Organic Synthesis in Ionic Liquids

A report submitted for the Degree of M.Sc.

By

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The work described in this report was carried out under the supervision of Dr. Joshua Howarth and Dr. Paraic James.

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Declaration:

I hereby certify that this material, which I now submit for assessment on the programme of study leading to the award of Degree of M.Sc. in Chemistry is entirely my own work and has not been taken from the work of others save and to the extent that such work has been cited and acknowledged within the text of my work.

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I.D No: 94362181

Date: 18/09/03

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Abstract: -

Solvents play an important role in organic chemistry. Most reactions must be carried out in organic solvents, thus chemists have to deal with large volumes of solvents everyday. Solvents are highly damaging chemicals for two main reasons; (a) they are used on a large scale and (b) they are volatile which makes storage and handling difficult. For environmental protection and reduction of damage to humans, clean technologies have become a major concern throughout both industry and academia. Therefore, the search for the replacement of damaging solvents has become a high priority.

Based on such an idea, reactions involving the room temperature and moisture stable 1,3-dialkylimidazolium ionic liquids, have been carried out in an effort to replace the common bench solvents. They are a new type of solvent with attractive properties allowing for their use as both solvent and catalyst in some cases.

Therefore, throughout this project the ambient temperature 1,3-dialkylimidazolium ionic liquid was employed firstly for the reduction of simple aldehydes and ketones. In the exploration of these ionic liquids as possible replacements for classical organic solvents, we discovered that the reduction of aldehydes and ketones with sodium borohydride in $[bmim]PF_6$ can be achieved. The ionic liquid can be recycled, and in some cases the product alcohol may be distilled directly from the ionic liquid eliminating classical organic solvents entirely.

Secondly, free radical addition reactions using tributyltin hydride, a variety of alkenes and alkyl halides were carried out in the ionic liquids $[bmim]BF_4$ and $[bmim]PF_6$. The reactions using tributyltin hydride were carried out under a number of experimental conditions but the toxicity of the tin by-products produced was a major concern. The ionic liquid was capable of dissolving all reactants and extraction of the products was efficient but the tin by-products proved extremely difficult to remove. (Tris)trimethylsilylsilane was then used in an effort to remove the toxicity and by-product problems. The hydrosilylated product was formed but

the target compound was not synthesised. The use of the ionic liquid in these radical reactions, although not a complete success, the hydrosilylated product was formed which suggests that the ionic liquid did stabilise radicals formed.

Finally, a novel type of ionic liquid was synthesised and investigated. These compounds were based on 1-vinylimidazole and the synthesis was very efficient and easily carried out. A series of 1-vinyl-3-alkyl-imidazolium bromide, tetrafluoroborate and hexafluorophosphate compounds were synthesised. It was hoped that the vinyl group of these ionic liquids could be used in a Diels-Alder synthesis using a variety of dienes.

Abbreviations:

[emim]	1-ethyl-3-methylimidazolium
VOC	Volatile Organic Compound
n-bpy	n-butylpyridinium
[emim]PF_6	1-ethyl-3-methylimidazolium hexafluorophosphate
[bmim]Br	1-butyl-3-methylimidazolium bromide
[mmim]	1-methyl-3-methylimidazolium
DMF	Dimethylformamide
[emim]BF_4	1-ethyl-3-methylimidazolium tetrafluoroborate
THF	Tetrahydrofuran
EAN	Ethylammonium nitrate
PTC	Phase Transfer Catalysis
HCl	Hydrochloric acid
DCM	Dichloromethane
RBF	Round bottomed flask
EPR	Electron Paramagnetic Resonance
AIBN	Azobisisobutyronitrile
SOMO	Singly Occupied Molecular Orbital
LUMO	Lowest Unoccupied Molecular Orbital
HOMO	Highest Occupied Molecular Orbital
TLC	Thin Layer Chromatography
NMR	Nuclear Magnetic Resonance
TTMSS	(tris)trimethylsilylsilane
DMSO	Dimethylsulphoxide
TFAA	Trifluoroacetic Acid

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1. Ionic Liquids- an overview:

Chemists, both in research laboratories and involved in bulk industrial processes are continually searching for new, improved and cleaner synthetic procedures. Since chemistry is dominated by the examination of species in solution, solvents, and their properties have the utmost importance for any synthetic reaction. Ionic liquids were discovered over five decades ago and investigation of them in the last three decades has taken place. It was recognised although not immediately that they had exciting potential in order to create new solvent systems for a wide range of synthetically useful reactions that are used commercially [39], [40], [42], [45], [49], [52]. Since their discovery there have been two main aims (i) understanding their physical properties and (ii) their use as solvents for classical reactions. It is the latter point which has been the most important use of these ionic liquids and also the main reason why chemists worldwide find these unique species so interesting

Ionic liquids are one of those odd species in chemistry, they are molten salts, colourless, fluidic and easily handled even at temperatures as low as -96°C [24]. They are nothing like molten salts such as NaCl which requires temperatures in excess of 800°C to break its very strong ionic lattices in order to reach its molten state. Ionic liquids have melting points at or below 298K. Low melting points are the main reason why ionic liquids can act as solvents for various synthetic reactions. The liquids are made up of ions rather than molecules, such reactions often give distinctive selectivities and reactivity when compared with conventional organic solvents. Initially, when ionic liquids were first discovered in the 1950's [6], [10] the emphasis was on their physical properties and not on their capability as new green, workable solvents. Only in the last two decades has extensive research been carried out investigating their use as solvents and their green chemistry capabilities [7], not to mention their use and excellent advantages for industrial processes, which will be discussed in more detail later. Industrial processes produce vast amounts of waste organic solvents. [1] A major environmental advantage of using ionic liquids is as replacements for volatile organic solvents (VOC's), which are used to the tune of about 5500m Euro per annum worldwide to synthesise organic chemicals and products .

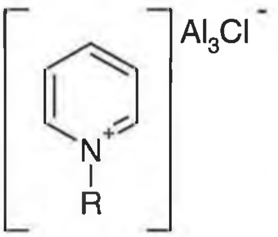
In essence, ionic liquids can be classified as one of two types; the moisture sensitive type or the room temperature moisture stable type, it is the room temperature moisture stable which are of interest in this research project but an overview of both types will be given later. They have no significant vapour pressure and thus create no volatile organic components. They also allow for ease of separation of organic molecules by direct distillation without loss of the ionic liquid. There are four types of ionic liquid grouped according to the cation and these are: alkylammonium (1), alkylphosphonium (2), N-alkylpyridinium (3) and N,N'-dialkylimidazolium (4) (*Scheme 1.*)

$R_nH_{4-n}N^+BR_4^-$

(1)

$[PR_nH_{4-n}]^+X^-$

(2)



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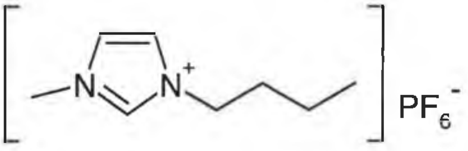


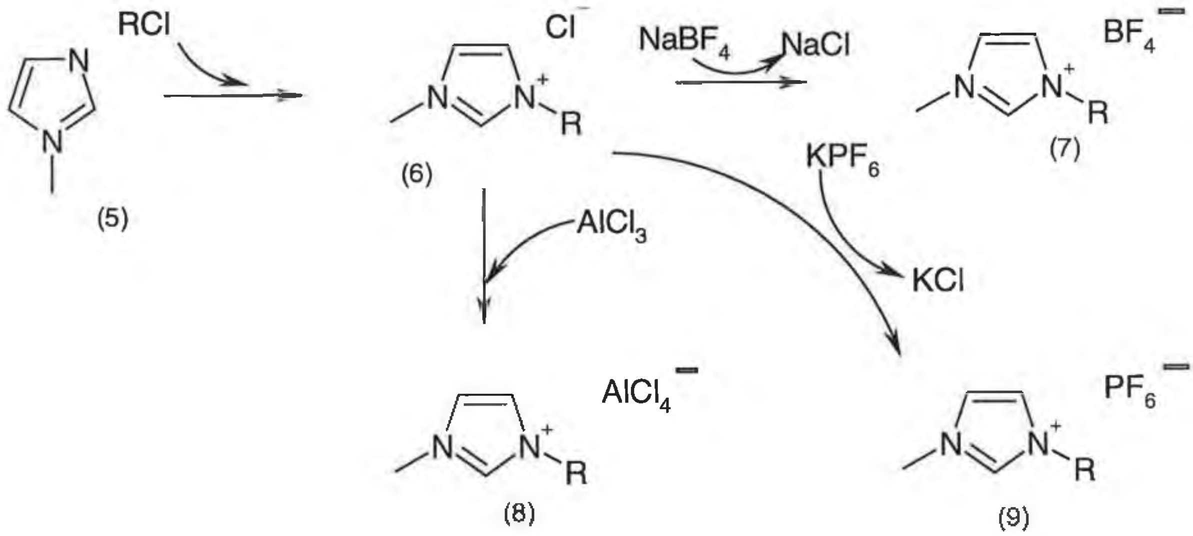
(4)

Scheme 1. Different Classes of Ionic Liquids

The counter anion X^- involved are poor nucleophilic anions such as $[BF_4]^-$, $[PF_6]^-$, $[CF_3CO_2]^-$, $[AlCl_4]^-$ and $[CF_3SO_3]^-$. The anions in these ionic liquids are what determines their physical properties [24], [25], [27]. The relative amounts of inorganic anions in the system make the liquid acidic, basic or neutral. The reason these ionic liquids do not arrange themselves as solids is that the organic cations are so big, compared to sodium for instance. A major factor in ionic liquid chemistry is that one can design an ionic liquid with the properties one desires for a specific synthesis, just by choosing the correct anion and cation. With reference to the four types mentioned above the tertraalkylammonium tetraalkylborides (1), despite being hydrophobic have limited applications due to their low conductivity, potential reactivity and difficulty of preparation [2,3]. The most widely used type now is the N,N'-dialkylimidazolium hexaflurophosphate/tetrafluoroborate (4) based on 1-methylimidazole (5)(*Scheme 2*). It should be mentioned that the most widely studied is the chloroaluminate based moieties.

2. Synthesis of Ionic Liquids:-

There are in fact four distinct methods of preparing ionic salts, the most important and most widely used being halide metathesis ie. adding two ionic compounds together in solution so that they can swap counterions with, for example, a silver, group 1 metal or ammonium salt of a desired anion. This is shown in *Scheme 2*, for the N,N'-dialkylimidazolium salt (6)



Scheme 2. Synthesis of Ionic Liquids(as shown for a N,N'-dialkylimidazolium salt)

The second method of synthesis is acid-base neutralisation, in which a basic salt, usually an alkylammonium salt is treated with an acid thereby providing the appropriate anion. Monoalkylammonium nitrate salts are prepared in this way, where aqueous solutions of the amine are neutralised with HNO_3 [4]. The ionic liquids are then isolated by removing excess water in vacuo. In an analogous reaction, treatment of tetraalkylammonium hydroxide with H_2SO_4, produces tetraalkylammonium sulfonates .

The third procedure for the preparation of ionic liquids is by quaternising the appropriate amine. Many 1-alkyl-3-methylimidazolium trifluoromethanesulphonate salts have been synthesised using this method [5]. The reaction involves methyl triflate and it should be noted that some reactions must be carried out under vacuum and also reactions involving methyl triflate and a stoichiometric amount of a 1-alkylimidazole in 1,1,1-trichloromethane require extremely anhydrous conditions.

The final method of synthesising ionic liquids is direct combination of a halide salt with a metal halide. The most commonly used metal halide is aluminium trichloride which has been used to produce imidazolium based chloroaluminates [3], the most common of these being (emim)Cl.$AlCl_3$. Chlorocuprate ionic liquids are also synthesised via this method.

3. Properties of Ionic Liquids:-

3.1 Chloroaluminate-based ionic liquids.

The first ionic liquids with chloroaluminate ions were developed in 1948 by Hurley and Weir [6] at the Rice Institute in Texas as bath solutions for electroplating aluminum. It was not until the late 1970's when Osteryoung and Wilkes's groups [7] rediscovered them. For the very first time they succeeded in preparing room temperature liquid chloroaluminate melts. In the early 1980's the groups of Seddon and Hussey [8] began to use chloroaluminate melts as non-aqueous polar solvents for the investigation of transition metal complexes. It was mainly due to Seddon's work that ionic liquids became of interest to chemists worldwide.

3.1.1 Lewis Acidity-Basicity:

Upon fusion, aluminum(III) chloride almost doubles in volume, yielding a liquid of low electrical conductance($<3 \times 10^{-7}\ \Omega cm^{-1}$) [9]. On X-ray analysis of the pure melt, a molecular liquid consisting of [Al_2Cl_6] dimers, comprising of two tetrahedra sharing an edge can be seen [10]. It should be noted that when these species were mixed with chloride ions the melt which formed were conducting, indicating the presence of ions [11]. Raman, ^{27}Al nmr and mass spectra all confirm that when $X(AlCl_3) < 0.5$ in a pure ionic liquid, $[AlCl_4]^-$ is the only chloroaluminate(III) species present [11,12,13]. All these observations conclude that the single compound formed is [cat][$AlCl_4$] where cat = $[emim]^+$ or $[n\text{-}bpy]^+$, which is indicated by local maxima in phase diagrams [14] of the chloroaluminate systems, when $X(AlCl_3) = 0.5$. Ions with the Al coordination number greater than four do not form, and excess Cl^- ions remain uncoordinated.

The chemistry of these chloroaluminate(III) ionic liquids is clearly dependent upon the specific composition of the ionic liquid. The aniodic chemistry of the addition of a chloride salt to aluminum(III) chloride is best shown by the three reactions below [15]

1. $[Al_2Cl_6] + Cl^- \rightarrow [Al_2Cl_7]^-$

2. $2[AlCl_4]^- \Leftrightarrow [Al_2Cl_7]^- + Cl^-$

3. $2[Al_2Cl_7]^- \Leftrightarrow [Al_3Cl_{10}]^- + [AlCl_4]^-$

In the ionic liquid, an analogy is often made between equilibrium 2 and the autosolvolysis reaction of water. As shown above Cl^- is a Lewis base and $[Al_2Cl_7]^-$ and $[Al_3Cl_{10}]^-$ are both Lewis acids, the Lewis acidity/basicity of the ionic liquid may be manipulated by altering its composition. This leads to a nomenclature of the liquids in which compositions with an excess of Cl^- ie $X(AlCl_3) < 0.5$, are called basic and those species with an excess of $[Al_2Cl_7]^-$ ie $X(AlCl_3) > 0.5$, are called acidic and those at the compound formation point ie. $X(AlCl_3) = 0.5$, are called neutral. The physical and chemical properties of these ionic liquids show major differences for example, [emim]Cl when combined with $AlCl_3$ in a 1:1 molar ratio has a melting point of 8°C whereas in a 2:1 molar ratio the melting point was found to be –98°C [16].

3.1.2 Water Sensitivity:

One major drawback of these aluminum(III) halides is that they are extremely sensitive to even trace amounts of water. Hence, when water is added to a chloroaluminate(III) ionic liquid of any composition, an exothermic reaction occurs with the evolution of HCl. The reaction produces (i) oxide and (ii) proton-containing species, both of which can interact with other solutes. It is this water sensitivity which hinders the use of these chloroaluminate(III) species in everyday synthesis. In carefully controlled systems oxide impurities are universally present, since water is present. However, it has been demonstrated that the presence of phosgene ($COCl_2$) will remove all oxide contamination from both basic and acidic chloroaluminate(III) ionic liquids [17,18]. Complete removal of proton-containing impurities from the chloroaluminate(III) ionic liquids has been demonstrated using ethyl aluminium(III) dichloride [19], although, it should be noted that care is required and the ethyl aluminium(III) dichloride must be titrated into the ionic liquid, as an excess of ethyl aluminium(III) dichloride cannot be removed. Ethyl aluminium(III) dichloride has to be handled with extreme care due to its toxicity. More recently it has been shown that it is possible to remove all proton impurities from both basic and acidic ionic liquids by prolonged pumping at $10^{-6} - 10^{-7}$ Torr [20]. So in conclusion, if an ionic liquid is treated with phosgene and then left on a pump overnight it can be virtually free of unadvantageous impurities which may hinder the use of the ionic liquid species.

3.2 Air and Moisture Stable Ionic Liquids:-

One of the major drawbacks which hinders the use of chloroaluminate(III) ionic liquids is their sensitivity to air and moisture. The development of ionic liquids that are air and moisture stable has provided renewed interest in ionic liquid chemistry.

The concept of ionic liquids received a substantial boost by the Wilkes group when they described in 1992 the synthesis of systems with significantly enhanced stability against hydrolysis, for example, low melting tetrafluoroborate melts [21],[22]. Based on the work carried out by Wilkes and his associates, it became clearly apparent that ionic liquids were by no means limited to chloroaluminate melts but that a whole range of cation/anion combinations can form low melting salts. These ionic liquids were initially based on the $[emim]^+$ salt system and the inert salts produced were shown to have low melting points. The $[emim]PF_6$ salt had a melting point 58-60°C while the BF_4^- and the CF_3COO^- salts had melting points of 15 and –45°C respectively.

Currently, the most popular and widely used cation is the $[bmim]^+$ system which was discovered by Suarez in 1995 and then in 1996 Bonhote *et al* [23] synthesised a series of 1,3-dialkylimidazolium salts. A wide range of cations with different alkyl groups at the C(2), C(4) and C(5) positions of the imidazole were combined with various inorganic anions such as CF_3COO^-, $C_4F_9SO_3^-$ and $(CF_3SO_2)_2N^-$. It was found that these species (34 in all were synthesised) had below room temperature melting points, low viscosities, were air and moisture stable and were easily and cheaply synthesised. They could also dissolve a wide range of organic and inorganic compounds which meant that they had applicabilty in organic synthesis. This opened up the avenue to use them as potential replacement solvents.

At present, the most widely used and most favourable group of ionic liquids are the species based on 1-methylimidazole [23]. One of the most popular being $[bmim]PF_6$ which is the one mostly used in this research project. It is a neutral stoichiometric compound, has a viscosity of 3.12 g/cm^3s at 30°C, is both air and moisture stable and is easily synthesised without great expense. It's synthesis is based on the metathesis method mentioned previously where the [bmim]Br salt is first synthesised by refluxing 1-methylimidazole and bromobutane in ethyl acetate and then treated with hexaflurophosphoric acid in water. The yield obtained varies from 85-95%.

3.2.1 Melting Points:

One of the most important criterion for the evaluation of an ionic liquid is, by definition, its melting point [24]. Of particular significance is the question of the relationship between the structure and the chemical composition of an ionic liquid and its melting point. Table 1. below shows the melting points of some chloride salts

Salt	**Melting point (^oC) [24]**
NaCl	803
KCl	772
[mmim]Cl	125
[emim]Cl	87
[bmim]Cl	65

Table 1. Melting points of chloride salts

On examination of the melting points in Table 1 the influence of the cation can clearly be seen. High melting points are characteristic of alkali metal chlorides while melting points are seen to be lower than 150^oC with suitable organic cations [25].

Not only the cation influences the melting point of ionic liquids, the anion also has a large influence, which cannot be overlooked, as shown in Table 2.

Imidazolium Salt	**Melting Point (^oC) [24]**
[emim]Cl	87
[emim]NO_2	55
[emim]NO_3	38
[emim]$AlCl_4$	7
[emim]BF_4	6
[emim]CF_3CO_3	-9
[emim]CF_3CO_2	-14

Table 2. Melting points of various imidazolium salts

Thus, on analysis of the above table, in can be concluded [24] that in most cases, an increasing size of anion with the same charge leads to a further decrease in melting point.

For ionic liquids prepared by reaction of a halide $[cation]^+X^-$ with a Lewis acid Mx_y, the mole ratio of the two reactants influences the melting point of the ionic liquid [26]. The conclusions drawn above about the factors influencing the melting point of ionic liquids are generalisations and cannot be applied to all ionic liquids. There are, of course, exceptions to these rules, but, in general the rules mentioned above can be applied to most ionic liquid species [24], [25].

3.2.2 Densities:

The density range of ionic liquids is 1.1 to 1.6 g/cm^{-3}. The density of an ionic liquid depends on the type of cation and anion used. The density of an ionic liquid decreases as the bulkiness of the organic cation increases. Slight structural changes in the cation allow a fine adjustment of the density to the desired amount for any given procedure. Table 3. below lists the densities of a few ionic liquids.

Ionic liquid	**Density (g/cm^{-3})**
[bmim]BF_4	1.320
[bmim]PF_6	1.510
[emim]Br	1.575
[emim]PF_6	1.426

Table 3. Densities of various Ionic Liquids

Varying the anion results in more obvious effects for example, with bromoaluminate melts, it was possible to achieve densities which were unusual for normal organic solvents [27]. Density measurements of ionic liquids with triflate or trifluoroacetate ions confirmed the more general result that a certain density range is established by choice of anion but fine adjustments of density are possible by careful and thoughtful choice of cation [24].

3.2.3 Viscosity:

The viscosity of an ionic liquid is essentially determined by their tendency to form hydrogen bonds and by the strength of their Van der Waals forces [28]. Comparison of the viscosity of different hydrophobic ionic liquids with [bmim]$^+$ ions emphasises the interplay between Van der Waals interactions and hydrogen bonding. Table 4. shows the viscosity of a few ionic liquids.

Anion $[A]^-$	**η(cP) [24]**
$CF_3SO_3^-$	90
n-$C_4F_9SO_3^-$	373
CF_3COO^-	73
n-$C_3F_7COO^-$	182
$(CF_3(SO_2)_2N^-$	52

Table 4. Viscosities of various anions

On analysis of Table 4 it can be seen that, on transition from the triflate ion to the n-$C_4F_9SO_3^-$ ion and from the trifluoracetate ion to the n-$C_3F_7COO^-$ ion a dramatic increase in viscosity is observed. From this, it appears that the stronger Van der Waals interactions in the case of the n-$C_4F_9SO_3^-$ and n-$C_3F_7COO^-$ ions result in higher viscosities. Comparison of [bmim]CF_3SO_3 with [bmim] $(CF_3(SO_2)_2N$ reveals a lower viscosity for the latter despite stronger Van der Waals interactions for ionic liquids with $(CF_3(SO_2)_2N^-$ ions.

The structure of the cation also influences viscosity. Low viscosities are usually obtained with $[emim]^+$ ion, in which a side chain with sufficient mobility is combined with a low molar mass. Longer or fluorinated alkyl chains result in higher viscosities because of stronger Van der Waals interactions [28]. Another point which should be made is that viscosities of ionic liquids may be lowered by only slight increases in temperature or by adding small amounts of organic co-solvents.

3.2.4 Solvation Strength and Solubility Characteristics:

As previously mentioned, the careful choice of cation and anion has a very important impact on the properties of ionic liquids, including the tuning of solubility properties, which is a large factor when using ionic liquids in any organic/inorganic synthesis. For example, the influence of the cation can be shown by investigations of the solubility of 1-octene in different tosylate melts [29]. It was shown that by increasing the non-polar character of the cation, the solubility of 1-octene in the ionic liquid increased, as shown in Table 5.

Solubility of x(octene)/mmol mol^{-1} in ionic liquid	**Cation**
0	$CH_3NEt_3^+$
500	$CH_3N\textit{n}Bu_3^+$
1000	$CH_3N\textit{n}Pent_3^+$
1500	$CH_3N\textit{n}Hex_3^+$

Table 5. Solubility of 1-octene in different tri-n-alkylmethylammonium tosylate melts at 80°C.

The influence of the anion on solubility of ionic liquids can be shown by investigating the water solubility of different melts containing the [bmim] ion. The ionic liquids [bmim]Br, [bmim]CF_3COO and [bmim]CF_3SO_3 , bearing the same cation are all highly water soluble but with PF_6^- and $(CF_3SO_2)_2N^-$ as ions biphasic mixtures with water are formed. It has been shown that the water content of the ionic liquid [bmim]$(CF_3SO_2)_2N$ at 20°C is only 1.4 weight percent [28].

Several ionic liquids, showing a miscibility gap with water have been considered as candidates for separation processes by liquid-liquid extraction. Rogers *et al* [30] investigated the solubility of different acids and bases in water/[bmim]PF_6 at different pH values of the aqueous phase. Their results reveal a higher solubility of neutral substances in the ionic liquid, while ionic species dissolve in the aqueous layer. It was concluded that the solubility properties of [bmim]PF_6 vs water show high similarities to organic solvents and this further adds to their possibilities of replacing volatile organic compounds (VOC's) in extractive separation processes. Without a doubt, the key to the successful use of ionic liquids lies in the skillful exploitation of their exceptional solubility characteristics. Table 6 shows a list of ionic liquids and their qualitative solubilities in various common organic solvents.

Ionic Liquid	**Molecular Weight**	**Solubility**						
		Water	**Methanol**	**Acetone**	**Chloroform**	**Pet. Ether**	**Hexane**	**Toluene**
[bmim]BF_4	226.02	s	s	s	s	I	i	i
[bmim]PF_6	284.18	i	s	s	s	i	i	i
[bmim]Cl/$ALCl_3$	154.01	r	r	s	s	i	i	s
[emim]PF_6	256.13	i	i	s	s	i	i	i
N-Butylpyridine/$AlCl_3$	152.50	r	r	s	i	i	i	s

s:- soluble, i:- insoluble, r:- may react with each other.

Table 6. Solubilities of various organic solvents in Ionic Liquids

3.2.5 Polarity:

Solvent polarity is the most commonly used solvent classification. The terms polar, non-polar and apolar are used indiscriminately to apply values of dielectric constants, dipole moments and polarisabilities, even though none of these are directly correlated in a simple way. The simplest definition of a polar solvent is a solvent that will dissolve and stabilise dipolar or charged solutes, and thus it is presumed ionic liquids will be polar solvents.

One of the most useful techniques for measuring the polarity of a substance is by using Reichardt's Dye (2,4,6-triphenylpyridinium) N-4-(2,6-diphenylphenoxide) betaine. This dye can register effects arising from solvent dipolarity, hydrogen bonding and Lewis acidity. The $E_{(T)}$ 30 scale was introduced by Dimroth *et al* in 1963 [31], but further developed by Reichardt in 1971. This method has been used to determine the polarity of a small number of ionic liquids. Tetra-n-hexylammonium benzoate has an $E_{(T)}$ 30 value of 0.41 which lies within the polarity range of DMF [32], ethyl ammonium nitrate has an $E_{(T)}$ 30 value of 0.95 which corresponds to a polarity between CF_3CH_2OH and water [33]. A value of [bmim]PF_6's $E_{(T)}$ 30 was found to have a polarity in the range corresponding to methanol [34]. The number of compounds tested is still limited but the results show that a wide range of polarities can be obtained depending on the structural content of the ionic liquid.

3.2.6 Vapour Pressure and Thermal Stability:

Ionic liquids have no measurable vapor pressure. From a process engineering point of view this is an exceptional advantage due to the fact that distillation may be used for product isolation. The well known problem of azeotrope formation between solvent and product does not arise.

The limitations of the thermal stability of ionic liquids are due to their heteroatom-carbon and heteroatom-hydrogen bonds. Ionic liquids synthesised via the direct protonation of an amine or phosphane display significantly restricted thermal stability. While 150°C has to be considered as the maximum working temperature for the vast majority of the quaternary ammonium chloride salts, [emim]BF_4 has been reported to be stable at 300°C [35] and [emim]$(CF_3SO_3)_2N$ is stable up to 400°C [28], which allows for further exploration into their synthetic utility.

4. Ionic Liquids as Solvents:

In recent years, significant progress has been made in the application of room temperature ionic liquids on catalytic processes, especially in homogenous catalysis [50]. There are many advantages of homogenous catalysis ie. selectivity, activity, low cost and mild, flexible conditions. A major factor which must be considered when using homogenous catalysis is the problem of separation of products from the reaction medium/solution. Removing the product from the catalyst after the reaction often requires techniques such as distillation and chromatography, all of which can add to the expense of the synthetic process and also the catalyst may degrade as may the product. Due to these factors heterogenous catalysis is chosen because this reduces cost and the number of steps in a process. Heterogenous catalysis involves anchoring the catalyst in one phase while the reactants and products are contained in the other. These two phases are then allowed to mix, the products decanted in one phase, while the catalyst is retained in the other, thus enabling recycling of the catalyst.

Ionic liquids have solved the hindrance of separation problems in homogenous catalysis. This is due to the fact that ionic liquids are ideal for biphasic catalysis, which is essentially a type of homogenous catalysis but the initial reactants or final products and catalyst are in two separate phases. Ionic liquids are suited to this task because;

- They have a wide liquid range (~300°C) with a melting point around room temperature. This allows for comfortable working conditions and also allows for distillation of compounds at higher temperatures.
- They have the ability to dissolve a wide range of materials including inorganic and organic materials. This allows for a vast range of possible chemical reactions to be carried out in ionic liquids.
- They have an excellent and variable Lewis/Bronsted acidity which means the required ionic liquid can be synthesised depending on the needs of the chemist for a particular chemical reaction.
- They have a negligible vapour pressure which means they are non volatile and can be used in high vacuum systems and distillation can be carried out which is not possible with conventional volatile organic solvents. Since ionic liquids do not evaporate there is no release of VOC's which serious industrial implications as mentioned previously.

- There is always the potential that the ionic liquid can be re-used and recycled. This drastically reduces the cost of any synthetic procedure.
- They are often composed of poorly coordinating ions so they can be highly polar but non-coordinating, activity of a catalyst is not hindered like in other organic solvents.

At present the applications of ionic liquids in catalysis as replacements to conventional solvents are concentrated in two distinct directions. One is to replace organic solvents due to their unique solvent properties and the other is to take the place of liquid acids, due to their variable acidities. The former applications include dimerisation reactions and the Heck reaction, while the latter includes alkylation reactions and Friedel-Crafts reactions [39], [40].

With regard to methods to reduce catalyst consumption, two aspects arise with the use of ionic liquids, namely the solubility characteristics of the ionic liquid allowing biphasic reaction procedures, which at present is the main focus regarding ionic liquids and a method of recycling catalysts is possible due to the miscibility gap between the ionic catalytic phase and the product. Secondly, the non-volatile nature enables a more effective product isolation by distillation.

5. Ionic Liquids as Green Solvents:

Clean technology concerns the reduction of waste from an industrial chemical process to a minimum: it requires the re-thinking and re-design of many current chemical processes. As defined by Roger Sheldon, the E-factor of a process is the ratio (by weight) of the by-products to the desired products [36]. Table 7. shows the E-factors of some industries.

Industry	Production/tons per annum	E factor
Oil refining	10^6-10^8	0.1
Bulk Chemicals	10^4-10^6	1-5
Fine Chemicals	10^2-10^4	5-50
Pharmaceuticals	10^1-10^3	25-100

Table 7. E factors of various industrial processes

The table shows that the relative "dirty" end of the chemical industry, where oil refining and bulk chemicals is actually remarkably waste conscious. It is the fine chemicals and pharmaceutical companies which use inefficient, dirty processes even though they are at a much smaller scale [37], much of the waste being due to solvent use. In order to reduce this waste factor, there are four main alternate strategies.

- Solvent free synthesis
- Water as a solvent
- Use of supercritical fluids as solvents
- Use of ionic liquids as solvents

The last strategy is the one of interest in this discussion. As mentioned previously ionic liquids have melting points beginning from –96°C [24]. By changing various anions and cations it is estimated that there are ~ 10^{18} (one trillion) accessible room temperature ionic liquids. The wide range of reactions (which shall be discussed later) that have been undertaken in low temperature ionic liquid solvents is quite amazing. Many of the processes which shall be mentioned which are now used in industry have been taken through the development process to the point of industrial commercialisation. They represent first generation ionic liquid processes, principally based on chloroaluminate III ionic liquids. These are now ready for industrial uptake at present. Following this closely is second generation ionic liquids, which are processes based on more benign ionic liquids and a vast amount of research in laboratories worldwide is ongoing.

Ziegler-Natta polymerisation of ethylene to linear α-olefins currently has a world capacity in excess of 1.6×10^6 tonnes per annum. The most common production methods involve the use of triethylaluminum catalysts at ~100°C and 100 atmospheres pressure. More modern processes make use of organic transition metals such as nickel and titanium based compounds, for example, the use of a mixed alkylchloroaluminum(III) and titanium(III) chloride catalyst in an organic solvent to produce exceptionally pure α-olefins. Ziegler-Natta polymerisation of ethylene has been reported in an ionic liquid [38], using dichloro-bis(n^5-cyclopentadienyl)titanium(IV) with an alkyl-chloro-aluminum(III) co-catalyst in an acidic [emim]Cl-$AlCl_3$ ionic liquid solvent.

The alkylation of benzene with a wide range of alkyl halides in acidic chloroaluminate(III) ionic liquids [39] leads to rapid and largely uncontrolled polyalkylation with evolution of hydrogen chloride. For example, the alkylation of benzene with chloromethane in an acidic ionic liquid gives a mixture of mono- to hexa-substituted products. The ionic liquid solvent/catalyst activates the reaction and the alkylation can be performed even at temperatures as low as –20°C. In the ionic liquid solvent, these products have a low solubility and thus are conveniently separated.

The two examples above which are being or already have been commercialised are very important if ionic liquids are to be of any real benefit commercially, as it is in industry they need to be beneficial. There are also many reactions which are still in the development stages in laboratories world-wide and it is hoped that with time and effort they will also be used in industry, reducing both cost and waste in various synthetic procedures. The ionic liquids based on the imidazole moiety are also being investigated. Many of these processes utilise the ability of ionic liquids to selectively immobilise transition metal catalysts for liquid-liquid two phase catalysis, while permitting ease of extraction of products. This alone would have great advantages in industrial processes involving liquid-liquid extraction. It is hoped that the ionic liquid may be recycled and used in a number of reactions which reduces the cost of the procedure by allowing for recycling of both solvent and catalyst and also waste problems may be reduced.

6. Applications of Ionic Liquids in Organic Synthesis:

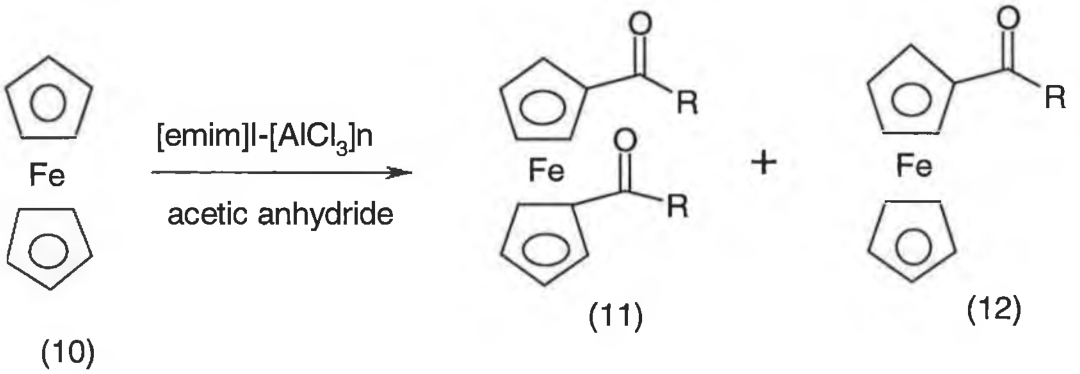
The study of the use of ionic liquids in synthetic procedures has received a vast amount of interest in the last ten years[21], [22], [23], [28]. The study of their use may be divided into two (i) their use as a solvent in classical organic reactions and (ii) their use in biphasic catalysis. The synthetic uses of both chloroaluminate and the imidazole based ionic liquids shall be discussed here with the latter group being the one favoured in this research project. The chloroaluminates were after all, the first discovered and the first reactions were carried out using these melts. In this discussion the chloroaluminates will be dealt with first followed by the imidazole-based salts.

6.1 Electrophilc Aromatic Substitution reactions in Chloroaluminate-based Salts:

The first type of reaction to be investigated in room temperature chloroaluminate(III) ionic liquids was electrophilic substitution reactions[39]. The high concentration of chloroaluminate(III) species coupled with the good solubility of simple arenes in the acidic ionic liquids makes them ideal for these reactions, using their function as a solvent and a catalyst. Of all the arenes tested by reaction with 1-chloropropane, nitrobenzene was the only one which failed to react. Just like the conventional reactions using bench solvents, polyalkylation was observed, for example, reaction of an excess of chloroethane with benzene led to a mixture of mono(12%), di(11%), tri(33%), tetra(24%), penta(17%) and hexa(2%) substituted products[39]. This polyalkylation can be kept to a minimum by using excess arene in the reaction. It should be noted that basic ionic liquids do not provide adequate catalytic activity for alkylation reactions to occur.

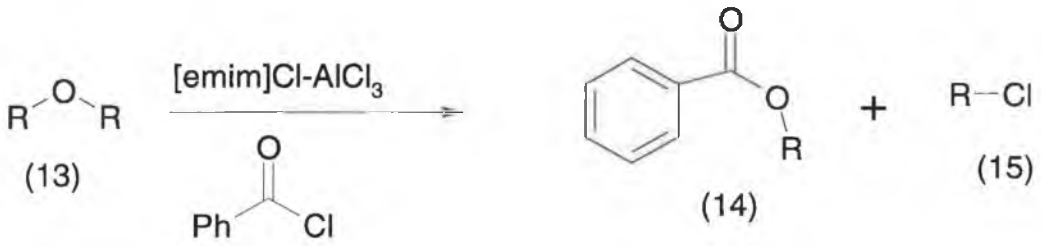
Friedel-Crafts alkylations and acylations are of great commercial importance and are among the earliest reported studies using ionic liquids as Lewis acid cataylsts [39]. The catalyst conventionally used in Friedel-Crafts reactions is $AlCl_3$ which gives rise to disposal and by-product problems. The Friedel-Crafts acylation was first carried out in the most widely used chloroaluminate(III) ionic liquid [emim]Cl-$AlCl_3$ by Wilkes and co workers [39]. Wilkes and his group carried out Friedel-Crafts alkylations using primary and secondary halides and simple benzene derivatives. It was Lewis acid equilibrium of the ionic liquid which was the main driving force of the reaction : $2AlCl_4$- $\Leftrightarrow$ $Al_2Cl_7^-$ + Cl^- where $Al_2Cl_7^-$ was the Lewis acid and Cl^- the Lewis base. They showed that it was the $Al_2Cl_7^-$ species present in the acidic mixture which was acting as the Lewis acid catalyst in the reaction. Thus it was proved the ionic liquid was not only the catalyst for the reaction but also the solvent.

The Friedel-Crafts acylation reaction of ferrocene with acetic anhydride in [emim] Cl-$AlCl_3$ as the ionic liquid was reported in 1996 [40]. The rate of the reaction was controlled by the $AlCl_3$ concentration in the melt, and it also determined whether a mono or bis substitution reaction took place. Scheme 3 below shows the acylation.



Scheme 3. Ferrocene acylation in Ionic Liquid.

The final synthesis in which the Lewis acidity of chloroaluminate(III) species is utilised is the acylative cleavage of cyclic and acyclic ethers. Several methods for cleaving ethers are available but a method to selectively cleave ether linkages had not been reported [41]. The ionic liquids derived from [emim]I/$AlCl_3$ have been used as solvents and Lewis acid catalysts for the acylative cleavage of a series of cylic and acyclic ethers such as THF, diethyl ether and diisopropyl ether. Green and co workers [41] had discovered another unique use of these chloroaluminate(III) melts in which there properties allowed for excellent results in synthetic chemistry.



Scheme 4. Acylative cleavage of ethers

6.2 Imidazole-based or Neutral Ionic Liquids:

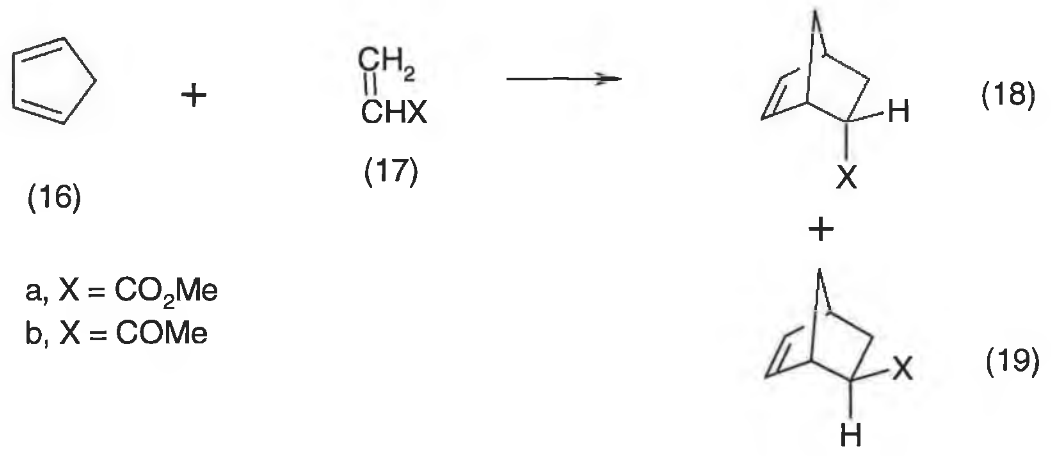
At present these ionic liquids are preferred due to their ease of preparation, handling and properties [21] [22]. A number of reactions have been carried out in these ionic liquids. Only the more recent reactions shall be discussed in this literature survey [24], although, the Diels-Alder reaction [42] shall be discussed as it was this reaction which had excellent results and opened the way for more synthetic procedures to be studied in the moisture stable room temperature ionic liquids

6.2.1 Diels-Alder Reaction:

The reaction of cyclopentadiene and methyl acrylate leads to exo and endo products as mentioned. The reaction has been investigated in a range of molecular solvents and solvent influences on the endo/exo selectivity of the reaction are well understood. "Polarity" of the solvent is thought to be responsible for the more polar (endo) activated complex. Recently, the effect has been attributed to solvophobic interactions that generate an internal pressure and promote the association of the reagents in the solvent cavity during the activation process. Due to their highly ordered hydrogen bonding systems, it was thought that ionic liquids would have great potential to have dramatic effects on Diels-Alder reactions.

The Diels-Alder reaction remains one of the most useful C-C bond formation reactions in organic chemistry. Water has been used as a solvent for the Diels-Alder reaction. Jaeger and co workers [42] used the ionic liquid ethylammonium nitrate (EAN), which is a low melting fused salt (melting point 12°C). EAN shares properties with water in that properties associated with its hydrophobic effect are very similar and it has a high cohesive energy.

The reactions studied were cyclopentadiene (16) with methyl acrylate (17a) and methyl vinyl ketone (17b) to give endo (18) and exo (19) cycloaddition products. Scheme 5 shows the Diels-Alder cycloaddition.



Scheme 5. Diels-Alder Reaction In Ionic Liquid

EAN gave endo selectivity enhancements for the reaction of (16) with (17a) and (17b), and a rate enhancement for the former (17a), relative to non-polar solvents [42]. The rate and endo selectivity of these reactions using EAN was not as good as water but however was a better reaction medium in one respect. In general, neutral organic compounds are more soluble in

EAN than in water[43]. In essence this led to use of EAN in Diels-Alder reactions involving water sensitive compounds. Currently EAN is not used due to it's potential explosive properties under certain conditions [44].

Ionic Liquid	**Conditions**	**Yield %**	**Endo/exo ratio**	**Product:dicyclo pentadiene**
[bmim]ClO_4	72hrs/25°C	75	5.3:1	97:3
[emim]CF_nSO_n	72hrs/25°C	56	4.9:1	93:7
[bmim]BF_4	72hrs/25°C	91	4.3:1	98:2
[emim]NO_n	72hrs/45°C	57	3.3:1	89:11
[emim]PF_6	72hrs/70°C	34	3.2:1	88:12
[$EtNH_n$]NO_n	72hrs/25°C	98	6.7:1	
$LiClO_4$	72hrs/25°C		7.2:1	
Water	72hrs/25°C		9:1	

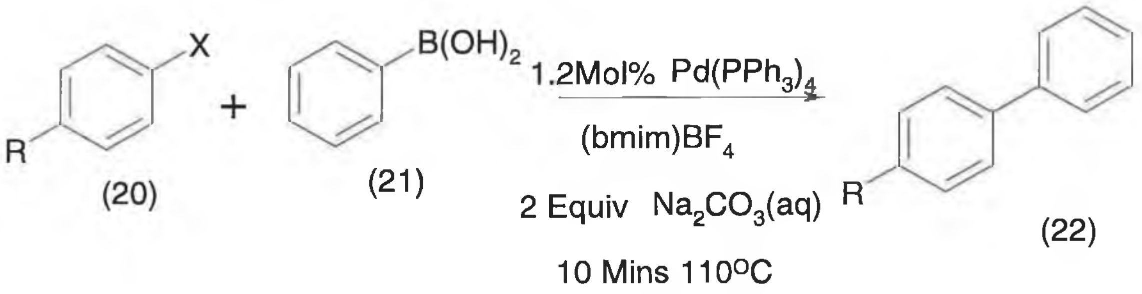
Table 8. Diels-Alder reaction in various ionic liquids

As can be seen from Table 8 above, room temperature ionic liquids gave substantial endo selectivity enhancements. As mentioned after the ethylammonium salts, moisture sensitive reagents may be used. It should be noted that although enhanced selectivities were obtained, these experiments did not produce a higher rate of reaction or endo selectivity as water and 5M $LiClO_4$ in diethyl ether, which is the most successful solvent system to date. On comparison with the results obtained for EAN, lower endo/exo selectivities were achieved possibly due to the more highly ordered structure of the ethylammonium salt, which is held together by N-H hydrogen bonds rather than the weaker C-H hydrogen bonds that dominate imidazolium salts.

6.2.2 *Suzuki Cross-Coupling Reaction:*

The Suzuki cross-coupling reaction is an extremely versatile method for the generation of new C-C bonds and is used most successfully in the synthesis of biaryls [45]. Although useful, the reaction does have a number of disadvantages; namely catalyst loss into the product, catalyst decomposition and poor reagent solubilities. It was hoped that ionic liquids would help to resolve these problems [46]. Stranforth and co workers [45] chose [bmim]BF_4 as the ionic liquid for the reaction due to its high liquid range.

4-Bromotoluene was reacted with phenylboric acid in [bmim]BF_4 using the original Suzuki conditions [47]. This yielded 4-methylbiphenyl in 30% yield after six hours with catalyst {1.2Mol% $Pd(PPh_3)_4$} decomposition. The procedure was modified and enhanced reaction rates were achieved and catalyst decomposition prevented. The new procedure (see Scheme 6) involved heating the catalyst with the aryl halide in [bmim]BF_4 at 110°C with vigorous stirring. The catalytic solution was then cooled to ambient temperature and the reaction was started by the addition of arylboronic acid and an aqueous solution of sodium carbonate. Table 9 overleaf shows the results obtained for the various arenes used.



X = I, Br, Cl
R = H, Cl, $COCH_3$, CH_3, OCH_3

Scheme 6. Suzuki-Cross Coupling In ionic liquid

Catalyst concentration was also reduced which resulted in improved yields. Overall, the Suzuki cross-coupling reaction was successfully carried out in the ambient temperature ionic liquid [bmim]BF_4, with a number of advantages;

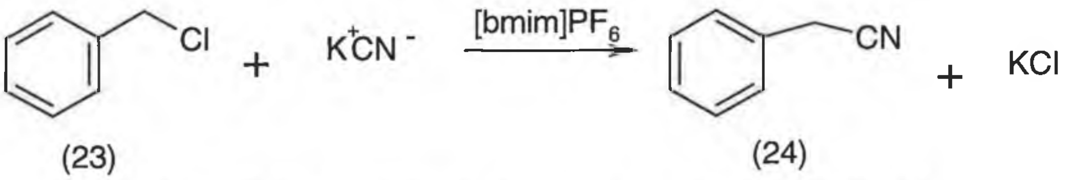
- Reaction showed a significant increase in reactivity at reduced catalyst concentration.
- Homo-coupled products can be eliminated, affording isolated products in relatively high purity.
- The reactions can be performed under air without loss of yield or catalyst decomposition.
- Catalyst can be recycled without loss of catalytic activity.

X	**R**	**Yield %**
I	H	86
Br	H	93
Cl	H	1
Br	Cl	17
Br	$COCH_3$	67
Br	OCH_3	81

Table 9. Results of Suzuki cross-coupling reactions in [bmim]BF_4

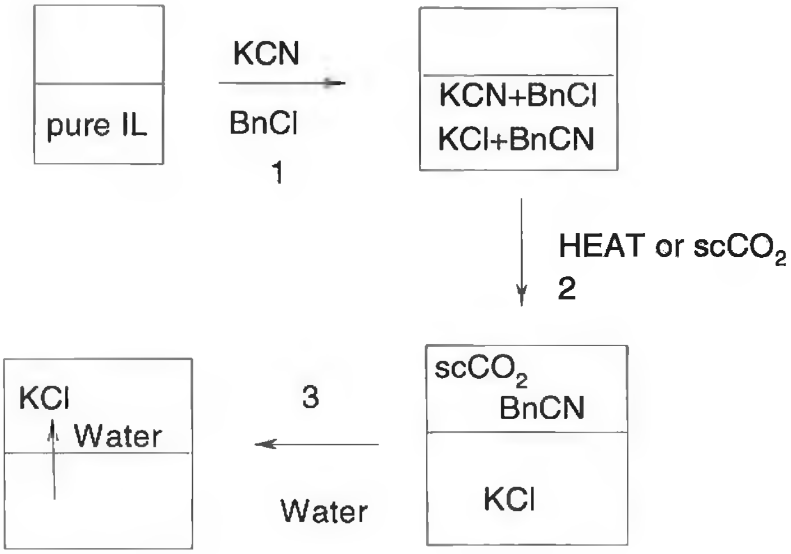
6.2.3 Nucleophilic Displacement Reactions:

Nucleophilic displacements are often carried out using phase transfer catalysis (PTC), see scheme 8, to facilitate the reaction between the organic reactants and the inorganic salts that provide the nucleophile [48]. The phase transfer catalyst, often a tetraalkylammonium salt, acts as a shuttle for the reactant anion between a polar phase that contains the salt and a non polar phase that contains the organic reactant. The use of ionic liquids in these reactions was studied by Wheeler and co workers[49]. They chose to displace the chloride of the benzyl chloride (23) using potassium cyanide to yield phenylacetonitrile (24) using [bmim]PF_6 as the ionic liquid.



Scheme 7. Nucleophilic displacement reaction in ionic liquid

Due to their bulky organic cations, ionic liquids seemed well suited for reactants where PTC is effective [49]. The ionic liquid based reaction was carried out at a range of temperatures and the rate of the reaction was highest at 80°C, due to the decrease in viscosity of the ionic liquid and increase in solubility of the KCN salt. In essence, it is clear that the use of ionic liquids in these PTC reactions seems favorable and the products were easily separated by benign methods. A major factor in this process was the fact that on completion of the reaction the ionic liquid could simply be washed with water which removed the inorganic salts and then used again in another reaction. This opens the opportunity for environmentally friendly processing, thus demonstrating the viability of ionic liquids as solvents for reactions between organic compounds and inorganic salts.



Scheme 8. Phase transfer catalysis for the reaction of benzyl chloride (23) and potassium cyanide (24)

6.2.4 Wittig Reaction:

The Wittig reaction is still one of the most popular methods for preparing alkenes, giving, in most cases good stereocontrol. The separation of the alkene from the by-product (Ph_3PO) is a classical problem, it is usually done by crystallisation and chromatography. It has been shown by Boulaire and co workers [50] that [bmim]BF_4 can be used as a medium to perform Wittig reactions using stabilised ylides (see scheme 9), allowing both easier separation of alkenes from Ph_3PO and also recycling of the ionic liquid [50].

$$\underset{(25)}{Ph_3P{=}CH\text{-}Y} \quad + \quad \underset{(26)}{PhCHO} \quad \Rightarrow \quad \underset{(27)}{PhCH{=}CH\text{-}Y} \quad + \quad \underset{(28)}{Ph_3PO}$$

a : $Y = COMe$ b : $Y = CO_2Me$ c : $Y = CN$

SCHEME 9. THE WITTIG REACTION

Y (ylide)	**Yield % of 27**
COMe	82
CO_2Me	90
CN	79
CN*	66

* reaction carried out in toluene for comparison

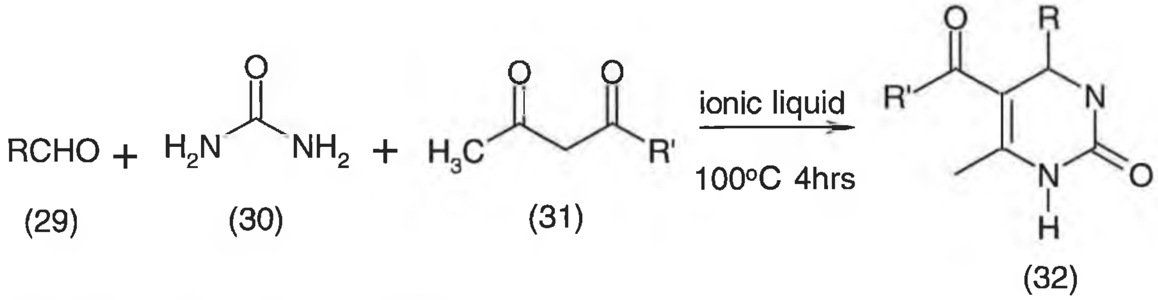
Table 10. Wittig reactions using various ylides in [bmim]BF_4

Table 10 shows the yields obtained for the various compounds used. A wide range of aldehydes were reacted using [bmim]BF_4 with (25a) to give the corresponding alkenes in good yield and selectivity. The only problem encountered was the use of a para-nitro derivative aldehyde which had low solubility in ether, thus giving a low yield (44%). In conclusion, the Wittig reaction can be carried out in ionic liquids and the problem of separation of alkene and Ph_3PO by-product is overcome due to the simple separation techniques. The ionic liquid was recycled six times without loss of reactivity which helps reduce disposal costs and thus improving the green chemistry use of the ionic liquids.

6.2.5 Biginelli Reaction using Ionic Liquids as Catalyst:

Recently, the interest in synthesis of 3,4-dihydropyrimidin-2(1H)-ones(32) (Biginelli compounds) and their derivatives is increasing due to their therapeutic and pharmacological properties [51]. Synthesis of the dihydropyrimidine nucleus involves one-pot to multi-step approaches. The classical Biginelli synthesis (scheme 10) is a one-pot condensation using β-dicarbonyl compounds with aldehydes (aromatic and aliphatic) and urea or thiourea in an ethanol solution containing catalytic amounts of acid [52]. Disadvantages of this method include; long reaction times, harsh reaction conditions and poor yields. It was reported by Hu and co workers [53] that Lewis acids in combination with transition metals and a proper proton source were effective catalysts for the reaction.

A new approach discovered by Peng [54] involved the use of room temperature ionic liquids [bmim]BF_4 and [bmim]PF_6 as catalysts for the Biginelli condensation under solvent-free conditions.



R = C_6H_5, 4-(CH_3O)-C_6H_4-Cl-C_6H_4
R' = OEt, CH_3

Scheme 10. Biginelli condensation reaction in ionic liquid

It was shown that by carrying the reaction in the absence of any ionic liquid, with just the reactants present, yielded no product, which proved a catalyst was necessary. A series of reactions were carried out using the ionic liquids ([bmim]BF_4 and [bmim]PF_6) as catalysts. The reaction was successfully carried out giving high yields for the first time, as good as 95% in some cases. The main advantages of the new reaction conditions were;

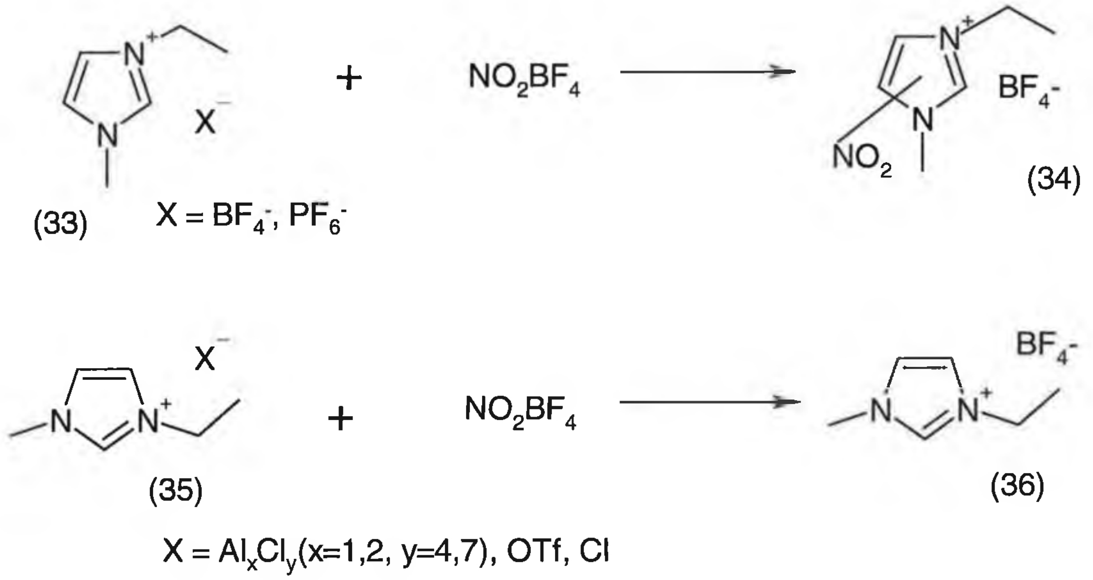
- Simple catalyst system was used
- Shorter reaction times
- Simple synthetic procedure

Although the ionic liquid isn't being used as a solvent in this reaction, its physical properties ie. cation/anion relationship allow for their successful use as a catalyst in the process.

6.2.6 Nitration Of Aromatic Compounds:

Nitration of aromatic compounds is a reaction of great importance to industry, the products of which are key organic intermediates. There is continuing concern over environmental aspects, disposal problems and regeneration of used acids, which using conventional solvents, the electrophilc aromatic nitration produces. The $ArNO_2$ products produced are generally soluble in concentrated nitric acid and this creates problems for product recovery. Also, the water by-product formed during mixed acid nitration ie H_2SO_4 and HNO_3, lowers the acidity and hence the efficiency for continuous operations. Boon and co-workers [55] carried out the earliest study of catalysis of electrophilic aromatic substitution reactions in acidic [emim] chloroaluminates using potassium nitrate.

Laali and co workers [56] explored the use of ionic liquids as solvents for aromatic nitration using several nitrating systems and various [emim]X compounds and aromatic substrates.



Scheme 11. Nitration with nitronium tetrafluorborate.

Ionic Liquid	**Yield %**
[emim]Cl	21
[emim]$AlCl_4$	47
[emim]BF_4	5
[emim]PF_6	19

Table 11. Nitration of toluene with nitronium tetraflouroborate and in the presence of an ionic liquid.

Table 11. shows the yields obtained for the nitration of toluene using nitronium tetraflouroborate in the presence of various ionic liquids. These systems proved to be unsuccessful for a number of reasons, mostly due to counterion exchange in the case of [emim]$AlCl_4$ where formation of [emim]BF_4 was noted.

A number of other nitrating systems were tested including (see table 12 below); NH_4NO_3/TFAA, isoamyl nitrate/$BF_3.Et_2O$, isoamyl nitrate/TfOH, $Cu(NO_3)$/TFAA and $AgNO_3/Tf_2O$. It was shown that the best systems for aromatic nitration in an ionic liquid were NH_4NO_3/TFAA with [emim]CF_3COO, [emim]NO_3 and isoamyl nitrate.$BF_3.Et_2O$ and isoamyl nitrate/TfOH with [emim]Otf

R-Ar	Ionic Liquid	Yield %
MeO	[emim]OTf	95
	[emim]CF_3COO	75
Me	[emim]CF_3COO	65
	[emim]OTf	60
1-MeO/4-Me	[emim]OTf	90
	[emim]CF_3COO	70

Table 12. Nitration of various aromatic compounds.

In conclusion, the use of ionic liquids for the nitration of arenes in the presence of a nitrating agent is useful and successful. Choice of nitrating system is very important as some systems proved very unreactive. The ionic liquids [emim]OTf, [emim]CF_3COO have been shown to be quite promising when used with the correct nitrating agent. Nitration using $[NO_2][BF_4]$ caused problems due to the fact that the imidazolium core itself was nitrated in a competition reaction, but, using the optimal nitrating systems mentioned above, nitration in ionic liquids was successful.

7. Reductions of aldehydes/ketones in Ionic Liquids using Sodium Borohydride:

7.1 Introduction- Hydride reducing agents

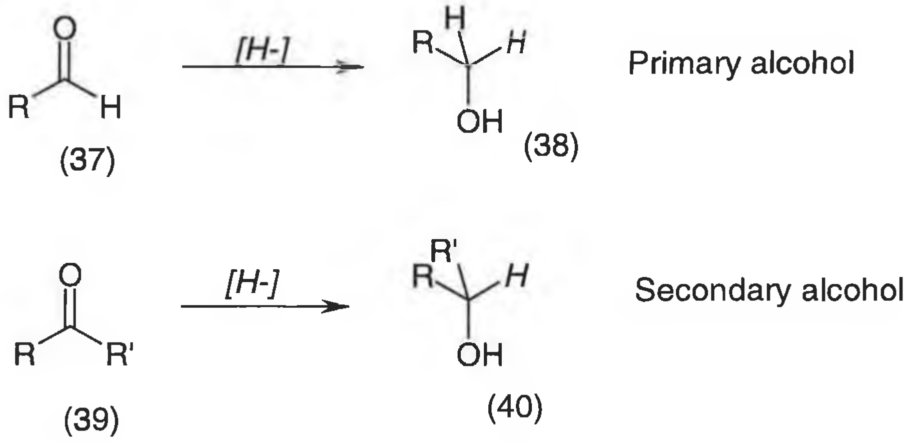
The most valuable method for preparing alcohols is by reduction of a carbonyl compound. In the scope of inorganic chemistry, reduction is defined as the gain of electrons and oxidation is defined as the loss of electrons, also, oxidation may be defined as a gain in oxygen or a loss of hydrogen. With organic chemistry it is sometimes difficult to determine whether an atom gains or loses electrons during a reaction. Hydride reducing agents, such as Lithium Aluminium hydride and Sodium borohydride form a major part of a chemist's arsenal of reducing agents employed in organic synthesis. Lithium aluminum hydride and sodium borohydride are widely used reducing agents. They were discovered and introduced by Schlesinger and Brown in 1943 [57,58]. Lithium aluminium hydride is useful due to the fact it can reduce so many compounds, although, it does lack selectivity. Sodium borohydride, which is milder and can be handled easier, reduced organic compounds in a more selective way.

As time went on, chemists began manipulating reducing agents by attaching organic ligands at the boron or aluminium atoms and, by also changing the metal counterion. Hence the scope of regio-and stereoselectivity of reductions could be modulated. Literally hundreds of substituted boron and aluminium hydrides have been synthesised and are all commercially available [59]. Transition metal salts have been used as catalysts or additives in conjunction with sodium borohydride and lithium aluminium hydride to modify and enhance their properties. At present, if a chemist has to carry out any given kind of reduction, even if the substrate is difficult to reduce, there is probably already an alumino or borohydride reducing agent and a set of reaction conditions that will carry out the required task. Such is the remarkable development in this field.

In general, $NaBH_4$ does not react with acids, esters, lactones, epoxides or nitriles. It should be noted that $LiAlH_4$ is extremely reactive and often when it is used it reduces groups which the chemist may not want reduced ie NO_2 or CN, the use of $NaBH_4$ allows selective reduction of compounds containing NO_2, Cl, COOR or CN. Another point is that sugars may also be reduced. They are not soluble in ether and since the use of $NaBH_4$ allows water and alcoholic solvents, these sugars are easily reduced.

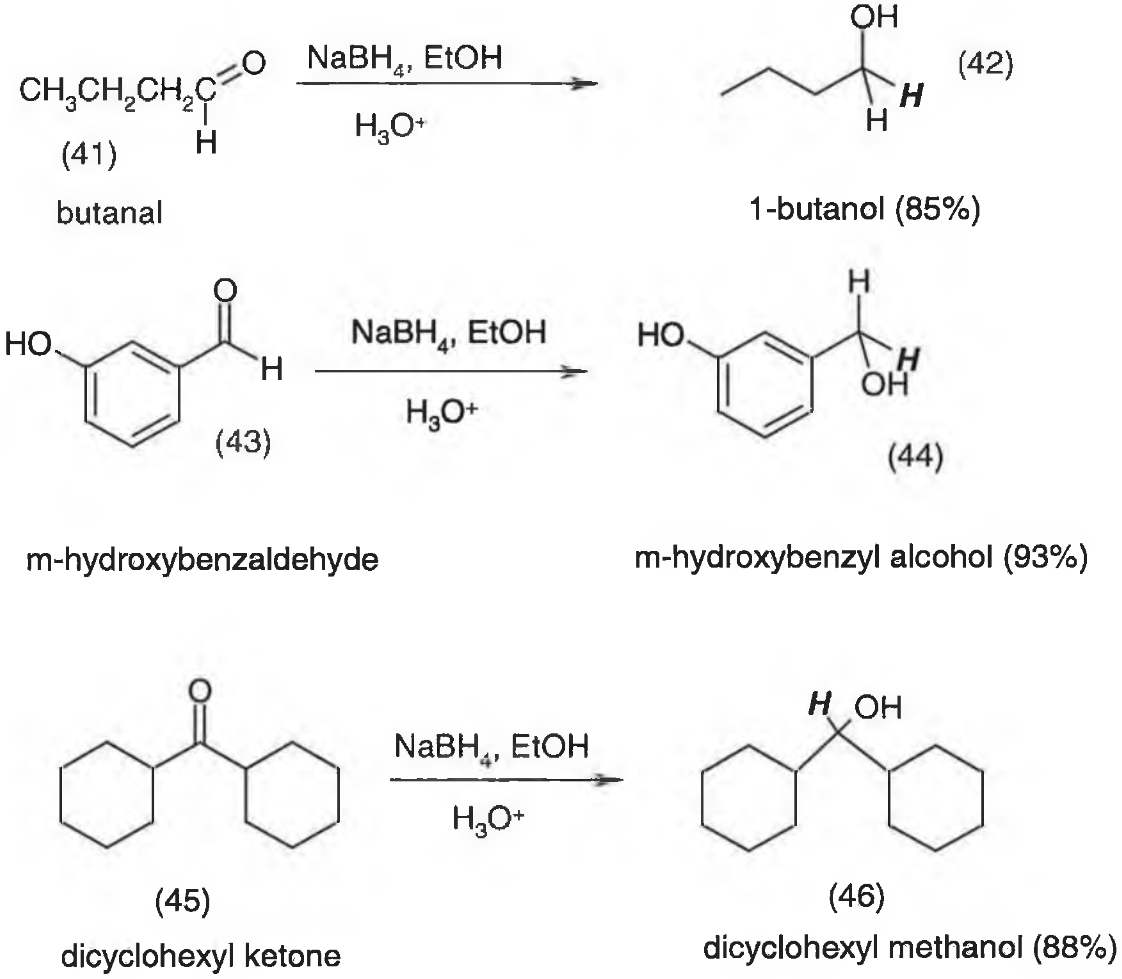
7.2 Reduction of Aldehydes and Ketones with Sodium Borohydride:

Aldehydes (37) and ketones (39) are easily reduced to yield alcohols. Aldehydes are converted into primary alcohols and ketones into secondary alcohols as shown in scheme 12 below.



Scheme 12. Reduction of aldehydes/ketones to primary and secondary alcohols

There are a vast number of reducing agents which are available for these reactions, but in general, sodium borohydride is chosen because of its safety and ease of handling. Sodium borohydride itself is a white crystalline solid, is soluble in water, alcohols, glymes and DMF. It can also be weighed in open atmosphere. Scheme 13 shows the $NaBH_4$ reduction of aliphatic and aromatic aldehydes and ketones yielding the corresponding alcohols.



(41) butanal

(42) 1-butanol (85%)

(43) m-hydroxybenzaldehyde

(44) m-hydroxybenzyl alcohol (93%)

(45) dicyclohexyl ketone

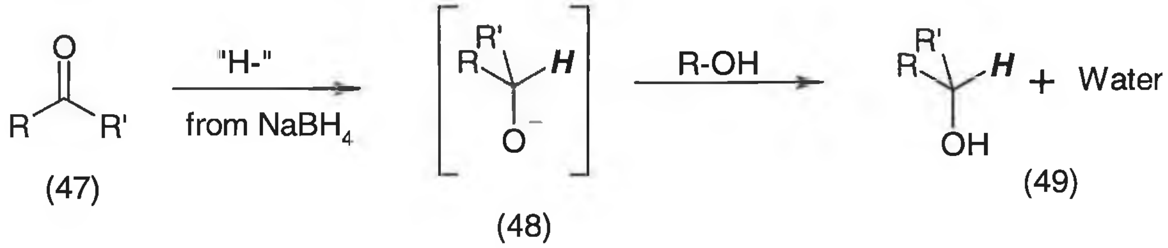
(46) dicyclohexyl methanol (88%)

Scheme 13. Various reductions using sodium borohydride

As the above examples exhibit, the yields obtained with $NaBH_4$ as a reducing agent are very high. The reduction of esters and carboxylic acids with $NaBH_4$ are much slower and much more difficult. $NaBH_4$ only very slowly reduces esters and does not reduce carboxylic acids at all. The stronger $LiAlH_4$ must be used for these transformations.

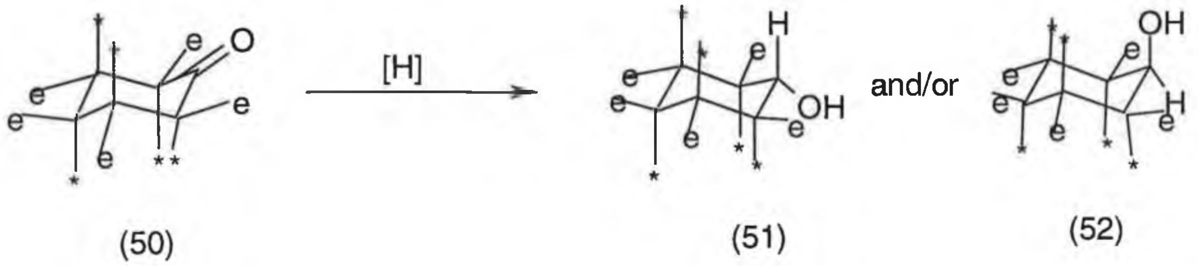
7.3 Stereochemical and Mechanistic studies of $NaBH_4$ Reductions

The basic reaction scheme of reduction using $NaBH_4$ is shown below (scheme 14).



Scheme 14. Basic reaction scheme of sodium borohydride reduction

The exact details of the carbonyl group reduction by $NaBH_4$ is complex but the fundamental step in this process is nucleophilic addition, which is what the scheme above represents. The precise mechanism and stereochemistry of these reductions has created some difficulty to chemists over the last forty years. From a stereochemical point of view, the interest was mainly on the reduction of six-membered ring ketones [60] as shown in scheme 15.



* - Axial hydrogens
e - equatorial hydrogens

Scheme 15. Stereochemical factors in cyclohexanone reduction

The two main variables affecting the stereochemistry are the structure of the cyclohexanone and the nature of the hydride reducing agent. In order for a proper rationalisation of stereochemistry of these reductions a number of factors must be discussed;

- Steric approach control interactions: interaction of the incoming reagent with bulky groups at C-3 and C-5 of the cyclohexanone.
- Effect of axial hydrogens: this rationalisation is based solely on steric strain, with various product ratios arising as a result of the balance between the effects of axial substituents at C-2 and C-6 (hindering equatorial attack) and axial substituents at C-3 and C-5 (hindering axial attack).
- Torsional strain : involves axial hydrogens at C-2 and C-6. Torsional strain involving partial bonds (in transition states) represents a substantial fraction of the strain between the fully formed bonds, thus preferential axial attack.
- Orbital interaction : axial attack predominates due to the orbital interaction of the p orbitals of the CO group with the σ orbitals of the β C-C bonds (C-2 C-3 and C-6 C-5) produces higher electron density on the equatorial face.
- Antiperiplanarity of the axial hydrogens at C-2 and C-6 : axial attack, antiperiplanarity is achievable whereas with equatorial it is not possible due to torsional strain.
- Steric effect of the axial hydrogen at C-4 : axial attack due to the hydrogens at C-2, C-4 and C-6, equatorial attack appears to be hindered.

As regards the correct mechanism of the borohydride reduction, once again a number of factors must be discussed;

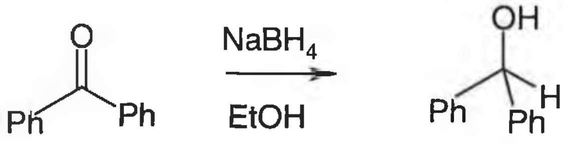
- The stoichiometry of reduction : since there is four hydrogens on $NaBH_4$, it is thought that four moles of ketone/aldehyde react with one borohydride [61]
- The question of disproportionation : this is the ease of transfer of the four hydrogens.
- Transition state geometry : three different geometries have been suggested [62]

8. Reductions of Aldehydes and Ketones in Ionic Liquids:

Reductions using organoborane reagents were studied by Kabalka and co workers [63]. They investigated the use of trialkylboranes eg tributylboranes $(CH_3(CH_2)_3)_3B$ in the reduction of initially, benzaldehyde and then a series of aldehydes. The use of trialkylboranes are known to require reaction temperatures in excess of 150°C [64]. They discovered [63] that ionic liquids such as [bmim]BF_4, [emim]BF_4 and [emim]PF_6 enhanced the rate of trialkylborane reductions. For example, tributylborane reduced benzaldehyde at room temperature in [emim]PF_6, although when the reaction was carried out at 100°C, reaction times were shorter. The yields obtained were extremely high (90-100%) although it was discovered that the presence of a para-substituted electron donating group on the aldehyde appeared to hinder the reaction, for example, *p*-$CH_3OC_4H_4CHO$ gave a yield of 40% in the presence of [bmim]BF_4. The reaction proceeded readily for aliphatic and aromatic aldehydes and the separation of the products from the ionic liquid was straightforward as was recycling of the solvent.

9. Results and Discussion:

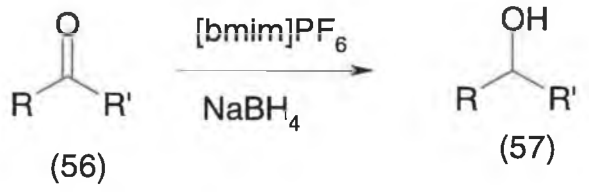
To investigate the use of ionic liquids in sodium borohydride reductions a series of reductions were carried out on a number of aldehydes and ketones. The method used was based on the standard procedure for experiments using $NaBH_4$ for reduction reactions. The solvents generally used in this procedure are ; water, ethanol and methanol and the $NaBH_4$ is added slowly either neat or dissolved in the solvent being used[57,58]. The reaction times can range from ten minutes to one hour depending on the aldehyde/ketone being used. A standard procedure for the reduction of benzophenone to diphenylmethanol uses ethanol as the solvent, the $NaBH_4$ was added, dissolved in water, very slowly. After all the $NaBH_4$ was added the reaction was stirred for 40 minutes and then poured into a beaker of ice with 1 ml of concentrated HCl added. The product precipitated and was filtered, dried over vacuum and then recrystalised from DCM. This procedure is both quick and easy to use.



Scheme 16. Standard procedure used for reduction of benzophenone to diphenylmethanol

The use of an ionic liquid would be advantageous due to the fact that ethanol and particularly methanol are potential poisons and their disposal has to be considered. The use of an ionic liquid would reduce disposal costs and there is also a possibility that the ionic liquid may be recycled as in previous experiments mentioned. It should be mentioned that these ionic liquids are expensive to buy commercially but there ease of synthesis makes them a good choice of solvent.

The ionic liquid chosen was the widely used [bmim]PF_6. A series of reactions were carried out on a variety of aldehydes and ketones (see scheme 17), using [bmim]PF_6 as the reaction solvent. The reaction scheme may be represented as follows ;



Scheme 17. Sodium borohydride reduction in [bmim]PF_6

The reaction conditions were as follows;

The aldehyde was added to the ionic liquid and the solution stirred until dissolution was complete. The $NaBH_4$ was then added slowly and the reaction left stirring for 1 hour, to ensure completion of reaction. Ice-cold water was then added to the reaction mixture and was rigorously stirred. The ionic phase was then extracted with Et_2O, dried over $MgSO_4$, filtered and evaporated to dryness. The products were then purified by either recrystallisation, short-path distillation or chromatography. All products were identified by their ^1H and ^{13}C NMR and all spectroscopic properties correlated with the data in the literature [65]. The results obtained for the various aldehyde/ketones used are shown in Table 13. below.

Aldehyde/Ketone	**Alcohol**	**Yield % with Ionic Liquid.**
Benzophenone	Diphenylmethanol	65
Benzaldehyde	Benzyl Alcohol	90
Benzoin	1,2-diphenyl-1,2-ethane diol (m.p 66-67°C)	70
Benzil	1,2-diphenyl-1,2-ethane diol (m.p 66-67°C)	70
3-Nitrobenzaldehyde	3-Nitrobenzyl alcohol (m.p 30-33°C)	75
Cyclohexanone	Cyclohexanol	55

Table 13. Results of $NaBH_4$ reductions in $[bmim]PF_6$

The above results show that the ionic liquid $[bmim]PF_6$ may be used as a solvent for $NaBH_4$ reductions of aldehyde/ketones. The reaction conditions are extremely mild and the reaction times are fast and efficient. The yields obtained are respectable and comparable to literature values [65]. Extraction of the products from the ionic liquid was easily carried out without complications.

A point which should be made is that, if volatile alcohols are produced the handling of these products is easily done by distilling them directly from the ionic liquid under high vacuum. This also increased the yield obtained where applicable in the above experiments. Thus eliminating the use of classical organic solvents completely from the procedure.

In conclusion, the advantages of using ionic liquids in the reduction of simple aldehydes and ketones are as follows:

- Toxic chemicals like methanol and ethanol need not be used
- Disposal of solvents does not apply
- Ionic liquid may be recycled and used for further reductions
- Volatile alcohol products may be distilled directly from the ionic liquid.

The ionic liquid [bmim]PF_6 may be used as a viable, efficient solvent for the $NaBH_4$ reductions of simple aldehydes and ketones. The ionic liquids clearly show that they would offer environmental and economical advantages over the solvents used presently.

9.1 Experimental:

^{1}H and ^{13}C NMR were obtained using a Bruker Avance 400 NMR spectrometer and were recorded at 400 and 100 MHz respectively. All reagents and chemicals were obtained from Aldrich Chemical company (UK) and were used as received.

Synthesis of [bmim]PF_6: (4)

1-methylimidazole (69.80g, 0.850mols) was added to 300cm^3 of ethyl acetate in a RBF fitted with a reflux condenser. Bromobutane (117g, 0.854mols) was added to the solution dropwise with stirring. The resulting solution was then heated at 70°C for 48 hours. The resulting viscous oil was then allowed to cool to room temperature and was then washed with ethyl acetate (2 x 300cm^3). The oil was then placed under vacuum overnight to remove any remaining ethyl acetate. Hexaflourophosphoric acid (125.68g, 0.861mols) was added to the prepared [bmim]Br in 500mls of water with vigorous stirring. This reaction mixture was left to stir overnight (12 hours). The upper aqueous layer was removed and the lower ionic layer was washed with water (10 x 200cm^3) until the washings were no longer acidic. The ionic liquid was then heated overnight at 60°C under vacuum to remove any excess water (120.20g , 63% yield) which is comparable to ref [23] (60-73%).

^{1}H NMR: (acetone-d^6, δ/ppm relative to TMS) : 9.00 (s, 1H), 7.90 (s, 1H), 7.80 (s, 1H), 4.30 (t, 2H, J=9.2Hz), 4.00 (s, 3H), 2.00 (m, 2H), 1.60 (m, 2H, J=9.4Hz), 1.00 (t, 3H, J=9.0Hz).
^{13}C NMR : (acetone-d^6) : 135, 126, 125, 50, 40, 35, 20, 15ppm. See appendix 1.

Procedure for $NaBH_4$ reduction of benzaldehyde to give benzyl alcohol:

Benzaldehyde (3.07g, 0.03mols) was dissolved in [bmim]PF_6 (10cm^3). $NaBH_4$ (3.00g, 0.08mols) was added slowly, with stirring, over a period of 30 minutes. The reaction was left to stir for 1 hour and then ice cold water was added (10cm^3). After 10 minutes the [bmim]PF_6 layer was separated from the aqueous layer and extracted with Et_2O (2 x 50cm^3). The combined extracts were dried ($MgSO_4$), and the solvent removed in vacuo to yield crude benzyl alcohol as a yellow liquid. After purification by short path distillation under vacuum, pure benzyl alcohol was obtained (2.82g, 90%). This work was published [66]

^{1}H NMR: ($CDCl_3$, δ/ppm relative to TMS) : 7.00-7.10 (m, 5H), 4.44 (s, 2H), 3.52 (s, 1H)
^{13}C NMR : ($CDCl_3$) : 140.3, 129.4, 128.7, 127.1, 65.5ppm.

Procedure for $NaBH_4$ reduction of benzophenone to give diphenylmethanol:

Benzophenone (1.82g, 0.01mols) was dissolved in [bmim]PF_6 (10cm^3). $NaBH_4$ (0.42g, 0.01mols) was added slowly, with stirring, over a period of 30 minutes. The reaction was left to stir for 1 hour and then ice cold water was added (10cm^3). After 10 minutes the [bmim]PF_6 layer was separated from the aqueous layer and extracted with Et_2O (2 x 50cm^3). The combined extracts were dried ($MgSO_4$), and the solvent removed in vacuo to yield crude diphenylmethanol as a yellow solid. After purification by recrystalisation, pure diphenylmethanol was obtained (1.19g, 65%). This work was published [66]

^{1}H NMR: ($CDCl_3$, δ/ppm relative to TMS) : 7.01-8.05 (m, 10H), 6.02 (s, 1H), 5.82 (s, 1H)
^{13}C NMR : ($CDCl_3$) : 146.1, 129.9, 128.9, 128.7, 128.4, 128.2, 127.2, 74.6ppm.

Procedure for $NaBH_4$ reduction of benzoin to give 1,2-diphenyl-1,2-ethane diol:

Benzoin (1.00g, 0.005mols) was dissolved in [bmim]PF_6 (10cm^3). $NaBH_4$ (0.42g, 0.01mols) was added slowly, with stirring, over a period of 30 minutes. The reaction was left to stir for 1 hour and then ice cold water was added (10cm^3). After 10 minutes the [bmim]PF_6 layer was separated from the aqueous layer and extracted with Et_2O (2 x 50cm^3). The combined extracts were dried ($MgSO_4$), and the solvent removed in vacuo to yield crude 1,2-diphenyl-1,2-ethane diol as a white solid. After purification by recrystalisation, pure 1,2-diphenyl-1,2-ethane diol was obtained (0.696g, 70%, m.p 66-67°C) This work was published [66]

^{1}H NMR: ($CDCl_3$, δ/ppm relative to TMS) : 7.2-7.4 (m, 10H), 4.5 (s, 2H)
^{13}C NMR : ($CDCl_3$) : 140.2, 128.4, 128.5, 78.5ppm.

Procedure for $NaBH_4$ reduction of benzil to give 1,2-diphenyl-1,2-ethane diol:

Benzil (1.06g, 0.005mols) was dissolved in [bmim]PF_6 (10cm^3). $NaBH_4$ (0.57g, 0.015mols) was added slowly, with stirring, over a period of 30 minutes. The reaction was left to stir for 1 hour and then ice cold water was added (10cm^3). After 10 minutes the [bmim]PF_6 layer was separated from the aqueous layer and extracted with Et_2O (2 x 50cm^3). The combined extracts were dried ($MgSO_4$), and the solvent removed in vacuo to yield crude 1,2-diphenyl-1,2-ethane diol as a white solid. After purification by recrystallisation, pure 1,2-diphenyl-1,2-ethane diol was obtained (0.75g, 70%). This work was published [66]

^{1}H NMR: ($CDCl_3$, δ/ppm relative to TMS) : 7.2-7.4 (m, 10H), 4.4 (s, 2H)
^{13}C NMR : ($CDCl_3$) : 140.1, 128.5, 128.3, 79.5ppm.

Procedure for $NaBH_4$ reduction of 3-nitrobenzaldehyde to give 3-nitrobenzyl alcohol:

3-nitrobenzaldehyde (1.52g, 0.01mols) was dissolved in [bmim]PF_6 (10cm^3). $NaBH_4$ (1.00g, 0.03mols) was added slowly, with stirring, over a period of 30 minutes. The reaction was left to stir for 1 hour and then ice cold water was added (10cm^3). After 10 minutes the [bmim]PF_6 layer was separated from the aqueous layer and extracted with Et_2O (2 x 50cm^3). The combined extracts were dried ($MgSO_4$), and the solvent removed in vacuo to yield crude 3-ntrobenzyl alcohol as a yellow oil. After purification by short path distillation under vacuum, pure 3-nitrobenzyl alcohol which solidified on cooling was obtained (1.15g, 75%, m.p 30-33°C). This work was published [66]

^{1}H NMR: ($CDCl_3$, δ/ppm relative to TMS) : 8.71 (s, 1H), 8.52 (d, 1H), 8.31 (d, 1H), 7.8 (t, 1H), 4.85 (s, 2H)
^{13}C NMR : ($CDCl_3$) : 148.6, 143.4, 133.1, 129.8, 122.7, 121.8, 64.1ppm.

Alternative procedure for volatile alcohols:

As above, but after the [bmim]PF_6 has been separated from the aqueous layer the [bmim]PF_6 was heated under high vacuum and the benzyl alcohol was distilled (75-80°C, 0.2 mmHg) directly from the [bmim]PF_6 in 70% yield using short path distillation apparatus. Cyclohexanol was distilled directly from the [bmim]PF_6 (50-54°C, 0.9 mmHg) in a similar manner, 78% yield. This work was published [66]

^{1}H NMR: ($CDCl_3$, δ/ppm relative to TMS) : 1.1-1.9 (m, 5H), 3.8 (s, 1H)
^{13}C NMR : ($CDCl_3$) : 71.0, 36.3, 26.2, 25.1ppm.

10. Free Radical Reactions in C-C bond formation:

Radical chemistry dates back to 1900 when Gomberg investigated the formation and reactions of the triphenylmethyl radical [67,68]. A crucial year was 1937 with the recognition that free radicals might be important in ordinary liquid-phase organic chemistry. It was in that year that Hey and Waters[69] suggested that the arylation of aromatics by benzoyl peroxide was a radical process and also Kharasch proposed that the abnormal addition of HBr to various alkenes, which he and Mayo had recognised in 1933, was a radical chain process [70]. The second world war was an important stimulus for the development of radical chemistry. The Japanese occupation of South East Asia cut off supplies of latex to the USA ; chemists were therefore called upon to find substitutes for natural rubber. Mayo, Walling and Lewis studied polymerisations of vinyl compounds, established rules of polymerisation, co-polymerisation and developed kinetic laws. Whereas uncharged free radicals were considered neutral species, these authors demonstrated their polar character in the reaction process, this character being expressed in the concept of electrophilic and nucleophilic radicals. It is now understood just how important this concept is for explaining the differences in selectivity and reactivity of free radicals. Up to a certain period these were expressed only in relative terms by considering a radical and several substrates or vice versa. Work at the time described mechanisms depending on the types of reaction, and established relative reactivity scales. For organic chemists at this time it proved difficult to control these reactions and led only to a mixture of products.

EPR first of all, made it possible to detect radicals, to identify them and determine their structures. EPR can be used to follow the appearance or the disappearance of radicals and therefore determine their kinetics. Flash photolysis later provided a valuable additional experimental tool. From the 1960's onward Keith Ingold, Fischer and Beckwith determined the absolute rate constants of the most important radical reactions in solution. From about the 1970's onwards, new synthetic methods using radical reactions were developed by various authors including ; Barton, Giese and Hart. It should be noted that cyclisation reactions, all aspects of which were studied in detail by Julia Surzur and co workers in the 1960's, were not, exploited as synthetic methods until the 1980's by Stork and Curran. The current output of publications concerning radical processes in synthesis is enormous. They are performed under mild conditions and, unlike ionic reactions, can be used to create complex structures by operating on molecules which have other functional groups without these being modified. Moreover they can be chemo-, regio-, and stereoselective.

10.1 Addition of Radicals to C=C bonds:

The rate of addition of radicals to C=C bonds depends on the substituents on the radical and the double bond.

Enthalpy:
In general, the addition of a carbon radical to a C=C bond is exothermic by about 20 kcal/mol, since a π bond is broken (54~59 kcal/mol) and a C-C bond is formed (~88 kcal/mol). The activation energies are of the order of 3~8 kcal/mol. Since their reaction becomes less exothermic as the stability of the attacking radical increases, the reaction may become reversible.

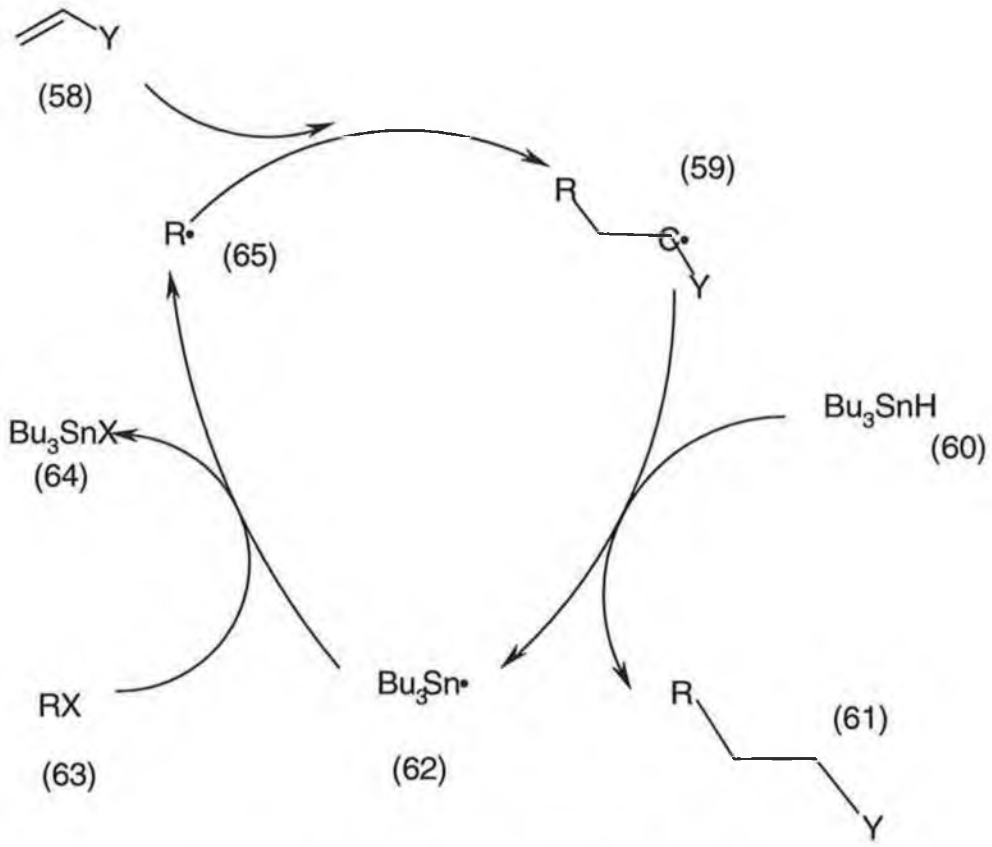
The reaction which is relevant for this research, is the reactions between radicals and non-radicals. These type of reactions have the following advantages :

- Radical character is not destroyed during the reaction which implies one can work with catalytic amounts of radical initiator.
- Most of the reactions are not diffusion controlled and the selectivity can be influenced by variations of the substituents.
- The concentrations of the non-radicals can be easily controlled.

In most cases, in order to apply reactions between radicals and non-radicals for synthesis, chain reactions have to be used. For successful use of these chain reactions, two conditions must be obeyed ;

(a) The selectivities of the radicals involved in the chain have to differ from each other.
(b) The reactions between radicals and non-radicals must be faster than radical combination reactions.

The reaction chosen for this research project was the addition of an alkyl halide to an alkene in the presence of tributyltin hydride to give an alkane (61)

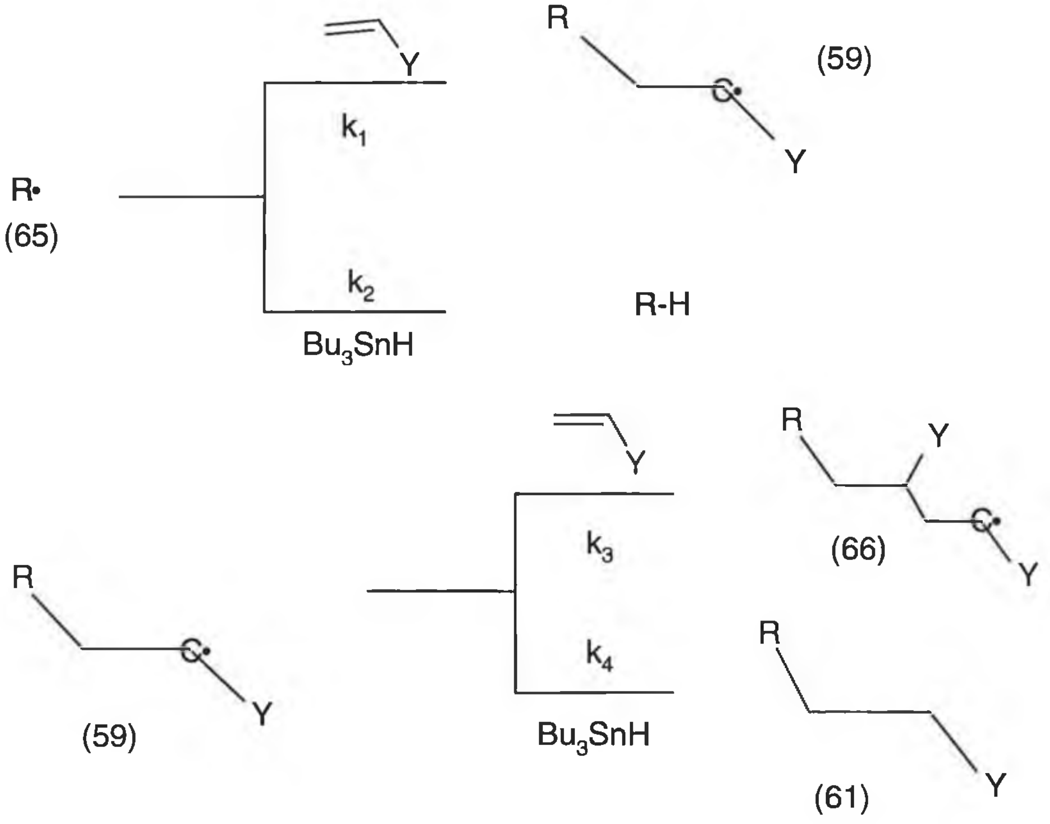


Scheme 18. Radical chain reaction for addition

For a successful application of the tin method, alkyl radicals (65), must attack alkenes (58) to form adduct radicals (59). Trapping of (59) with tributyltin hydride yields products (61) and tributyltin radicals (62), which react with alkyl halides (63) to give back adduct radicals (65). The tin method can be synthetically useful only if these reactions are faster than all other possible reactions of radicals (65), (59) and (62). This shows the certain selectivity and reactivity requirements the radicals in the chain must meet.

10.1.1 Selectivity Requirement:

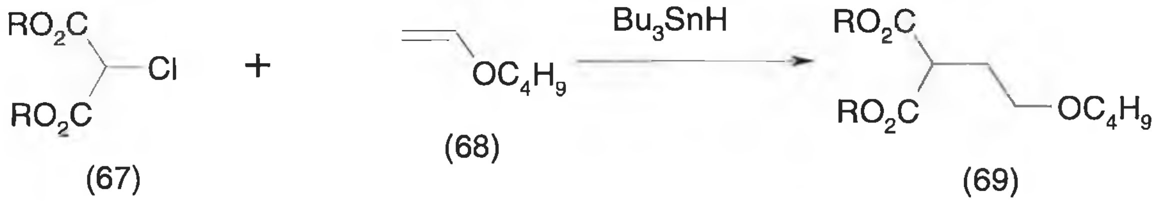
Radicals (65), (59) and (62) are all simultaneously present during the formation of product (61) from alkyl halides (63), alkene (58) and tributyltin hydride (60). These radicals face competition with other radicals generated for reaction completion, but for a successful synthesis, each radical must react with a specific adduct. Radical (65) must add to an alkene, adduct radical (59) has to abstract a hydrogen atom from tributyltin hydride and tin radical (62) must react with an alkyl halide. All this means that all the radicals in the chain must have different selectivities. If the adduct radical (59) had the same selectivity as radicals (65) ie $k1/k2 = k3/k4$, polymerisation of alkenes ($k1/k2 >> 1$), reduction of alkyl halides ($k1/k2 << 1$) or formation of a product mixture would result. See scheme 19 below



Scheme 19. Selectivity requirements

This can be prevented by choosing a suitable substituent on the alkene that changes the selectivity of radical (59) compared to radical (65). Alkyl radicals, substituted with electron releasing groups (alkoxy, alkyl) behave like nucleophiles and react very rapidly with electrons and alkenes substituted with electron withdrawing substituents (nitrile, ketone)

[71]. Although, on the other hand, radicals with electron withdrawing substituents behave like electrophiles and react faster with electron rich alkenes [71]. Therefore, the synthetic application of the tin method is possible, only with those halides (63) and alkenes (58) which lead to radicals (65) and (59) with different or opposite polarity, for example, cyclohexyl iodide/acrylonitrile [72] or chloromalonic ester/enol ether, shown in Scheme 20 below.

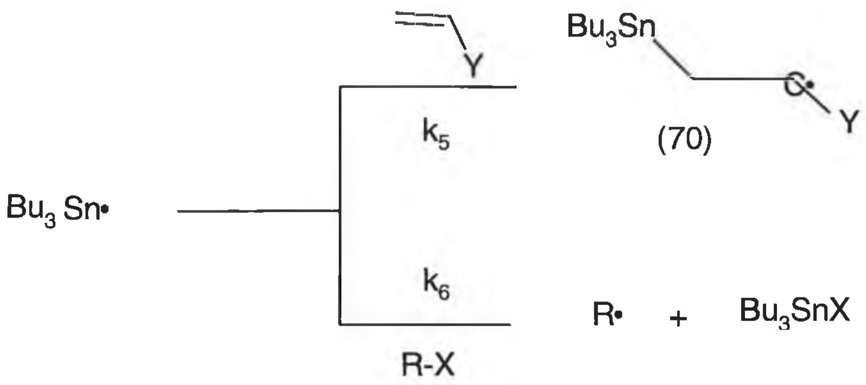


Scheme 20. Free Radical addition using tributyltin hydride

One must also make sure that the desired reaction dominates the various competitive reactions. At room temperature, alkyl radicals add to alkenes such as acrylonitrile with rate coefficients of about 10^5-10^6 (l/mol.s) [73], whereas nitrile substituted radicals react with acrylonitrile about 10^4 times slower. The selectivities of alkyl radicals (65) and adduct radicals (59) in the competition system $H_2C{=}CHCN/Bu_3SnH$ are $k_1/k_2 = 1$ and $k_3/k_4 = 10^{-4}$. In order to form a C-C bond, the reaction between radical (65) and the alkene has to be faster than the reduction of (65) by Bu_3SnH. This is possible only with a $H_2C{=}CHCN/Bu_3SnH$ concentration ratio of at least 10 – 100, because the competition constant is ~1.

In essence, one must work with an excess of acrylonitrile or with low concentrations of Bu_3SnH. Low Bu_3SnH concentration is obtained by adding the tin hydride slowly or by working with a catalytic amount of tin salts and equimolar amounts of $NaBH_4$, which generates the tin hydride in situ. When a $H_2C{=}CHCN/Bu_3SnH$ ratio of 10^2 is used, polymerisation does not occur because the competition coefficient k_4/k_3 is ~10^4. The rate ratio r_4/r_3, which takes the concentrations into account is 10^2, therefore, the adduct radical (59) reacts predominantly with Bu_3SnH to yield product (61). If the excess of $H_2C{=}CHCN$ is too large, the (59) reacts noticeably with acrylonitrile. A major factor in radical synthesis is to find the optimum concentration ratio for the synthesis in question.

Finally, the third radical in the chain is the tributyltin radical (62). The selectivity in the competition system alkene/tributyltin hydride is of no importance, because the reaction of (62) with the tin hydride regenerates the tin radical. Competition between alkene addition and halogen abstraction from the alkyl halide is synthetically important.



Scheme 21. Tributyltin hydride selectivity requirements

Since there is an excess of $H_2C{=}CHCN$ in the synthesis, the undesired addition of tin radicals (62) to alkenes can not be greatly influenced by varying the concentration ratio of alkene/alkyl halide. It is much more favorable to discard alkyl bromides and use the 10-100 times more reactive alkyl iodides [74]. C-C bond formation does not take place with less reactive alkyl halides such as alkyl chlorides and isonitriles. Their use leads to tin hydride addition products on the alkene.

10.1.2 Reactivity Requirement:

Chain reactions are terminated by combination of the radicals. Therefore, the rate of chain propagation between radicals and non- radicals (r_p) must be higher than that of chain termination between radicals (r_t).

$$r_p = k_p.[R^*].[X] \qquad (a)$$

$$r_t = k_t.[R^*].[R^*] \qquad (b)$$

$$1 < r_p/r_t = k_p.[X]/k_t.[R^*] \qquad (c)$$

Equations (a) and (b) are the analytical expressions for these reactions where k_p and k_t are the rate constants for chain propagation and termination steps. R^* represents all radicals that are present in the chain and X the added reagents. The reactivity requirement that must be satisfied is given by (c).

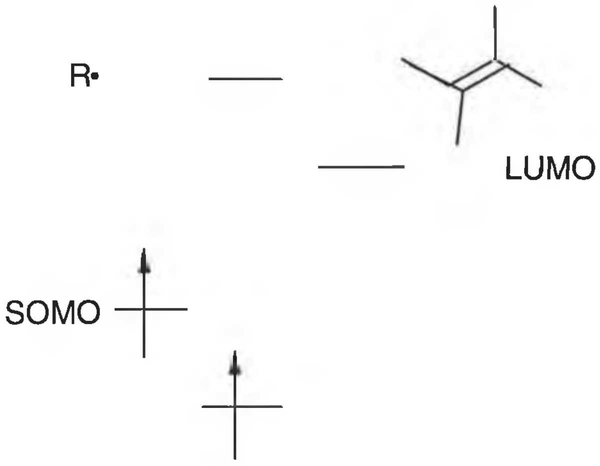
In most cases, carbon-centered radicals react with each other with diffusion controlled rates ; the rate coefficients k_t, which have small temperature dependence, are 10^9-10^{10} (l/mol.s) in the liquid phase [75]. The concentration of X depends on the reaction conditions, but in syntheses, these concentrations are often approximately one molar. The concentrations of the radicals in chain reactions also depends on the conditions, for example, the rate of the decomposition of the initiator. Generally, concentrations of radicals in chain reactions are ~10^{-7}-10^{-8} mol/l.

$$k_p > 10^2 \quad (\text{l/mol.s}) \qquad (d)$$

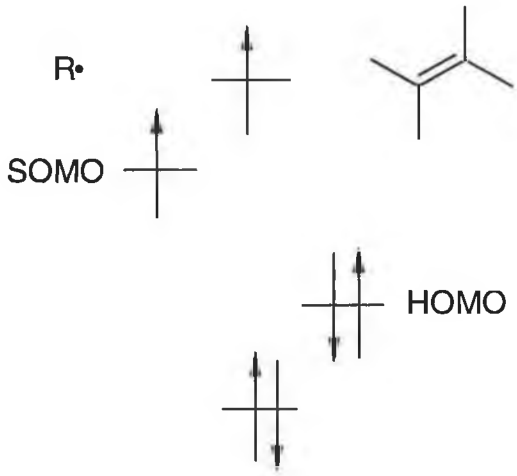
According to eq. (d), only those propagation steps whose coefficients k_p are larger than 10^2 can be used for synthesis.

11. Addition: Frontier Orbital theory

Addition of radicals to alkenes is an excellent method of C-C bond formation in which a σ C-C bond is made from a π C=C bond in an exothermic reaction. As already stated the rate of addition of a radical to an alkene depends on the substituents on the radical and the alkene and these effects can be described by FMO theory [71].



Orbital interaction between a nucleophilic radical and an electron poor alkene



Orbital interaction between an electrophilic radical and an electron rich alkene

It should be mentioned that all the radicals have singly occupied molecular orbitals (SOMO), this is so due to the fact they have an orbital containing one electron. The singly occupied orbital (SOMO) of the radical interacts with the highest occupied orbital (HOMO) of the C-C multiple bond. Radicals with high lying SOMO interact preferentially with the LUMO of the alkene.

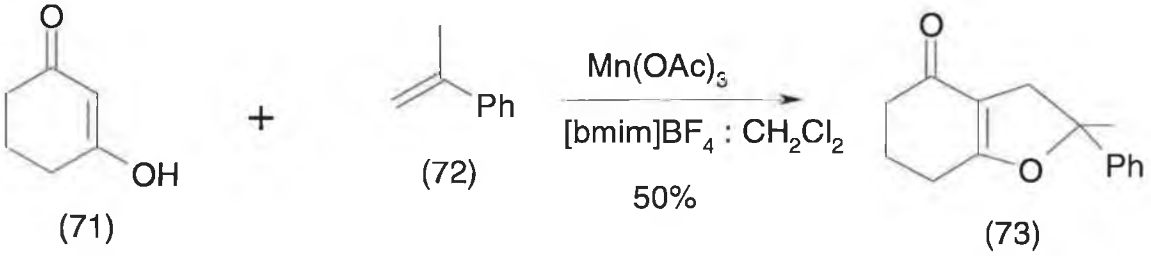
Electron withdrawing groups on the alkene, which lower the LUMO energy, increase the addition rate by reducing the SOMO-LUMO difference, therefore cyclohexyl radicals react 8500 times faster with acrolein than 1-hexene [76].

These orbital effects are so important that a tert-butyl radical reacts faster than a primary or secondary radical with alkenes like vinylphosphonic ester or acrylonitrile [77]. Thus, the increase in SOMO energy in going from primary to tertiary radicals has a larger effect on the rate than the decrease in the strength of the bonds that are formed. This implies that alkyl, alkoxyalkyl, aminoalkyl are nucleophilic radicals.

On the other hand, radicals with electron withdrawing groups attached have SOMO energies so low that the SOMO-HOMO interaction dominates. These radicals react like electrophiles; that is, electron donating groups at the alkenes increase the rate.

12. Free Radical Reactions in Ionic Liquids:

Free radical reactions in ionic liquids has not been investigated extensively except for the manganese(III) acetate mediated radical reactions carried out by Bar and co workers [78]. Scheme 23 below shows the radical reaction.



Scheme 23. Free radical reaction in ionic liquid

Manganese(III) acetate is known to oxidise a variety of carbonyl compounds including β-diketones and β-keto esters, to form radicals [79]. These α-carbonyl radicals can undergo cyclisation or intermolecular addition reactions to form radical adducts, which may be oxidised by a second equivalent of manganese(III) acetate.

Manganese(III) acetate is inexpensive and thus is an attractive oxidant for C-C bond formation, but a major drawback to its use is the harsh reaction conditions necessary. Manganese(III) acetate has poor solubility in organic solvents. Acetic acid is used [78,79] which severely limits the range of substrates which can be employed, especially as many reactions require heating in excess of 70°C.

Another disadvantage with the use of acetic acid is the separation and recovery of the manganese acetate at the end of the reaction. It was suggested that the use of the air and moisture stable ionic liquids would be suited for these manganese(III) mediated radical reactions. Bar and co workers [78] initially tried the reactions in neat [bmim]BF_4, but discovered they were low yielding. They found that cyclised products could be isolated in good yield when 1,3-dicarbonyl compounds and alkenes were reacted in a mixed [bmim]BF_4-DCM solvent system. The reaction conditions were much milder and yields varied from 30-50% depending on the solvent system used. The use of the ionic liquid in this instance allowed more substrates to be used than with the use of acetic acid.

With regards to this research project, the study of C=C bond forming radical reactions using tributyltin hydride and tristrimethylsilyl silane as initiators were chosen. The reasoning behind this was the fact that there was no mention of the use of Ionic Liquids in these type of radical reactions. The actual reactions chosen to study can be seen in scheme 24. The ionic liquids chosen were [bmim]BF_4 and [bmim]PF_6.

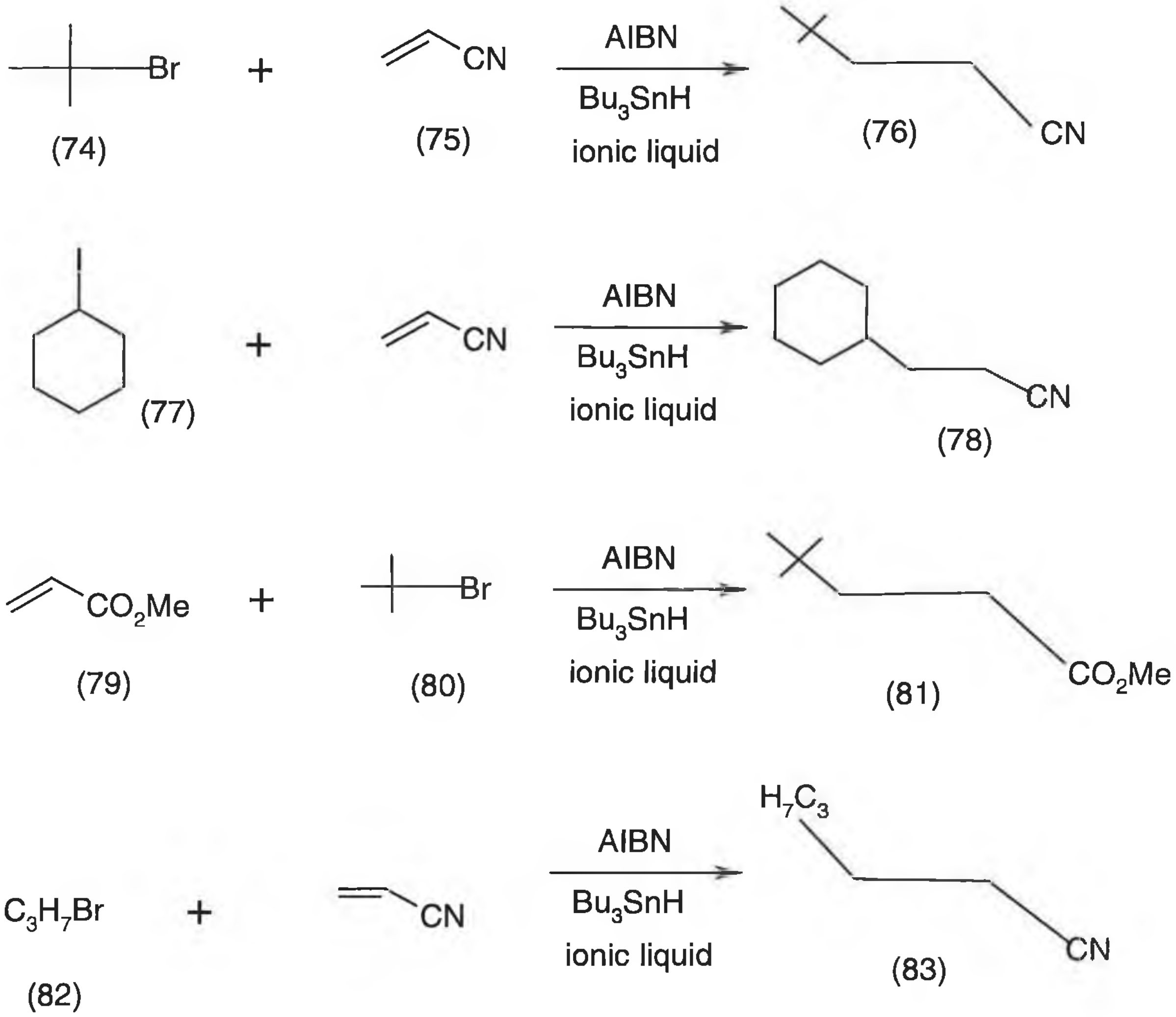
13. Results and Discussion:

The solvents normally used for this type of synthesis are dried toluene and benzene with a reaction time varying from 1 – 10 hours and a reaction temperature of 80-90°C. A standard procedure using conventional solvents was used [80] to incorporate the ionic liquids as solvents into these tributyltin hydride-based radical addition reactions. The standard procedure for a radical addition reaction to an alkene is as follows;

To a solution of a cyclohexyl bromide/iodide in dry benzene and an alkene was added tributyltin hydride and AIBN slowly over a period of ~ 1 hour. Stirring is continued for 1 hour after addition was complete. The reaction mixture was worked up via the KF (potassium fluoride) method, which involved evaporation of excess solvent and the residue then taken up in diethyl ether. An excess of potassium fluoride is added along with a drop of water and this solution was stirred for 3 hours at room temperature. The mixture is filtered through a pad of anhydrous magnesium sulphate, the solution evaporated and the residue purified by chromatography.

The use of an ionic liquid in this procedure would be useful in the sense that extraction of products may be easier and the reaction conditions ie high temperatures may not be necessary. Also, the use of benzene and toluene, both of which are suspect carcinogens would no longer be necessary. Thus the procedure would be environmentally cleaner and hopefully more efficient. By using an ionic liquid disposal costs may be reduced and like in previous experiments mentioned earlier, using ionic liquids, they may be recycled.

The free radical haloalkane-alkene reactions investigated are shown in scheme 25. The ionic liquids chosen for use where [bmim]PF_6 and [bmim[BF_4. The products expected from the reactions in the scheme below were not synthesised. The reaction procedure was manipulated in a number of ways in order for the desired products to be obtained. These manipulations shall be discussed later.



Scheme 25.Free radical haloalkane-alkene reactions in the ionic liquids [bmim]BF_4 and [bmim]PF_6

The general reaction conditions were as follows;

The ionic liquid was degassed overnight. The alkene and the alkyl bromide/iodide were added to the ionic liquid and the solution was stirred gently over nitrogen and heated to 50°C. Tributyltin hydride and AIBN were dissolved in benzene/toluene, these were also added neat in an attempt to yield the desired products and then added dropwise over a period of 1 hour with stirring. After addition of the tributyltin hydride/AIBN the reaction was cooled to room temperature and allowed to stir for a further hour. The ionic layer was extracted with diethyl ether and the ether layer was then dried over $MgSO_4$. The ether was then removed in vacuo and the residue was taken up in ether and an excess of KF was added and the mixture was stirred for 3 hours. The mixture was then filtered and the solvent was removed in vacuo. TLC analysis was carried out and ^1H and ^{13}C NMR spectra were then obtained. TLC analysis was inconclusive but the NMR data obtained showed a large tributyltin hydride peak and no evidence of product was seen.

It should be noted that the above procedure was altered a number of times to try and obtain the optimum experimental conditions in order for the reaction to take place (see experimental section). In the neat addition of the AIBN and tributyltin hydride dissolution problems were encountered. The ionic liquid would not dissolve the AIBN. Overall, the following observations were made as regards the reactions using tributyltin hydride and $[bmim]BF_4$ and $[bmim]PF_6$ as solvents.

Initially, the Bu_3SnH/AIBN solution was added dropwise manually which proved very tedious and also a uniform amount of the solution was not being added to the reaction. A syringe pump was then used which allowed for an addition of Bu_3SnH/AIBN at a controlled rate. As mentioned previously, there must be an excess of alkene to alkyl halide and the Bu_3SnH concentration has to be kept low for the reaction to take place and the desired product formed. With this in mind, a number of experiments were carried out where the ratios of reactants was altered in an attempt to find the correct reaction ratio. The ratio's used varied from experiment to experiment.

The AIBN was added directly to the ionic liquid/alkene/alkyl halide solution and then the Bu_3SnH was then added neat and extremely slowly. It was hoped that this would help with the initiation step and the Bu_3Sn^* radical would form and the required reaction would take place. The reaction temperature was another factor which was also altered. In the normal solvents, the temperature used was 80-90°C. In an attempt to carry out the reaction under milder conditions the reaction was carried out initially at room temperature and then over a range of temperatures (30-100°C). Thus far the ratio has been altered, the Bu_3SnH/AIBN addition controlled, AIBN added before Bu_3SnH to help initiation step and finally the temperature was altered. All starting materials were distilled before use also. The KF work-up was also left out and the residues obtained were subjected to flash chromatography.

The TLC, ^1H and ^{13}C NMR data obtained from the reactions was compared with the data obtained from the reactions carried out using the conventional solvents ie benzene/toluene. Each of the reactions in scheme 25 gave the desired products in benzene/toluene. These reactions were used as reference points.

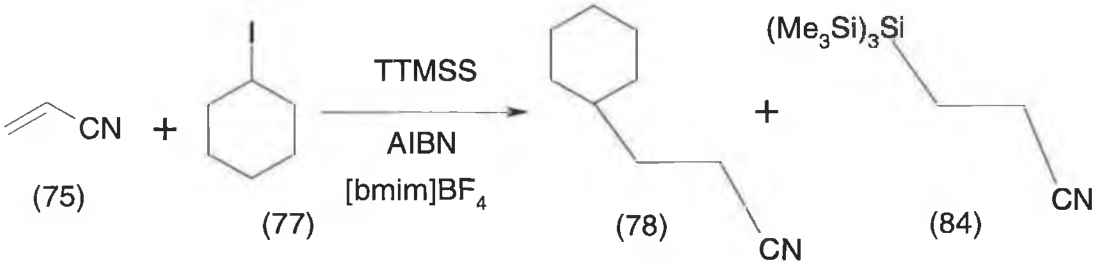
Analysis of each TLC, ^1H and ^{13}C NMR of the ionic liquid reactions showed the presence of Bu_3SnX and this proved extremely difficult to remove. The KF work up failed, chromatography failed and every alteration made to experimental procedure failed to give the desired product. The same results were obtained for both ionic liquids used and all the alkene/alkyl halide combinations. The tin by-products produced were just too difficult to remove which is a factor when the normal solvents are used, but they can be removed in these via the KF work-up. The use of ionic liquids in the synthesis seems to have failed maybe due to the following reasons;

- The initiation step may not be taking place at all in the ionic liquid which implies the Bu_3Sn* was not formed and thus no reaction can take place. The ionic liquid may not facilitate the formation of this radical.
- Since the ionic liquid can't be completely dried properly, trace amounts of water present may be affecting the reaction.
- A major factor in using tributyltin hydride in addition reactions is that its concentration must be kept low or the tributyltin hydride radical would react directly with the alkene and not the alkyl halide. Even though a syringe pump was used for a controlled rate of addition it appears that tin by-products are the only compound being formed so maybe

an even slower addition rate should be employed. These tin by-products are extremely difficult to remove and are also toxic.

With all that in mind, a new method in the synthesis was attempted which made use of TTMSS instead of Bu_3SnH. Although it has not been fully tested, TTMSS has been used in place of Bu_3SnH in radical addition reactions in an effort to eliminate the problem of tin by-products and also the toxicity of Bu_3SnH itself. The same reagents and experiments were carried out using the same ionic liquids. The equivalent ratio of Bu_3SnH to alkene in a free radical reaction was low. A 1:1 ratio of TTMSS and alkene was used or sometimes even a small excess of TTMSS.

As with Bu_3SnH, the experimental procedure was altered in an effort to try and achieve the desired product. The TTMSS/AIBN solution was added via syringe pump, the ratios were altered, the temperature was varied and the work up did not involve the KF method, the excess ether was simply reduced in vacuo and the residue was subjected to flash chromatography. The end result was basically the same as before, the product obtained was $(Me_3Si)_3Si\text{-}X$ which was clearly seen in ^1H NMR spectra.



Scheme 26. Free radical addition in ionic liquid using tris(trimethylsilyl)silane

Unlike the Bu_3SnH experiments, NMR analysis did suggest that the product formed was (84), which suggest that a radical reaction did indeed take place and the hydrosilylated product was formed. Product (78) was not formed as the desired NMR spectra was not obtained compared to the reference experiment carried out using conventional solvents.

13.1 Experimental:-

Synthesis of [bmim]BF_4 :

The ionic liquid [bmim]Br (100g, 0.457mols) was dissolved in 250mls of acetone in a RBF with stirring. $NaBF_4$ (50.16g, 0.457mols) was added neat to this solution. The reaction was left to stir for 12 hours at room temperature. The mixture was then filtered through a bed of celite. The acetone was then removed in vacuo to yield 1-butyl-3-methylimidazolium tetrafluoroborate (87.78g, 85%).

^{1}H NMR :- (acetone-d^6, δ/ppm relative to TMS): 10.17 (s, 1H), 8.00 (s, 1H), 7.95 (s, 1H), 4.40 (t, 2H, J=9.2Hz), 4.15 (s, 3H), 1.95 (m, 2H), 1.35-1.36 (m, 2H, J=9.5Hz), 0.95 (t, 3H, J=9.1Hz)
^{13} C NMR :- (acetone-d^6) 130.2, 120.4, 118.5, 47.9, 36.2, 30.5, 19.7, 13.8ppm.

Synthesis of tert butyl cyanoethane (76):

A solution of tert butyl bromide (0.34g, 2.5mmols) and acrylonitrile (1.33g, 25mmols) was heated to 60°C over nitrogen in [bmim]PF_6 (50mls) in a RBF fitted with a reflux condenser. Bu_3SnH (0.54mls, 2mmols) and AIBN (0.02g, 0.1mmols) were dissolved in benzene (25cm^3) and added to the reaction mixture over a period of 2 hours via syringe pump. The reaction was heated for a further hour after addition was complete. The reaction was then allowed to cool to room temperature and then extracted with Et_2O (3 x 50mls). The Et_2O extracts were combined and dried over $MgSO_4$. The ether layer was then filtered and then removed in vacuo and a yellow oil was obtained (2.13g).

NMR analysis showed only Bu_3Sn-X products obtained even after KF work-up
The above reaction with the same conditions and ratios was tried in [bmim]BF_4 and the results were the same.

The procedure above was carried out using a range of ratios of reactants as shown below. A temperature range of 30-100°C was also investigated. The synthesis of cyanopentane was also carried out by varying ratios, temperatures and reaction times.

tert butyl bromide (0.34g, 2.5mmols)
acrylonitrile (0.85g, 16mmols)
Bu_3SnH (0.54mls, 2mmols)
AIBN (0.05g, 0.3 mmols)

tert butyl bromide (0.29mls, 2.5mmols)
Acrylonitrile (0.75g, 14mmols)
Bu_3SnH (0.52mls, 1.93mmols)
AIBN (0.05g, 0.3mmols)

After KF work up and chromatography NMR analysis gave the same results ie Bu_3SnX products obtained.

Synthesis of cylohexylcyanoethane (78):

Cyclohexyl iodide (0.41g, 3.2mmols) and acrylonitrile (0.85g, 16mmols) were added to [bmim]PF_6 (20mls) in a RBF fitted with a reflux condenser and heated to 60°C. Bu_3SnH (0.86mls, 3.2mmols) and AIBN 0.11g, 0.68mmols) were dissolved in toluene (5mls) and added to the solution dropwise via a syringe pump. The addition took 2 hours to complete. After addition was complete, the reaction had an orange colour and was left to stir for a further 1 hour. The ionic layer was then extracted with diethyl ether (3 x 35mls) and then the ether was removed in vacuo. A yellow oil (1.03g) was obtained and this was subjected to flash chromatography using pentane.

As before, the above reaction was repeated using a temperature range of 30-100°C and a range of ratios of reactants.[bmim]BF_4 was also used in the series of reactions. NMR showed similar results for all attempts with large Bu_3SnX peaks present in all spectra.

Free radical addition using (tris)trimethylsilylsilane:-

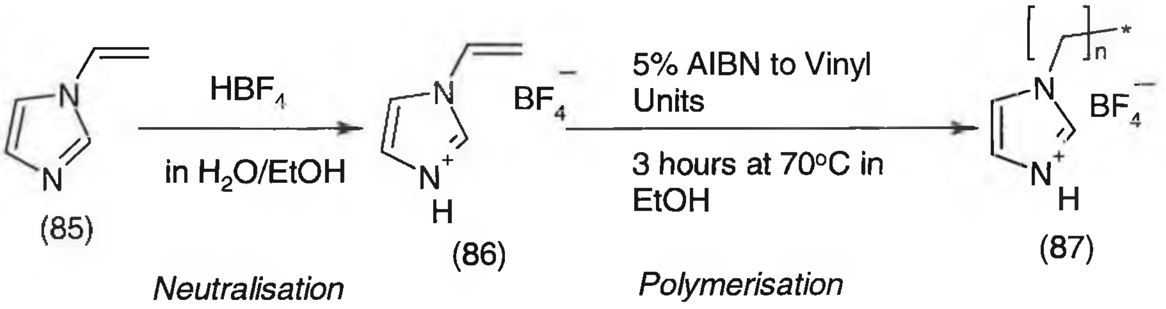
Cyclohexyl iodide (0.52mls, 2 mmols) and acrylonitrile (0.13mls, 2mmols) were added to [bmim]PF_6 (30mls) in a RBF fitted with a reflux condenser and heated to 100°C. (Tris)trimethylsilylsilane (0.595g, 2.4mmols) and AIBN (78.8mgs, 0.48mmols) were dissolved in toluene (3mls) and added dropwise to the ionic solution via a syringe pump. The addition took 1.5 hours to complete. After the addition the reaction was allowed stir for a further hour, it had a yellow colour. The ionic liquid was extracted with diethyl ether (3 x 35mls). The ether was removed in vacuo yielding a yellow/orange oil (2.86g)

The same procedure was used altering the temperature (60-100°C) and the ionic liquid [bmim]BF_4 was also used. The TTMSS and AIBN was also added neat in an effort to yield the desired products. A small excess of TTMSS was also tried to try to improve the chances of a the desired radical reaction taking place.

In the experiments carried out using TTMSS, the hydrosilylated product seems to have been formed and not the desired alkane.

14. Ionic Liquids based on 1-Vinylimidazole:

The ionic liquids used thus far have all been based on 1-methylimidazole, where [bmim]PF_6 and [bmim]BF_4 were the ionic liquids of choice due to their ease of synthesis and handling. A new type of ionic liquid was then investigated using 1-vinylimidazole as the staring material as opposed to 1-methylimidazole. Hirao and co workers [81] had worked with N-vinylimidazolium tetrafluoroborate, preparing it via a neutralisation of tetrafluoroboronic acid and polymerisation technique to obtain salt polymers as shown in scheme 26



Scheme 27. Preparation of N-vinylimidazolium salts

The basis of their work was on measuring the ionic conductivity of these polymeric ionic compounds which were solids. They showed that polymerisation decreased the ionic conductivity as the ions were no longer as mobile in the polymerised state, although addition of lithium salts did increase conductivity.

Ionic conductivity is not really relevant in this synthetic research project so it was hoped that a series of these 1-vinylimidazolium compounds could be synthesized and used in various organic synthetic procedures. The preparation above would need to be altered and the polymerisation step would not be necessary. It was also hoped that by varying the chain length of a second substituent on the 3-nitrogen would give less viscous and more workable ionic compounds, which would be easier to work with in organic reactions [50]. A series of compounds were synthesised by adding a number of substituents on the 3-nitrogen of the 1-vinylimidazole, ranging from 3-methyl to 3-decyl-1-vinylimidazolium compounds.

15. Results and Discussion:

The original procedure [81] for the synthesis of these 1-vinylimidazolium compounds made use of a neutralisation step then a polymerisation step. For the synthesis of a series of such compounds polymerisation was deemed to be unnecessary. The original procedure used by Hirao and co workers [81] was as follows:
Aqueous solutions of N-vinylimidazole and HBF_4 were prepared. The aqueous solution of 1-vinylimidazole was then added dropwise to the HBF_4 solution in an ice bath. After stirring for 12 hours at 0^oC, the water was removed by evaporation at 40^oC under reduced pressure. The salt obtained was washed twice with diethyl ether to remove residual 1-vinylimidazole. The 1-vinylimidazolium tetrafluoroborate was then dried for 24 hours at ambient temperature.

The above procedure was altered for the synthesis of the series of compounds based on 1-vinylimidazole (scheme 27) as the use of the water system was causing difficulties as the removal of the water was not that easy. An alternative procedure was devised to make the synthesis far more workable. The general reaction conditions were as follows:-

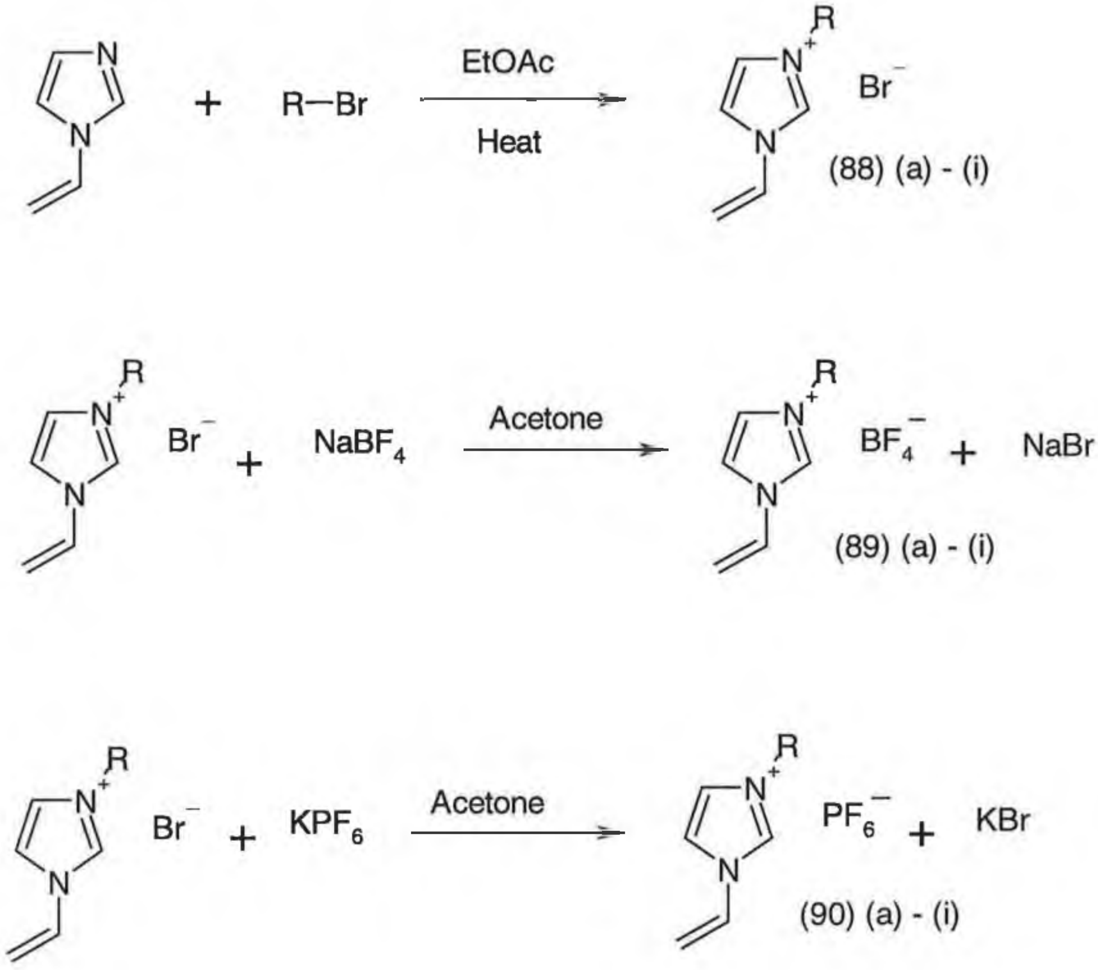
1-Vinylimidazole was added to ethyl acetate and the solution was stirred until the 1-vinylimidazole dissolved fully. The bromoalkane was then added dropwise to the ethyl acetate/1-vinylimidazole solution. The reaction mixture was then stirred, brought to reflux slowly and was left to reflux overnight. The reaction mixture was then allowed to cool to room temperature, two distinct phases were observed. The lower ionic phase was separated off, and washed twice with ethyl acetate to remove any 1-vinylimidazole. Excess solvent was then removed in vacuo. The 1-vinyl-3-alkyllimidazolium bromide was then dissolved in acetone and sodium tetrafluoroborate was added slowly. The solution was then allowed to stir for 12 hours. The NaBr was then filtered through a bed of activated celite as the NaBr salts were not fully removed using filter paper, the excess acetone was removed in vacuo. The hexafluorophosphate derivatives of the 1-vinyl-3-alkylimidazolium bromide compounds were synthesised as per the method used to produce 1-vinyl-3-alkylimidazolium tetrafluoroborate except KPF_6 was used in the place of $NaBF_4$. The compounds based on KPF_6 although novel, were all very viscous compounds and proved difficult to work with. It was decided to continue with the compounds based on $NaBF_4$. All products were identified by ^1H NMR and ^{13}C NMR.

The polymerisation step (scheme 26) was not carried out but the compounds were tested in the Diels-Alder reaction. It was hoped the vinyl group would take part in the Diels-Alder reaction using various dienes. 1,3-butadiene, cyclopentadiene and furan were all tested in a Diels-Alder synthesis using various 1-vinyl-3-alkyl imidazolium tetrafluoroborate compounds. Initially the compounds were added together and left stir at room temperature for 12 hours. No reaction took place as analysis by NMR showed that the vinyl group remained.

The reaction was then carried out under reflux, but the same result was obtained. 1,3-butadiene, cyclopentadiene and furan all failed to react in a Diels-Alder reaction with any of the 1-vinyl-3-alkyl imidazolium tetrafluoroborate compounds. It seems the vinyl group is not reactive enough due to the presence of the imidazolium ring and the tetrafluoroborate anion to form a Diels-Alder adduct. See Table 14.

Diene	**1-vinyl-3-alkylimidazolium tetrafluroborate**
Cyclopentadiene	1-vinyl-3-heptylimidazolium
Cyclopentadiene	1-vinyl-3-butylimidazolium
Cyclopentadiene	1-vinyl-3-pentylimidazolium
Cyclopentadiene	1-vinyl-3-hexylimidazolium
1,3 Butadiene	1-vinyl-3-pentylimidazolium
1,3 Butadiene	1-vinyl-3-butylimidazolium
1,3 Butadiene	1-vinyl-3-heptylimidazolium
Furan	1-vinyl-3-heptylimidazolium
Furan	1-vinyl-3-pentylimidazolium

Table 14. Dienes and Ionic liquids used in Diels-Alder reactions



(88) (a) - (i)

(89) (a) - (i)

(90) (a) - (i)

R = Ethyl (a), propyl (b), butyl (c), pentyl (d), hexyl (e), heptyl (f), octyl (g), nonyl (h) and decyl (i)

Scheme 28. Synthesis of N-vinylimidazolium compounds

These are all new compounds and the respective yields are shown in Table 15 .

Cation of Ionic Compound	**Yield % of the Bromide anion (Br^-) ionic compound**	**% Yield of the Tetrafluorborate anion (BF_4^-) ionic compound**
1-vinyl-3-ethyl imidazolium	75	58
1-vinyl-3-propyl imidazolium	71	60
1-vinyl-3-butyl imidazolium	78	52
1-vinyl-3-pentyl imidazolium	51	51
1-vinyl-3-hexyl imidazolium	65	66
1-vinyl-3-heptyl imidazolium	53	41
1-vinyl-3-octyl imidazolium	40	55
1-vinyl-3-nonyl imidazolium	60	40
1-vinyl-3-decyl imidazolium	55	50

Table15. Results of 1-vinylimidazolium compounds synthesis

As can be seen on analysis of the table above, the yields obtained varied. It should be noted that the 1-vinyl-3-ethyl, propyl and butylimidazolium bromide compounds were all obtained as solids. The rest of the compounds were obtained as brown oils, some of which were extremely viscous and hard to work with (nonyl and decyl compounds). All the 1-vinyl-3-alkylimidazolium bromide compounds were dark brown in colour and after conversion to the tetrafluoroborate compounds they were lighter in colour and the viscosity of the compounds was reduced slightly.

15.1 Experimental:

Procedure for the Synthesis of 1-vinyl-3-decyl-imidazolium bromide:- (88) (i)

1-Vinylimidazole (3g, 0.032mols), was dissolved in ethyl acetate (50cm^3) in a RBF fitted with a reflux condenser. 1-Bromodecane (7.05g, 6.6mls, 0.032mols) was added dropwise to the 1-vinylimidazole solution.

The reaction was then heated to reflux and left heating for 12 hours. The reaction was then allowed to cool to room temperature. Two distinct layers were observed, the lower ionic layer was separated and washed with ethyl acetate (2 x 50cm^3) to remove any residual 1-vinylimidazole. The ionic layer was then reduced in vacuo to remove any remaining ethyl acetate. A dark brown viscous oil was obtained (55% yield).

^{1}H NMR :- (DMSO-d^6, δ/ppm relative to TMS): 9.66 (s, 1H), 8.26 (s, 1H), 7.98 (s, 1H), 7.33 (q, 1H), 6.00 (d, 1H), 5,42 (d, 1H), 4.22 (t, 2H), 1.83 (t, 2H), 1.24 (m, 14H), 0.85 (t, 3H)

^{13}C NMR (DMSO-d^6, δ/ppm relative to TMS): 135.66, 129.23, 123.61, 119.51, 108.95, 49.54, 31.63, 29.44, 29.24, 29.15, 29.01, 28.73, 25.83, 22.44, 14.36ppm.

Procedure for the Synthesis of 1-vinyl-3-ethyl-imidazolium bromide:- (88) (a)

As per (88) (i) except ethyl bromide (2.5cm^3, 0.032mols) was used. (75% Yield)

^{1}H NMR :- (DMSO-d^6, δ/ppm relative to TMS): 9.94 (s, 1H), 8.37 (s, 1H) 8.10 (s, 1H) 7.38(q, 1H) 6.06 (d, 1H) 5.39 (d, 1H) 4.31 (t, 2H) 1.44 (t, 3H)

^{13}C NMR (DMSO-d^6, δ/ppm relative to TMS): 135.34, 129.02, 123.28, 119.55, 109.00, 44.96, 15.22 ppm

Procedure for the Synthesis of 1-vinyl-3-propyl-imidazolium bromide:- (88) (b)

As per (88) (i) except bromopropane (3.94g, 0.032mols) was used. (71% Yield)

^{1}H NMR :- (DMSO-d^6, δ/ppm relative to TMS): 9.90 (s, 1H), 8.32 (s, 1H) 8.03 (s, 1H) 7.42(q, 1H) 6.47 (d, 1H) 5.59 (d, 1H) 4.41 (t, 2H) 3.67 (t, 2H) 1.34 (t, 3H)

^{13}C NMR (DMSO-d^6, δ/ppm relative to TMS): 136.56, 130.32, 125.74, 121.65, 112.34, 46.79, 17.12 ppm

Procedure for the Synthesis of 1-vinyl-3-butyl-imidazolium bromide:- (88) (c)

As per (88) (i) except butyl bromide (3.4cm^3, 0.032mols) was used. (78% Yield)

^{1}H NMR :- (DMSO-d^6, δ/ppm relative to TMS): 9.46 (s, 1H), 8.02 (s, 1H), 7.51 (s, 1H), 7.09 (q, 1H), 5.76 (d, 1H), 5.17 (d, 1H), 3.98 (t, 2H), 1.57 (t, 2H), 1.04 (m, 2H), 0.65 (t, 3H)

^{13}C NMR (DMSO-d^6, δ/ppm relative to TMS): 153.66, 129.22, 123.61, 119.53, 108.98, 49.27, 31.40, 19.14, 14.31 ppm

Procedure for the Synthesis of 1-vinyl-3-pentyl-imidazolium bromide:- (88) (d)

As per (88) (i) except pentyl bromide (2.6cm^3, 0.032mols) was used. (51% Yield)

^{1}H NMR :- (DMSO-d^6, δ/ppm relative to TMS): 9.71 (s, 1H) 8.27 (s, 1H), 8.00 (s, 1H), 7.32 (q, 1H), 6.01 (d, 1H), 5.41 (d, 1H), 4.22 (t, 2H), 1.83 (t, 2H), 1.27 (m, 4H), 0.87 (t, 3H)

^{13}C NMR (DMSO-d^6, δ/ppm relative to TMS): 135.61, 129.18, 123.60, 119.54, 109.00, 49.52, 29.14, 27.95, 21.85, 14.08 ppm

Procedure for the Synthesis of 1-vinyl-3-hexyl-imidazolium bromide:- (88) (e)

As per (88) (i) except hexyl bromide (3.65cm^3, 0.032mols) was used. (65% Yield)

^{1}H NMR :- (DMSO-d^6, δ/ppm relative to TMS): 9.46 (s, 1H), 8.02 (s, 1H), 7.75 (s, 1H), 7.09 (q, 1H), 5.75 (d, 1H), 5.17 (d, 1H), 3.96 (t, 2H), 1.01 (m, 8H), 0.60 (t, 3H)

^{13}C NMR (DMSO-d^6, δ/ppm relative to TMS): 135.65, 129.21, 123.60, 119.53, 108.95, 101.30, 49.52, 30.89, 29.40, 25.49, 22.20, 14.22 ppm

Procedure for the Synthesis of 1-vinyl-3-heptyl-imidazolium bromide:- (88) (f)

As per (88) (i) except heptyl bromide (3.34cm^3, 0.021mols) was used. (53% Yield)

^1H NMR :- (DMSO-d^6, δ/ppm relative to TMS): 9.70 (s, 1H), 8.28 (s, 1H), 8.00 (s, 1H), 7.34 (q, 1H), 6.01 (d, 1H), 5.42 (d, 1H), 4.22 (t, 2H), 1.83 (t, 2H), 1.26 (m, 8H), 0.84 (t, 3H)

^{13}C NMR (DMSO-d^6, δ/ppm relative to TMS): 135.65, 129.21, 123.60, 119.52, 108.96, 49.53, 31.36, 29.45, 25.80, 22.33, 14.26 ppm.

Procedure for the Synthesis of 1-vinyl-3-octyl-imidazolium bromide:- (88) (g)

As per (88) (i) except octyl bromide (3.63cm^3, 0.021mols) was used. (40% Yield)

^1H NMR :- (DMSO-d^6, δ/ppm relative to TMS): 9.79 (s, 1H), 8.31 (s, 1H), 8.03 (s, 1H), 7.36 (q, 1H), 6.03 (d, 1H), 5,41 (d, 1H), 4.23 (t, 2H), 1.82 (t, 2H), 1.22 (m, 10H), 0.83 (t, 3H)

^{13}C NMR (DMSO-d^6, δ/ppm relative to TMS): 135.65, 129.19, 123.61, 119.52, 108.96, 49.53, 31.36, 29.45, 28.78, 28.39, 25.80, 22.33, 14.26 ppm.

Procedure for the Synthesis of 1-vinyl-3-nonyl-imidazolium bromide:- (88) (h)

As per (88) (I) except nonyl bromide (4.01cm^3, 0.021mols) was used. (60% Yield)

^{1}H NMR :- (DMSO-d6, δ/ppm relative to TMS): 9.66 (s, 1H), 8.26 (s, 1H), 7.98 (s, 1H), 7.33 (q, 1H), 6.00 (d, 1H), 5.42 (d, 1H), 4.22 (t, 2H), 1.84 (d, 2H), 1.24 (m, 12 H), 0.85 (t, 3H).

^{13}C NMR (DMSO-d^6, δ/ppm relative to TMS): 135.66, 129.23, 123.61, 119.51, 108.95, 49.54, 31.59, 29.44, 29.10, 28.94, 28.73, 25.83, 22.43, 14.30 ppm

Procedure for the Synthesis of 1-vinyl-3-decyl-imidazloium tetrafluoroborate :- (89) (i)

1-Vinyl-3-decyl imidazolium bromide (1.5g, 0.005mols) was dissolved in acetone (40cm^3) in a conical flask. $NaBF_4$ (0.52g, 0.005mols) was added to the solution and left to stir for 12 hours. The solution was then left to settle and then the precipitated NaBr salt was filtered through a pad of activated celite. The acetone was then removed in vacuo yielding a light brown viscous oil (50% yield).

^{1}H NMR :- (DMSO-d^6, δ/ppm relative to TMS): 9.55 (s, 1H), 8.10 (s, 1H), 7.88 (s, 1H), 7.28 (q, 1H), 5.95 (d, 1H) 5.36 (d, 1H), 4.19 (t, 2H), 1.84 (t, 2H), 1.20 (m, 14H), 0.79 (t, 3H)

^{13}C NMR (DMSO-d^6, δ/ppm relative to TMS): 135.62, 129.20, 123.57, 119.48, 108.95, 48.45, 31.68, 29.42, 29.21, 29.23, 29.00, 28.73, 25.83, 22.44, 14.30 ppm.

See Appendix for examples of NMR spectra of various 1-vinyl-alkylimidazolium bromide/hexaflurophosphate/tetrafluoroborate.

Procedure for the Diels-Alder reaction of Cyclopentadiene and 1-vinyl-3-heptylimidazolium tetrafluoroborate :-

1-Vinyl-3-heptyl imidazolium tetrafluoborate (2.06g, 7.4mmols) was dissolved in ethanol (50cm^3). Upon dissolution cyclopentadiene (0.49g, 7.4mmols) was added dropwise to the

ionic liquid solution over a period of 20minutes. The reaction was left stir for 24 hours. The same procedure was followed except the solution was refluxed for 24 hours.
No reaction took place in either instance. Furan and 1,3 butadiene were experimented with but both gave the same results, no reaction took place.

16. Conclusions:-

In can be concluded that, the reduction of simple aldehydes and ketones was a success in the ionic liquid [bmim]PF_6. The yields obtained were satisfactory and the reaction procedure was not complicated and easily carried out. All the properties which were discussed proved to be advantageous in this type of synthesis in the ionic liquids.

The ionic liquid proved successful due to a number of factors. Firstly, [bmim]PF_6 is air and moisture stable so this allowed the reductions to be carried out without an inert atmosphere. The final step in the reaction procedure was the addition of iced water to the ionic phase. The ionic liquid [bmim]PF_6 is moisture stable so this important protonation step was carried out without any detrimental effects to the ionic liquid. If the ionic liquid used was air and moisture sensitive like the chloroaluminate-based ionic liquids the reductions would not have been carried out using this method, as addition of water would cause a reaction between the water and the chloroaluminate ionic liquid. An inert atmosphere would also have been necessary which would have made the reaction somewhat more troublesome.

Another important factor was that [bmim]PF_6 is not that viscous and this allowed the reaction mixture to be stirred properly, which allowed a uniform mixture of aldehyde/ketone and sodium borohydride which is necessary for complete reduction to take place. The solubility properties of [bmim]PF_6 also played a large role in the success of this synthesis as a range of aldehydes and ketones were used, all of which were readily soluble in the ionic liquid with stirring. This was a major factor as if the aldehyde or ketone was not soluble in the ionic liquid, reduction would not have taken place completely and yields would have been substantially lower. The polar nature of [bmim]PF_6 was also essential. The ions produced during the reduction were obviously stabilised in the [bmim]PF_6 and this property allowed for the reduction to proceed and the charges of the various ions produced were stable enough to form the desired products.

Another point which should be noted is that the thermal stability and lack of vapor pressure of [bmim]PF_6 was very important as during the addition of the sodium borohydride there was a slight exotherm which had no adverse effects to the [bmim]PF_6 whatsoever. Using conventional solvents such as ethanol may have caused thermal instability of the solvent and some product may have been lost. Although, a controlled rate of addition of sodium borohydride is still necessary.

Finally, the ionic liquid was recycled 8-10 times in these reduction processes without any major loss of reactivity. This is a very important point as this has a major environmental impact. The green chemistry of ionic liquids is one of there most important and industrially attractive properties. The use of bulk solvents costs companies millions of euro in disposal costs, using ionic liquids in industrial reduction processes could reduce the overall cost of the procedure.

The free radical synthesis proved unsuccessful. A number of factors were altered in an effort to achieve the required goal. In all, over 100 reactions were carried out, varying temperature, time, ratios etc but the end result was the same. Even the use of the new compound (tris)trimethylsilylsilane proved unsuccessful but this reaction should be tested again when the compound becomes available commercially again. The hydrosilylated product was observed from the reactions, so a radical reaction did indeed take place even though it was not the desired one. A better method for drying the ionic liquids has to be investigated to completely eliminate water from them, possibly a freeze-dry technique could be incorporated into the synthesis. Water present may be affecting the radical chain reaction. Even though these radical reactions were not successful, a vast amount of knowledge has been obtained about the use of ionic liquids in these radical reactions ie the problems which have to be overcome; absolute drying of the ionic liquid and the reaction conditions which don't allow radicals to form in ionic liquids.

The synthesis of the series of 1-vinyl-3-alkylimidazolium tetrafluorborate compounds was a success and all the compounds were characterised by nmr. The Diels-Alder reaction was not a success but these compounds are a novel type of ionic liquid and may be manipulated for other chemical procedures.

So in conclusion, sodium borohydride reductions were very successfully carried in ionic liquids. The free radical addition reactions although unsuccessful, a lot of information has been learned about ionic liquids and free radical reactions in general. Although the free radical reactions were not successful vital information was obtained about the characteristics of ionic liquids in free radical addition reactions. There is a vast amount of reactions that have possibilities in ionic liquids and further investigation has to be carried out in the future.

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carbonate(5.3mmols, 2 equiv.) and toluene-water-ethanol 4:2:1, heated at 110°C for 6 hours. *Synthetic Commun.*, (1981), 11, 513, Suzuki, A, Yanagi, T

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18. Appendix 1:

NMRs

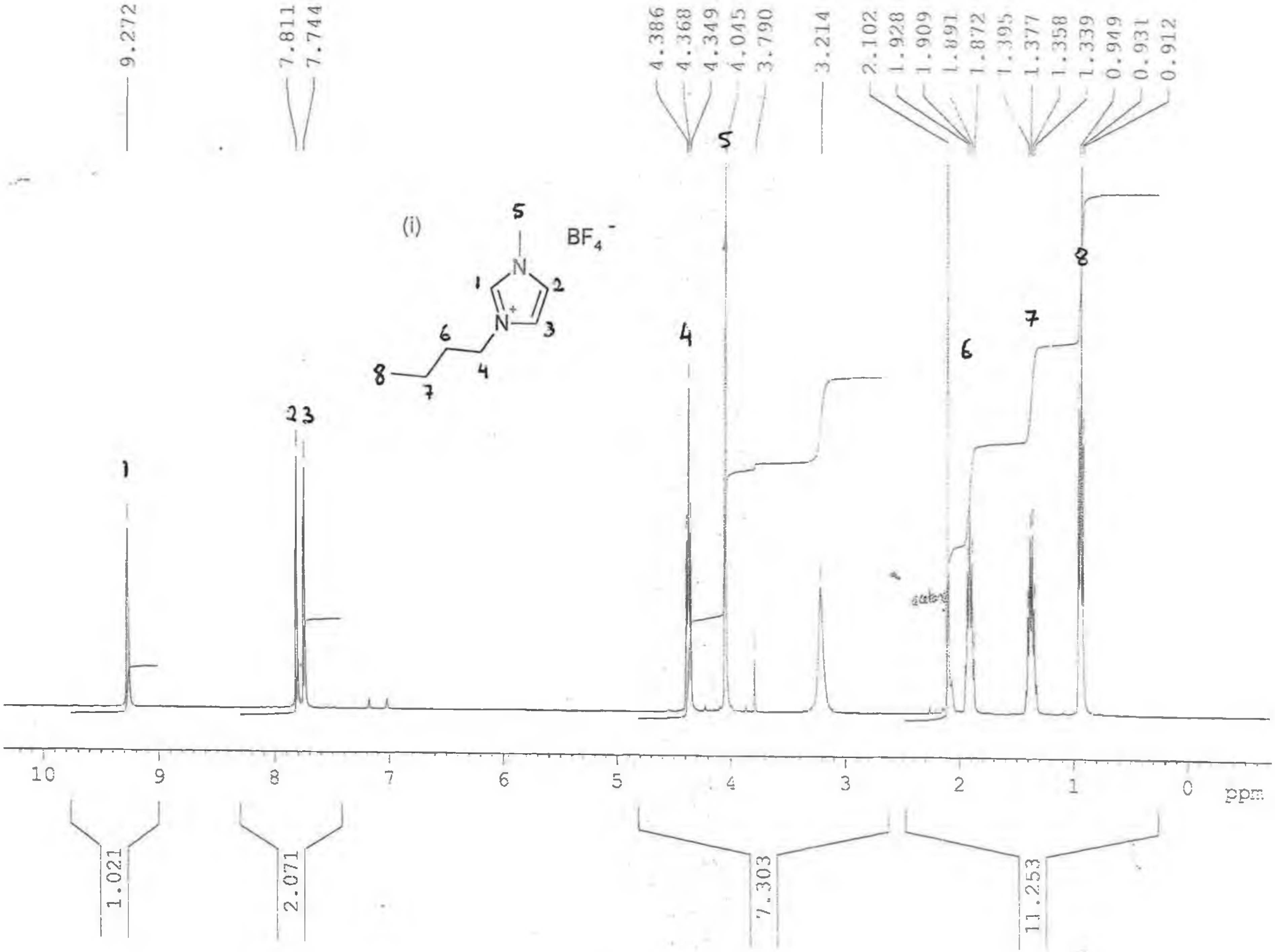
(i) ^{1}H and ^{13}C NMR of 1-butyl-3-methyl-imidazolium hexafluorophosphate (4)

(ii) ^{1}H and ^{13}C NMR of 1-butyl-3-methyl-imidazolium tetrafluoroborate (7)

(iii) ^{1}H and ^{13}C NMR of 1-vinyl-3-pentyl-imidazolium bromide (88)

19. Appendix 2:

Publication.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1.339
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0.931
0.912
(i)
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3
6
4
8
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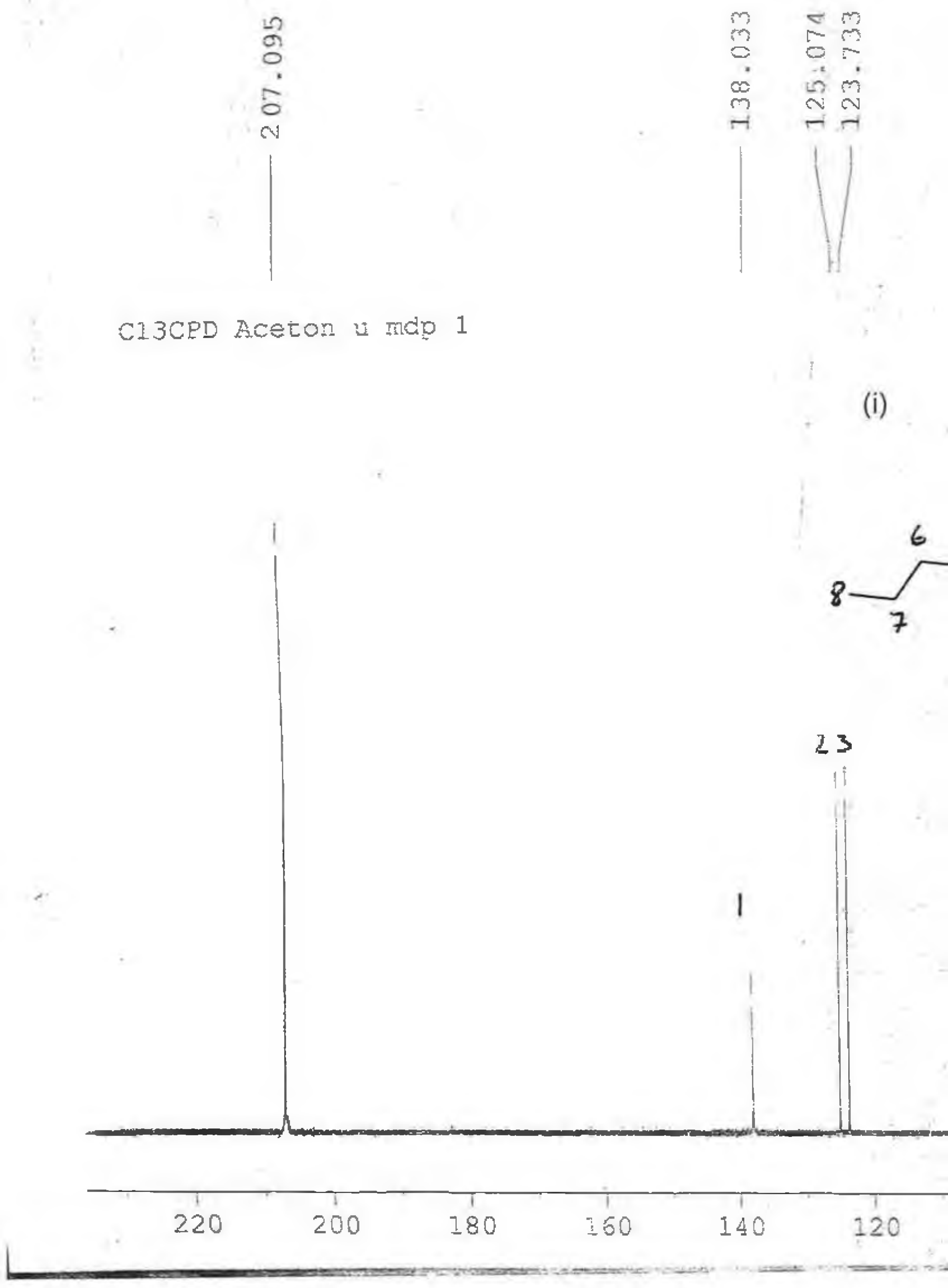

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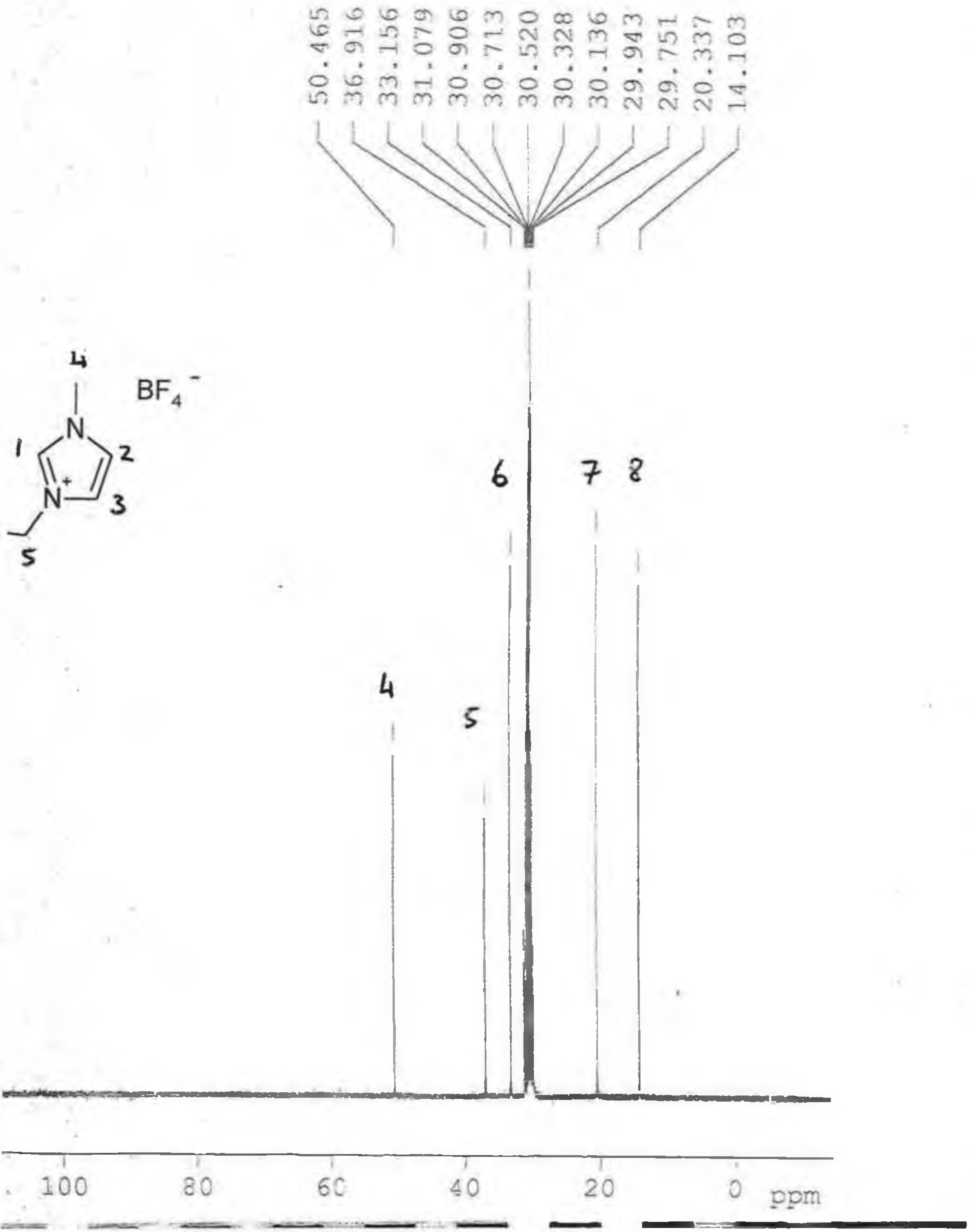
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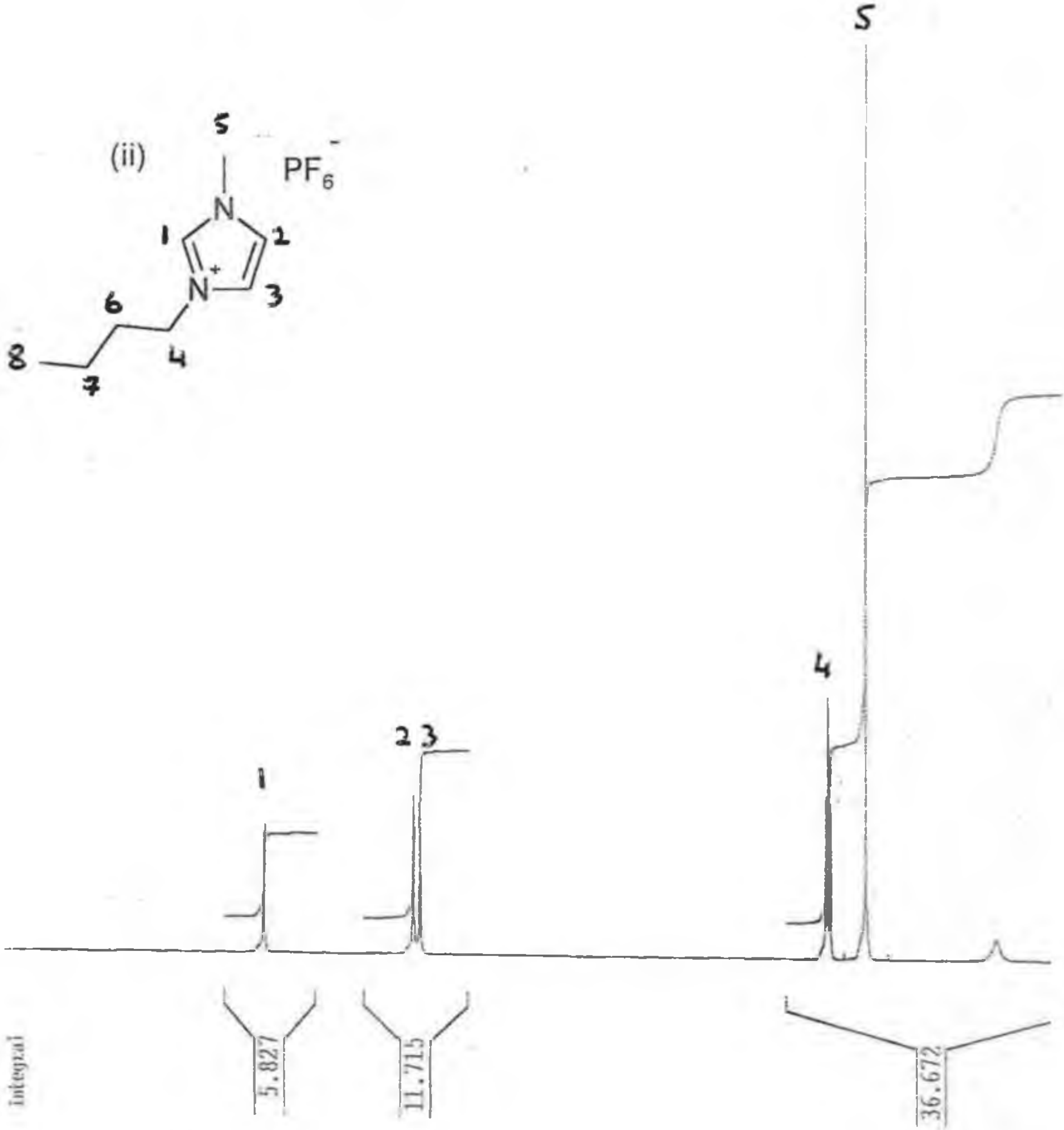
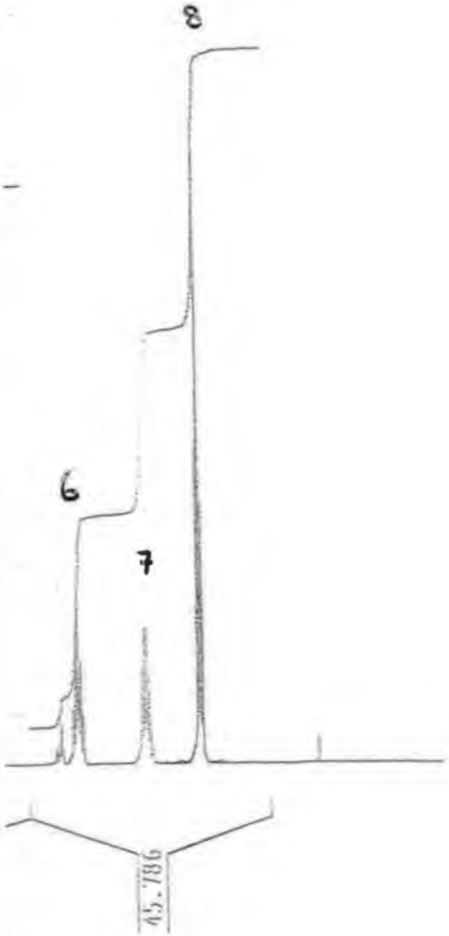
(ii)





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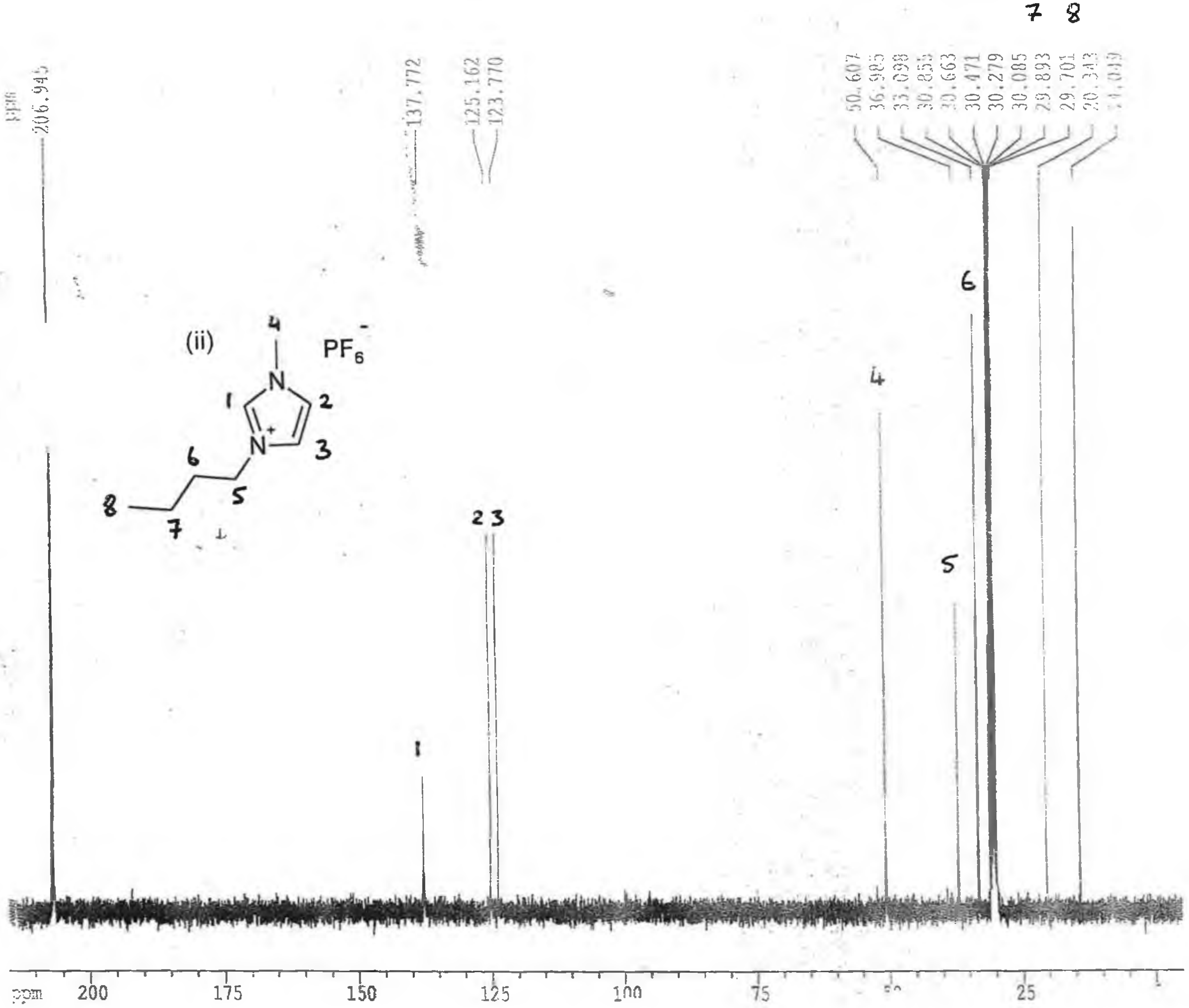

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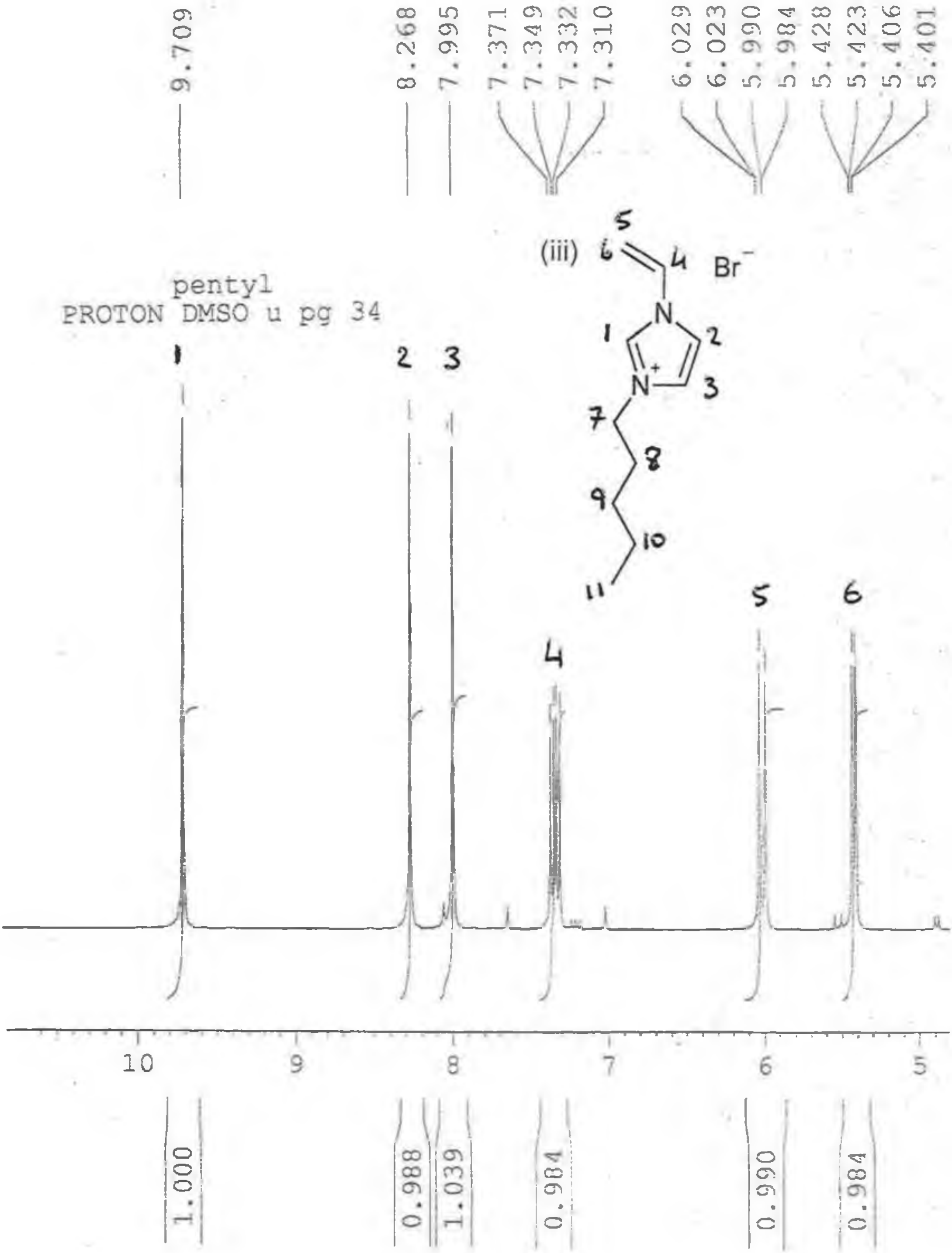
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(iii)
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N+
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4
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10
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pentyl
PROTON DMSO u pg 34
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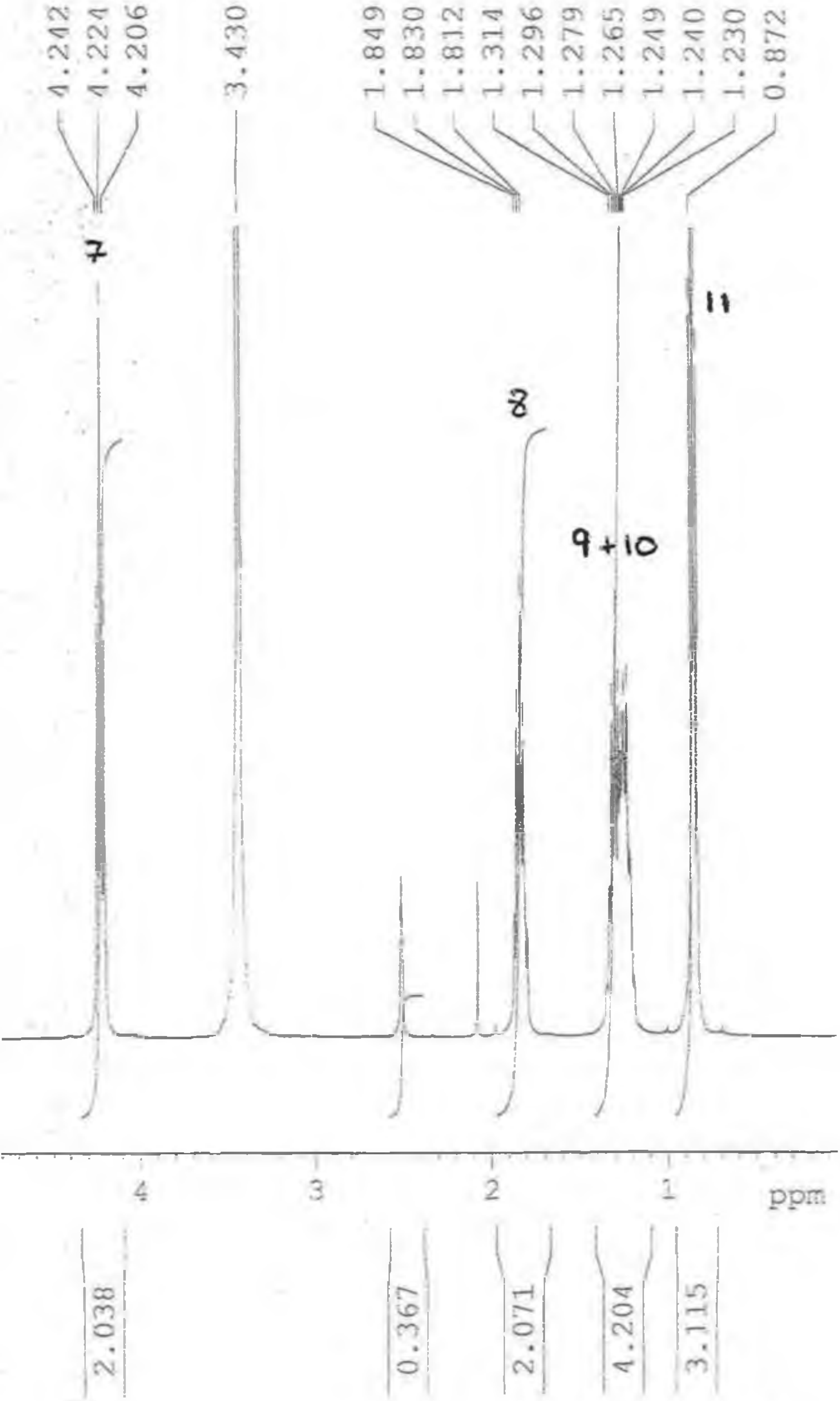
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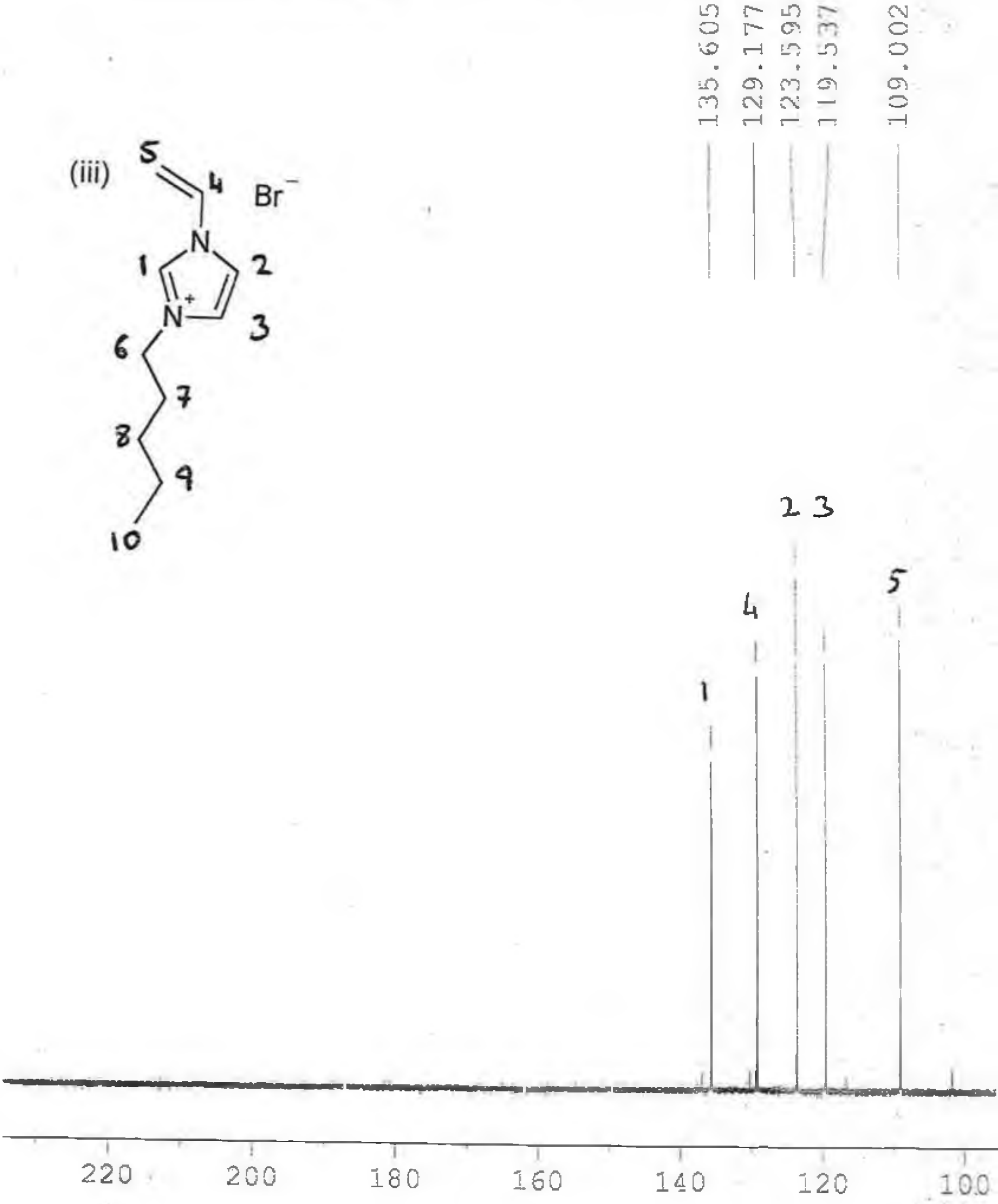

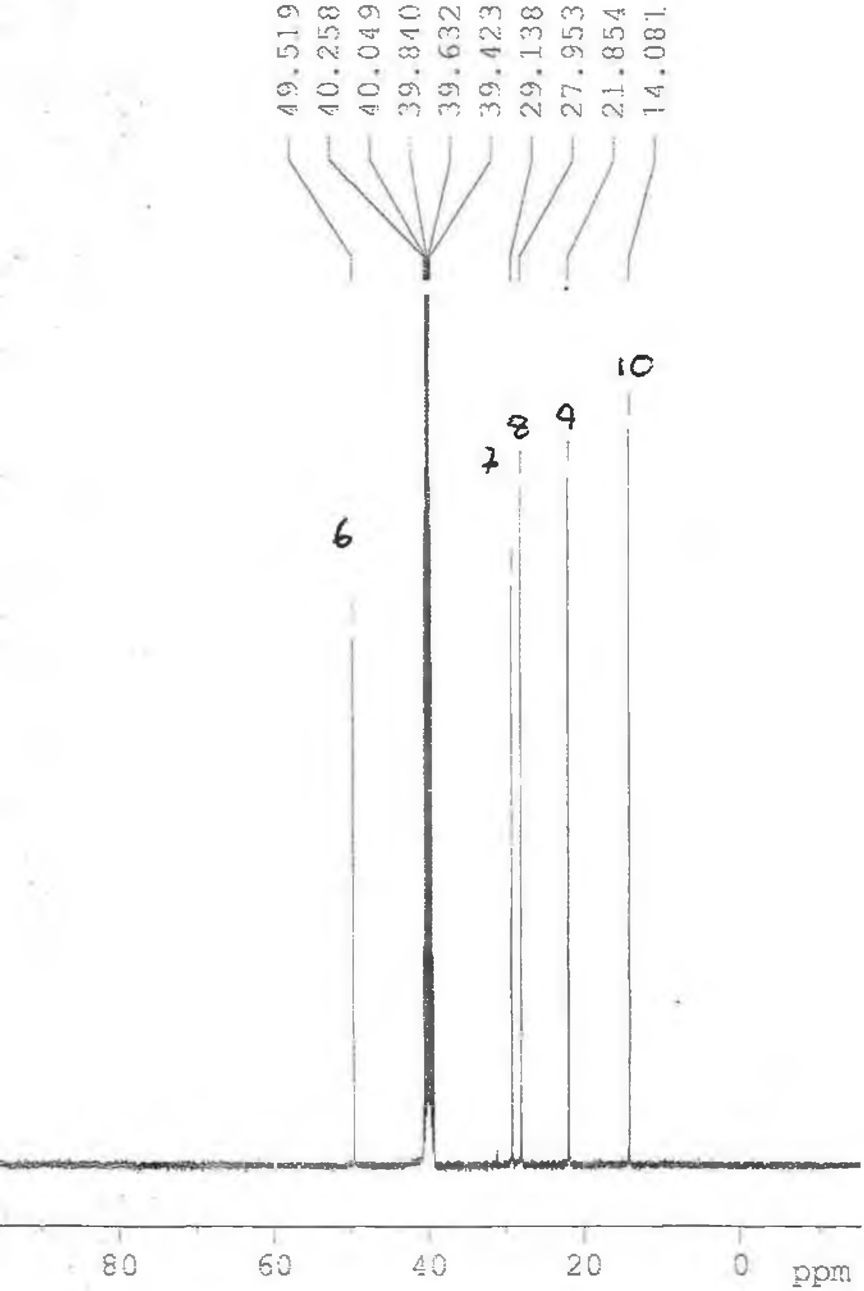
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ppm

SYNTHETIC COMMUNICATIONS, 31(19), 2935–2938 (2001)

SODIUM BOROHYDRIDE REDUCTION OF ALDEHYDES AND KETONES IN THE RECYCLABLE IONIC LIQUID [BMIM]PF_6

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University, Dublin 9, Ireland

ABSTRACT

In our exploration of the new ionic liquid solvents as possible replacements for classical organic solvents, we have found that the reduction of aldehydes and ketones with $NaBH_4$ in the ionic liquid [bmim]PF_6 can be achieved. The ionic liquid can be recycled, and in some cases the product alcohol may be distilled directly from the ionic liquid eliminating classical organic solvents entirely.

The ionic liquids [emim]PF_6 and [emim]BF_4, where $[emim]^+$ is the 1-ethyl-3-methylimidazolium cation, were first discovered in 1994 and 1992 respectively.[1] The analogous [bmim]PF_6 **1** and [bmim]BF_4 ionic liquids, where $[bmim]^+$ is the 1-butyl-3-methylimidazolium cation, followed shortly after.[2] These liquids have several very interesting properties; they

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*Corresponding author.

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can solvate a wide range of organic and inorganic materials, they are highly polar yet non-coordinating, they are immiscible with a wide range of organic solvents, and they have a nonvolatile nature. It is also possible to vary their immiscibility with water and other solvents by varying the counter ion, allowing for the possibility of biphasic reactions. Thus for example $[bmim]PF_6$ is water immiscible and $[bmim]BF_4$ is water miscible.

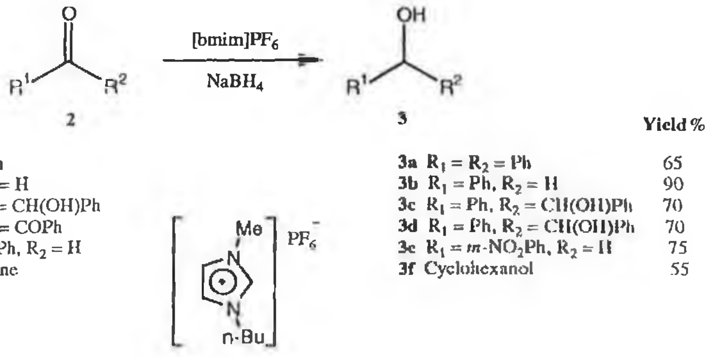
One of the prime concerns of industry and academia is the search for replacements to the environmentally damaging solvents used on a large scale, especially those that are volatile and difficult to contain. Moisture stable ionic liquids, with their unique properties, provide the promise of a credible alternative. As such a rapid growth in the investigation of the $[bmim]PF_6$ and $[bmim]BF_4$ type ionic liquids as substitutes for classical solvents is underway.

To date some of the more important reactions that have been carried out and investigated in $[bmim]PF_6$ and $[bmim]BF_4$ are a simple Diels–Alder reaction between cyclopentadiene and methyl methacrylate,[3] *N*-alkylation of indole and *O*-alkylation of 2-naphthol,[4] hydrogenations,[5] hydroformylation,[6] dimerization of olefins,[7] oxidation of aromatic aldehydes,[8] and the Heck reaction.[9]

Herein we report, as far as we are aware, the results of the first sodium borohydride reduction to be carried out in the new and versatile solvent $[bmim]PF_6$, a further, important example of the general application of this type of solvent. The sodium borohydride reduction has many precedents in synthetic chemistry,[10] its widespread use makes it an ideal reaction to test the versatility of the new $[bmim]PF_6$ ionic liquid solvent, as a replacement for classical organic solvents. As such we took six common aldehydes and ketones **2a–f**, and using the procedure given below we reduced them to the corresponding alcohols **3a–f**. The results of these reductions are given in Scheme 1.

General procedure for the reduction of aldehydes and ketones in $[bmim]PF_6$, using benzaldehyde as an example. Benzaldehyde (3.07 g, 0.03 mol) was dissolved in $[bmim]PF_6$ (10 mL).[11] Sodium borohydride (3.00 g, 0.08 mol) was added slowly, with stirring, over a period of 0.5 h. The reaction was left to stir for 1 h and then ice cold water was added (10 mL). After 10 min the $[bmim]PF_6$ layer was separated from the aqueous layer and extracted with diethyl ether (2 × 50 mL). The combined extracts were dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*, to yield the crude benzyl alcohol as a yellow liquid. After purification by short path distillation under vacuum pure benzyl alcohol **3b** was obtained (2.82 g, 90% yield).[12]

Alternative procedure for volatile product alcohols. As above, but after the $[bmim]PF_6$ has been separated from the aqueous layer the $[bmim]PF_6$



2 → **3**

2a $R_1 = R_2 = Ph$
2b $R_1 = Ph, R_2 = H$
2c $R_1 = Ph, R_2 = CH(OH)Ph$
2d $R_1 = Ph, R_2 = COPh$
2e $R_1 = m\text{-}NO_2Ph, R_2 = H$
2f Cyclohexanone

	Yield %
3a $R_1 = R_2 = Ph$	65
3b $R_1 = Ph, R_2 = H$	90
3c $R_1 = Ph, R_2 = CH(OH)Ph$	70
3d $R_1 = Ph, R_2 = CH(OH)Ph$	70
3e $R_1 = m\text{-}NO_2Ph, R_2 = H$	75
3f Cyclohexanol	55

Scheme 1.

was heated under high vacuum and the benzyl alcohol **3b** was distilled (75–80°C, 0.2 mmHg) directly from the [bmim]PF$_6$ in 70% yield using short path distillation apparatus. Cyclohexanol **3f** was distilled directly from the [bmim]PF$_6$ (50–54°C, 0.9 mmHg) in a similar manner, 78% yield.

The yields obtained using this procedure are better than with extraction, and this procedure eliminates the use of all classical organic solvents from the reaction if volatile alcohols are produced from the aldehydes or ketones being reduced.

Compounds **3a**, benzhydrol, and **3e**, *m*-nitrobenzyl alcohol, were purified by recrystallisation with melting points of 66–67°C (Lit. mp[13] 65–67°C) and 30–33°C (Lit. mp[14] 30–32°C) respectively. Compounds **3c,d** were purified by silica gel flash chromatography.

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