_3COO]^-$
10			 (3.3.10)	Yes	25 °C	2.5 h	95	$[MeOEtMIM]^+[CF_3COO]^-$
11	 2-Mercaptopyrimidine		 (3.3.11)	No	25 °C	30 min	98	$[MeOEtMIM]^+[CF_3COO]^-$

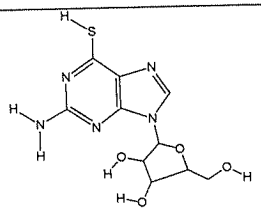
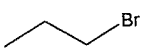
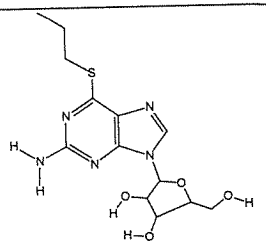
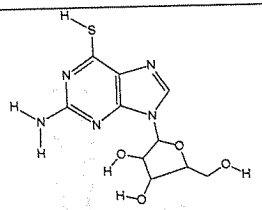
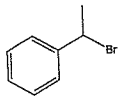
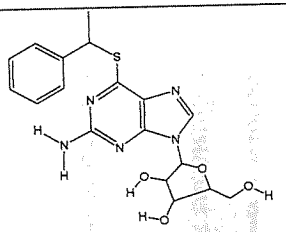
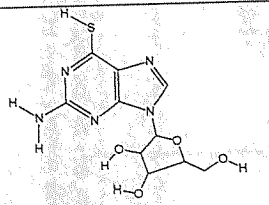
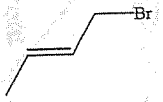
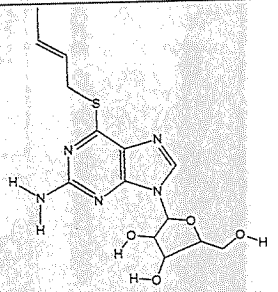
12			 (3.3.12)	No	25 °C	20 h	90	$[MeOEtMIM]^+[CF_3COO]^-$
13			 (3.3.13)	Yes	25 °C	2 h	75	$[MeOEtMIM]^+[CF_3COO]^-$
14			 (3.3.14)	Yes	25 °C	3 h	51	$[MeOEtMIM]^+[CF_3COO]^-$
15			 (3.3.15)	Yes	25 °C	48 h	83	$[MeOEtMIM]^+[CF_3COO]^-$

16	 2-Thiocytosine		 (3.3.16)	No	25 °C	30 min	98	$[MeOEtMIM]^+[CF_3COO]^-$
17			 (3.3.17)	Yes	25 °C	2.5 h	93	$[MeOEtMIM]^+[CF_3COO]^-$
18			 (3.3.18)	Yes	25 °C	2 h	91	$[MeOEtMIM]^+[CF_3COO]^-$
19			 (3.3.19)	Yes	25 °C	2 h	99	$[MeOEtMIM]^+[CF_3COO]^-$

20	 6-Aza-2-thiothymine		 (3.3.20)	No	25 °C	2 h	82	$[MeOEtMIM]^+[CF_3COO]^-$
21		CH_3I	 (3.3.21)	Yes	25 °C	20 h	57	$[MeOEtMIM]^+[CF_3COO]^-$
22			 (3.3.22)	Yes	25 °C	20 h	80	$[MeOEtMIM]^+[CF_3COO]^-$
23	 2-Thiouracil	CH_3I	 (3.3.23)	Yes	25 °C	6 h	53	$[MeOEtMIM]^+[CF_3COO]^-$

24			 (3.3.24)	Yes	25 °C	24 h	81	$[MeOEtMIM]^+[CF_3COO]^-$
25			 (3.3.25)	Yes	25 °C	24 h	80	$[MeOEtMIM]^+[CF_3COO]^-$
26	 4-Thiouracil		 (3.3.26)	Yes	25 °C	24 h	79	$[MeOEtMIM]^+[CH_3SO_3]^-$
27			 (3.3.27)	Yes	25 °C	24 h	82	$[MeOEtMIM]^+[CF_3COO]^-$

28	 6-Mercaptopurine riboside		 (3.3.28)	No	25 °C	1 h	89	$[MeOEtMIM]^+[CF_3COO]^-$
29			 (3.3.29)	Yes	25 °C	2 h	97	$[MeOEtMIM]^+[CF_3COO]^-$
30			 (3.3.30)	Yes	25 °C	4 h	92	$[MeOEtMIM]^+[CF_3COO]^-$

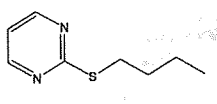
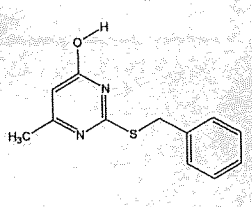
31	 Thioguanosine		 (3.3.31)	Yes	25 °C	4 h	81	$[MeOEtMIM]^+[CF_3COO]^-$
32			 (3.3.32)	Yes	25 °C	3 h	96	$[MeOEtMIM]^+[CF_3COO]^-$
33			 (3.3.33)	Yes	25 °C	2.5 h	96	$[MeOEtMIM]^+[CF_3COO]^-$

In addition, the methylation products were obtained at lower yields (Table 3.3, Entry 2, 21, 23). This was because the extraction of these products from the reaction mixtures was not very efficient. After many extractions (6-7), TLC plate still showed the product spot in the aqueous ionic liquid layer. For the products of thiouracil analogues, if the crude product was purified by flash column chromatography, a large amount of ethyl acetate was required to dissolve the product which reduced separation efficiency. To overcome this problem an alternative approach was used (see experimental section 3.3.23). A small amount of silica was added to the product/ethyl acetate solution in a round bottom flask and the mixture was evaporated to dryness. The dried powder was added to the top of the prepared column and then the column was eluted with ethyl acetate. The eluted product was isolated in high purity and good yield.

3.2.3 Modification of thionucleobases in various solvents

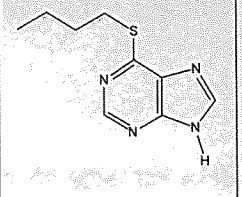
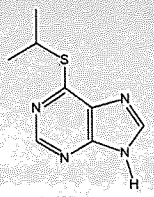
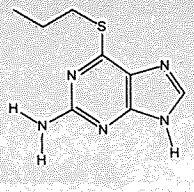
To compare different RTILs for the modification of the thionucleobases, and also compare RTILs with traditional organic solvents as the reaction medium, some thionucleobase-modification reactions were investigated in various ionic liquids and organic solvents. The results are illustrated in Tables 3.4 and 3.5 and in Figure 3.4.

Table 3.4 Alkylation of thionucleobases in the presence of triethylamine in various solvents

Product / Reaction Solvent	Yield (%)  (3.3.13)	Product / Reaction Solvent	Yield (%)  (3.3.20)
$[MeOEtMIM]^+$ $[CF_3COO]^-$	75	$[MeOEtMIM]^+$ $[CF_3COO]^-$	82
DMSO	72	CH_3OH	51

Triethylamine (20 % mol/mol) was used.The reactions were carried out in the same conditions as in Table 3.3, only the solvent was different. The yields of the products were shown above.

Table 3.5 Alkylation of thionucleobases in the presence of triethylamine in various solvents

Product / Reaction Solvent	Yield (%)  (3.3.4)	Yield (%)  (3.3.5)	Yield (%)  (3.3.8)
$[MeOEtMIM]^+[CF_3COO]^-$	96	76	88
$[MeOEtMIM]^+[CH_3SO_3]^-$	95	58	60
$[BMIM]^+[CF_3COO]^-$	85	61	47
DMSO	91	66	67
DMF	64	14	insoluble

Triethylamine (20 % mol/mol) was used.The same reactions were carried out in the same conditions as in Table 3.3, only the solvents were different. The yields of the products were shown above. Insoluble: thionucleobase was insoluble in the solvent.

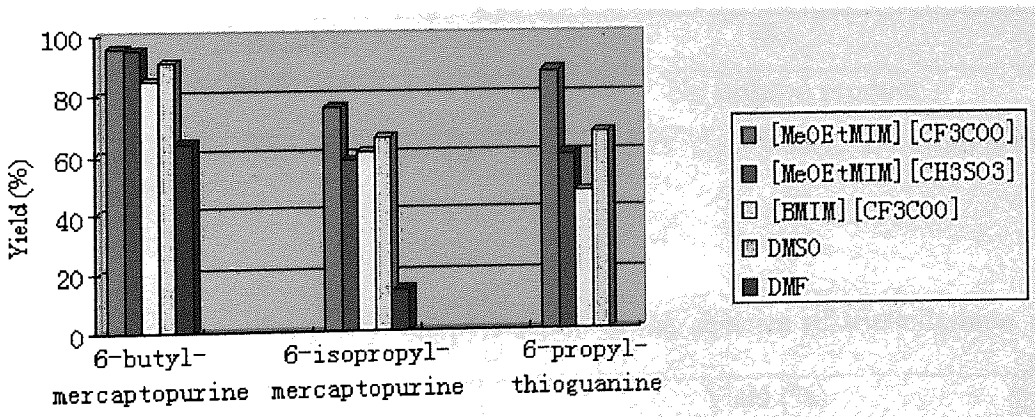
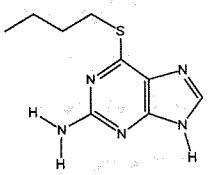


Figure 3.4 Reaction yields in various solvents

In the presence of triethylamine, the alkylation reactions of thionucleobases proceeded smoothly within a short period of time in both RTILs and DMSO. High yields of products were obtained with $[MeOEtMIM]^+[CF_3COO]^-$. Low yields of products were obtained with organic solvents such as methanol (Table 3.4) and DMF (Table 3.5).

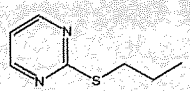
Later, it was found that ionic liquids had some catalytic activity to promote the thionucleobase reactions. In order to prove this catalytic activity, two reactions were carried out in various RTILs without the addition of any other catalysts (Table 3.6 and Table 3.7).

Table 3.6 Preparation of 6-butyl-thioguanine in the absence of triethylamine in various solvents

Product / Reaction Solvent	Yield (%)  (3.3.9)
$[MeOEtMIM]^+[CF_3COO]^-$	93
$[MeOMeOEtMIM]^+[CF_3COO]^-$	72
$[BMIM]^+[CF_3COO]^-$	85
$[PhOPMIM]^+[CF_3COO]^-$	80
$[EtOEtBuMIM]^+[CF_3COO]^-$	75
$[MeOEtMIM]^+[CH_3SO_3]^-$	78
DMSO	No isolated product

Reaction of 6-thioguanine and 1-iodobutane was carried out at 25 °C for 6 hours. The yields of the products were shown above.

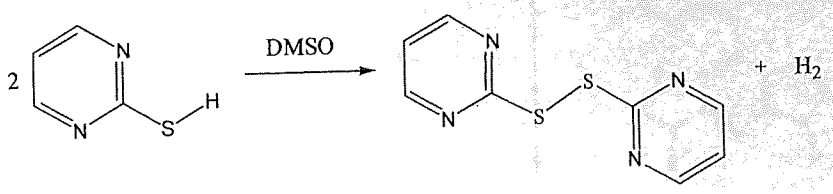
Table 3.7 Preparation of 6-propyl-thiopyrimidine in the absence of triethylamine in various solvents

Product / Reaction Solvent	Yield (%)  (3.3.12)
$[MeOEtMIM]^+[CF_3COO]^-$	90
$[PhOPMIM]^+[CF_3CF_2COO]^-$	92
$[BMIM]^+[CF_3COO]^-$	80
DMSO	No isolated product

Reaction of 2-mercaptopyrimidine and 1-bromopropane was carried out at 25 °C for 20 hours. The yields of the products were shown above.

These reactions could be carried out more efficiently in the ionic liquids than in the traditional solvents such as DMSO. High yields of the products were obtained in $[MeOEtMIM]^+[CF_3COO]^-$, $[BMIM]^+[CF_3COO]^-$ and $[PhOPMIM]^+[CF_3COO]^-$. Although $[MeOEtMIM]^+[CH_3SO_3]^-$ and $[MeOMeOEtMIM]^+[CF_3COO]^-$ had a quite good solubility for thionucleobases, it was difficult to dissolve alkyl halides in these two solvents, which became more obvious when the alkyl chain of haloalkanes increases. Therefore, a lower yield of the product 3.3.9 (6-butyl-thioguanine) was observed in both of the ionic liquids (Table 3.6).

In addition, with no triethylamine, high yields of the products were still obtained when these reactions were carried out in RTILs. However, no product was isolated in the absence of triethylamine under the same reaction conditions in DMSO (see table 3.6 and table 3.7). When 2-mercaptopyrimidine was reacted with bromopropane in DMSO without triethylamine, no expected product was obtained, but a yield (27%) of byproduct "bis(2-pyrimidinyl) disulfide" (product 3.3.34) was observed. These results proved that ionic liquids have a certain catalytic ability to promote these alkylation reactions.

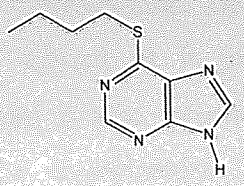


Scheme 3.3 Bis(2-pyrimidinyl) disulfide

3.2.4 Modification of thionucleobases in recycled RTILs

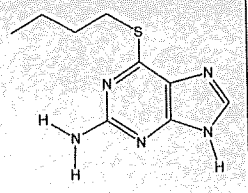
RTILs have gained wide popularity in organic chemistry. One of its important properties is that they can be recycled and reused. In order to determine whether ionic liquids could be reused, and whether recovered ionic liquids would affect the reaction rates or the yields of the products, the thionucleobase reactions were carried out in the recycled ionic liquids $[MeOEtMIM]^+[CF_3COO]^-$ and $[MeOEtMIM]^+[CH_3SO_3]^-$ with triethylamine (table 3.8) or without triethylamine (table 3.9).

Table 3.8 Preparation of 6-butyl-mercaptopurine with triethylamine in the recycled ionic liquids

Product / Reaction Solvent	Yield (%)  (3.3.4)
$[MeOEtMIM]^+[CF_3COO]^-$ (Fresh)	96
$[MeOEtMIM]^+[CF_3COO]^-$ (Recycled)	94
$[MeOEtMIM]^+[CH_3SO_3]^-$ (Fresh)	95
$[MeOEtMIM]^+[CH_3SO_3]^-$ (Recycled)	87

Reaction of 6-mercaptopurine and iodobutane with triethylamine (20 % mol/mol) was carried out at room temperature for 2 hours. The yields were shown above.

Table 3.9 Preparation of 6-butyl thioguanine without triethylamine in the recycled ionic liquid $[MeOEtMIM]^+[CF_3COO]^-$

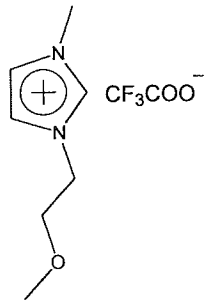
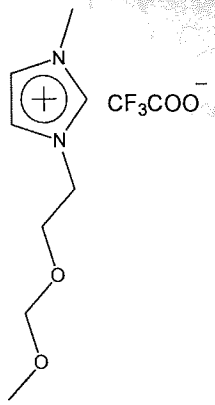
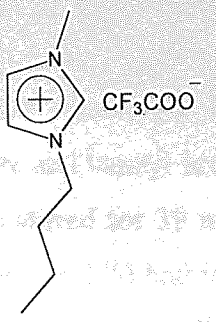
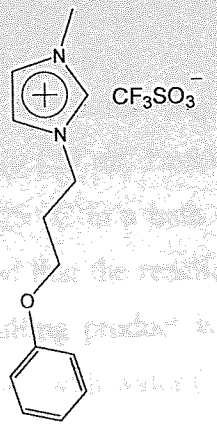
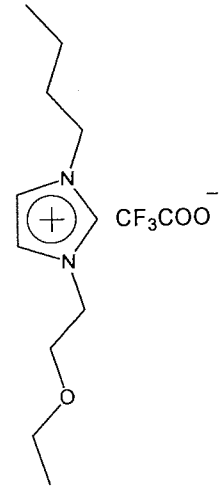
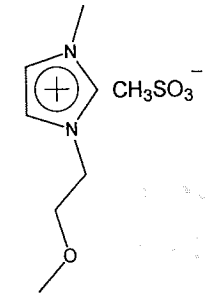
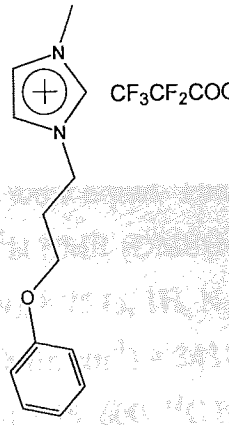
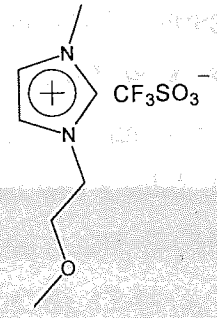
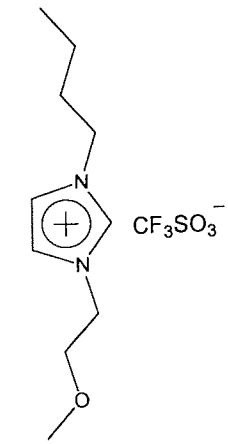
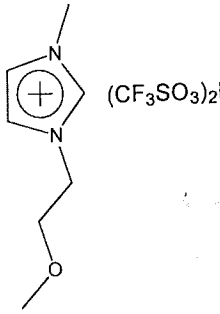
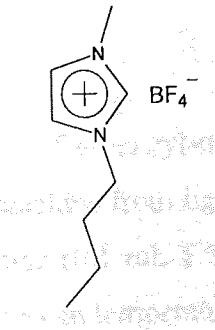
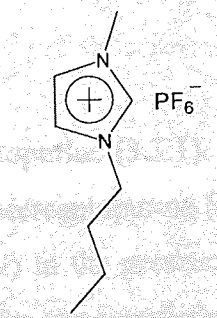
Product / Reaction Solvent	Yield (%)  (3.3.9)
$[MeOEtMIM]^+[CF_3COO]^-$ (Fresh)	93
$[MeOEtMIM]^+[CF_3COO]^-$ (Recycled 1)	91
$[MeOEtMIM]^+[CF_3COO]^-$ (Recycled 2)	84

Reaction of 6-thioguanine and iodobutane was carried out at room temperature for 6 hours. The yields were shown above.

The reactions proceeded efficiently in the recovered ionic liquids. RTILs could be reused without any obvious decrease in both the product yields and the reaction rates. All the resulting products were analyzed by IR, MS, ^{1}HNMR and ^{13}CNMR.

In summary, most of the thionucleobases and thionucleosides have a good solubility in RTILs. These thio-alkylation reactions could be carried out effectively and efficiently in RTILs with or without the organic base triethylamine. The ionic liquid $[MeOEtMIM]^+[CF_3COO]^-$ is an excellent reaction solvent as it provides good solubility for thionucleobases and thionucleosides and it also generates excellent catalytic ability to promote these reactions. The experimental approach is straightforward. Ionic liquids are environmentally friendly and they can be reused, Thionucleobases and thionucleosides with different substituents are produced with excellent yields. However, due to the limited time available, these chemicals are not tested for their biological activity.

Table 3.10 Structures of RTILs used in studies described in chapter 3

$[MeOEtMIM]^+$ $[CF_3COO]^-$ 	$[MeOMeOEtMIM]^+$ $[CF_3COO]^-$ 	$[BMIM]^+$ $[CF_3COO]^-$ 	$[PhOPMIM]^+$ $[CF_3COO]^-$ 
$[EtOEtBuMIM]^+$ $[CF_3COO]^-$ 	$[MeOEtMIM]^+$ $[CH_3SO_3]^-$ 	$[PhOPMIM]^+$ $[CF_3CF_2COO]^-$ 	$[MeOEtMIM]^+$ $[CF_3SO_3]^-$ 
$[MeOEtBuMIM]^+$ $[CF_3SO_3]^-$ 	$[MeOEtMIM]^+$ $[(CF_3SO_2)_2N]^-$ 	$[BMIM]^+[BF_4]^-$ 	$[BMIM]^+[PF_6]^-$ 

3.3 Experimental section

3.3.1: 6-Benzyl-mercaptopurine

6-Mercaptopurine (0.19 g, 1 mmol) was dissolved in 3 ml ionic liquid $[MeOEtMIM]^+[CH_3SO_3]^-$ at room temperature and benzyl bromide (0.135 ml, 1 mmol) was added to the solution. The mixture was stirred for 30 min at 25 °C in a bath of aluminium. When TLC analysis ($MeOH/CHCl_3$ = 1/5) had indicated that the reaction was completed, water (5 ml) was added to the mixture. The resulting product was extracted with ethyl acetate (3 × 10 ml) and the extraction was washed with water (2 × 10 ml). Ethyl acetate was removed by rotary evaporation. The crude product was further purified by flash column chromatography (methanol/chloroform = 1/5). The fractions containing the product were combined and the solvent was removed by rotary evaporation under reduced pressure. The product was further dried overnight under vacuum. The ionic liquid/water was collected together, filtered off twice, and then washed with ethyl acetate (2 × 10 ml). Water was removed under high vacuum rotary evaporation to afford the recovered ionic liquid. The product was a solid. The yield was 0.15 g (94%). Mp: 193-194 °C. ^{1}H NMR (DMSO-d_6): 4.66 (s, 2H, S-CH_2-), 7.22-7.51 (m, 5H, Ph), 8.47(s, 1H, N-CH-N), 8.75 (s, 1H, N-CH-N-C-S), 13.44 (s, 1H, N-H). MS APCI$^+$ (m/z): = 243(M+H). IR (KBr, cm^{-1}) = 3431, 3067, 2935, 2771, 2657, 1570, 1383, 1328, 1233, 951, 896, 841, 714, 646, 600. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 137.86(Ph), 31.60 (S-CH_2-). Negative peaks: δ = 151.41(N-CH-N), 128.96(Ph), 128.47(Ph), 127.15(Ph).

3.3.2: 6-Methyl-mercaptopurine

A similar method was used for the synthesis of 6-benzyl-mercaptopurine (3.3.1). The exception was that this reaction should be shielded from light. 6-Mercaptopurine (0.27 g, 1.5 mmol) was reacted with methyl iodide (0.1 ml, 1.5 mmol) in the presence of triethylamine (20 % mol/mol) for 30 min at room temperature. After the completion of the reaction, a saturated NaCl aqueous solution (10 ml) was added to the mixture. The resulting product was extracted with ethyl acetate (6 × 10 ml) and the extraction was

washed with water. Ethyl acetate was removed by rotary evaporation under reduced pressure to afford a solid product (0.14g, 53%). Further purification followed the similar procedures as used for 6-benzyl-mercaptopurine (3.3.1). Mp: 220-221 °C. ^{1}H NMR (DMSO-d_6): 2.67 (s, 3H, S-CH_3), 8.45 (s, 1H, N-CH-N), 8.71 (s, 1H, N-CH-N-C-S), 13.47 (s, 1H, N-H). MS APCI^{+} (m/z): = 167(M+H). IR (KBr, cm^{-1}) = 3412, 3049, 2925, 2783, 2677, 2567, 1814, 1575, 1383, 1323, 1245, 992, 946, 845, 643. ^{13}C NMR (DMSO-d_6): Negative peaks: δ = 151.50(N-CH-N), 11.16(S-CH_3).

3.3.3: 6-Propyl-mercaptopurine

A similar method was used for the synthesis of 6-benzyl-mercaptopurine (3.3.1). 6-Mercaptopurine (0.22 g, 1.3 mmol) was reacted with propyl bromide (0.12 ml, 1.3 mmol) in the presence of triethylamine (20 % mol/mol) for 3 h at 25 °C to give a solid product (0.22 g, 83%). Mp: 173-174 °C. ^{1}H NMR (DMSO-d_6): 1.02 (t, 3H, J = 7.27Hz, -CH_3), 1.74 (sext, 2H, J = 7.27Hz, -CH_2-), 3.33 (t, 2H, J = 7.27Hz, S-CH_2-), 8.44 (s, 1H, N-CH-N), 8.69 (s, 1H, N-CH-N-C-S), 13.51 (s, 1H, N-H). MS APCI^{+} (m/z): = 195(M+H), 153(M-$CH_2CH_2CH_3$). IR (KBr, cm^{-1}) = 3445, 3054, 2964, 2773, 2659, 2559, 1773, 1568, 1382, 1327, 1232, 950, 845, 645, 600. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 29.59(S-CH_2-), 22.60(-CH_2-). Negative peaks: δ = 151.43(N-CH-N), 13.20(-CH_3).

3.3.4: 6-Butyl-mercaptopurine

A similar method was followed to that for 6-benzyl-mercaptopurine (3.3.1). 6-Mercaptopurine (0.16 g, 1 mmol) was reacted with butyl iodide (0.11 ml, 1 mmol) in the presence of triethylamine (20 % mol/mol) for 2 h at 25 °C to give a solid product (0.18 g, 96%). Mp: 144-146 °C. ^{1}H NMR (DMSO-d_6): 0.92 (t, 3H, J=7.27Hz, -CH_3), 1.46 (sext, 2H, J=7.27Hz, S-CH_2CH_2-CH_2-), 1.70 (quint, 2H, J=7.43H, S-CH_2-CH_2-), 3.35 (t, 3H, J=7.27Hz, S-CH_2-), 8.46 (s, 1H, N-CH-N), 8.70 (s, 1H, N-CH-N-C-S), 13.44 (s, 1H, N-H). MS APCI^{+} (m/z): = 209(M+H), 153(M-$CH_2CH_2CH_2CH_3$). IR (KBr, cm^{-1}) = 3441, 3059, 2959, 2773, 2659, 2559, 1773, 1568, 1377, 1318, 1236, 950, 845, 645, 595. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 31.24(S-CH_2-),

27.46(S-CH_2-CH_2-), 21.39(S-CH_2CH_2-CH_2-). Negative peaks: δ = 151.44(N-CH-N), 13.50(-CH_3).

3.3.5: 6-Isopropyl-mercaptopurine

A similar method was used for the synthesis of 6-benzyl-mercaptopurine (3.3.1). 6-Mercaptopurine (0.34 g, 2 mmol) was reacted with isopropyl iodide (0.21 ml, 2 mmol) in the presence of triethylamine (20 % mol/mol) for 3 h at 25 °C to give a solid product (0.30 g, 76%). Mp: 233-235 °C. ^{1}H NMR (DMSO-d_6): 1.42 (s, 3H, -CH_3), 1.45 (s, 3H, -CH_3), 4.30 (septuplet, 1H, J = 6.95Hz, S-CH-), 8.45 (s, 1H, N-CH-N), 8.70 (s, 1H, N-CH-N-C-S), 13.54 (s, 1H, N-H). MS APCI$^+$ (m/z): = 195(M+H), 167(M-CH-CH_3), 153(M-$(CH)_2CH_3$). IR (KBr, cm^{-1}) = 3432, 3058, 2964, 2774, 2662, 2563, 1774, 1571, 1382, 1319, 1242, 945, 837, 643, 594. ^{13}C NMR (DMSO-d_6): Negative peaks: δ = 151.47(N-CH-N), 33.60(S-CH-), 23.03(-CH_3).

3.3.6: 6-Crotyl-mercaptopurine

A similar method was used for the synthesis of 6-benzyl-mercaptopurine (3.3.1). 6-Mercaptopurine (0.35 g, 2 mmol) was reacted with crotyl bromide (0.22 ml, 2 mmol) in the presence of triethylamine (20 % mol/mol) for 2.5 h at 25 °C to give a solid product (0.39 g, 92%). Mp: 179-180 °C. ^{1}H NMR (DMSO-d_6): 1.65 (d, 3H, J = 6.16Hz, -CH_3), 4.00 (d, 2H, J = 6.79Hz, S-CH_2-), 5.57-5.69 (m, 1H, CH=CH), 5.78-5.86 (m, 1H, CH=CH), 8.45 (s, 1H, N-CH-N), 8.70 (s, 1H, N-CH-N-C-S), 13.56(s, 1H, N-H). MS APCI$^+$ (m/z): (M+1) = 207(M+H), 153(M-CH_2CH=CHCH_3). IR (KBr, cm^{-1}) = 3440, 3054, 2939, 2769, 2650, 2553, 1571, 1378, 1318, 1236, 946, 841, 648, 602. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 29.92(S-CH_2-). Negative peaks: δ = 151.40(N-CH-N), 128.95(CH_2-CH=CH), 126.24 (CH=CH-CH_3), 17.51(-CH_3).

3.3.7: 6-Benzyl-thioguanine

6-Thioguanine (0.10 g, 0.5 mmol) was dissolved in 5 ml ionic liquid

$[MeOEtMIM]^+[CF_3COO]^-$ at 50 °C and the solution was cooled until room temperature. After that, benzyl bromide (0.07 ml, 0.5 mmol) was added.The reaction mixture was stirred for 30 min at 3 °C in an ice bath. When TLC analysis ($MeOH/CHCl_3$ = 1/5) had indicated that the reaction was completed, water (5 ml) was added to the mixture. The resulting product was extracted with ethyl acetate (3 × 10 ml) and the extraction was washed with water (2 × 10 ml). Ethyl acetate was removed by rotary evaporation. The crude product was further purified by flash column chromatography (methanol/chloroform = 1/5). The fractions containing the product were combined and the solvent was removed by rotary evaporation. The product was further dried overnight under vacuum. The solution of ionic liquid/water was collected together, filtered off twice, and then washed with ethyl acetate (2 × 10 ml). Water was removed in high vacuum rotary evaporation to afford the recovered ionic liquid. The yield of 6-benzyl thioguanine was 0.13 g (88%). Mp: 209-210 °C. ^1H NMR (DMSO-d_6): 4.54 (s, 2H, S-CH_2-), 6.46 (s, 2H, NH_2), 7.52-7.19 (m, 5H, Ph), 7.90 (s, 1H, N-CH-N), 12.57 (s, 1H, N-H). MS $APCI^+$ (m/z): = 258(M+H). IR (KBr, cm^{-1}) = 3391, 3086, 2986, 2814, 1559, 1359, 1264, 914, 827, 700. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 159.55(-C-NH_2), 138.71(Ph), 31.00(S-CH_2-). Negative peaks: δ = 129.15(Ph), 128.39(Ph), 126.90(Ph).

3.3.8: 6-Propyl-thioguanine

A similar method was followed to that for 6-benzyl-thioguanine (3.3.7). 6-Thioguanine (0.14 g, 0.9 mmol) was reacted with methyl iodide (0.08 ml, 0.9 mmol in the presence of triethylamine (20 % mol/mol) for 4 h at 25 °C to give a solid product (0.39 g, 88%). Mp: 179-181 °C. ^1H NMR (DMSO-d_6): 0.99 (t, 3H, J = 7.27Hz, -CH_3), 1.68 (sext, 2H, J = 7.27Hz, -CH_2-), 3.23 (t, 2H, J = 7.27Hz, S-CH_2-), 6.33 (s, 2H, NH_2), 7.89 (s, 1H, N-CH-N), 12.58 (s, 1H, N-H). MS $APCI^+$ (m/z): = 210(M+H), 168(M-$CH_2CH_2CH_3$). IR (KBr, cm^{-1}) = 3488, 3295, 3178, 2967, 2810, 1612, 1558, 1495, 1459, 1356, 1307, 1257, 916, 817, 638. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 159.54(-C-NH_2), 29.25(S-CH_2-), 22.72(-CH_2-). Negative peaks: δ = 13.23(-CH_3).

3.3.9: 6-Butyl-thioguanine

The synthesis was followed as described for 6-benzyl-thioguanine (3.3.7). 6-Thioguanine (0.07 g, 0.4 mmol) was reacted with butyl iodide (0.05 ml, 0.4 mmol) for 6 h at 25 °C to afford a solid product (0.08 g, 93%). Mp: 197-199 °C. ^{1}H NMR (DMSO-d_6): 0.92 (t, 3H, J = 7.58Hz, -CH_3), 1.43 (sext, 2H, J = 7.58Hz, S-$CH_2$$CH_2$-$CH_2$-), 1.65 (quint, 2H, J = 7.58Hz, S-CH_2-CH_2-), 3.26 (t, 2H, J = 7.58Hz, S-CH_2-), 6.35 (s, 2H, NH_2), 7.90 (s, 1H, N-CH-N), 12.53 (s, 1H, 1H, N-H). MS ES^{+} (m/z): = 224(M+H). IR (KBr, cm^{-1}) = 3498, 3306, 3178, 2964, 2924, 2684, 1609, 1560, 1498, 1453, 1356, 1302, 1262, 929, 787, 644, 547. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 159.55(-C-NH_2), 158.90(S-C-), 151.59(S-C-**C**=C-N), 123.86(S-C-C=**C**-N), 31.40(S-CH_2-), 27.00(S-CH_2-**C**H_2-), 21.38(S-$CH_2$$CH_2$-**C**$H_2$-). Negative peaks: δ = 138.62(N-CH-N), 13.57(-CH_3).

3.3.10: 6-(1-Methylbenzyl)-thioguanine

This preparation was followed as described for 6-benzyl-thioguanine (3.3.7). 6-Thioguanine (0.19 g, 1 mmol) was reacted with α-methyl-benzyl bromide (0.16 ml, 1 mmol) in the presence of triethylamine (20 % mol/mol) for 2.5 h at 25 °C to give a solid product (0.3 g, 95%). Mp: 99-100 °C. ^{1}H NMR (DMSO-d_6): 1.73 (d, 3H, J = 7.27Hz, -CH_3), 5.43 (q, 1H, J = 7.11Hz, S-CH-), 6.45 (s, 2H, NH_2), 7.70-7.19 (m, 5H, Ph), 8.30 (s, 1H, N-CH-N). MS APCI^{+} (m/z): = 272(M+H), 168(M-(CH_3-CH-Ph)). IR (KBr, cm^{-1}) = 3327, 3086, 2973, 2786, 1564, 1350, 1259, 909, 704. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 159.36(-C-NH_2), 158.04(S-C-), 152.04(S-C-**C**=C-N), 143.22(Ph), 122.39(S-C-C=**C**-N). Negative peaks: δ = 128.39(Ph), 127.36(Ph), 127.11(Ph), 40.95(S-CH-), 22.18(-CH_3).

3.3.11: 2-Benzyl-mercaptopyrimidine

2-Mercaptopyrimidine (0.11 g, 1 mmol) was dissolved in 10 ml ionic liquid [MeOEtMIM]$^{+}$[CF_3COO]$^{-}$ at room temperature and benzyl bromide (0.12 ml, 1 mmol) was added. The mixture was stirred for 30 min at 25 °C in a bath of aluminium. When

TLC analysis (TLC developing solvent was chloroform) had indicated that the reaction was completed, water (5 ml) was added to the mixture. The resulting product was extracted with ethyl acetate (3 × 10 ml) and the extraction was washed with water (2 × 10 ml). Ethyl acetate was removed by rotary evaporation. The crude product was further purified by flash column chromatography (chloroform). The fractions containing the desired product were combined and the solvent was removed. The product was further dried overnight under vacuum. The removed ionic liquid/water was collected, filtered off twice, and then washed with ethyl acetate (2 × 10 ml). Water was removed in high vacuum rotary evaporation to afford ionic liquid for reuse. The yield of 2-benzyl mercaptopyrimidine was 0.19g (98%). Mp: 48-51 °C. ^{1}H NMR (DMSO-d_6): 4.42 (s, 2H, S-CH_2-), 7.24 (t, 1H, J = 4.90Hz, CH-CH-CH), 7.20-7.50 (m, 5H, Ph), 8.67 (d, 2H, J = 4.90Hz, CH-CH-N). MS APCI$^+$ (m/z): = 203(M+H). IR (KBr, cm^{-1}) = 3435, 3026, 1543, 1387, 1203, 1167, 767, 698. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 170.62(-C-S), 137.59(Ph), 34.00(S-CH_2-). Negative peaks: δ = 157.86(C-CH-C), 128.96(Ph), 128.39(Ph), 127.08(Ph), 117.32(CH-CH-N).

3.3.12: 2-Propyl-mercaptopyrimidine

A similar method was used as described in section 3.3.11. 2-Mercaptopyrimidine (0.1 g, 1 mmol) was reacted with propyl bromide (0,09 ml, 1 mmol) for 20 h at 25 °C to give a liquid product (0.17 g, 90%). ^{1}H NMR (DMSO-d_6): 0.98 (t, 3H, J=7.27Hz, -CH_3), 1.67 (sext, 2H, J = 7.27Hz, -CH_2-), 3.08 (t, 2H, J = 7.27Hz, S-CH_2-), 7.20 (t, 1H, J = 4.90Hz, CH-CH-CH), 8.63 (d, 2H, J = 4.90Hz, CH-CH-N). MS ES$^+$ (m/z): = 155(M+H). IR (cm^{-1}) = 2966, 2930, 1564, 1542, 1384, 1191, 795, 773, 751, 629. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 171.13(-C-S), 31.84(S-CH_2-), 22.17(-CH_2-). Negative peaks: δ = 157.71(C-CH-C), 117.03(CH-CH-N), 13.20(-CH_3).

3.3.13: 2-Butyl-mercaptopyrimidine

A similar method was followed to that for 2-benzyl-mercaptopyrimidine (3.3.11). 2-Mercaptopyrimidine (0.15 g, 1.4 mmol) was reacted with butyl bromide (0.16 ml, 1.4 mmol) in the presence of triethylamine (20 % mol/mol) for 2 h at 25 °C to give a

liquid product (0.17 g, 75%). ^{1}H NMR (DMSO-d_6): 0.90 (t, 3H, J = 7.11Hz, -CH_3), 1.41 (sext, 2H, J = 7.11Hz, S-CH_2-CH_2-CH_2-), 1.65 (quint, 2H, J = 7.11Hz, S-CH_2-CH_2-), 3.11 (t, 2H, J = 7.27Hz, S-CH_2-), 7.21 (t, 1H, J = 4.90Hz, CH-CH-CH), 8.64 (d, 2H, J = 4.90Hz, CH-CH-N). MS APCI$^+$ (m/z): = 169(M+H), 113(M-$CH_2CH_2CH_2CH_3$). IR (cm^{-1}) = 2961, 1567, 1545, 1381, 1199, 773, 631. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 171.18(-C-S), 30.81(S-CH_2-), 29.69(S-CH_2-CH_2-), 21.43(S-CH_2CH_2-CH_2-). Negative peaks: δ = 157.67(C-CH-C), 116.95(CH-CH-N), 13.55(-CH_3).

3.3.14: 2-Cyclopentyl-mercaptopyrimidine

A similar method was used for the synthesis of 2-benzyl-mercaptopyrimidine (3.3.11). 2-Mercaptopyrimidine (0.12 g, 1 mmol) was reacted with cyclopentyl bromide (0.13 ml, 1 mmol) in the presence of triethylamine (20 % mol/mol) for 3 h at 25 °C to give a liquid product (0.0965 g, 51%). ^{1}H NMR (DMSO-d_6): 1.47-1.79 (m, 6H, -$CH_2CH_2CH_2$-), 2.11-2.26 (m, 2H, CH_2), 3.96 (quint, 1H, J = 6.79Hz, S-CH-), 7.20 (t, 1H, J = 4.90Hz, CH-CH-CH), 8.64 (d, 2H, J = 4.90Hz, CH-CH-N). MS APCI$^+$ (m/z): = 181(M+H), 113(M-cyclopentyl). IR (cm^{-1}) = 3400, 2954, 1564, 1536, 1382, 1191, 768, 632. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 171.74(-C-S), 32.69(-CH_2-), 24.24(-CH_2-). Negative peaks: δ = 157.48(C-CH-C), 116.95(CH-CH-N), 42.82(S-CH-).

3.3.15: 1,4-Bis(2-mercaptopyrimidinyl) butane

A similar method was followed as described for the synthesis of 2-benzyl-mercaptopyrimidine (3.3.11). 2-Mercaptopyrimidine (0.14 g, 1.2 mmol) was reacted with 1, 4-dibromobutane (0.08 ml, 0.6 mmol) in the presence of triethylamine (20 % mol/mol) for 48 h at 25 °C to give a solid product (0.14 g, 83%). Mp: 63-64 °C. ^{1}H NMR (DMSO-d_6): 1.77-1.90 (m, 4H, -CH_2CH_2-), 3.11-3.23 (m, 4H, S-CH_2-, -CH_2-S), 7.21 (t, 2H, J = 4.90Hz, CH-CH-CH), 8.63 (d, 4H, J = 4.90Hz, CH-CH-N). MS APCI$^+$ (m/z): = 279(M+H), 167(M-mercaptopyrimidinyl). IR (KBr, cm^{-1}) = 3432, 2936, 1550, 1391, 1182, 768, 627. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 170.99(-C-S),

29.50(S-CH_2-), 28.00(-CH_2-). Negative peaks: δ = 157.67(C-CH-C), 117.13(CH-CH-N).

3.3.16: 2-Benzyl-thiocytosine

2-Thiocytosine (0.12 g, 1 mmol) was dissolved in $[MeOEtMIM]^+[CF_3COO]^-$ (3 ml) and benzyl bromide (0.11 ml, 1 mmol) was added to the solution. The mixture was stirred for 30 min at 25 °C to give a solid product (0.28 g, 98%). The product was further purified by flash column chromatography (ethyl acetate). The fractions containing the product were combined and the solvent was removed by rotary evaporation. The product was further dried overnight under vacuum. Mp: 111-112 °C. ^{1}H NMR (DMSO-d_6): 4.31 (s, 2H, S-CH_2-), 6.17 (d, 1H, J = 6.00Hz, -CH-C), 7.04 (s, 2H, NH_2), 7.19-7.52 (m, 5H, Ph), 7.93 (d, 1H, J = 5.85Hz, N-CH). MS APCI$^+$ (m/z): = 218(M+H). IR (KBr, cm^{-1}) = 3458, 3293, 3155, 1644, 1539, 1461, 1327, 1236, 813, 703, 570. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 169.12(-C-NH_2), 163.11(N-C-S), 138.53(Ph), 33.62(S-CH_2-). Negative peaks: δ = 154.66(N-CH-CH), 128.96(Ph), 128.39(Ph), 126.90(Ph), 101.37(CH-CH-C).

3.3.17: 2-Propyl-thiocytosine

A similar method was used for the synthesis of 6-benzyl-thiocytosine (3.3.16). 2-Thiocytosine (0.12 g, 1 mmol) was reacted with propyl bromide (0.09 ml, 1 mmol) in the presence of triethylamine (20 % mol/mol) for 2.5 h at 25 °C to give a solid product (0.15 g, 93%). Mp: 60-62 °C. ^{1}H NMR (DMSO-d_6): 0.95 (t, 3H, J = 7.42Hz, -CH_3), 1.63 (sext, 2H, J = 7.27Hz, -CH_2-), 2.99 (t, 2H, J = 7.42Hz, S-CH_2-), 6.15 (d, 2H, J = 6.00Hz, -CH-C), 7.04 (s, 2H, NH_2), 7.90 (d, 1H, J = 5.85Hz, N-CH). MS APCI$^+$ (m/z): = 170(M+H), 128(M-$CH_2CH_2CH_3$). IR (KBr, cm^{-1}) = 3424, 3306, 3157, 1638, 1542, 1325, 1248, 976, 813, 717, 577. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = = 169.49(-C-NH_2), 163.11(N-C-S), 31.56(S-CH_2-), 22.55(-CH_2-). Negative peaks: δ = 154.10(N-CH-CH), 101.00(CH-CH-C), 13.17(-CH_3).

3.3.18: 2-(1-Methylbenzyl)-thiocytosine

A similar method was followed to that for 6-benzyl-thiocytosine (3.3.16). 2-Thiocytosine (0.14 g, 1 mmol) was reacted with α-methylbenzyl bromide (0.15 ml, 1 mmol) in the presence of triethylamine (20 % mol/mol) for 2 h at 25 °C to give a solid product (0.24 g, 91%). Mp: 125-126 °C. ^{1}H NMR (DMSO-d_6): 1.67 (d, 3H, J = 7.58Hz, -CH_3), 4.95 (q, 1H, J = 6.95Hz, S-CH-), 6.14 (d, 1H, J = 5.69Hz, -CH-C), 6.98 (s, 2H, NH_2), 7.21-7.55 (m, 5H, Ph), 7.61 (d, 1H, J = 5.69Hz, N-CH). MS APCI^{+} (m/z): = 232(M+H), 128(M-(CH_3-CH-Ph)). IR (KBr, cm^{-1}) = 3449, 3315, 3163, 1636, 1578, 1537, 1466, 1331, 1255, 763. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 169.29(-C-NH_2), 163.07(N-C-S), 143.25(Ph). Negative peaks: δ = 154.90(N-CH-CH), 128.39(Ph), 127.30(Ph), 101.26(CH-CH-C), 42.66(S-CH-), 22.31(-CH_3).

3.3.19: 2-Crotyl-thiocytosine

A similar method was used for the synthesis of 6-benzyl-thiocytosine (3.3.16). 2-Thiocytosine (0.2 g, 1.6 mmol) was reacted with crotyl bromide (0.05 ml, 1.6 mmol) in the presence of triethylamine (20 % mol/mol) for 2 h at 25 °C to give a liquid product (0.29 g, 99%).^{1}H NMR (DMSO-d_6): 1.64 (d, 3H, J = 6.32Hz, -CH_3), 3.64 (d, 2H, J = 6.95Hz, S-CH_2-), 5.49-5.75 (m, 2H, CH=CH), 6.14 (d, 1H, J = 5.69Hz, -CH-C), 6.94 (s, 2H, NH_2), 7.90 (d, 1H, J = 6.32Hz, N-CH). MS APCI^{+} (m/z): = 182(M+H), 128(M-CH_2CH=CHCH$_3$). IR (cm^{-1}) = 3317, 3175, 2927, 1632, 1579, 1544, 1464, 1340, 1256, 1211, 1065, 967, 812, 724. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = = 169.37(-C-NH_2), 163.02(N-C-S), 31.78(S-CH_2-). Negative peaks: δ = 154.84(N-CH-CH), 127.84(CH_2-CH=CH), 126.92(CH=CH-), 101.17(CH=CH-CH_3), 17.50(-CH_3).

3.3.20: 6-Aza-2-benzyl-thiothymine

A similar method was followed as described for the synthesis of 6-benzyl-thiocytosine (3.3.16). 6-Aza-2-thiothymine (0.12 g, 0.8 mmol) was reacted with benzyl bromide (0.1 ml, 0.8 mmol) in the presence of triethylamine (20 % mol/mol) for 2 h at 25 °C to

give a solid product (0.15 g, 82%). Mp: 182-185 °C. ^{1}H NMR (DMSO-d_6): 4.41(s, 2H, S-CH_2-), 2.12(s, 3H, C-CH_3), 7.27-7.51 (m, 5H, Ph), 13.76(s, 1H, OH). MS APCI$^+$ (m/z): = 234(M+H). IR (KBr, cm^{-1}) = 3435, 2774, 2710, 1621, 1516, 1456, 1360, 1263, 1015, 698, 551. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 32.69(S-CH_2-). Negative peaks: δ = 128.96(Ph), 128.58(Ph), 127.46(Ph), 16.74(C-CH_3).

3.3.21: 6-Aza-2-methyl-thiothymine

A similar method was followed as described for the synthesis of 2-benzyl-thiocytosine (3.3.16). Light should be avoided for this reaction. 6-Aza-2-thiothymine (0.21 g, 1.5 mmol) was reacted with methyl iodide (0.1 ml, 1.6 mmol) in the presence of triethylamine (20 % mol/mol) for 20 h at 25 °C to give a solid product (0.14 g, 57%). Mp: 147-149 °C. ^{1}H NMR (DMSO-d_6): 2.11(s, 3H, C-CH_3), 2.47(s, 3H, S-CH_3), 13.71(s, 1H, OH). MS APCI$^+$ (m/z): =186(M+H), 144(M-CH_3). IR (KBr, cm^{-1}) = 3436, 2773, 2714, 1614, 1523, 1454, 1354, 1268, 1241, 1041, 786, 545. ^{13}C NMR (DMSO-d_6): Negative peaks: δ = 16.69(C-CH_3), 12.06(S-CH_3).

3.3.22: 6-Aza-2-isopropylbenzyl-thiothymine

A similar method was used for the synthesis of 2-benzyl-thiocytosine (3.3.16). 6-Aza-2-thiothymine (0.24 g, 1.7 mmol) was reacted with isopropyl iodide (0.17 ml, 1.7 mmol) in the presence of triethylamine (20 % mol/mol) for 20 h at 25 °C to give a solid product (0.25 g, 80%). Mp: 224-226 °C. ^{1}H NMR (DMSO-d_6): 1.36 (d, 6H, J = 6.95Hz, -CH_3CHCH_3-), 2.11 (s, 3H, C-CH_3), 3.89 (7, 1H, J = 6.95Hz, S-CH), 13.64 (s, 1H, OH). MS APCI$^+$ (m/z): = 158(M+H). IR (KBr, cm^{-1}) = 3436, 2691, 2636, 1604, 1532, 1454, 1364, 1268, 1018, 782, 550. ^{13}C NMR (DMSO-d_6): Negative peaks: δ =35.66(S-CH-), 22.70(CH-CH_3), 16.77(C-CH_3).

3.3.23: 2-Methyl-thiouracil

2-Thiouracil (0.31 g, 2.4 mmol) was dissolved in 3 ml ionic liquid [MeOEtMIM]$^+$ [CF_3COO]$^-$ at 25 °C and methyl iodide (0.16 ml, 2.5 mmol) and triethylamine (20 %

mol/mol) were added. The mixture was stirred for 6 h at 25 °C in a bath of aluminium. TLC monitored the reaction progress (TLC developing solvent was ethyl acetate). After the completion of the reaction, water (5 ml) was added to the mixture. The resulting product was extracted with ethyl acetate (3 × 10 ml) and the extraction was washed with water (2 × 10 ml). Ethyl acetate was removed by rotary evaporation. When the crude product was purified by flash column chromatography, large amount of ethyl acetate was required to dissolve the product which reduced separation efficiency. To overcome this problem an alternative method was used. A small amount of silica was added to the product/ethyl acetate solution in a round bottom flask and the mixture was evaporated to dryness. The dried powder was added onto the top of the pre-prepared column and then the column was eluted with ethyl acetate. The yield of 2-methyl thiouracil was 0.17 g (53%). The product was a solid. Mp: 200-202 °C. ^{1}H NMR (DMSO-d_6): 2.54 (s, 3H, S-CH_3), 6.16 (d, 1H, J = 6.38Hz, C-CH), 7.93 (d, 1H, J = 6.32Hz, N-CH), 12.79 (s, 1H, OH). MS APCI$^+$ (m/z): = 143(M+H), 129(M-CH_3). IR (KBr, cm^{-1}) = 3433, 2803, 1651, 1507, 1538, 1461, 1284, 1184, 1062, 980, 822, 531. ^{13}C NMR (DMSO-d_6): Negative peaks: δ = 12.80(S-CH_3).

3.3.24: 2-Butyl-thiouracil

A similar method was used for the synthesis of 2-methyl-thiouracil (3.3.23). 2-Thiouracil (0.14 g, 1.1 mmol) was reacted with butyl iodide (0.13 ml, 1.1 mmol) in the presence of triethylamine (20 % mol/mol) for 24 h at 25 °C to give a solid product (0.16 g, 81%). Mp: 93-95 °C. ^{1}H NMR (DMSO-d_6): 0.89 (t, 3H, J = 7.27Hz, -CH_3), 1.37 (sext, 2H, J = 7.74Hz, S-CH_2CH_2-C**H**$_2$-), 1.61 (quint, 2H, J = 7.74Hz, S-CH_2-C**H**$_2$-), 3.10 (t, 2H, J = 7.27Hz, S-CH_2-), 6.08 (d, 1H, J = 6.63Hz, C-CH), 7.85 (d, 1H, J = 6.63Hz, N-CH), 12.59 (s, 1H, OH). MS APCI$^+$ (m/z): = 185(M+H), 129(M-$CH_2CH_2CH_2CH_3$). IR (KBr, cm^{-1}) = 3427, 2959, 2864, 1664, 1464, 1282, 982, 827, 532. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 30.81(S-CH_2-), 29.31(S-CH_2-**C**H_2-), 21.25(S-CH_2CH_2-**C**H_2-). Negative peaks: δ = 13.36(-CH_3).

3.3.25: 2-Cyclopentyl-thiouracil

A similar method was followed as described for the synthesis of 2-methyl-thiouracil (3.3.23). 2- Thiouracil (0.18 g, 1.4 mmol) was reacted with cyclopentyl bromide (0.04 ml, 1.4 mmol) in the presence of triethylamine (20 % mol/mol) for 24 h at 25 °C to give a solid product (0.2421 g, 80%). Mp: 135-137 °C. ^{1}H NMR (DMSO-d_6): 1.43-1.77 (m, 6H, -$CH_2CH_2CH_2$-), 2.04-2.26 (m, 2H, -CH_2-), 3.96 (quint, 1H, J = 6.95Hz, S-CH-), 6.08 (d, 1H, J = 6.48Hz, C-CH), 7.86 (d, 1H, J = 6.32Hz, N-CH), 12.69 (s, 1H, OH). MS APCI$^+$ (m/z): = 197(M+H), 129(M-cyclopentyl). IR (KBr, cm^{-1}) = 3437, 2962, 2865, 1655, 1539, 1468, 1287, 1061, 981, 821, 533. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 32.73(-CH_2-), 24.23(-CH_2-). Negative peaks: δ = 42.98(S-CH-).

3.3.26: 4-Propyl-thiouracil

A similar method was followed as described for the synthesis of 2-methyl-thiouracil (3.3.23). 4-Thiouracil (0.16 g, 1.2 mmol) was reacted with propyl bromide (0.11 ml, 1.2 mmol) in the presence of triethylamine (20 % mol/mol) for 24 h at 25 °C to give a solid product (0.16 g, 79%). Mp: 138-141 °C. ^{1}H NMR (DMSO-d_6): 0.97 (t, 3H, J = 6.95Hz, -CH_3), 1.63 (sext, J = 6.95Hz, -CH_2CH_2-S), 3.06 (t, 2H, J = 6.95Hz, -CH_2-S), 6.27 (d, 1H, J = 6.32Hz, C-CH), 7.35 (d, 1H, J = 6.95Hz, N-CH), 11.48 (s, 1H, OH). MS APCI$^+$ (m/z): = 171(M+H), 129(M-$CH_2CH_2CH_3$). IR (KBr, cm^{-1}) = 3454, 2925, 2845, 1618, 1416, 1242, 1094, 982, 790, 588. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 30.22(S-CH_2-), 22.00(-CH_2-). Negative peaks: δ = 101.98(CH-CH-C), 13.17(-CH_3).

3.3.27: 4-Butyl-thiouracil

A similar method was used for the synthesis of 2-methyl-thiouracil (3.3.23). 4-Thiouracil (0.12 g, 1 mmol) was reacted with butyl iodide (0.11 ml, 1 mmol) in the presence of triethylamine (20 % mol/mol) for 24 h at 25 °C to give a solid product (0.14 g, 82%). Mp: 131-132 °C. ^{1}H NMR (DMSO-d_6): 0.88 (t, 3H, J = 7.27Hz, -CH_3), 1.37 (sext, 2H, J = 7.42Hz, S-CH_2CH_2-CH_2-), 1.58 (quint, 2H, J = 7.42Hz,

S-CH_2-C**H**$_2$-), 3.07 (t, 2H, J = 7.11Hz, S-CH_2-), 6.25 (d, 1H, J = 6.79Hz, C-CH), 7.61 (d, 1H, J = 6.79Hz, N-CH), 11.56 (s, 1H, OH). MS APCI$^+$ (m/z): = 184(M+H), 129(M-$CH_2CH_2CH_2CH_3$). IR (KBr, cm^{-1}) = 2927, 2864, 1645, 1418, 1241, 1095, 782, 595. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 177.00(-C-OH), 154.29(-C-S), 30.63(S-CH_2-), 28.00(S-CH_2-**C**H_2-), 21.43(S-CH_2CH_2-CH_2-). Negative peaks: δ = 143.22(N-CH-CH), 101.93(CH-CH-C), 13.55(-CH_3).

3.3.28: 6-Benzyl-mercaptopurine riboside

A similar method was followed as described for the synthesis of 6-benzyl-mercaptopurine (3.3.1). 6-Mercaptopurine riboside (0.14 g, 0.5 mmol) was reacted with benzyl bromide (0.6 ml, 0.5 mmol) for 1 h at 25 °C to give a solid product (0.17 g, 89%). Mp: 115-116 °C. ^{1}H NMR (DMSO-d_6): 3.50-3.76 (m, 2H, sugar ring), 3.95-4.03 (q, 1H, sugar ring), 4.15-4.23 (m, 1H, sugar ring), 4.60 (q, 1H, J=5.37Hz, sugar ring), 4.67 (s, 2H, S-CH_2-), 5.15 (t, 1H, J = 5.69Hz, sugar ring), 5.28 (d, 1H, J = 5.06Hz, sugar ring), 5.57 (d, 1H, J = 5.84Hz, sugar ring), 6.00 (d, 1H, J = 5.53Hz, sugar ring), 7.25-7.53 (m, 1H, Ph), 8.73 (s, 1H, 1H, N-CH-N), 8.80 (s, 1H, N-CH-N-C-S). MS APCI$^+$ (m/z): = 375(M+H), 243(M-sugar ring). IR (KBr, cm^{-1}) = 3366, 2925, 1566, 1433, 1337, 1208, 1116, 951, 703. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 159.14(S-C-), 148.25(S-C-C=C-N), 137.74(Ph), 130.90(S-C-C=C-N), 61.17(sugar ring), 31.56(S-CH_2-). Negative peaks: δ = 128.95(Ph), 128.48(Ph), 128.01(Ph), 87.77(sugar ring), 85.66(sugar ring), 73.74(sugar ring), 70.21(sugar ring).

3.3.29: 6-Butyl-mercaptopurine riboside

A similar method was followed as described for the synthesis of 6-benzyl-mercaptopurine (3.3.1). 6-Mercaptopurine riboside (0.22 g, 0.8 mmol) was reacted with butyl iodide (0.09 ml, 0.8 mmol) in the presence of triethylamine (20 % mol/mol) for 2 hr at 25 °C to give a solid product (0.3 g, 97%). Mp: 57-59 °C. ^{1}H NMR (DMSO-d_6): 0.92 (t, 3H, J = 7.27Hz, -CH_3), 1.44 (sext, 2H, J = 7.27Hz, S-CH_2CH_2-C**H**$_2$-), 1.70 (quint, 2H, J = 7.27Hz, S-CH_2-C**H**$_2$-), 3.37 (t, 2H, J = 7.27Hz, S-CH_2-), 3.53-3.74 (m, 2H, sugar ring), 3.95-4.01 (m, 1H, sugar ring), 4.15-4.23 (m,

1H, sugar ring), 4.61 (q, 1H, J = 5.21Hz, sugar ring), 5.16 (t, 1H, J = 5.37Hz, sugar ring), 5.28 (d, 1H, J = 4.90Hz, sugar ring), 5.57 (d, 1H, J = 6.00Hz, sugar ring), 6.00 (d, 1H, J = 5.53Hz, sugar ring), 8.72 (s, 1H, N-CH-N), 8.74 (s, 1H, N-CH-N-C-S). MS APCI$^+$ (m/z): = 341(M+H), 209(M-sugar ring). IR (KBr, cm^{-1}) = 3323, 2936, 1573, 1427, 1336, 1218, 1114, 945, 636. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 159.92(S-C-), 148.09(S-C-**C**=C-N), 131.21(S-C-C=**C**-N), 61.21(sugar ring), 31.19(S-CH_2-), 27.43(S-CH_2-**C**H_2-), 21.43(S-CH_2CH_2-**C**H_2-). Negative peaks: δ = 87.67(sugar ring), 85.61(sugar ring), 73.79(sugar ring), 70.22(sugar ring), 13.55(-CH_3).

3.3.30: 6-Cyclopentyl-mercaptopurine riboside

A similar method was used for the synthesis of 6-benzyl-mercaptopurine (3.3.1). 6-Mercaptopurine riboside (0.14 g, 0.5 mmol) was reacted with cyclopentyl bromide (0.06 ml, 0.5 mmol) in the presence of triethylamine (20 % mol/mol) for 4 hr at 25 °C to give a solid product (0.2 g, 92%). Mp: 60-62 °C. ^1H NMR (DMSO-d_6): 1.55-1.82 (m, 6H, -$CH_2CH_2CH_2$-), 2.18-2.31 (m, 2H, -CH_2-), 3.53-3.74 (m, 2H, sugar ring), 3.94-4.02 (m, 1H, sugar ring), 4.15-4.22 (m, 1H, sugar ring), 4.35 (quint, 1H, J = 6.16Hz, sugar ring), 4.61 (q, 1H, J = 5.06Hz, sugar ring), 5.18 (t, 1H, J = 6.00Hz, sugar ring), 5.28 (d, 1H, J = 5.05Hz, sugar ring), 5.57 (d, 1H, J = 5.84Hz, sugar ring), 5.99 (d, 1H, J = 5.69Hz, sugar ring), 8.71 (s, 1H, 1H, N-CH-N), 8.74 (s, 1H, N-CH-N-C-S). MS APCI$^+$ (m/z): = 353(M+H), 221(M-sugar ring), 153(M-sugar ring-cyclopentyl). IR (KBr, cm^{-1}) = 3377, 2954, 1573, 1423, 1332, 1209, 1082, 941, 636. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 160.67(S-C-), 148.09(S-C-**C**=C-N), 131.02(S-C-C=**C**-N), 61.21(sugar ring), 33.06(-CH_2-), 24.43(-CH_2-). Negative peaks: δ = 87.67(sugar ring), 85.61(sugar ring), 73.79(sugar ring), 70.22(sugar ring), 41.32(S-CH-).

3.3.31: 6-Propyl-thioguanosine

A similar method was used for the synthesis of 6-benzyl-mercaptopurine (3.3.1). 6-Thioguanosine (0.27 g, 1 mmol) was reacted with propyl bromide (0.09 ml, 1 mmol)

in the presence of triethylamine (20 % mol/mol) for 4 hr at 25 °C to give a solid product (0.24 g, 81%). Mp: 89-91 °C. ^{1}H NMR (DMSO-d_6): 1.00 (t, 3H, J = 6.95Hz, -CH_3), 1.69 (q, 2H, J = 6.95Hz, -CH_2-), 3.26 (t, 2H, J = 6.95Hz, S-CH_2-), 3.49-3.70 (m, 2H, sugar ring), 3.88-3.92 (m, 1H, sugar ring), 4.09-4.14 (m, 1H, sugar ring), 4.44-4.51 (m, 1H, sugar ring), 5.10 (t, 1H, J = 5.68Hz, sugar ring), 5.18 (d, 1H, J = 4.42Hz, sugar ring), 5.46 (d, 1H, J = 5.68Hz, sugar ring), 5.83 (d, 1H, J = 5.68Hz, sugar ring), 6.54 (s, 2H, NH_2), 8.19 (s, 1H, N-CH-N). MS APCI^{+} (m/z): = 298(M+H), 208(M-sugar ring). IR (KBr, cm^{-1}) = 3387, 1565, 1462, 1410, 1212, 1086, 922. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 159.43(S-C-, 150.86(-C-NH_2), 124.23(S-C-C=C-N), 61.33(sugar ring), 29.25(S-CH_2-), 22.72(-CH_2-). Negative peaks: δ = 86.40(sugar ring), 85.25(sugar ring), 73.44(sugar ring), 70.33(sugar ring), 13.22(-CH_3).

3.3.32: 6-(1-Methylbenzyl)-thioguanosine

A similar method was followed as described for the synthesis of 6-benzyl-mercaptopurine (3.3.1). 6-Thioguanosine (0.21 g, 0.7 mmol) was reacted with α-methylbenzyl bromide (0.13 ml, 0.7 mmol) in the presence of triethylamine (20 % mol/mol) for 3 hr at 25 °C to give a solid product (0.24 g, 96%). Mp: 102-103 °C. ^{1}H NMR (DMSO-d_6): 1.74 (d, 3H, J = 7.27Hz, -CH_3), 3.48-3.69 (m, 2H, sugar ring), 3.86-3.94 (m, 1H, sugar ring), 4.08-4.16 (m, 1H, sugar ring), 4.42-4.52 (m, 1H, sugar ring), 5.11 (t, 1H, J = 5.37Hz, sugar ring), 5.16-5.22 (m, 1H, sugar ring), 5.42 (q, 1H, J = 7.27Hz, S-CH-), 5.44-5.48 (m, 1H, sugar ring), 5.76-5.84 (m, 1H, sugar ring), 6.64 (s, 2H, NH_2), 7.20 -7.58 (m, 5H, Ph), 8.19 (s, 1H, N-CH-N). MS APCI^{+} (m/z): = 404(M+H), 272(M-sugar ring), 168(M-sugar ring-(CH_3-CH-Ph)). IR (KBr, cm^{-1}) = 3350, 2923, 1564, 1400, 1214, 1082, 927, 700. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 159.36(S-C-), 151.10(-C-NH_2), 143.22(S-C-C=C-N), 123.89(S-C-C=C-N), 61.21(sugar ring). Negative peaks: δ = 128.39(Ph), 127.46(Ph), 127.11(Ph), 86.54(sugar ring), 85.23(sugar ring), 73.41(sugar ring), 70.22(sugar ring), 40.76(S-CH-), 22.18(-CH_3).

3.3.33: 6-Crotyl-thioguanosine

A similar method was followed as described for the synthesis of 6-benzyl-mercaptopurine (3.3.1). 6-Thioguanosine (0.16 g, 0.5 mmol) was reacted with crotyl bromide (0.07 ml, 0.5 mmol) in the presence of triethylamine (20 % mol/mol) for 2.5 hr at 25 °C to give a solid product (0.18 g, 96%). Mp: 89-91 °C. ^{1}H NMR (DMSO-d_6): 1.64 (d, 2H, J = 5.69Hz, -CH_3), 3.17 (d, 2H, J = 5.21Hz, S-CH_2-), 3.48-3.70 (m, 2H), 3.87-3.95 (m, 3H), 4.07-4.22 (m, 1H), 4.42-4.53 (m, 1H), 5.11 (m, 1H, 5.69Hz), 5.17-5.23 (m, 1H), 5.44-5.51 (m, 1H), 5.51-5.80 (m, 2H, CH=CH), 5.74-5.83 (m, 1H), 6.59 (s, 2H, NH_2), 8.19 (s, 1H, N-CH-N). MS APCI^{+} (m/z): = 354(M+H), 222(M-sugar ring), 168(M-sugar ring-CH_2CH=$CHCH_3$). IR (KBr, cm^{-1}) = 3350, 2918, 1559, 1400, 1214, 1086, 927, 636. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 159.36(S-C-), 150.92(-C-NH_2), 124.08(S-C-C=C-N), 61.40(sugar ring), 29.50(S-CH_2-). Negative peaks: δ = 128.58(CH_2-CH=CH), 126.71(CH=CH-), 86.36(sugar ring), 85.24(sugar ring), 73.41(sugar ring), 70.41(sugar ring), 17.49(-CH_3).

3.3.34: Bis(2-pyrimidinyl) disulfide

A similar method was followed as described for the synthesis of 2-propyl-mercaptopyrimidine (3.3.12). 2-Mercaptopyrimidine (0.1 g, 0.9 mmol) was treated with propyl bromide (0.09 ml, 0.9 mmol). DMSO was used as a solvent and no triethylamine was added. The product was a solid. The yield was 0.05 g (27%). Mp: 128-131 °C. ^{1}H NMR (DMSO-d_6): 7.39 (t, 2H, J=4.42Hz), 8.73 (d, 4H, J=4.42Hz). MS ES^{+} (m/z): = 223 (M+H). IR (KBr, cm^{-1}) = 3443, 1554, 1370, 1163, 737, 649. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 167.74(-C-S). Negative peaks: δ = 158.53(C-CH-C), 119.10(CH-CH-N).

Chapter 4

Use of Room Temperature Ionic Liquids for Knoevenagel Condensation Reactions

4.1 Introduction

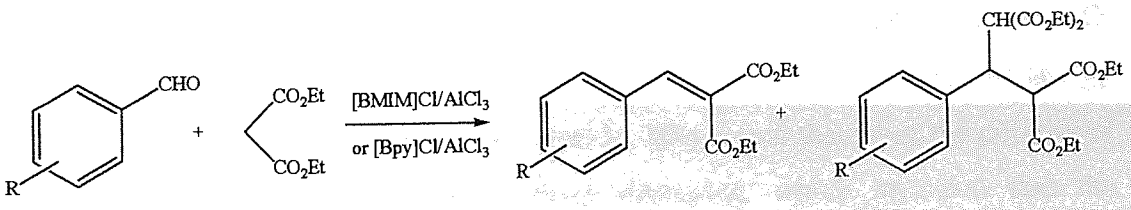
The Knoevenagel condensation reaction is an important, useful and widely employed method for carbon-carbon bond formation in organic reactions (Jones, 1967). It has been widely used in organic synthesis to prepare coumarins and their derivatives, which are important intermediates in the synthesis of cosmetics, perfumes and pharmaceuticals (Tietze and Beifuss, 1991; Bigi et al., 1999; Yu et al., 2000; Balalaie and Nemati, 2001).

The Knoevenagel condensation reaction is generally carried out in the presence of a weak base such as ethylenediamine, piperidine or amino acids such as glycine, β-alanine and L-proline under homogeneous conditions (Allen and Spangler, 1955; Rand et al., 1962; Acker and Hertler, 1962; Bastus, 1963; Cardillo et al., 2003). In recent years, many more catalysts such as calcium phosphate/potassium fluoride (Sebti et al., 2002) and triphenylphosphate (Yadav et al., 2004) have been found to promote the Knoevenagel condensation. Tetra-n-butylammonium hydroxide (TBAH) has also been reported to catalyze the condensation of alkyl cyanoacetates with several aromatic aldehydes in water/ethanol (Balalaie and Bararjanian, 2006). However, in many reported approaches, the reactions usually take a long time, organic solvents are always used and high reaction temperatures may be required. Moreover, less work has been done on the Knoevenagel condensation involving ketones, as sterically hindered ketones are not very reactive reagents in these reactions.

Recently, room temperature ionic liquids as "green solvents" have gained wide popularity for their increasing applications in the areas of synthetic and biological chemistry as they possess a number of interesting properties, especially their lack of

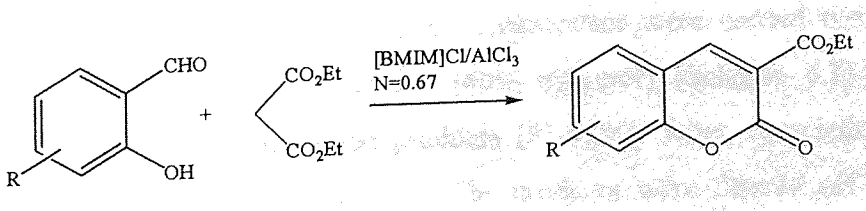
vapor pressure and lack of flammability, a widely accessible temperature range and ease of reuse. Therefore they are considered to be environmentally friendly reaction media, which initiate a tremendous growth in the interest of the application of RTILs for Knoevenagel condensation reactions.

Harjani et al. (2002) reported Knoevenagel condensation in Lewis acidic ionic liquids 1-butyl-3-methylimidazolium chloroaluminate [BMIM]Cl/$AlCl_3$, N=0.67 (N refers to the mole fraction of $AlCl_3$) and 1-butylpyridinium chloroaluminate [bpy]Cl/$AlCl_3$, N=0.67 (Scheme 4.1). The two ionic liquids acted as the catalyst and the solvent for the condensation of benzaldehyde or substituded benzaldehyde with diethyl malonate to give benzylidene malonates. The conversions were 70-95% after 5 minutes. A small amount of Michael addition product was formed as well, which depended on the Lewis acidity of ionic liquids. As Lewis acidity increased, the reaction conversion increased and the ratio of Knoevenagel condensation product/Michael addition product decreased.



Scheme 4.1 Reaction of benzaldehyde or substituted benzaldehyde with diethyl malonate in [BMIM]Cl/$AlCl_3$ or [bpy]Cl/$AlCl_3$

In addition, 3-ethoxycarbonyl coumarin was synthesized via Knoevenagel condensation by 2-hydroxybenzaldehyde with diethyl malonate in the Lewis acidic ionic liquid [BMIM]Cl/$AlCl_3$, N=0.67 (Scheme 4.2). Good yields (78-92%) of coumarins were produced within a few minutes.



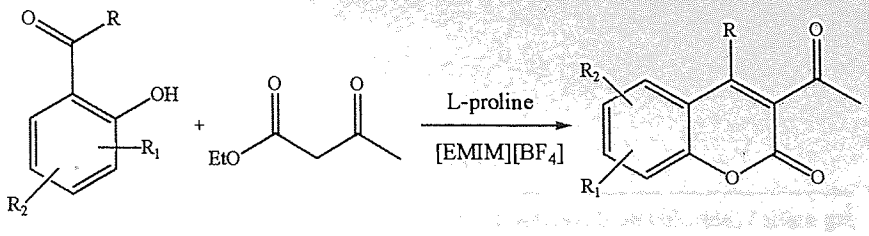
Scheme 4.2 Coumarin synthesis via Knoevenagel condensation of 2-hydroxy benzaldehydes with diethyl malonate in [BMIM]Cl/$AlCl_3$

Lewis acid-based ionic liquids are moisture sensitive. Therefore, air and water stable ionic liquids as solvents in the presence of a catalyst have received much attention for organic synthesis.

L-proline has been proposed to act as a recyclable chiral base for Knoevenagel condensation reactions. Wang and co-workers (Wang et al., 2006) described several Knoevenagel reactions catalyzed by L-proline in two ionic liquids $[EMIM]^+[BF_4]^-$ and $[BMIM]^+[BF_4]^-$. The reaction of diethylmalonate with benzaldehyde proceeded smoothly at 50 °C for 12 hours. The yield of the product was about 90% in either $[BMIM]^+[BF_4]^-$ or $[EMIM]^+[BF_4]^-$. Substituted benzaldehydes such as 4-chloro and 4-hydroxyl only afforded products with a yield of 50% and for 4-nitrobenzaldehyde the yield was much lower at 20%. However, the yields of those products in the ionic liquids were still higher than in common solvents such as H_2O, DMSO and CH_3OH under the same reaction conditions. The catalyst and the ionic liquid could be reused at least four times with no significant decrease in the yields. Additionally, Wang calculated solvation energies of the reactants and products in solvents such as H_2O, DMSO, and CH_3OH with the Gaussian 98 suite of the program. However, the energy value could not be calculated in the ionic liquids. They found that when the polarity of the solvent increased, the solvation energy decreased, which indicated that the reactants and products were more stabilized with the increased polarity of the solvents. Ionic liquids consist of cations and anions and they have high polarity. Therefore, the reactants such as starting materials, catalyst and intermediates would be expected to be more stable in the ionic liquids than in common solvents.

Another significant work was done by Liu et al. (2008). They studied L-proline as a promoter for the synthesis of coumarins in an ionic liquid 1-ethyl-3-methyl-imidazolium tetrafluoroborate $[EMIM]^+[BF_4]^-$. Knoevenagel reactions of salicylaldehyde or its derivatives with ethyl acetoacetate were carried out at room temperature in the presence of L-proline (40% mol/mol) (Scheme 4.3) and this approach achieved high yields of the products (81-95%). After completion of the reaction, water was added to the mixture. The products were filtered off from the water solution and L-proline and the ionic liquid remained in the water. The ionic liquid containing L-proline could be recycled and reused for several times without

noticeably decreasing in reactivity. The L-proline/$[EMIM]^+[BF_4]^-$ system provided a clean, efficient method for the synthesis of coumarines.

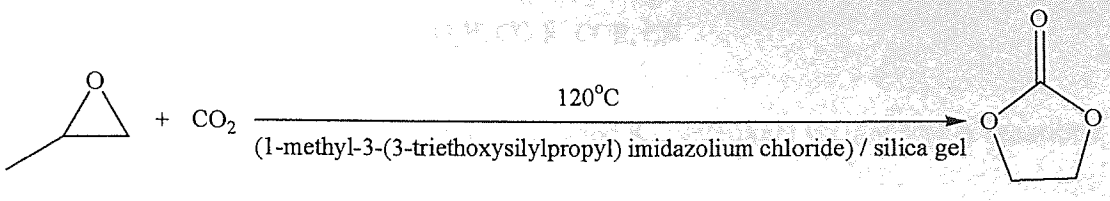


Scheme 4.3 Coumarin synthesis via Knoevenagel reactions in $[EMIM]^+[BF_4]^-$

An efficient catalyst for Knoevenagel condensation reactions in ionic liquids was found by Su et al. (2003). Their work showed that ethylenediammonium diacetate (EDDA) was an effective catalyst for Knoevenagel reactions in $[BMIM]^+[BF_4]^-$ and $[BMIM]^+[PF_6]^-$. The reactions of aldehydes and ketones with methylene compounds proceeded well in these two ionic liquids. They compared the traditional solvents with ionic liquids and found that a longer reaction time was required and a lower yield was obtained with the common organic solvents such as CH_2Cl_2 and MeOH than in ionic liquids. For example, when benzaldehyde was treated with ethyl cyanoacetate with the catalyst EDDA, the reaction was complete within 1 hour and the yield of the product was 95% and 92% in $[BMIM]^+[BF_4]^-$ and $[BMIM]^+[PF_6]^-$ respectively. In contrast, the reaction took 4 hours with a yield of 82% in CH_2Cl_2 and 8 hours with a yield of 87% in MeOH. This study clearly demonstrated that, with the same catalyst, ionic liquids can be more effective than common organic solvents.

In recent years, some groups have investigated a functionalized imidazolium ionic liquid that was immobilized on to silica gel to produce a recyclable system for Knoevenagel reactions. Lai et al. (2006) reported their work on Knoevenagel condensation of benzaldehyde or 2-, 4- substituted benzaldehyde with ethyl cyanoacetate and also cycloaddition of propylene oxide with carbon dioxide in an imidazolium cation based ionic liquid (1-methyl-3-(3-triethoxysilylpropyl) imidazolium chloride) immobilized on silica gel, which acted as a catalyst and a fixed solvent. A relatively high reaction temperature (100 °C) was required and the reaction time was 4-5 hours for the condensation of aldehydes. This imidazolium ionic liquid

was more effective with the addition of catalyst zinc chloride for the cycloaddition of carbon dioxide with propylene (Scheme 4.4). This cycloaddition reaction was performed at 120 °C for 8 hours in this ionic liquid/silica gel system.



Scheme 4.4 Cycloaddition of propylene oxide with carbon dioxide

In 2007, Paun et al. (2007) reported Knoevenagel reactions in several recyclable specific basic ionic liquids such as BIL1, BIL2, BIL3 (Figure 4.1) or non-basic ionic liquids including 1-butyl-1-methylpyrrolidilium bis[(trifluoromethyl)sulfonyl] imide ([C_4mpyrr][NTf_2]), 1-butyl-3-methylimidazolium bis[(trifluoromethyl)sulfonyl] imide ([C_4mim][NTf_2]) and 1-butyl-2,3-dimethyl imidazlolium bis[(trifluoromethyl) sulfonyl] imide ([C_4dmim][NTf_2]) (Schem 4.5).

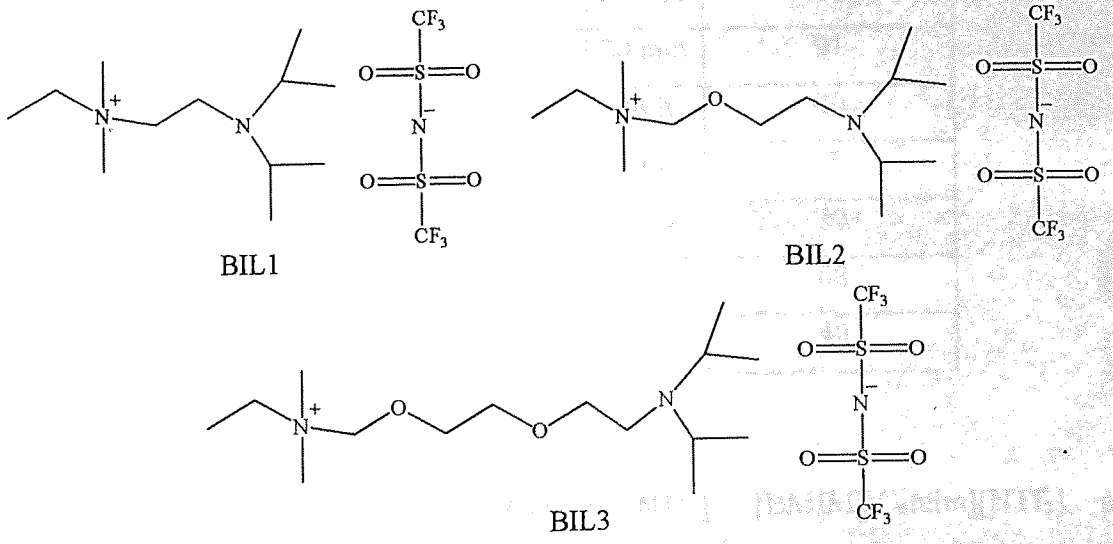
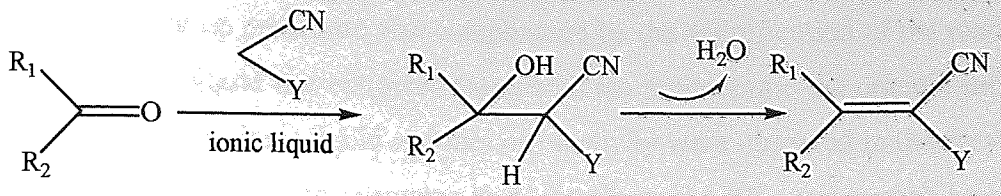


Figure 4.1 Structures of specific basic ionic liquids



R1, R2 = H, alkyl, aryl Y = CO_2H, CO_2R, COR, CN

Scheme 4.5 Specific basic ionic liquid-catalyzed Knoevenagel condensation reactions

One of the specific basic ionic liquids or the non-basic ionic liquids described above was used to form a homogeneous system without the addition of other solvents. In each case, 10% (mol/mol) of the ionic liquid was used. The experimental results for the reaction of heptaldehyde with ethyl cyanoacetate were summarized in Table 4.1.

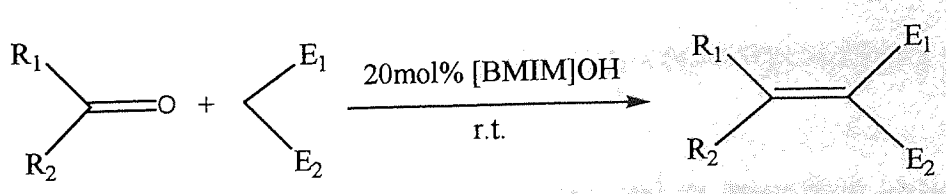
Table 4.1 Specific basic ionic liquids and non-basic ionic liquids-catalyzed the reaction of heptaldehyde with ethyl cyanoacetate at room temperature

Entry	System	Time	Conversion (%)
1	BIL1	60 min	50
2	BIL2	20 min	87
3	BIL3	20 min	91
4	$[C_4mpyrr][NTf_2]$	24 h	40
5	$[C_4mim][NTf_2]$	24 h	7
6	$[C_4dmim][NTf_2]$	24 h	30
7	Silica supported BIL2	1 h	68
8	BIL2/cyclohexene	1 h	40

When ionic liquids such as $[C_4mpyrr][NTf_2]$, $[BMIM][C_4mim][NTf_2]$ or $[C_4dmim][NTf_2]$ were used, a low conversion rate was observed even after a reaction time of 24 hours at room temperature (Entry 4-6). In contrast, the reactions catalyzed by basic ionic liquids proceeded efficiently with high yields within 1 hour (Entry 1-3). The conversion rate increased in the order of basic ionic liquids BIL1<BIL2< BIL3.

However, the work-up procedure was complicated by the solidification of the reaction mixture. The ionic liquid was extracted along with the product into the organic solvent. In addition, the loss of ionic liquid and loss of reactivity were observed in the recycled ionic liquids. In an attempt to overcome these problems the BIL was immobilized on silica with a pH value of 4. This silica did not catalyze the condensation even after a long reaction time without the presence of BIL. BIL in an immiscible solvent such as cyclohexene was also used to form a biphasic system for Knoevenagel reactions. The reactions in the heterogeneous system showed a lower reactivity than in the homogeneous system (Entry 7, 8), but the recycling potential was much improved. After recycling for five times, there was no significant loss of reactivity and loss of the recovered basic ionic liquids. However, the reactions of alkyl ketones with ethyl cyanoacetate did not proceed in all of these homogeneous and heterogeneous systems. Very low yields of products (10-20%) were obtained from the reactions of cycloketones with ethyl cyanoacetate in the homogeneous system (Paun et al., 2007).

Currently, task specific ionic liquids are being developed for organic synthesis. A basic ionic liquid $[BMIM]^+[OH]^-$ was reported by Ranu and Jana (2006). Reactions of aliphatic and aromatic aldehydes and ketones with active methylene compounds catalyzed by $[BMIM]^+[OH]^-$ were carried out in solvent-free conditions at room temperature (Scheme 4.6). The procedure was straightfoward. The reaction proceeded quickly within 10-30 minutes at room temperature. The products were obtained in high yields (75-96%). This method avoids the use of an additional catalyst. It is applicable to a wide range of aldehydes and methylene compounds.



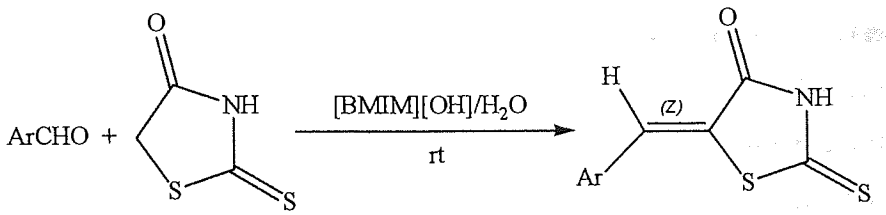
R1, R2 = alkyl, aryl, H

E1, E2 = CN, COMe, COOMe, COOEt, COOH

Scheme 4.6 $[BMIM]^+[OH]^-$-catalyzed Knoevenagel condensation reactions

Other groups have also reported the use of $[BMIM]^+[OH]^-$. Li et al. (2007) demonstrated that the basic ionic liquid $[BMIM]^+[OH]^-$ could be used as a catalyst for Knoevenagel reactions and Perkin reactions. Knoevenagel reactions proceeded within 10-30 minutes with a typical product yield of 85-95%.

Gong et al. (2008) described Knoevenagel condensation of rhodanine with aromatic aldehydes catalyzed by $[BMIM]^+[OH]^-$ in water. The reaction time was only 10-90 minutes and the product yield was over 80% (Scheme 4.7).

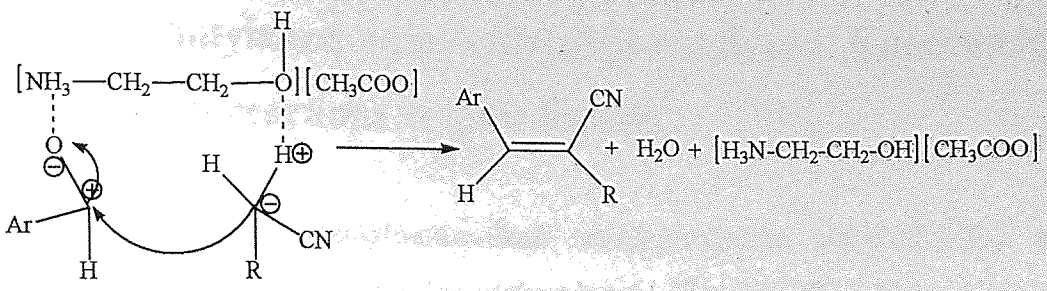


Scheme 4.7 $[BMIM]^+[OH]^-$-catalyzed reaction of rhodanine with aromatic aldehydes in water

$[BMIM]^+[OH]^-$ can catalyze Knoevenagel condensation reaction because of its basic anion. Another task specific ionic liquid was designed to achieve the catalytic activity with its cation. In 2008, Yue et al. (2008) synthesized a special ionic liquid $[H_3N^+–CH_2–CH_2–OH][CH_3COO^-]$ (Scheme 4.8).

Scheme 4.8 Synthesis of ionic liquid $[H_3N^+–CH_2–CH_2–OH][CH_3COO^-]$

This specific ionic liquid involves a hydroxyl group and an ammonium group. The hydroxyl group interacts with the hydrogens on the active methylene group to activate methylene compounds and the ammonium group interacts with the carbonyl group to activate the aromatic aldehydes. The mechanism is illustrated in Scheme 4.9.



Scheme 4.9 $[H_3N^+–CH_2–CH_2–OH][CH_3COO^-]$-catalyzed Knoevenagel sondensation reactions

The Knoevenagel condensation of aromatic aldehydes with ethyl cyanoacetate or malononitrile was catalyzed by the above specific ionic liquid under solvent-free condition at room temperature. Most of the reactions were completed within 1-15 minutes for benzaldehyde and 2- or 4-chlorobenzaldehyde. The reaction of 4-methoxy benzaldehyde with ethyl cyanoacetate required over 1 hour. Carbonyl products were obtained in good yields (82-98%). E-isomers were detected for all the products. No ketones were involved in this work. The ionic liquids were reused with no noticeably decrease of the catalytic activity.

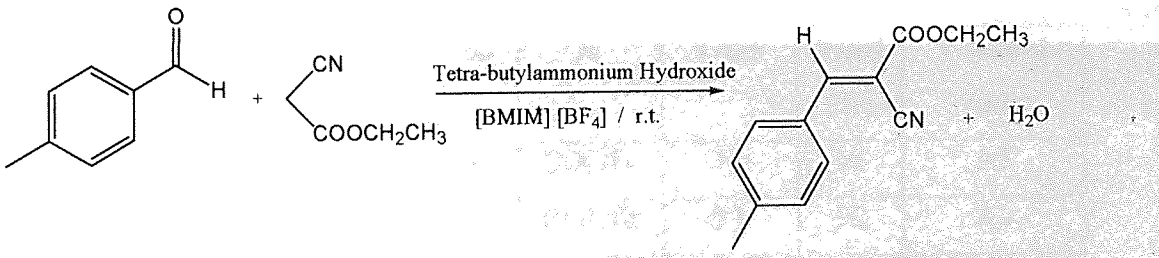
At the start of this project in 2006, there had not been many reports in the literature about Knoevenagel condensation reaction in RTILs. One interesting study was reported by Su and co-workers (Su et al., 2003). They investigated Knoevenagel reactions of a wide range of aldehydes and ketones with methylene compounds catalyzed by ethylenediammonium diacetate (EDDA) in $[BMIM]^+[BF_4]^-$ and $[BMIM]^+[PF_6]^-$ and found that, with the same catalyst (EDDA), the reactions were completed more rapidly in the ionic liquids than in organic solvents. Balalaie and Bararjanian (2006) studied the use of tetrabutylammonium hydroxide (TBAH) to catalyze Knoevenagel reactions in water/ethanol and indicated that TBAH was an efficient catalyst. However, only a few reactions were carried out and there was no description of reactions involving ketones. Considering the two significant studies discussed above, we decided to investigate Knoevenagel reactions in ionic liquids using TBAH as a catalyst.

4.2 Tetra-butylammoium hydroxide-catalyzed Knoevenagel condensation reactions in ionic liquids

Ionic liquids 1-butyl-3-methylimidazolium tetrafluoroborate $[BMIM]^+[BF_4]^-$ and 1-butyl-3-methylimidazolium hexafluorophosphorate $[BMIM]^+[PF_6]^-$ have been used as solvents for the Knoevenagel condensation reactions with tetrabutylammonium hydroxide (TBAH) as a catalyst to afford substituted olefins.

4.2.1 Results and Discussion

Generally, the catalyst is used in 20% (mol/mol) of one of the starting materials in a typical reaction. In order to determine the optimum amount of the catalyst, different amounts of TBAH were tested with the reaction of 4-methyl benzaldehyde with ethyl cyanoacetate in $[BMIM]^+[BF_4]^-$ (Scheme 4.10). The yields of the products with different amounts of TBAH as a catalyst are shown in Figure 4.2.



Scheme 4.10 Reaction of 4-methyl bezaldehyde with ethyl cyanoacetate catalyzed by TBAH in $[BMIM]^+[BF_4]^-$

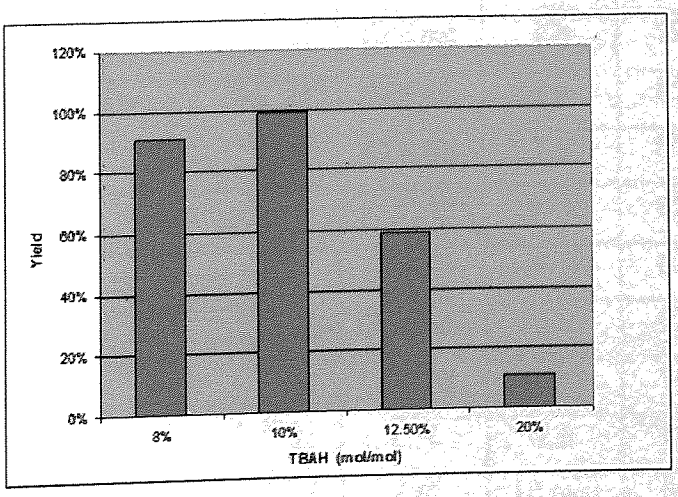
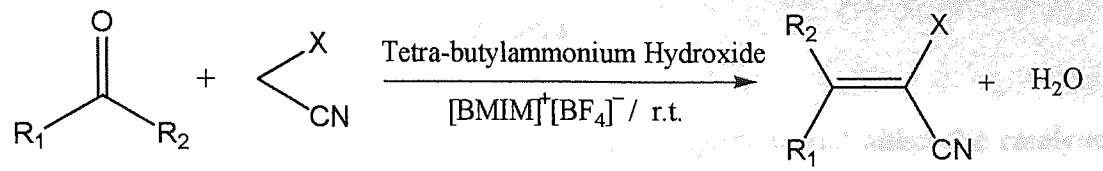


Figure 4.2 Comparison of the different amounts of TBAH used for the reaction of 4-methyl bezaldehyde with ethyl cyanoacetate in $[BMIM]^+[BF_4]^-$

Using TBAH at a concentration of 10 % (mol/mol) with respect to the starting material gave the best yield of product. Therefore, TBAH was used at this concentration for the following reactions. The reactions of aromatic aldehydes with different active methylene compounds were carried out in $[BMIM]^+[BF_4]^-$. The reaction scheme (Scheme 4.11) and the product yields (Table 4.2) are shown below.



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Scheme 4.11 Knoevenagel condensation reactions catalyzed by TBAH in $[BMIM]^+[BF_4]^-$

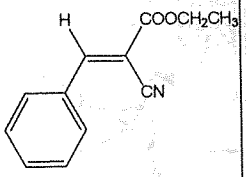
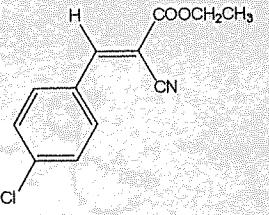
Table 4.2 Knoevenagel condensation reactions catalyzed by TBAH in $[BMIM]^+[BF_4]^-$ at room temperature

Entry	R_1	R_2	X	Time	Yield (%)	Product code
1	Ph	H	COOEt	3 h	98	A1
2	4-Cl-C_6H_4	H	COOEt	3 h	92	A2
3	4-MeO-C_6H_4	H	COOEt	3 h	82	A3
4	4-Me-C_6H_4	H	COOEt	1 h	97	A4
5	4-(Me_2N)-C_6H_4	H	COOEt	1 h	79	A5
6	3,4,5-MeO-C_6H_4	H	COOEt	3 h	85	A6
7	4-NO_2-C_6H_4	H	COOEt	1 h	87	A7
8	-$(CH_2)_4$-		COOEt	20 h	49	A8
9	-$(CH_2)_5$-		COOEt	20 h	62	A9
10	Ph	H	COOMe	2 h	93	A10
11	4-Cl-C_6H_4	H	COOMe	20 min	90	A11
12	Ph	H	CN	2 h	82	A12
13	4-Cl-C_6H_4	H	CN	10 min	80	A13

The above results demonstrated that the Knoevenagel condensation reactions of aromatic aldehydes with various substituents and different active methylene compounds proceeded effectively with TBAH as the catalyst in $[BMIM]^+[BF_4]^-$ at room temperature. High yields of the products were obtained. For cycloketones, a longer reaction time (20 hours) was required with moderate yields (Table 4.2, Entry 8, 9). The synthetic methods were straightforward, and the products were easily isolated from the RTILs with good to excellent yields.

In order to determine whether the recovered ionic liquids would affect the catalytic activity of TBAH, reactions of benzaldehyde or chlorobenzaldehyde with ethyl cyanoacetates were carried out in the recycled ionic liquids $[BMIM]^+[BF_4]^-$ and $[BMIM]^+[PF_6]^-$. The results (Table 4.3) showed that these reactions were still effective and efficient in recovered $[BMIM]^+[BF_4]^-$ and $[BMIM]^+[PF_6]^-$.

Table 4.3 Knoevenagel condensation reactions catalyzed by TBAH in recycled $[BMIM]^+[BF_4]^-$ or $[BMIM]^+[PF_6]^-$

Entry	Ionic liquid	Yield (%)  (A1)	Yield (%)  (A2)
1	$[BMIM]^+[BF_4]^-$ (Fresh)	97	91
2	$[BMIM]^+[BF_4]^-$ (cycle1)	96	92
3	$[BMIM]^+[BF_4]^-$ (cycle2)	97	90
4	$[BMIM]^+[PF_6]^-$ (Fresh)	95	89
5	$[BMIM]^+[PF_6]^-$ (cycle1)	94	88
6	$[BMIM]^+[PF_6]^-$ (cycle2)	94	91

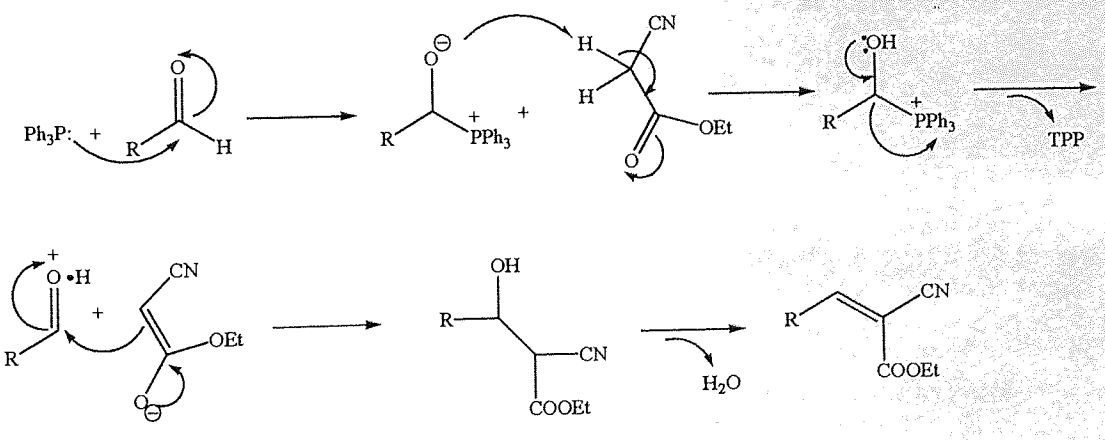
The reactions were carried out in the same conditions as in Table 4.2.

Balalaie reported TBAH-catalyzed Knoevenagel condensation of a few aromatic aldehydes with alkyl cyanoacetates in water/ethanol (Balalaie and Bararjanian, 2006). There was no report of reactions involving ketones in Balalaie's work. Condensations

of alkyl cyanoacetates with cycloketones catalyzed by TBAH could be carried out in $[BMIM]^+[BF_4]^-$ at room temperature.

To summarize the above results, tetrabutylammonium hydroxide was a good catalyst for Knoevenagel condensation reaction. The reactions of aldehydes and cyclic ketones with methylene compounds such as methyl- and ethylcyanoacetate, malononitrile could be carried out effectively in $[BMIM]^+[BF_4]^-$ and $[BMIM]^+[PF_6]^-$. Both of the ionic liquids as solvents significantly promoted the reaction rate and gave high yields of the products. $[BMIM]^+[BF_4]^-$ and $[BMIM]^+[PF_6]^-$ were recycled several times with no obvious decrease in the reaction rates and the product yields.

Yadav et al. (2004) reported the use of triphenylphosphine (TPP) to catalyze Knoevenagel condensation of aromatic and heterocyclic aldehydes with ethyl cyanoacetate and malononitrile under solvent-free condition. Good results were obtained when the reactions were carried out at 75-80 °C with 20% (mol/mol) TPP as the catalyst. The proposed mechanism of the reaction is illustrated in Scheme 4.12.



Scheme 4.12 Mechanism of TPP-catalyzed Knoevenagel condensation reactions

Based on the proposed mechanism, it was reasoned that if triphenylarsine (TPA) was to be used in the place of TPP the reaction rate and, possibly, the yield could be further improved as TPA is a better leaving group compared with TPP. So TPA-catalyzed

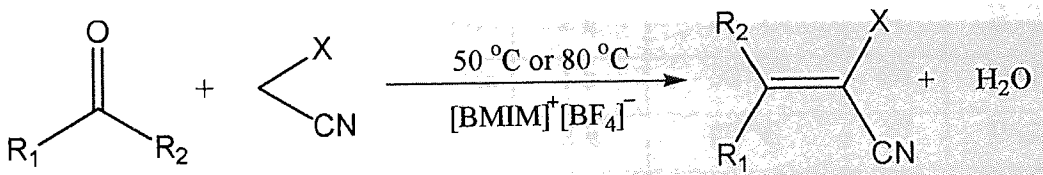
Knoevenagel reactions were investigated in $[BMIM]^+[BF_4]^-$ at room temperature. However, for the reaction of benzaldehyde with ethyl acetate, after the mixture was stirred for 3-4 hours at room temperature, no product was observed with TLC analysis. When the reaction temperature was increased to 80 °C, the reaction proceeded and the product was observed. Later it was unexpectedly discovered that the reaction also occurred at 80 °C in the absence of "catalyst" TPA. Further investigations revealed that $[BMIM]^+[BF_4]^-$ had some catalytic activity to promote Knoevenagel reactions. Therefore more research work was carried out using ionic liquids as both a solvent and a catalyst for Knoevenagel reactions. The details are described in the following sections.

4.3 $[BMIM]^+[BF_4]^-$ or $[BMIM]^+[PF_6]^-$ as a solvent and a catalyst for Knoevenagel condensation reactions

Knoevenagel condensation reactions were investigated in an ionic liquid $[BMIM]^+[BF_4]^-$ or $[BMIM]^+[PF_6]^-$ without the addition of any other catalysts.

4.3.1 Results and Discussion

Adehydes or ketones, and methylene compounds were mixed in $[BMIM]^+[BF_4]^-$ and stirred for an appropriate time. The reactions occurred in $[BMIM]^+[BF_4]^-$ at 50 °C or 80 °C. When the reactions were completed, the products were extracted with diethyl ether and washed with water and then further purified by recrystallization or flash column chromatography. The reaction scheme (Scheme 4.13) and results (Table 4.4) are shown below.



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Scheme 4.13 Knoevenagel condensation reaction in $[BMIM]^+[BF_4]^-$

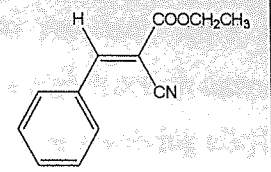
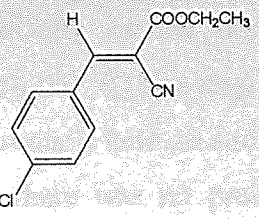
According to the results in Table 4.4 $[BMIM]^+[BF_4]^-$ acted as a solvent and a catalyst for the Knoevenagel condensations. The products were isolated in excellent yields. The reactions involving cycloketones required a longer reaction time (48 hours).

Table 4.4 Knoevenagel condensation of aldehydes or ketones with methylene compounds in $[BMIM]^+[BF_4]^-$

Entry	R_1	R_2	X	Time	Reaction temperature	Yield (%)	Product code
1	Ph	H	COOEt	3 h	80 °C	97	B1
2	4-Cl-C_6H_4	H	COOEt	3 h	80 °C	95	B2
3	4-MeO-C_6H_4	H	COOEt	3 h	80 °C	94	B3
4	3,4,5-MeO-C_6H_4	H	COOEt	3 h	80 °C	79	B4
5	4-Me-C_6H_4	H	COOEt	3 h	80 °C	90	B5
6	4-(Me_2N)-C_6H_4	H	COOEt	2 h	80 °C	98	B6
7	4-NO_2-C_6H_4	H	COOEt	1 h	50 °C	86	B7
8	-$(CH_2)_4$-		COOEt	48 h	80 °C	31	B8
9	-$(CH_2)_5$-		COOEt	48 h	80 °C	83	B9
10	Ph	H	COOMe	2 h	80 °C	86	B10
11	4-Cl-C_6H_4	H	COOMe	1 h	50 °C	66	B11
12	Ph	H	CN	2 h	80 °C	87	B12
13	4-Cl-C_6H_4	H	CN	20 min	50 °C	88	B13

In order to determine whether ionic liquids could be reused, and whether recovered ionic liquids would affect the reaction rates or the yields of the products, the Knoevenagel condensation reactions were carried out in the recycled ionic liquid $[BMIM]^+[BF_4]^-$ or $[BMIM]^+[PF_6]^-$. The results (Table 4.5) showed that these reactions were still effective in recycled $[BMIM]^+[BF_4]^-$ and $[BMIM]^+[PF_6]^-$. Slightly reduced yields of products were observed when the reactions were carried out in these two recovered ionic liquids.

Table 4.5 Knoevenagel condensation reactions in the recycled ionic liquids $[BMIM]^+[BF_4]^-$ and $[BMIM]^+[PF_6]^-$

Ionic liquid	Reaction time	Yield (%)  (B1)	Yield (%)  (B2)
$[BMIM]^+[BF_4]^-$ (Fresh)	3 h	97	95
$[BMIM]^+[BF_4]^-$ (cycle1)	3 h	96	81
$[BMIM]^+[BF_4]^-$ (cycle2)	3 h	90	84
$[BMIM]^+[PF_6]^-$ (Fresh)	4 h	96	94
$[BMIM]^+[PF_6]^-$ (cycle1)	4 h	86	85
$[BMIM]^+[PF_6]^-$ (cycle2)	4 h	55	65

The reactions were carried out in the same conditions as in Table 4.4.

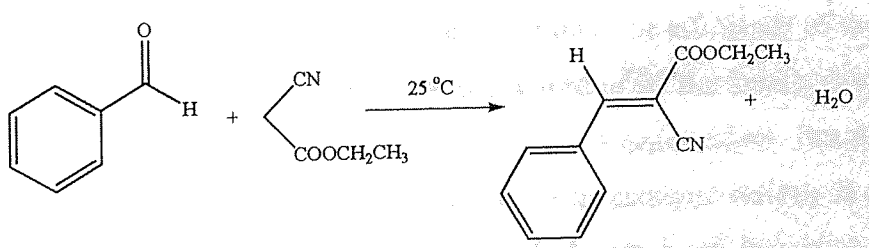
In summary, for the first time, neutral ionic liquids $[BMIM]^+[BF_4]^-$ and $[BMIM]^+[PF_6]^-$ have been demonstrated to have catalytic activity for Knoevenagel reactions. Reactions of aldehydes and cycloketones with methylene compounds could be carried out effectively in $[BMIM]^+[BF_4]^-$ and $[BMIM]^+[PF_6]^-$.

4.4 Various room temperature ionic liquids as solvents and catalysts for Knoevenagel condensation reactions

Although Knoevenagel condensation reactions were successfully carried out in $[BMIM]^+[BF_4]^-$ and $[BMIM]^+[PF_6]^-$, a high reaction temperature (80 °C) was required for the most of the reactions. The reactions involving alkyl or aromatic ketones such as butanone and acetophenone did not proceed. For example, there was no product observed when the reaction of acetophenone with methyl- or ethyl cyanoacetate was carried out for 3 days at 80 °C. Moreover, the reaction with low boiling reagents such as acetone is difficult to be carried out at relatively high temperature. In order to find an ionic liquid in which these reactions can occur at room temperature and be completed in a short reaction time, a range of ionic liquids were investigated for these Knoevenagel reactions.

4.4.1 Results and Discussion

The reaction outlined in Scheme 4.14 was investigated in various ionic liquids in order to identify an appropriate RTIL. Benzaldehyde and ethyl cyanoacetate were mixed in one of the ionic liquids listed in Table 4.6 and stirred for an appropriate time at 25 °C.



Scheme 4.14 Reaction of benzaldehyde with ethyl cyanoacetate in various RTILs

The results in Table 4.6 demonstrated that benzaldehyde reacted effectively with ethyl cyanoacetate in all the tested RTILs. In contrast, no desired product was gained when the reaction was carried out in methanol. Excellent yields of the products were obtained in the following ionic liquids $[MeOEtMIM]^+[CF_3COO]^-$, $[MeOMeOEtMIM]^+[CF_3COO]^-$, $[BMIM]^+[CF_3COO]^-$ and $[MeOEtMIM]^+[CH_3SO_3]^-$.

The reaction took a relatively long time when it was carried out in $[BMIM]^+[BF_4]^-$ or $[BMIM]^+[PF_6]^-$.

Table 4.6 Knoevenagel condensation of benzaldehyde with ethyl cyanoacetate in various ionic liquids at 25 °C

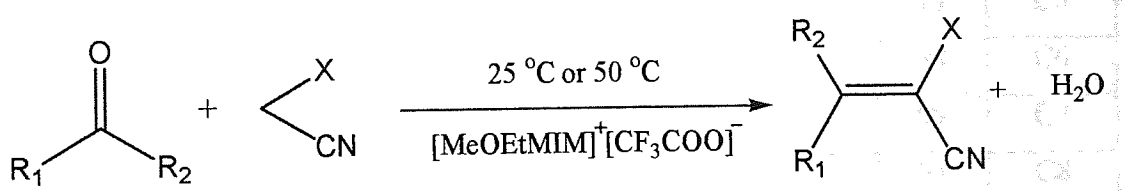
Entry	Solvent	Reaction time	Yield (%)
1	$[MeOEtMIM]^+[CF_3COO]^-$	40 min	99
2	$[MeOMeOEtMIM]^+[CF_3COO]^-$	40 min	95
3	$[BMIM]^+[CF_3COO]^-$	50 min	98
4	$[PhOPMIM]^+[CF_3CF_2COO]^-$	4 h	90
5	$[MeOEtMIM]^+[CH_3SO_3]^-$	1 h	97
6	$[MeOEtMIM]^+[CF_3SO_3]^-$	2 h	81
7	$[MeOEtBuMIM]^+[CF_3SO_3]^-$	1 h	54
8	$[BMIM]^+[BF_4]^-$	24 h	85
9	$[BMIM]^+[PF_6]^-$	22 h	63
10	Methanol	24 h	0

It also can be seen from Table 4.6 that when the reaction was carried out in RTILs that have the same cation but with a different anion, the reaction time and the yield of the product varied greatly with the different type of anions. In contrast, when the reaction proceeded in RTILs that have the same anion but with a different cation, the reaction time and the yield of the product were similar. Therefore, the efficiency of the reaction depends on the type of anions in RTILs. Various anions of RTILs have a crucial effect on the catalytic activity of RTILs. Cations do not have a major effect. But the type of cations significantly affects the viscosity of RTILs. This catalytic cativity is due to the basicity of the anion of ionic liquids and also the hydrogen bond formation ability of the C-2 hydydrogen.

An ideal ionic liquid for Knoevenagel condensation reactions should have a lower viscosity, a strong catalytic capability, and is not expensive for industrial production. According to the yields of the reaction, $[MeOEtMIM]^+[CF_3COO]^-$, $[MeOMeOEtMIM]^+[CF_3COO]^-$ and $[BMIM]^+[CF_3COO]^-$ seemed better options compared with others. However, $[MeOMeOEtMIM]^+[CF_3COO]^-$ is more viscous than

$[MeOEtMIM]^+[CF_3COO]^-$ and the price of starting material for its preparation is higher than for the preparation of other two ionic liquids. A further experiment was carried out in order to differentiate the two ionic liquids. When the reaction of 4-methylbenzaldehyde with ethyl cyanoacetate was carried out in $[BMIM]^+[CF_3COO]^-$, the reaction time was 30 minutes and the yield was 74%. When the same reaction was carried out in $[MeOEtMIM]^+[CF_3COO]^-$, the reaction time was 20 minutes and the yield was 89%.

Considering the above results, $[MeOEtMIM]^+[CF_3COO]^-$ seems to be a good choice for Knoevenagel reactions. A wide range of aldehydes and ketones with methylene compounds (Scheme 4.15) were investigated in $[MeOEtMIM]^+[CF_3COO]^-$. The reaction results are shown below (Table 4.7).



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Scheme 4.15 Knoevenagel condensation reactions in $[MeOEtMIM]^+[CF_3COO]^-$

It can be seen from Table 4.7 that all the reactions proceeded smoothly in $[MeOEtMIM]^+[CF_3COO]^-$. Aldehydes with various substituents reacted rapidly with active methylene compounds at room temperature and the resulting products were obtained in excellent yields (Entry 1-10). For ketones, higher temperature and longer reaction times were needed with moderate yields (Entry 11-17). All the products were characterized by ^1H NMR, ^{13}C NMR, IR, MS. These reactions were usually highly stereo-selective and most products were the E-geometry as confirmed with nuclear overhauser enhancement spectroscopy (NOESY) experiments. However, two isomers (E & Z) were obtained when butanone or acetophenone was reacted with methylene compounds as revealed by ^1H NMR and ^{13}C NMR. It was difficult to isolate the two isomers on flash column chromatography, as they showed only one spot on TLC plate with various developing solvents. From NMR analysis of the reaction mixture the ratio

of E : Z isomer was 17 : 5 and 14 : 5 for the reaction of acetonephenone with methyl- and ethyl cyanoacetate respectively. The ratio of E : Z was 6 : 5 and 3 : 2 for the reaction of butanone with methyl- and ethyl cyanoacetate respectively.

Table 4.7 Knoevenagel condensation of aldehydes or ketones with methylene compounds in $[MeOEtMIM]^+[CF_3COO]^-$

Entry	R1	R2	X	Time	Reaction temperature	Yield (%)	Product code
1	Ph	H	COOEt	40 min	25 °C	99	C1
2	4-Cl-C_6H_4	H	COOEt	5 min	25 °C	97	C2
3	4-Me-C_6H_4	H	COOEt	20 min	25 °C	89	C3
4	4-NO_2-C_6H_4	H	COOEt	10 min	25 °C	81	C4
5	4-COOH-C_6H_4	H	COOEt	50 min	25 °C	77	C5
6	Naphthalene	H	COOEt	15 min	25 °C	98	C6
7	3-Cl-C_6H_4	H	COOMe	2 min	25 °C	99	C7
8	4-Me-C_6H_4	H	COOMe	10 min	25 °C	91	C8
9	4-MeO-C_6H_4	H	COOMe	35 min	25 °C	78	C9
10	4-OH-C_6H_4	H	COOMe	40 min	25 °C	83	C10
11a	-$(CH_2)_4$-		COOMe	16 h	25 °C	11	C11
11b	-$(CH_2)_4$-		COOMe	16 h	50 °C	23	C11
11c	-$(CH_2)_4$-		COOMe	48 h	50 °C	85	C11
12a	-$(CH_2)_5$-		COOMe	16 h	25 °C	56	C12
12b	-$(CH_2)_5$-		COOMe	16 h	50 °C	61	C12
13	CH_3	CH_3	COOEt	65 h	25 °C	90	C13
14	CH_3CH_2CO	CH_3	COOMe	48 h	50 °C	55	C14
15	CH_3CH_2CO	CH_3	COOEt	60 h	50 °C	40	C15
16	Ph	CH_3	COOMe	48 h	50 °C	47	C16
17	Ph	CH_3	COOEt	45 h	50 °C	40	C17

The NOESY spectrum of ethyl-2-cyano-3-phenyl-2-propenoate is shown in Figure 4.4. No spot between C(3)H (Figure 4.3) and CH_2CH_3 is shown in Figure 4.4, which proves that there is no coupling between C(3)H and CH_2CH_3, therefore this compound is trans-formation.

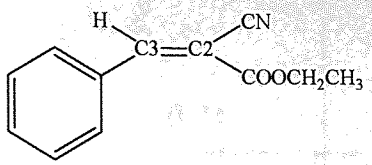


Figure 4.3 Ethyl-2-cyano-3-phenyl-2-propenoate

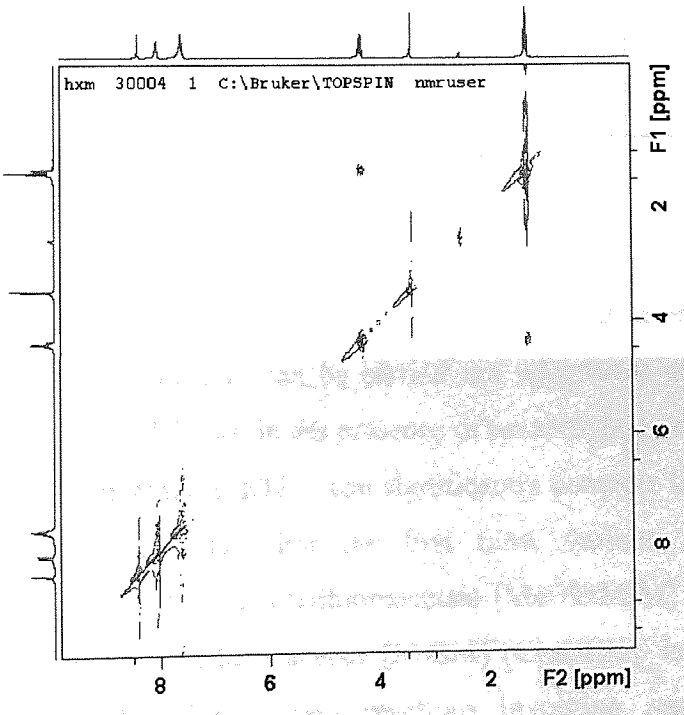
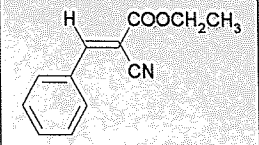
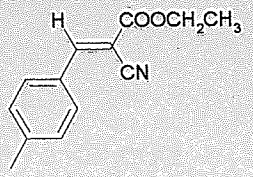


Figure 4.4 NOESY spectrum of ethyl-2-cyano-3-phenyl-2-propenoate

In order to determine whether ionic liquids could be reused, and whether recovered ionic liquids would affect the reaction rates and the product yields, the Knoevenagel condensation reactions were carried out in recycled $[MeOEtMIM]^+[CF_3COO]^-$. The results (Table 4.8) showed that these reactions were still effective in recycled $[MeOEtMIM]^+[CF_3COO]^-$.

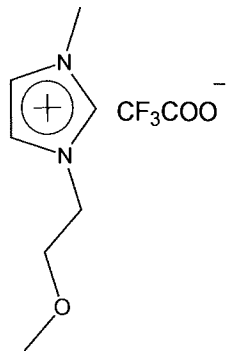
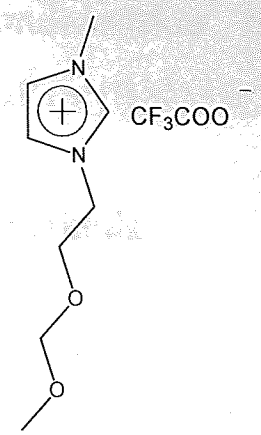
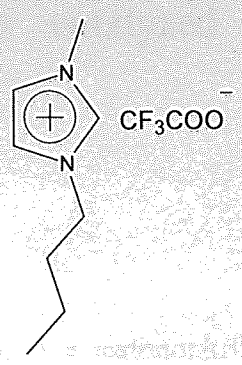
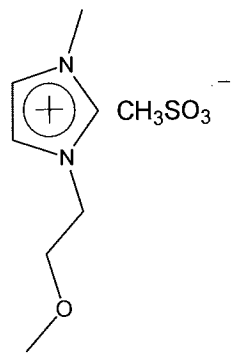
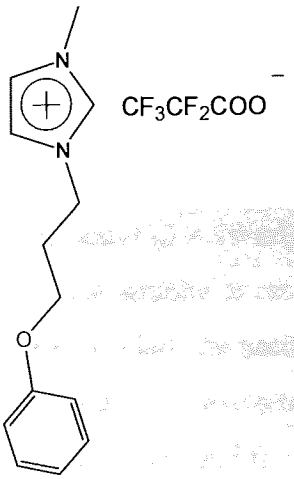
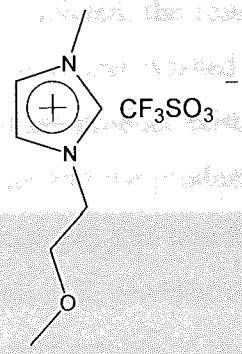
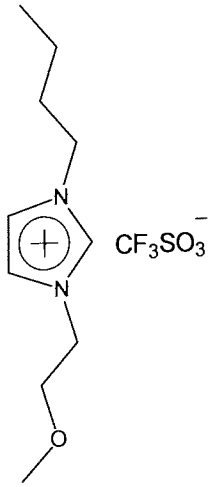
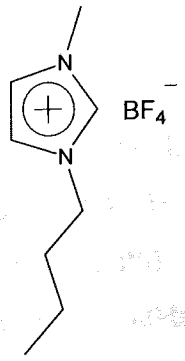
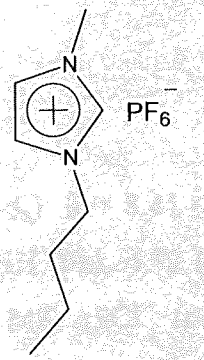
Table 4.8 Knoevenagel condensation reactions in recycled $[MeOEtMIM]^+[CF_3COO]^-$

Ionic liquid	Reaction time	Yield (%)  (C1)	Reaction time	Yield (%)  (C3)
$[MeOEtMIM]^+$ $[CF_3COO]^-$ (Fresh)	40 min	99	20 min	89
$[MeOEtMIM]^+$ $[CF_3COO]^-$ (cycle1)	40 min	91	30 min	86
$[MeOEtMIM]^+$ $[CF_3COO]^-$ (cycle2)	40 min	88	50 min	81

The reactions were carried out in the same conditions as in Table 4.7.

In summary, RTILs as "green solvents" have many applications in organic reactions. Knoevenagel condensation reaction can be carried out effectively and efficiently in $[BMIM]^+[BF_4]^-$ and $[BMIM]^+[PF_6]^-$ in the presence of tetrabutylammonium hydroxide as a catalyst at room temperature. RTILs can significantly promote the reaction rates and improve the product yields. For the first time, various RTILs such as 1-methoxyethyl-3-methylimidazolium trifluoroacetate $[MeOEtMIM]^+[CF_3COO]^-$ and 1-butyl-3-methylimidazolium trifluoroacetate $[BMIM]^+[CF_3COO]^-$ have been used as catalysts and solvents for Knoevenagel reactions involving not only aromatic aldehydes but also ketones to afford substituted olefins at room temperature with good to excellent yields. This catalytic cativity is due to the basicity of the anion of ionic liquids and also the hydrogen bond formation ability of the C-2 hydydrogen. RTILs could be reused and with no significant difference in the yields. RTILs as "green solvent" have great potential in the area of organic synthesis.

Table 4.9 Structures of RTILs used in studies described in this chapter

$[MeOEtMIM]^+[CF_3COO]^-$ 	$[MeOMeOEtMIM]^+$ $[CF_3COO]^-$ 	$[BMIM]^+[CF_3COO]^-$ 
$[MeOEtMIM]^+[CH_3SO_3]^-$ 	$[PhOPMIM]^+$ $[CF_3CF_2COO]^-$ 	$[MeOEtMIM]^+[CF_3SO_3]^-$ 
$[MeOEtBuMIM]^+$ $[CF_3SO_3]^-$ 	$[BMIM]^+[BF_4]^-$ 	$[BMIM]^+[PF_6]^-$ 

4.5 Experimental section

4.5.1 Knoevenagel condensation reactions catalyzed by TBAH in $[BMIM]^+[BF_4]^-$ or $[BMIM]^+[PF_6]^-$

4.5.1.1 Chemicals and methods

An aldehyde or a ketone (5 mmol) and an alkylcyanoacetate or a malononitrile (5 mmol) together with TBAH (10% mol/mol) were mixed in one of the ionic liquids $[BMIM]^+[BF_4]^-$ and $[BMIM]^+[PF_6]^-$ (5 ml). The reaction mixture was stirred for an appropriate time (Table 4.2) at room temperature. When TLC analysis (diethyl ether/ petroleum ether=1/2, 1/4 or 1/6) indicated the reaction was completed, the resulting product was extracted with ether (3 × 10 ml), and the extraction was washed with water (3 × 10 ml). Ether was removed by rotary evaporation. If the product existed as a solid in the ionic liquid, 10 ml water was added to the mixture and the product was filtered off directly and washed with water (3 × 10 ml). The crude product was further purified by either flash column chromatography or recrystallization in petroleum ether or ether. If the ionic liquid was to be recycled, the used ionic liquid was added to water (5 ml) and washed with ether (3 × 10 ml), then extracted with dichloromethane (1 × 10 ml). After that, dichloromethane was removed and the ionic liquid was kept under high vacuum (5 mm Hg) at 80 °C for 3 h for reuse.

4.5.1.2 Experimental data

A1: (E) Ethyl-2-cyano-3-phenyl-2-propenoate: Solid.
Mp: 47-49 °C (47-48 °C, Su et al., 2003). ^{1}H NMR (DMSO-d_6): δ = 8.41 (s, 1H, H-C=C), 8.06 (dd, J = 6.32, 1.26Hz, 2H, Ph), 7.69-7.56 (m, 3H, Ph), 4.32 (q, J = 7.58Hz, 2H, COO-CH_2-), 1.31 (t, J = 7.58Hz, 3H, -CH_3). MS APCI$^+$ (m/z): = 202(M+H), 174(M-CH_2CH_3), 156(M-CH_2CH_3-COO-HC=C). IR (KBr, cm^{-1}): 3431, 2976, 2223, 1727, 1603, 1442, 1254, 1194, 1089, 1006, 763, 685. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 161.73(-COO), 131.46(Ph), 115.47(-CN),

102.58(C=C-CN), 62.48(COO-CH_2-). Negative peaks: δ = 155.01(H-C=C), 133.42(Ph), 130.90(Ph), 129.21(Ph), 13.97(-CH_3).

A2: (E) Ethyl-2-cyano-3-(4-chlorophenyl)-2-propenoate: Solid.
Mp: 91-92 °C (90 °C, Su et al., 2003). ^{1}H NMR (DMSO-d_6): δ = 8.41 (s, 1H, H-C=C), 8.07 (d, J = 8.7Hz, 2H, Ph), 7.68 (d, J = 8.7Hz, 2H, Ph), 4.32 (q, J = 7.11Hz, 2H, COO-CH_2-), 1.31 (t, J = 7.11Hz, 3H, -CH_3). MS APCI$^+$ (m/z): = 236(M+H), 208(M-CH_2CH_3), 190(M-CH_2CH_3-COO-HC=C). IR (KBr, cm^{-1}): 3431, 2990, 2227, 1723, 1612, 1589, 1497, 1263, 1079, 1011, 836, 501. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 161.62(-COO), 138.05(-C-Cl), 130.26(Ph), 115.34(-CN), 103.23(C=C-CN), 62.36(COO-CH_2-). Negative peaks: δ = 153.62(H-C=C), 132.43(Ph), 129.39(Ph), 13.92(-CH_3).

A3: (E) Ethyl-2-cyano-3-(4-methoxyphenyl)-2-propenoate: Solid.
Mp: 81-82 °C (79-80 °C, Su et al., 2003). ^{1}H NMR (DMSO-d_6): δ = 8.29 (s, 1H, H-C=C), 8.08 (d, J = 8.53Hz, 2H, Ph), 7.14 (d, J = 8.53Hz, 2H, Ph), 4.30 (q, J = 7.11Hz, 2H, COO-CH_2-), 3.87 (s, 3H, -OCH_3), 1.30 (t, J = 7.11Hz, 3H, -CH_3). MS APCI$^+$ (m/z): = 232(M+H), 204(M-CH_2CH_3), 186(M-CH_2CH_3-COO-HC=C). IR (KBr, cm^{-1}): 3408, 2994, 2216, 1715, 1583, 1556, 1515, 1433, 1260, 1178, 1019, 837, 555. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 163.51(-COO), 162.27(-C-OCH_3), 123.96(Ph), 116.15(-CN), 98.42(C=C-CN), 62.06(COO-CH_2-). Negative peaks: δ = 154.47(H-C=C), 133.54(Ph), 114.91(Ph), 55.68(-O-CH_3), 14.00(-CH_3).

A4: (E) Ethyl-2-cyano-3-(4-methylphenyl)-2-propenoate: Solid.
Mp: 93-94 °C (90-92 °C, Yaday et al., 2004). ^{1}H NMR (DMSO-d_6): δ = 8.34 (s, 1H, H-C=C), 7.97 (d, J = 8.36Hz, 2H, Ph), 7.39 (d, J = 8.36Hz, 2H, Ph), 4.31 (q, J = 7.90Hz, 2H, COO-CH_2-), 2.410 (s, 3H, Ph-CH_3), 1.31 (t, J = 7.90Hz, 3H, -CH_3). MS APCI$^+$ (m/z): = 216(M+H), 188(M-CH_2CH_3), 170(M-CH_2CH_3-COO-HC=C). IR (KBr, cm^{-1}): 3431, 2994, 2214, 1727, 1594, 1268, 1203, 1190, 1093, 818, 496. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 161.96(-COO), 144.35(-C-CH_3), 128.58(Ph), 115.74(-CN), 101.06(C=C-CN), 62.18(COO-CH_2-). Negative peaks: δ = 154.99(H-C=C), 130.99(Ph), 129.86(Ph), 21.27(Ph-CH_3), 13.94(-CH_3).

A5: (E) Ethyl-2-cyano-3-(4-N,N-dimethylaminophenyl)-2-propenoate: Solid.
Mp: 123-124 °C (125 °C, Balalaie and Bararjanian, 2006). ^{1}H NMR (DMSO-d_6): δ = 8.09 (s, 1H, H-C=C), 7.95 (d, J = 8.69Hz, 2H, Ph), 6.82(d, J = 8.69Hz, 2H, Ph), 4.25 (q, J = 7.11Hz, 2H, COO-CH_2-), 3.08 (s, 6H, N-$(CH_3)_2$), 1.28 (t, J = 7.11Hz, 3H, -CH_3). MS APCI$^+$ (m/z): = 245(M+H), 217(M-CH_2CH_3), 199(M-CH_2CH_3-COO-HC=C). IR (KBr, cm^{-1}): 3395, 2990, 2211, 1706, 1570, 1524, 1388, 1274, 1228, 1174, 1092, 819, 509. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 163.43(-COO), 153.66(-C-N), 118.30(Ph), 117.62(-CN), 92.03(C=C-CN), 61.39(COO-CH_2-). Negative peaks: δ = 154.16(H-C=C), 133.79(Ph), 111.73(Ph), 39.50(N-$(CH_3)_2$), 14.08(-CH_3).

A6: (E) Ethyl-2-cyano-3-(3,4,5-trimethoxyphenyl)-2-propenoate: Solid.
Mp: 80-81 °C. ^{1}H NMR (DMSO-d_6): δ = 8.30 (s, 1H, H-C=C), 7.49 (s, 2H, Ph), 4.31 (q, J = 6.95Hz, 2H, COO-CH_2-), 3.81 (s, 6H, (-OCH_3)$_2$), 3.79 (s, 3H, -OCH_3), 1.31 (t, J = 6.95Hz, 3H, -CH_3). MS APCI$^+$ (m/z): = 292(M+H), 264(M-CH_2CH_3). 246(M-CH_2CH_3-COO-HC=C). IR (KBr, cm^{-1}): 3436, 2980, 2216, 1729, 1579, 1501, 1333, 1256, 1128, 996, 837, 755, 627. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 161.93(-COO), 152.80(-C-O), 141.91(-C-O), 126.46(Ph), 116.10(-CN), 100.65(C=C-CN), 62.20(COO-CH_2-). Negative peaks: δ = 154.91(H-C=C), 108.73(Ph), 60.27((-OCH_3)$_2$), 55.88(-OCH_3), 13.92(-CH_3).

A7: (E) Ethyl-2-cyano-3-(4-nitrophenyl)-2-propenoate: Solid.
Mp: 170-171 °C (170-171 °C, Su et al., 2003). ^{1}H NMR ($CDCl_3$): δ = 8.13 (s, 1H, H-C=C), 8.18 (d, J = 9.48Hz, 2H, Ph), 7.96 (d, J = 9.48Hz, 2H, Ph), 4.25 (q, J = 7.58Hz, 2H, COO-CH_2-), 1.24 (t, J = 7.58Hz, 3H, -CH_3). MS APCI$^+$ (m/z): = 247(M+H), 219(M-CH_2CH_3). IR (KBr, cm^{-1}): 3417, 2994, 2227, 1722, 1617, 1594, 1516, 1346, 1263, 1199, 1006, 868, 767, 680. ^{13}C NMR ($CDCl_3$): Positive peaks: δ = 161.45(-COO), 149.73(-C-NO_3), 136.98(Ph), 114.56(-CN), 107.32(C=C-CN), 63.37(COO-CH_2-). Negative peaks: δ = 151.80(H-C=C), 131.63(Ph), 124.39(Ph), 14.07(-CH_3).

A8: Ethyl-2-cyano-3-cyclopentanyl-2-propenoate: Solid.
Mp: 54-56 °C. ^{1}H NMR (DMSO-d_6):δ= 4.21 (q, J = 7.58Hz, 2H, COO-CH_2-), 2.91 (t,

J = 7.58Hz, 2H, -CH_2-C=C), 2.75 (t, J = 7.58Hz, 2H, -CH_2-C=C), 1.83-1.68 (m, 4H, -CH_2-CH_2-), 1.25 (t, J = 7.58Hz, 3H, -CH_3). MS APCI$^+$ (m/z): = 180(M+H), 152(M-CH_2CH_3), 135(M-CH_2CH_3-COO). IR (KBr, cm^{-1}): 3431, 2981, 2227, 1732, 1617, 1268, 1034, 772. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 188.64(CH_2-C=C), 161.41(-COO), 115.68(-CN), 99.43(C=C-CN), 61.22(COO-CH_2-), 37.44(-CH_2-), 35.20(-CH_2-), 26.06(-CH_2-), 24.64(-CH_2-). Negative peaks: δ = 14.07(-CH_3).

A9: Ethyl-2-cyano-3-cyclohexanyl-2-propenoate: Liquid.
^{1}H NMR (DMSO-d_6): δ = 4.22 (q, J = 6.95Hz, 2H, COO-CH_2-), 2.95 (t, J = 6.32Hz, 2H, -CH_2-C=C), 2.62 (t, J = 6.32Hz, 2H, -CH_2-C=C), 1.82-1.53 (m, 6H, -CH_2-CH_2-CH_2-), 1.26 (t, J = 6.95Hz, 3H, -CH_3). MS APCI$^+$ (m/z): = 194(M+H), 166(M-CH_2CH_3), 149(M-CH_2CH_3-COO). IR (KBr, cm^{-1}): 3440, 2939, 2225, 1729, 1601, 1447, 1215, 1096, 1028, 778. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 180.33(CH_2-C=C), 161.35(-COO), 115.18(-CN), 100.90(C=C-CN), 61.39(COO-CH_2-), 36.15(-CH_2-), 30.87(-CH_2-), 28.14(-CH_2-), 27.66(-CH_2-), 24.84(-CH_2-). Negative peaks: δ = 13.81(-CH_3).

A10: (E) Methyl-2-cyano-3-phenyl-2-propenoate: Solid.
Mp: 87-89 °C (87 °C, Balalaie and Bararjanian, 2006). ^{1}H NMR (DMSO-d_6): δ = 8.42 (s, 1H, H-C=C), 8.06 (dd, J = 7.58, 1.26Hz, 2H, Ph), 7.69-7.55 (m, 3H, Ph), 3.87 (s, 3H, -CH_3). MS APCI$^+$ (m/z): = 188(M+H), 156(M-CH_3-COO-HC=C). IR (KBr, cm^{-1}): 3440, 3036, 2223, 1727, 1608, 1447, 1428, 1263, 1203, 1089, 960, 767, 685. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 162.28(-COO), 131.26(Ph), 115.61(-CN), 102.29(C=C-CN). Negative peaks: δ = 155.26(H-C=C), 133.45(Ph), 130.82(Ph), 129.36(Ph), 53.28(-CH_3).

A11: (E) Methyl-2-cyano-3-(4-chlorophenyl)-2-propenoate: Solid.
Mp: 126-127 °C. ^{1}H NMR (DMSO-d_6): δ = 8.43 (s, 1H, H-C=C), 8.08 (d, J = 7.58Hz, 2H, Ph), 7.69 (d, J = 8.21Hz, 2H, Ph), 3.87 (s, 3H, -CH_3). MS APCI$^+$ (m/z): = 222(M+H), 190(M-CH_3-COO-HC=C). IR (KBr, cm^{-1}): 3432, 3077, 3032, 2959, 2223, 1723, 1614, 1586, 1427, 1282, 1204, 1086, 841, 495. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 153.84(-COO), 132.42(-C-Cl), 129.50(Ph), Negative peaks: δ = 162.11(H-C=C), 138.10(Ph), 130.15(Ph), 53.40(-CH_3).

A12: 1,1-Dicyano-2-phenylethylene: Solid.

Mp: 82-83 °C (83 °C, Balalaie and Bararjanian, 2006). ^{1}H NMR (DMSO-d_6): δ = 8.55 (s, 1H, H-C=C), 7.96 (dd, J = 6.95, 1.0Hz 2H, Ph), 7.74-7.57 (m, 3H, Ph). MS APCI^{+} (m/z): = 155(M+H). IR (KBr, cm^{-1}): 3453, 3031, 2223, 1585, 1566, 1451, 1217, 956, 753, 675, 616. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 131.24(Ph), 114.24(-CN), 113.17(-CN), 81.60(C=C-CN). Negative peaks: δ = 161.58(H-C=C), 134.31(Ph), 130.48(Ph), 129.56(Ph).

A13: 1,1-Dicyano-2-(4-chlophenyl)-ethylene: Solid.

Mp: 162-163 °C. ^{1}H NMR (DMSO-d_6): δ = 8.55 (s, 1H, H-C=C), 7.95 (d, J = 8.21Hz, 2H, Ph), 7.71 (d, J = 8.85Hz, 2H, Ph). MS APCI^{+} (m/z): = 189(M+H). IR (KBr, cm^{-1}): 3435, 3031, 2227, 1585, 1401, 1217, 1093, 827, 616, 519. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 138.99(-C-Cl), 130.11(Ph), 114.08(-CN), 112.99(-CN), 82.17(C=C-CN). Negative peaks: δ = 160.16(H-C=C), 132.13(Ph), 129.64(Ph).

4.5.2 $[BMIM]^{+}[BF_4]^{-}$ or $[BMIM]^{+}[PF_6]^{-}$ as a solvent and a catalyst for Knoevenagel condensation reactions

4.5.2.1 Chemicals and Methods

An aldehydes or a ketones (5 mmol) and an alkylcyanoacetate or a malononitrile (5 mmol) were mixed in either $[BMIM]^{+}[BF_4]^{-}$ or $[BMIM]^{+}[PF_6]^{-}$ (3 ml or 5 ml). The reaction mixture was stirred for an appropriate time (Table 4.4) at 50 °C or 80 °C. TLC (diethyl ether/petroleum ether = 1/2, 1/4 or 1/6) monitored the reaction progress. After the completion of the reaction, the resulting product was extracted with ether (3 × 10 ml), and the extraction was washed with water (3 × 10 ml). Ether was removed by rotary evaporation. The product was further purified by recrystallization in one of the following solvents: petroleum ether, ether, ethyl acetate.

4.5.2.2 Experimental data

B1: (E) Ethyl-2-cyano-3-phenyl-2-propenoate: Solid.

Mp: 47-48 °C. ^{1}H NMR (DMSO-d_6): δ = 8.40 (s, 1H, H-C=C), 8.06 (dd, J = 6.1, 1.4Hz, 2H, Ph), 7.68-7.55 (m, 3H, Ph), 4.32 (q, J = 7.1Hz, 2H, COO-CH_2-), 1.31 (t, J = 7.1Hz, 3H, -CH_3). MS APCI$^+$ (m/z): = 202(M+H), 174(M-CH_2CH_3), 156(M-CH_2CH_3-CO**O**-**H**C=C). IR (KBr, cm^{-1}): 3424, 2976, 2216, 1719, 1599, 1437, 1261, 1194, 1095, 762, 678. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 161.76(-COO), 131.32(Ph), 115.56(-CN), 102.57(C=C-CN), 62.36(COO-CH_2-). Negative peaks: δ = 155.07(H-C=C), 133.38(Ph), 130.78(Ph), 129.29(Ph), 13.94(-CH_3).

B2: (E) Ethyl-2-cyano-3-(4-chlorophenyl)-2-propenoate: Solid.

Mp: 91-92 °C. ^{1}H NMR (DMSO-d_6): δ = 8.41 (s, 1H, H-C=C), 8.07 (d, J = 8.5Hz, 2H, Ph), 7.68 (d, J = 8.5Hz, 2H, Ph), 4.32 (q, J = 7.1Hz, 2H, COO-CH_2-), 1.32 (t, J = 7.1Hz, 3H, -CH_3). MS APCI$^+$ (m/z): = 236(M+H), 208(M-CH_2CH_3), 190(M-CH_2CH_3-CO**O**-**H**C=C). IR (KBr, cm^{-1}): 3424, 2984, 2216, 1727, 1607, 1592, 1496, 1272, 1207, 1075, 836, 492 ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 161.59(-COO), 138.00(-C-Cl), 130.19(Ph), 115.39(-CN), 103.17(C=C-CN), 62.44(COO-CH_2-). Negative peaks: δ = 153.64(H-C=C), 132.42(Ph), 129.45(Ph), 13.94(-CH_3).

B3: (E) Ethyl-2-cyano-3-(4-methoxyphenyl)-2-propenoate: Solid.

Mp: 79-81 °C. ^{1}H NMR (DMSO-d_6): δ = 8.26 (s, 1H, H-C=C), 8.05 (d, J = 8.8Hz, 2H, Ph), 7.12 (d, J = 8.8Hz, 2H, Ph), 4.28 (q, J = 7.1Hz, 2H, COO-CH_2-), 3.85 (s, 3H, -OCH_3), 1.29 (t, J = 7.1Hz, 3H, -CH_3). MS APCI$^+$ (m/z): = 232(M+H), 204(M-CH_2CH_3), 186(M-CH_2CH_3-CO**O**-**H**C=C). IR (KBr, cm^{-1}): 3408, 2996, 2209, 1711, 1588, 1565, 1507, 1426, 1256, 1187, 1022, 832, 546. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 163.49(-COO), 162.31(-C-OCH_3), 123.89(Ph), 116.16(-CN), 98.43(C=C-CN), 62.01(COO-CH_2-). Negative peaks: δ = 154.33(H-C=C), 133.47(Ph), 114.84(Ph), 55.68(-OCH_3), 13.95(-CH_3).

B4: (E) Ethyl-2-cyano-3-(4-methylphenyl)-2-propenoate: Solid.

Mp: 93-94 °C. ^{1}H NMR (DMSO-d_6): δ = 8.34 (s, 1H, H-C=C), 7.97 (d, J = 8.4Hz, 2H, Ph), 7.40 (d, J = 8.4Hz, 2H, Ph), 4.31 (q, J = 7.1Hz, 2H, COO-CH_2-), 2.39 (s, 3H, Ph-CH_3), 1.31 (t, J = 7.1Hz, 3H, -CH_3). MS APCI$^+$ (m/z): = 216(M+H), 188(M-CH_2CH_3), 170(M-CH_2CH_3-CO**O**-**H**C=C). IR (KBr, cm^{-1}): 3424, 2988, 2209, 1719, 1588, 1264, 1202, 1183, 1086, 809, 489. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 161.97(-COO), 144.39(-C-CH_3), 128.66(Ph), 115.77(-CN), 101.07(C=C-CN), 62.23(COO-CH_2-). Negative peaks: δ = 154.92(H-C=C), 130.97(Ph), 129.94(Ph), 21.33(Ph-CH_3), 13.96(-CH_3).

B5: (E) Ethyl-2-cyano-3-(4-N,N-dimethylaminophenyl)-2-propenoate: Solid.

Mp: 124-125 °C. ^{1}H NMR (DMSO-d_6): δ = 8.10 (s, 1H, H-C=C), 7.96 (d, J = 9.1Hz, 2H, Ph), 6.82 (d, J = 9.1Hz, 2H, Ph), 4.25 (q, J = 7.0Hz, 2H, COO-CH_2-), 3.08 (s, 6H, N-$(CH_3)_2$), 1.28 (t, J = 7.0Hz, 3H, -CH_3). MS APCI$^+$ (m/z): = 245(M+H), 217(M-CH_2CH_3), 199(M-CH_2CH_3-CO**O**-**H**C=C). IR (KBr, cm^{-1}): 3426, 2982, 2205, 1702, 1571, 1529, 1380, 1276, 1224, 1170, 1083, 821, 512. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 163.45(-COO), 153.69(-C-N), 118.27(Ph), 117.55(-CN), 91.96(C=C-CN), 61.41(COO-CH_2-). Negative peaks: δ = 154.14(H-C=C), 133.78(Ph), 111.67(Ph), 39.57(N-$(CH_3)_2$), 14.13(-CH_3).

B6: (E) Ethyl-2-cyano-3-(3,4,5-trimethoxyphenyl)-2-propenoate: Solid.

Mp: 80-81 °C. ^{1}H NMR (DMSO-d_6): δ = 8.32 (s, 1H, H-C=C), 7.50 (s, 2H, Ph), 4.31 (q, J = 7.1Hz, 2H, COO-CH_2-), 3.82 (s, 6H, (-OCH_3)$_2$), 3.78 (s, 3H, -OCH_3), 1.31 (t, J = 7.1Hz, 3H, -CH_3). MS APCI$^+$ (m/z): = 292(M+H), 264(M-CH_2CH_3). 246(M-CH_2CH_3-CO**O**-**H**C=C). IR (KBr, cm^{-1}): 3432, 2983, 2215, 1725, 1581, 1506, 1340, 1253, 1121, 992, 836, 753, 636. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 162.02(-COO), 152.82(-C-O), 141.97(-C-O), 126.43(Ph), 116.04(-CN), 100.68(C=C-CN), 62.24(COO-CH_2-). Negative peaks: δ = 154.91(H-C=C), 108.77(Ph), 60.30((-OCH_3)$_2$), 55.98(-OCH_3), 13.99(-CH_3).

B7: (E) Ethyl-2-cyano-3-(4-nitrophenyl)-2-propenoate: Solid.

Mp: 170-171 °C. ^{1}H NMR ($CDCl_3$): δ = 8.21 (s, 1H, H-C=C), 8.26 (d, J = 8.8Hz, 2H, Ph), 8.04 (d, J = 9.1Hz, 2H, Ph), 4.32 (q, J = 7.1Hz, 2H, COO-CH_2-), 1.32 (t, J =

7.1Hz, 3H, -CH_3). MS $APCI^+$ (m/z): = 247(M+H), 219(M-CH_2CH_3). IR (KBr, cm^{-1}): 3420, 2990, 2223, 1717, 1619, 1596, 1511, 1345, 1264, 1205, 1004, 861, 763, 684. ^{13}C NMR ($CDCl_3$): Positive peaks: δ = 63.38(COO-CH_2-). Negative peaks: δ = 151.75(H-C=C), 131.53(Ph), 124.36(Ph), 14.13(-CH_3).

B8: Ethyl-2-cyano-3-cyclopentanyl-2-propenoate: Solid.
Mp: 53-54 °C. ^1H NMR (DMSO-d_6): δ= 4.21 (q, J = 7.1Hz, 2H, COO-CH_2-), 2.91 (t, J = 6.0Hz, 2H, -CH_2-C=C), 2.75 (t, J = 6.5Hz, 2H, -CH_2-C=C), 1.84-1.66 (m, 4H, -CH_2-CH_2-), 1.25 (t, J = 7.1Hz, 3H, -CH_3). MS $APCI^+$ (m/z): = 180(M+H), 152(M-CH_2CH_3), 135(M-CH_2CH_3-COO). IR (KBr, cm^{-1}): 3428, 2971, 2229, 1723, 1615, 1264, 1037, 765. ^{13}C NMR (DMSO-d_6): Positive peaks: 188.56(CH_2-C=C), 161.38(-COO), 115.56(-CN), 99.49(C=C-CN), 61.21(COO-CH_2-), 37.44(-CH_2-), 35.28(-CH_2-), 26.01(-CH_2-), 24.57(-CH_2-). δ = Negative peaks: δ = 13.98(-CH_3).

B9: Ethyl-2-cyano-3-cyclohexanyl-2-propenoate: Liquid.
^1H NMR (DMSO-d_6): δ = 4.22 (q, J = 7.1Hz, 2H, COO-CH_2-), 2.94 (t, J = 6.6Hz, 2H, -CH_2-C=C), 2.61 (t, J = 6.5Hz, 2H, -CH_2-C=C), 1.78-1.50 (m, 6H, CH_2-CH_2-CH_2-), 1.25 (t, J = 7.1Hz, 3H, -CH_3). MS $APCI^+$ (m/z): = 194(M+H), 166(M-CH_2CH_3), 149(M-CH_2CH_3-COO). IR (KBr, cm^{-1}): 3438, 2940, 2221, 1725, 1598, 1445, 1218, 1101, 1025, 780. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 180.59(CH_2-C=C), 161.41(-COO), 115.42(-CN), 100.89(C=C-CN), 61.46(COO-CH_2-), 36.19(-CH_2-), 30.95(-CH_2-), 28.12(-CH_2-), 27.78(-CH_2-), 24.87(-CH_2-). Negative peaks: δ = 13.87(-CH_3).

B10: (E) Methyl-2-cyano-3-phenyl-2-propenoate: Solid.
Mp: 88-89 °C. ^1H NMR (DMSO-d_6): δ = 8.42 (s, 1H, H-C=C), 8.06 (dd, J = 6.5, 1.1Hz, 2H, Ph), 7.68-7.56 (m, 3H, Ph), 3.87 (s, 3H, -CH_3). MS $APCI^+$ (m/z): = 188(M+H), 156(M-CH_3-COO-HC=C). IR (KBr, cm^{-1}): 3438, 3031, 2227, 1725, 1604, 1450, 1428, 1264, 1202, 1087, 969, 769, 680. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = = 162.31(-COO), 131.31(Ph), 115.58(-CN), 102.29(C=C-CN). Negative peaks: δ = 155.19(H-C=C), 133.44(Ph), 130.80(Ph), 129.32(Ph), 53.35(-CH_3).

B11: (E) Methyl-2-cyano-3-(4-chlorophenyl)-2-propenoate: Solid.
Mp: 125-126 °C. ^{1}H NMR (DMSO-d_6): δ = 8.44 (s, 1H, H-C=C), 8.08 (d, J = 8.7Hz, 2H, Ph), 7.70 (d, J = 8.5Hz, 2H, Ph), 3.87 (s, 3H, -CH_3). MS APCI$^+$ (m/z): = 222(M+H), 190(M-CH_3-COO-HC=C). IR (KBr, cm^{-1}): 3429, 3075, 3030, 2957, 2218, 1724, 1601, 1588, 1429, 1275, 1207, 1085, 835, 491. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 153.79(-COO), 132.45(-C-Cl), 129.49(Ph). Negative peaks: δ = 162.15(H-C=C), 138.03(Ph), 130.21(Ph), 53.41(-CH_3).

B12: 1,1-Dicyano-2-phenylethylene: Solid.
Mp: 81-82 °C. ^{1}H NMR (DMSO-d_6): δ = 8.57 (s, 1H, H-C=C), 7.96 (dd, J = 6.7, 1.0Hz, 2H, Ph), 7.74-7.59 (m, 3H, Ph). MS APCI$^+$ (m/z): = 155(M+H). IR (KBr, cm^{-1}): 3432, 3029, 2221, 1588, 1569, 1452, 1214, 960, 757, 680, 619. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 131.27(Ph), 114.19(-CN), 113.21(-CN), 81.59(C=C-CN). Negative peaks: δ = 161.56(H-C=C), 134.37(Ph), 130.47(Ph), 129.52(Ph).

B13: 1,1-Dicyano-2-(4-chlophenyl)-ethylene: Solid.
Mp: 161-162 °C. ^{1}H NMR (DMSO-d_6): δ = 8.56 (s, 1H, H-C=C), 7.96 (d, J=8.4Hz, 2H, Ph), 7.73 (d, J=8.7Hz, 2H, Ph). MS APCI$^+$ (m/z): = 189(M+H). IR (KBr, cm^{-1}): 3418, 3029, 2229, 1587, 1405, 1212, 1097, 825, 619, 522. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 138.99(-C-Cl), 130.08(Ph), 114.05(-CN), 113.01(-CN), 82.25(C=C-CN). Negative peaks: δ = 160.10(H-C=C), 132.13(Ph), 129.72(Ph).

4.5.3 Various RTILs as solvents and catalysts for Knoevenagel condensation reactions

4.5.3.1 Chemicals and methods

An aldehyde or a ketone (5 mmol) and an alkylcyanoacetate (5 mmol) were mixed in one of the ionic liquids (3-5 ml) listed in Table 4.6. The reaction mixture was stirred for an appropriate time (Table 4.7) at 25 °C or 50 °C. When TLC analysis (diethyl ether/petroleum ether = 1/2, 1/4 or 1/6) indicated the reaction was completed, the resulting product was extracted with ether (3 × 10 ml), and the extraction was washed

with water (3 × 10 ml). Ether was removed by rotary evaporation. The product was further purified by recrystallization. To recycle the ionic liquid, the used ionic liquid was washed with ethyl acetate (3 × 10 ml) and then was kept under high vacuum (4 mm Hg) at 80 °C for 3 h.

4.5.3.2 Experimental data

C1: (E) Ethyl-2-cyano-3-phenyl-2-propenoate: Solid.
Mp: 47-48 °C. ^{1}H NMR (DMSO-d_6): δ = 8.39 (s, 1H, H-C=C), 8.14-8.02 (m, 2H, Ph), 7.74-7.54 (m, 3H, Ph), 4.31 (q, J = 7.11Hz, 2H, COO-CH_2-), 1.30 (t, J = 7.11Hz, 3H, -CH_3). IR (KBr, cm^{-1}): 3426, 2980, 2220, 1724, 1601, 1438, 1256, 1196, 1078, 1005, 769, 678, 477. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 161.72(-COO), 131.27(Ph), 115.52(-CN), 102.52(C=C-CN), 62.33(COO-CH_2-). Negative peaks: δ = 155.02(H-C=C), 133.35(Ph), 130.74(Ph), 129.25(Ph), 13.90(-CH_3).

C2: (E) Ethyl-2-cyano-3-(4-chlorophenyl)-2-propenoate: Solid.
Mp: 91-92 °C. ^{1}H NMR (DMSO-d_6): δ = 8.39 (s, 1H, H-C=C), 8.05 (d, J = 8.53Hz, 2H, Ph), 7.66 (d, J = 8.53Hz, 2H, Ph), 4.31 (q, J = 7.11Hz, 2H, COO-CH_2-), 1.30 (t, J = 7.11Hz, 3H, -CH_3). IR (KBr, cm^{-1}): 3434, 2989, 2225, 1717, 1609, 1586, 1488, 1263, 1200, 1074, 1007, 827, 755, 499. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 161.56(-COO), 137.99(-C-Cl), 130.14(Ph), 115.35(-CN), 103.11(C=C-CN), 62.42(COO-CH_2-). Negative peaks: δ = 153.60(H-C=C), 132.39(Ph), 129.41(Ph), 13.91(-CH_3).

C3: (E) Ethyl-2-cyano-3-(4-methylphenyl)-2-propenoate: Solid.
Mp: 92-93 °C. ^{1}H NMR (DMSO-d_6): δ = 8.32 (s, 1H, H-C=C), 7.95 (d, J = 8.21Hz, 2H, Ph), 7.39 (d, J = 8.21Hz, 2H, Ph), 4.30 (q, J = 7.11Hz, 2H, COO-CH_2-), 2.39 (s, 3H, Ph-CH_3), 1.30 (t, J = 7.11Hz, 3H, -CH_3). IR (KBr, cm^{-1}): 3440, 2997, 2218, 1727, 1591, 1273, 1206, 1179, 1094, 816, 758, 494. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 161.95(-COO), 144.37(-C-CH_3), 128.62(Ph), 115.75(-CN), 101.01(C=C-CN), 62.22(COO-CH_2-). Negative peaks: δ = 154.88(H-C=C), 130.94(Ph), 129.90(Ph), 21.30(Ph-CH_3), 13.93(-CH_3).

C4: (E) Ethyl-2-cyano-3-(4-nitrophenyl)-2-propenoate: Solid.

Mp: 170-171 °C. ^{1}H NMR (DMSO-d_6): δ = 8.55 (s, 1H, H-C=C), 8.40 (d, J = 9.00Hz, 2H, Ph), 8.24 (d, J = 9.00Hz, 2H, Ph), 4.34 (q, J = 7.11Hz, 2H, COO-CH_2-), 1.32 (t, J = 7.11Hz, 3H, -CH_3). IR (KBr, cm^{-1}): 3451, 2991, 2226, 1718, 1621, 1590, 1510, 1342, 1262, 1205, 1196, 865, 763, 688. ^{13}C NMR ($CDCl_3$): Positive peaks: δ = 161.10(-COO), 149.19(-C-NO_3), 137.23(Ph), 114.92(-CN), 106.62(C=C-CN), 62.71(COO-CH_2-). Negative peaks: δ = 152.66(H-C=C), 131.64(Ph), 124.13(Ph), 13.91(-CH_3).

C5: (E) Ethyl-2-cyano-3-(4-carboxyphenyl)-2-propenoate: Solid.

Mp: 232-234 °C. ^{1}H NMR (DMSO-d_6): δ = 13.42 (s, 1H, COOH), 8.46 (s, 1H, H-C=C), 8.13 (d, J = 8.67Hz, 2H, Ph), 8.08 (d, J = 8.53Hz, 2H, Ph), 4.33 (q, J = 7.11Hz, 2H, COO-CH_2-), 1.32 (t, J = 7.11Hz, 3H, -CH_3). MS ES^- (m/z) = 244(M-H). IR (KBr, cm^{-1}): 3424, 2992, 2205, 1733, 1702, 1612, 1421, 1283, 1196, 1006, 850, 768, 686, 543. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 166.36(Ph-COO), 161.40(-COO), 135.02(-C-COO), 134.22(Ph), 115.20(-CN), 104.73(C=C-CN), 62.52(COO-CH_2-). Negative peaks: δ = 153.80(H-C=C), 130.69(Ph), 129.82(Ph), 13.90(-CH_3).

C6: (E) Ethyl-2-cyano-3-naphthalene-2-propenoate: Solid.

Mp: 111-112 °C. ^{1}H NMR (DMSO-d_6): δ = 8.60 (s, 1H, H-C=C), 8.53(s, 1H), 8.26-7.99 (m, 4H, Ph), 7.78-7.61 (m, 2H, Ph), 4.34 (q, J = 6.95Hz, 2H, COO-CH_2-), 1.33 (t, J = 6.95Hz, 3H, -CH_3). IR (KBr, cm^{-1}): 3439, 2981, 2222, 1724, 1598, 1248, 1181, 817, 750, 476. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 161.90(-COO), 134.76(Ph), 132.29(Ph), 128.91(Ph), 115.77(-CN), 102.28(C=C-CN), 62.36(COO-CH_2-). Negative peaks: δ = 154.92(H-C=C), 134.43(Ph), 129.27(Ph), 129.24(Ph), 128.95(Ph), 127.81(Ph), 127.41(Ph), 124.48(Ph), 13.97(-CH_3).

C7: (E) Methyl-2-cyano-3-(3-chlorophenyl)-2-propenoate: Solid.

Mp: 111-112 °C. ^{1}H NMR (DMSO-d_6): δ = 8.42 (s, 1H, H-C=C), 8.09 (t, J = 1.90Hz, 1H, Ph), 8.05-7.99 (m, 1H, Ph), 7.73-7.58 (m, 2H, Ph), 3.87 (s, 3H, -CH_3). IR (KBr, cm^{-1}): 3431, 3059, 2218, 1722, 1612, 1562, 1433, 1272, 1208, 1093, 781, 680. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 161.89(-COO), 133.80(Ph), 133.24(Ph),

115.18(-CN), 103.95(C=C-CN). Negative peaks: δ = 153.44(H-C=C), 132.74(Ph), 131.07(Ph), 130.16(Ph), 128.94(Ph), 53.42(-CH_3).

C8: (E) Methyl-2-cyano-3-(4-methylphenyl)-2-propenoate: Solid.
Mp: 108-110 °C. ^{1}H NMR (DMSO-d_6): δ = 8.37 (s, 1H, H-C=C), 7.99 (d, J = 8.21Hz, 2H, Ph), 7.41 (d, J = 8.06Hz, 2H, Ph), 3.86 (s, 3H, -CH_3), 2.40 (s, 3H, Ph-CH_3). IR (KBr, cm^{-1}): 3434, 2952, 2218, 1722, 1590, 1435, 1271, 1209, 1183, 1094, 811, 489. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 162.51(-COO), 144.46(-C-CH_3), 128.64(Ph), 115.80(-CN), 100.77(C=C-CN). Negative peaks: δ = 155.07(H-C=C), 130.08(Ph), 129.95(Ph), 53.25(-CH_3), 21.33(Ph-CH_3).

C9: (E) Methyl-2-cyano-3-(4-methoxyphenyl)-2-propenoate: Solid.
Mp: 102-103 °C. ^{1}H NMR (DMSO-d_6): δ = 8.31 (s, 1H, H-C=C), 8.09 (d, J = 9.00Hz, 2H, Ph), 7.15 (d, J = 9.00Hz, 2H, Ph), 3.87 (s, 3H, -OCH_3), 3.84 (s, 3H, -CH_3). IR (KBr, cm^{-1}): 3434, 2949, 2213, 1720, 1585, 1554, 1509, 1423, 1257, 1208, 1168, 1024, 840, 548. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 163.53(-COO), 162.84(-C-OCH_3), 123.87(Ph), 116.19(-CN), 98.13(C=C-CN). Negative peaks: δ = 154.51(H-C=C), 133.51(Ph), 114.91(Ph), 55.71(-OCH_3), 53.07(-CH_3).
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C10: (E) Methyl-2-cyano-3-(4-hydroxyphenyl)-2-propenoate: Solid.
Mp: 213-214 °C. ^{1}H NMR (DMSO-d_6): δ = 10.89 (s, 1H, OH), 8.26(s, 1H, H-C=C), 8.00 (d, J = 8.85Hz, 2H, Ph), 6.95 (d, J = 8.64Hz, 2H, Ph), 3.83 (s, 3H, -CH_3). MS ES^- (m/z) = 202(M-H). IR (KBr, cm^{-1}): 3338, 2222, 1724, 1590, 1434, 1270, 1209, 1170, 1088, 815, 513. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 163.10(-COO), 162.08(-C-OH), 122.42(Ph), 116.45(-CN), 96.59(C=C-CN). Negative peaks: δ = 154.79(H-C=C), 133.00(Ph), 111.36(Ph), 53.00(-CH_3).

C11: Methyl-2-cyano-3-cyclopentanyl-2-propenoate: Solid.
Mp: 23-25 °C. ^{1}H NMR (DMSO-d_6): δ= 3.75 (s, 2H, -CH_3), 2.91 (t, J = 6.95Hz, 2H, -CH_2-C=C), 2.75 (t, J = 7.11Hz, 2H, C=C-CH_2-), 1.85-1.69 (m, 4H, -CH_2-CH_2-). MS ES^- (m/z) = 164(M-H). IR (KBr, cm^{-1}): 3440, 2957, 2224, 1727, 1612, 1439, 1279, 1203, 1088, 1026, 773. ^{13}C NMR (DMSO-d_6): Positive peaks: 188.79(CH_2-C=C),

161.77(-COO), 115.45(-CN), 99.15(C=C-CN), 37.39(-CH_2-), 35.25(-CH_2-), 25.97(-CH_2-), 24.56(-CH_2-). Negative peaks: δ = 52.28(-CH_3).

C12: Methyl-2-cyano-3-cyclohexanyl-2-propenoate: Liquid.
^{1}H NMR (DMSO-d_6): δ = 3.76 (s, 3H, -CH_3), 2.95 (t, J = 5.61Hz, 2H, -CH_2-C=C), 2.62 (t, J = 5.85Hz, 2H, C=C-CH_2-), 1.78-1.57 (m, 6H, CH_2-CH_2-CH_2-). MS ES^- (m/z) = 178(M-H). IR (cm^{-1}): 3446, 2940, 2222, 1734, 1601, 1437, 1269, 1216, 1096, 1012, 777. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 180.95(CH_2-C=C), 161.85(-COO), 115.41(-CN), 100.56(C=C-CN), 61.43(COO-CH_2-), 36.19(-CH_2-), 30.92(-CH_2-), 28.12(-CH_2-), 27.77(-CH_2-), 24.83(-CH_2-). Negative peaks: δ = 52.53(-CH_3).

C13: Ethyl-2-cyano-3-methyl-2-butyrate: Solid.
Mp: 23-25 °C. ^{1}H NMR (DMSO-d_6): 4.21 (q, J = 7.11Hz, 2H, COO-CH_2-), 2.36(s, 3H, C=C-CH_3), 2.27(s, 3H, C=C-CH_3), 1.25 (t, J = 7.11Hz, 3H, COOCH_2-CH_3). MS ES^- (m/z) = 152(M-H). IR (KBr, cm^{-1}): 3431, 2990, 2225, 1724, 1606, 1438, 1369, 1233, 1083, 773. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 175.37(-COO), 115.69(-CN), 103.45((CH_3)$_2$-C=), 62.35(=C-CN), 61.31(COO-CH_2-). Negative peaks: δ = 26.92(C=C-CH_3), 22.44 (C=C-CH_3), 13.89(COOCH_2-CH_3).

C14: Methyl-2-cyano-3-methyl-2-pentenoate: Liquid.
^{1}H NMR (DMSO-d_6): 3.76 (s, 6H, COO-CH_3), 2.75 (q, J = 7.58Hz, 1.7H, C=C-CH_2-), 2.53 (q, J = 7.58Hz, 2.3H, C=C-CH_2-), 2.36 (s, 3.3H, C=C-CH_3), 2.27 (s, 2.7H, C=C-CH_3), 1.12 (t, J = 7.58Hz, 3.3H, C=CCH_2-CH_3), 1.07 (t, J = 7.58Hz, 2.7H, C=CCH_2-CH_3). MS ES^- (m/z) = 152(M-H). IR (cm^{-1}): 2982, 2224, 1734, 1600, 1435, 1227, 1098, 777. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 180.30(-COO), 180.06(-COO), 161.89(CH_3CH_2-C=), 161.40(CH_3CH_2-C=), 115.68(-CN), 115.27(-CN), 102.92(=C-CN), 102.68(=C-CN), 33.18(-CH_2-C=), 28.13(-CH_2-C=). Negative peaks: δ = 52.39(COO-CH_3), 24.41(C=C-CH_3), 20.13(C=C-CH_3), 11.98 (C=CCH_2-CH_3), 11.72 (C=CCH_2-CH_3).

C15: Ethyl-2-cyano-3-methyl-2-pentenoate: Liquid.
^{1}H NMR (DMSO-d_6): 4.21 (q, J = 6.95Hz, 4H, COO-CH_2-), 2.74 (q, J = 7.58Hz, 1.7H, C=C-CH_2), 2.52 (q, J = 7.58Hz, 2.3H, C=C-CH_2), 2.35 (s, 3.5H, C=C-CH_3), 2.26(s,

2.3H, C=C-CH_3), 1.25 (t, J = 6.95Hz, 6H, $COOCH_2$-CH_3), 1.12 (t, J = 7.58Hz, 3.6H, C=CCH_2-CH_3), 1.07 (t, J = 7.58Hz, 2.3H, C=CCH_2-CH_3). MS ES^- (m/z) = 166(M-H). IR (cm^{-1}): 2981, 2223, 1727, 1607, 1446, 1372, 1222, 1094, 777. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 180.38(-COO), 180.13(-COO), 161.90(CH_3CH_2-C=), 161.41(CH_3CH_2-C=), 115.72(-CN), 115.31(-CN), 102.88(=C-CN), 102.65(=C-CN), 33.18(-CH_2-C=), 28.13 (-CH_2-C=). Negative peaks: δ = 52.45($COOCH_2$-CH_3), 52.44($COOCH_2$-CH_3), 24.45(C=C-CH_3), 20.18(C=C-CH_3), 12.02(C=CCH_2-CH_3), 11.76 (C=CCH_2-CH_3).

C16: Methyl-2-cyano-3-phenyl-2-butyrate: Liquid.
^1H NMR (DMSO-d_6): 7.63-7.28 (m, 10H, Ph), 3.82 (s, 4.5H, -CH_3), 3.58 (s, 1.3H, -CH_3), 2.66 (s, 4.2H, CH_3-C=C), 2.52 (s, 1.4H, CH_3-C=C). MS ES^- (m/z) = 200(M-H). IR (cm^{-1}): 3424, 2976, 2216, 1719, 1599, 1437, 1261, 1194, 1095, 762, 678. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 173.02(-COO), 162.19(C=C), 138.49(Ph), 116.15(-CN), 103.99(C=C-CN). Negative peaks: δ = 130.31(Ph), 129.48(Ph), 128.55(Ph), 128.07(Ph), 127.19(Ph), 126.59(Ph), 52.77(COO-CH_3), 26.65(C=C-CH_3), 23.14(C=C-CH_3).

C17: Ethyl-2-cyano-3-phenyl-2-butyrate: Liquid.
^1H NMR (DMSO-d_6): δ = 7.70-7.27 (m, 10H, Ph), 4.29 (q, J = 6.95Hz, 2.8H, COO-CH_2-), 4.00 (q, J = 6.95Hz, 1.0H, O-CH_2-), 2.65 (s, 4H, CH_3-C=C), 2.52 (s, 1.9H, CH_3-C=C), 1.29 (t, J = 6.95Hz, 4.4H, -CH_3), 0.91 (t, J = 6.95Hz, 1.6H, -CH_3). MS ES^- (m/z) = 214(M-H). IR (cm^{-1}): 2985, 2225, 1729, 1592, 1442, 1369, 1242, 1137, 1046, 764, 700. ^{13}C NMR (DMSO-d_6): Positive peaks: δ = 172.67(-COO), 170.07(-COO), 161.71(C=C), 161.11(C=C), 140.13(Ph), 138.67(Ph), 116.10(-CN), 115.74(-CN), 104.75(C=C-CN), 104.29(C=C-CN), 61.73(COO-CH_2-), 61.46(COO-CH_2-). Negative peaks: δ = 133.12(Ph), 130.23(Ph), 129.38(Ph), 128.53(Ph), 128.06(Ph), 127.15(Ph), 126.52(Ph), 26.48(C=C-CH_3), 23.12(C=C-CH_3), 13.87($COOCH_2$-CH_3).

Conclusions

In this project, some common and new ionic liquids were synthesized. Knoevenagel condensation reactions were successfully carried out in these ionic liquids. For the first time, RTILs such as 1-methoxyethyl-3-methylimidazolium trifluoroacetate $[MeOEtMIM]^+[CF_3COO]^-$ and 1-butyl-3-methylimidazolium trifluoro acetate $[BMIM]^+[CF_3COO]^-$ have been used as catalysts and solvents for Knoevenagel condensation of aldehydes and ketones with active methylene compounds such as methyl- and ethylcyanoacetate, malononitrile.

In addition, nucleoside reactions have been investigated in these prepared ionic liquids. Most thionucleobases and thionucleosides had a good solubility in RTILs. Triethylamine was an efficient organic base to promote the alkylation of thio-substituted nucleobases and nucleosides. These nucleoside reactions could be carried out effectively in RTILs, especially in $[MeOEtMIM]^+[CF_3COO]^-$. The experimental approach was straightforward. These ionic liquids are environmentally friendly and can be recycled. Thionucleosides with various substituents were produced with excellent yields. RTILs have a great potential of use in nucleoside chemistry.

There is an urgent need to develop alternative solvents and "green procedure" for industrial chemical production. Current approaches using organic solvents have caused environmental pollutions in many countries, both in the developing and developed countries. Most of the organic solvents are flammable, volatile, harmful or toxic. In recent years, room temperature ionic liquids, a new class of reaction media, have received much attention as alternative solvents due to their interesting properties such as low vapor pressure, no flammability and ease of reuse. Through the combination of various cations and anions, an extremely large numbers and varieties of ionic liquids can be constructed. The properties of ionic liquids can be controlled by varying their cations or anions. Many ionic liquids are commercially available in research quantities now.

Ionic liquids as environmentally friendly solvents have many applications. Most applications take advantages of their unique physical and chemical properties. Some promising results have already been obtained. Ionic liquids are used in batteries, fuel cells, capacitors, and sensors in electrochemical field. They are also used in a variety of applications such as lubricants for engineering and stationary phases for gas chromatography in analytic chemistry. One of the great potential applications of ionic liquids is in organic synthesis. Their good solubility and catalytic capability provide great opportunity in this area. A large number of organic reactions have been successfully carried out in ionic liquids. Additionally, the recent work with enzymatic catalysis in ionic liquids has presented an entirely new range of biochemical applications. The combination of $scCO_2$ and ionic liquids provide an attractive approach for biphasic catalysis (Gordon, 2001).

More recently, three important and interesting applications of ionic liquids have been reported, which indicates that ionic liquids can be applied in a very diverse area. One is an ionic liquid thermometer designed by Roger group in USA in 2008 (Rodriguez, 2008). Two ionic liquids tris(2-hydroxyethyl)methylammonium methylsulfate and trihexyl(tetradecyl) phosphonium bis[(trifluoromethyl)sulfonyl]amide were used as thermometric fluids in liquid-in-glass thermometers. They used a red color dye to make the ionic liquids visible. These ionic liquids have a faster temperature response time compared with mercury and they operate at a wider range of temperatures than ethanol. They are far less toxic than mercury and obviously eliminate the risk of mercury contamination due to the breakage of a glass thermometer.

The second interesting project has been reported by Borra et al. (Borra et al., 2007). They proposed to use an ionic liquid 1-ethyl-3-methylimidazolium ethylsulphate $[EMIM]^+[EtOSO_3]^-$ to make liquid mirrors for telescopes.

Cosmologists assumed that a telescope on the Moon with a large liquid mirror could provide unprecedented views of deep optical fields and would be ideally suitable for studying very distant structures of the universe.

Most liquid mirror telescopes on Earth use mercury. Mercury is molten at room temperature, and it reflects about 75% of incoming light, which is similar to silver. But mercury is unsuitable on the Moon, because it is very dense, expensive and it evaporates quickly if exposed to the lunar vacuum. Borra explained that ionic liquids were molten salts even at low temperature. They had low vapor, thus they would not evaporate into the lunar vacuum. Borra and co-workers tested several ionic liquids and identified an ionic liquid 1-ethyl-3-methylimidazolium ethylsulphate. They spray-coated the surface of this ionic liquid with silver and they found that the reflectivity of light in infrared region was improved compared to silver coating polyethylene glycol. This ionic liquid mirror is close to the requirements for Moon-based telescope and this potential application is continued (Gross, 2007; Bell, 2008).

The third significant report is that ionic liquids have been proposed to be used in drug delivery, for example, lidocaine docusate, an ionic liquid based on a common local anaesthetic (Hough et al., 2007). This report indicates that not only physical and chemical properties but also biological properties of ionic liquids have been targeted for some applications.

Therefore, the unique physical, chemical and biological properties of ionic liquids have great potentials to be used in various areas. With different cations and anions, a large number of ionic liquids can be synthesized with a wide range of properties. These ionic liquids can be investigated to replace traditional solvents for organic reactions. New applications will be identified as the range of ionic liquids is extended and explored. Another aspect of the future work is that to satisfy a particular purpose, an ionic liquid could be designed to achieve specific properties. Ionic liquids will be designed and optimized for the best performance in their intended application. At the moment, there is a lack of understanding of the full role played by ionic liquids for organic synthesis. Future studies and investigations are needed to determine the complex nature of ionic liquids. The results from the future studies will certainly help us to further broaden the applications of ionic liquids.

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