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Janne Asikkala

APPLICATION OF IONIC LIQUIDS AND MICROWAVE ACTIVATION IN SELECTED ORGANIC REACTIONS

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JANNE ASIKKALA

APPLICATION OF IONIC LIQUIDS AND MICROWAVE ACTIVATION IN SELECTED ORGANIC REACTIONS

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Abstract

Ionic liquids and microwave heating have been studied in four different reactions namely esterifications, etherifications and ene and sulfonylation reactions. These techniques revealed several advantages over conventional methods.

In esterification of alcohols with anhydrides in ionic liquid solvents, the low boiling acid by-product could be removed before product recovery. The acid by-product could be regenerated back to the anhydride. Similar or higher yields were observed from esterifications with acetic anhydride of carbohydrates than with conventional methods. Even cellulose and starch could be esterificated in ionic liquids in the homogenous phase.

The etherification reaction in ionic liquid was challenging, due to the basic reaction conditions needed. 1-Methyl-3-butylimidazolium -cations ([BMIM]) could not be used in basic conditions. The new information was that [BMIM]-cation could not be used with epichlorohydrin.

The ene reaction was carried out with microwave heating in various solvents. Ionic liquids could be used as a solvent, but the ene reaction between allyl benzene. The best results were obtained without additional solvent. The yields by using microwave heating were high and reaction times were relatively short.

The sulfonylation reaction of aromatics could be catalyzed by metal bistriflimide complexes. Even chlorobenzene could be sulfonylated when Bi-complex was used as a catalyst. Ionic liquids could be used as a solvent, but sulfonylations were best carried out without additional solvents.

Keywords: ionic liquid, microwave

To my Grandfather

Acknowledgements

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Oulu 2008 Janne Asikkala

Symbols and Abbreviations

IL	Ionic liquid
[EMIM]	1-Ethyl-3-methylimidazolium
[BMIM]	1-Butyl-3-methylimidazolium
[HMIM]	1-Hexyl-3-methylimidazolium
[DCA]	Dicyanoamine
[NTf_2]	Bis(trifluoromethanesulfonyl)amine
[EPy]	Ethylpyridinium
[BPy]	Butylpyridinium
[HPy]	Hexylpyridinium
MeI	Methyl iodide
Dabco	1,4-Diaza-bicyclo[2.2.2]octane
Ac_2O	Acetic anhydride
[OAc]	Acetic acid
[OTf]	Trifluoromethanesulfonic acid
TFAA	Trifluoroacetic acid
Tf_2O	Trifluoromethanesulfonic anhydride
TMSCl	Trimethylsilylchloride
DMAc	*N*,*N*-dimethylacetamide
[B-3-MPy]	3-Methyl-*N*-butylpyridium
[BDTAC]	Benzyldimethyl(tetradecyl)ammonium
DMAP	*N*,*N*-dimethyl-4-aminopyridine
[MMSIM]	1-Methyl-3-(methylsulfonyl)imidazolium
[MESIM]	1-Methyl-3-(ethylsulfonyl)-imidazolium
[MEEIM]	1-(Ethoxyethanol)-3-methylimidazolium
[TBA]	Tetrabutylammonium
[AMIM]	1-Allyl-3-methylimidazolium
[BDMIM]	1-butyl-2,3-dimethylimidazole
[AdMIM]	1-*N*-allyl-2,3-dimethylimidazolium
[BBIM]	1,3-Dibutylimidazolium
pentaerythritol	2,2-Bis(hydroxymethyl)-1,3-propanediol
TMP	2-Ethyl-2-hydroxymethyl-propane-1,3-diol
PMA	Phosphomolybdic acid
DP	Degree of polymerization
DS	Degree of substitution
ee	Enantiomeric excess

TLC	Thin layer chromatography
MS	Mass spectrometry
ESI	Electrospray ionization
NMR	Nuclear magnetic resonanse
T_g	Glass transition temperature

Contents

1 Introduction

The aim of the study was to find out if the microwave technique and ionic liquids could be used together to improve the efficiency of chemical reactions. To do this, four different reaction types were chosen as models where the effects of microwaves and ionic liquids were studied. The reactions included esterification, etherification, the ene reaction and the sulfonylation reaction.

1.1 Background of the selected reactions

The selection criteria of the reactions were established according to both academic and industrial interests toward the developed techniques. Thus, esterification and etherification studies were collaborated on with Kemira Oyj Espoo Research Center. The esterification reaction studies lead to two invention notifications to Kemira Oyj. The ene reaction was collaborated on with The University of Helsinki Drug Discovery and Technology Development Centre. I had the privileged opportunity to work in Queen's University Ionic Liquid Laboratory (QUILL, at University of Belfast), where the sulfonylation studies were carried out.

1.2 Green Chemistry

After the book Silent Spring (44) awakening of the general public toward environmentalism was realized. After the book was released in 1962, huge numbers of laws against chemical release and safety have been enacted. The environmental laws generated new ways of thinking about chemical safety and the environmental aspects of chemicals. It was recognized that chemistry is one of the key sciences in taking care of the environmental problems created by chemicals.

The term green chemistry was a counter attack against the bad reputation of chemists and chemicals. Since there is no going back to the time before chemicals, it is imperative that chemicals are produced in a sustainable way and that they are safe to use. Green chemisty (10, 294) is defined as the "Approach to synthesis, processing and use of chemicals that reduces risks to humans and the environment".

Green chemistry has been one of the keywords when microwaves and especially ionic liquids have been introduced. It is misleading to state that

microwaves and ionic liquids are “green chemistry” by themselves. Ionic liquids can have a positive environmental effect on the synthesis and processing of chemicals if they are chosen correctly, but at the same time they are chemicals which have to be dealt with. Microwaves do not change chemical reactions, but they can greatly increase the energy efficiency of the process.

It is hard to immediately see where microwaves are located in the field of green chemistry. The value of microwaves is that they usually reduce reaction time by efficient heating and ease the path to high temperature reactions. In drug discovery the screening of promising drug candidates is done from 100 to 10 000 molecule libraries. The synthesis of such amounts of molecules takes considerable amout of time and by reducing the reaction time from 1 hour to 10 minutes libraries are synthesized much faster. This saves on labor costs significantly and at the same time less energy is used in synthesis. Cost savings are actually one of the key points in green chemistry, since if synthesis is not economically feasible it is not green even if it produces less waste and uses microwaves and ionic liquids.

Usually it is simply stated that ionic liquids do not evaporate and that is the reason why they are green. Actually the release of volatile organic compounds (VOC) from chemical plants is not a concern anyway. Another statement which is usually made about ionic liquids is that they are recyclable, but their recyclability is rarely tested. In most cases it is just assumed that since products could be recovered from ILs, they are recyclable. It was found during this work that ionic liquids recyclability is not necessarily achieved after a product is recovered, especially if basic reaction conditions are used with imidazolium cation. The environmental impact of ionic liquids is very rarely green when fluorinated anions or cations are used since the fluorination process usually releases fluorinated hydrocarbons. Fluorinated hydrocarbons are one of the worst gases to induce ozone depletion in the upper atmosphere. So there is still room for new inventions to produce reusable and environmentally safe ionic liquids.

This work has been carried out with green chemistry principles in mind. The use of energy was reduced and the reaction modifications concentrate on finding recyclable solvents.

2 Microwaves

Microwaves are electromagnetic radiation with a frequency range from 300 to 300 000 MHz, with free space wavelengths of 1 m to 1 mm. The energy of microwaves is so low that only molecular rotation could be induced. Microwaves have no effect on molecular bonds or electron clouds such as infrared (IR) or the visible region of electromagnetic radiation has. The frequency used in heating applications is usually 2 450 MHz (wavelength 12.2 cm) and for industrial heating applications 915 MHz (wavelength 32.8 cm) can also be used.

The development of microwave technology was initiated by the invention of radar. Radar applications needed single frequency microwaves and this demand lead to the development of the magnetron. The heating effect of microwaves was discovered by accident. Percy Spencer from Raytheon Company was the first to realize the potential of microwaves as an every day life application. Spencer's invention lead to the first commercial microwave oven in 1954. (275, 276, 277) The search for industrial applications of microwave heating started in the 1940s. The first applications were removal of organic sulphur from coal, tempering of frozen food, vulcanization of rubber and drying of pasta products. Microwave heating has been intensively used in analytical applications since the early days. (149)

Probably the first publication on the use of microwaves in the heating of organic reactions is the modification of starch in 1974. (310) According to most publications the first reactions to use microwave heating have been carried out in 1986. (94, 98) It took some time before microwave heating was widely accepted in organic synthesis, maybe due to the non-reproducible results of the domestic microwave oven. After microwave reactors were developed specially for organic chemistry (pressure, temperature and power can be precisely measured and adjusted) microwave heating has reached ever-growing popularity, especially in pharmaceutical industry. Over the last decade microwaves have been intensively used in organic chemistry as a heating method, mainly because it is fast. There are many excellent reviews on different applications where microwaves can be used. (63, 71, 112, 136, 164, 165, 172, 176, 180, 184, 190, 227, 279)

Scale-up is one of the key questions in the microwave technique but not too many articles have been published yet on the subject. One of the drawbacks of microwaves is the penetration depth of radiation. When polar absorbing solvent is used as a reaction medium, the microwave power halves for every 2.5 cm travelled in medium. This feature limits the reactor diameter, which is a problem

in scale-up. The penetration depth depends on the used wavelength, with lower wavelengths having higher penetration but at the same time longer wavelengths having lower energy. So by changing the wavelength it is possible to build bigger reactors. Another way to get around penetration problems is to build flow-through reactors. (85, 133, 149, 184)

2.1 Microwave heating

Dielectric loss is the amount of electromagnetic energy absorbed by molecules. Its origin is in how microwave energy is obstructed by matter (dielectric constant) and how energy is dissipated in the sample. (85, 133, 149, 184)

Molecular dipoles are normally randomly orientated, but they orientate themselves according to the external electric field. For small non-associated molecules (molecular weight < few hundred, no hydrogen bonding) dielectric relaxation times are so short that they follow the external electric field of microwaves and do not heat. Small associated and large molecules (dipoles) have such long relaxation times that they do not have time to orient themselves and thus the rapidly changing electric field cause heating when dipoles hit each other when some are relaxing and some are excited again (see Fig. 1). (149)

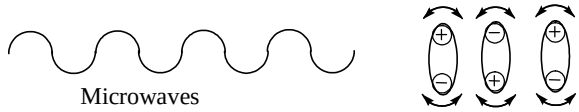


Fig. 1. Microwave induced dipole rotation.

Free ions in solution (in liquid or in ionic liquid) tend to follow the changing electric field by migrating with the field. This migration causes a current, which results in losses caused by resistance. Energy is then released in the form of heat. All ions migrate during irradiation, but only a fraction of the current is carried away by the medium. Therefore losses by ionic conduction depend on the concentration, size and charge of ionic species (see Fig. 2). (149)

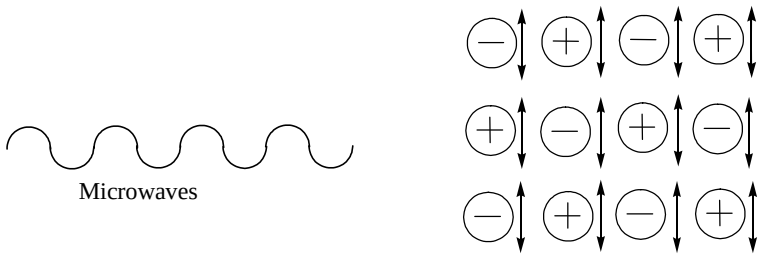


Fig. 2. Microwave induced ionic conduction.

2.2 Heating effect of microwaves

It is well known that microwaves enhance reaction rates, increase selectivities and yields. Every time when discussing with people with little or no experience in microwave heating at some point of the discussion a question about the "microwave effect" comes up. It is one of those questions which are quite hard to answer, because it is case dependent. (23, 57, 91, 156, 166, 238, 242, 278, 280)

The easiest case to explain the microwave heating effect is when a reaction is done in a polar microwave absorbing solvent. There is no microwave effect since the solvent absorbs most of the microwave energy and there is no additional energy going to the reactants. So, no matter what kind of reaction is done, no rate enhancement is detected due the microwave effect. Sometimes, however, it has been reported that rate enhancements was detected. Usually rate enhancements can be explained by superheating of the solvent. It is possible to achieve 10-15 °C higher boiling points in polar solvents when they are heated with microwaves compared to conventional heating. (184)

Polar absorbing reagents in non-absorbing solvent are a considerably harder case to explain. In this case microwave energy is mostly absorbed by reactants. The solvent acts as a heat sink, which cools the reactants down. Sometimes in these systems selectivity and yield can be lot better than in conventional heating, because overall temperature is lower than the temperature of the reactants. This prevents products from reacting further to by-products, because the solvent is cooler than the reactants and thus has a lower amount of energy to be released to by-product formation. (184)

The reaction mechanism plays an important role when polar reagents are used in non-polar solvents. The reaction is "pushed" toward products if the transition

state has a long enough lifetime it can absorb energy from microwaves and energy can be transferred to the activated complex. (184)

Microwave effect(s) can be seen in rare cases when the reactant acts as a solvent and no additional solvents are added. Reaction coordinates play an even more important role in this case, since reactants absorbs the microwave energy. This increases the probability of meeting of the activated complexes. There is a proposal that “hot spots” are generated in the reaction mixture and the reaction would take place mostly in the “hot spots”. The existence of “hot spots” has been proved in solid and highly viscous materials, but the existence of “hot spots” in liquids is still under debate. (112, 184)

As a conclusion, using microwaves usually has a beneficial effect on reaction if a reaction needs heating. The specific microwave effect depends on different factors, but it is quite hard to actually rule out the existence or lack of microwave effect. Generally reactions give higher selectivity and yields when microwave heating is used.

3 Ionic liquids

The history of ionic liquids (ILs) starts from 1914 when the synthesis of ethyl ammonium nitrate was carried out. (296) The first ILs with chloroaluminate anion were published in 1948. (122, 311) Spectroscopy and electrochemical studies were carried out in the 1970s (50, 87, 249), and solvent properties were studied in the 1980s. (13, 62, 124, 160, 256, 257, 312) In 1967 liquid salt based on tetrahexyl ammonium benzoate was reported. (282) It was not until 1980 that interest toward ionic liquids was really awoken. Interesting properties and applications were reported and the awareness of the environmental impacts of organic solvents was noted and ionic liquids were one new option for traditional solvents. Most of the IL research carried out before 1992 was done by using chloroaluminate anions. Chloroaluminates are water sensitive and must be handled in a dry atmosphere. In 1992 a new generation of ionic liquids were reported. (313) These ionic liquids were insensitive to water and were made from 1-ethyl-3-methylimidazolium cation ([EMIM]) and tetrafluoroborate and acetate anions. After the first water insensitive IL was reported the number of new ILs has exploded. There are review articles on ionic liquids used as a solvent in catalysis (118, 229, 261, 270, 305, 307, 308) and in synthesis (48, 129), as electrolytes (88), ILs with fluorine containing anions (107, 323), metal containing anions (181), chiral ILs (20, 21), actinide chemistry (39), and also task-specific ionic liquids (175). All previous review articles have been about single ionic liquids, though there has also been one article about the properties of a mixture of different ILs. (194) There are also books about ionic liquids. (250, 251, 306)

As can be seen from different review articles ILs could be used for different kinds of purposes. Their properties could be tuned to fit certain needs from simple solvents to chiral coordinating solvents with carefully designed environment and complete life cycle analysis.

In the following chapters the main focus is on the introduction of general properties of ionic liquids. The newest generation (water insensitive) of ionic liquids has been considered, since the information on older ILs can be found from previous review articles. Also more attention has been on the ILs, which have been used in the practical part of this thesis.

3.1 Salt or ionic liquid

A typical characteristic of a salt is a high melting point and usually matter which contains only ions is considered to be a salt. Ions in salt consist of small symmetric ions which have a high charge density and thus they can be effectively packed into a crystal lattice. When an ionic liquid is constructed, the size of the ion/ions is changed. (153) For example NaCl has a melting point of about 800 °C, but when sodium is changed to 1-butyl-3-methylimidazolium ([BMIM]) the melting point decreases to about 60 °C.

When Na is changed to [BMIM] the size of the cation is increased from 102 pm (103) (6-coordinate ionic radius of sodium) to 350 pm (157) (distance of imidazolium rings face to face in crystal lattice). Charge density is decreased. Crystal lattice packing is affected, since sodium is a symmetrical ion (spherical) and imidazolium is a bulky asymmetrical ion. The crystal packing energy with [BMIM] is much higher and thus the melting point is lower.

Similar changes occur on the anion part of ionic liquids. 1-Ethyl-3-methylimidazolium chloride ([EMIM][Cl]) has a melting point of 89 °C and [EMIM] bis(trifluoromethanesulfonyl)amine ([NTf_2]) has a melting point of -15 °C. The same explanation of the melting point shift is valid for the anions as for the cations. Increasing the size of the anion lowers the charge density. A bulkier anion also decreases the attractive forces between anions and cations and lowers the melting point.

3.2 Protic ionic liquids

The simplest way to make ionic liquid is to neutralize Brønsted acid with Brønsted base. The first ionic liquid (ethylammonium nitrate) was made this way. (122) In order to make ionic liquids from acids and bases the pK_a difference must be enough, so that the acid and base are mostly in ionized form. When the pK_a difference of an acid and a base is more than 10, the change in vapor pressure temperature is more than 300 °C in most cases. Increase in the vapor pressure temperature indicates that most acid and base molecules are in ionized state and the resulting liquid can be called ionic liquid. (330)

3.3 Aromatic heterocyclic cations

Aromatic heterocyclic cations are probably the most studied and used cation type at the moment; especially imidazolium-based cations have gained very much attention.

3.3.1 Imidazolium based cations

The reason for popularity of imidazolium (Fig. 3.) as an IL cation is due to the features which can be achieved. It is easy to modify, stable under acidic conditions, and its charge density is low due to the aromatic system. The low charge density means that it is relatively easy to construct low melting salts from imidazolium.

One problem associated with imidazolium derivatives are the acidic protons of the heterocyclic ring. Acidic protons tend to come loose when imidazolium is used under basic conditions.

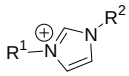


Fig. 3. The imidazolium cation (R^1 = H or -alkyl-chain, R^2 = H or alkyl-chain).

Table 1 summarizes the most important physical properties (melting point, degradation temperature and viscosity) of imidazolium based ionic liquids. The table shows that in general the melting point decreases when unsymmetry of the cation ([Cl] salts entries 1, 11, 22) or anion increases ([EMIM] salts entries 1, 4-10).

Table 1. Physical properties of 1-ethyl-3-methylimidazolium ([EMIM]), 1-butyl-3-methylimidazolium ([BMIM]) and 1-hexyl-3-methylimidazolium –based ([HMIM]) ionic liquids.

Entry	Cation	Anion	Melting point (°C)	Degradation temperature (°C)	Viscosity at 20 °C (cP)
1	[EMIM]	[Cl]	89 (220)	285 (220) (onset TGA)	
2	[EMIM]	[Br]	79 (220)		
3	[EMIM]	[I]	79 (220)	303 (220)	
4	[EMIM]	$[CF_3CO_2]$	-14 (261)		35 (27)
5	[EMIM]	$[NTf_2]$	-15 (220)	455 (220)	34 (27)
6	[EMIM]	$[BF_4]$	11 (147)	420 (332)	66.5 (260)
7	[EMIM]	$[PF_6]$	62 (220)		
8	[EMIM]	$[CF_3SO_3]$	-9 (261)		45 (27)
19	[EMIM]	$[AlCl_4]$	84 (74)		
10	[EMIM]	[DCA]	-21 (187)		17 (22 °C) (326)
11	[BMIM]	[Cl]	65 (312)	254 (121)	
12	[BMIM]	[Br]		273 (81)	1462 (25 °C) (150)
13	[BMIM]	[I]		265 (121)	963 (25 °C) (154)
14	[BMIM]	$[CF_3CO_2]$	-78 (T_g)	176 (291)	73 (27)
15	[BMIM]	$[NTf_2]$	-2 (81)	422 (81)	52 (27)
16	[BMIM]	$[BF_4]$	-82 (220)	425 (220)	154 (260)
17	[BMIM]	$[PF_6]$	10 (121)	349 (121)	371 (260)
18	[BMIM]	$[CF_3SO_3]$	13 (81)	-	60 (27)
19	[BMIM]	$[CH_3SO_3]$	76 (157)	-	
20	[BMIM]	$[AlCl_4]$	65 (74)	-	
21	[BMIM]	[DCA]	-6 (81)	300 (81)	
22	[HMIM]	[Cl]	-70 (106)	253 (121)	
23	[HMIM]	[Br]	-49 (T_g) (54)	276 (54)	
24	[HMIM]	[I]	-	-	1439 (25 °C) (154)
25	[HMIM]	$[CF_3CO_2]$	-	-	
26	[HMIM]	$[NTf_2]$	-7 (54)	428 (54)	60 (125)
27	[HMIM]	$[BF_4]$	-81 (106)	358 (54)	314 (260)
28	[HMIM]	$[PF_6]$	-61 (106)	417 (121)	680 (260)
29	[HMIM]	$[CF_3SO_3]$	-	-	
30	[HMIM]	$[CH_3SO_3]$	-	-	

Increasing side chain length has a dual effect on the melting point of imidazolium salts (see Fig. 1). If R^1 remains constant and R^2 is changed, the melting point starts to decrease (Table 1, entries 1, 11, 22) until a certain chain length is achieved and then starts to increase again. Short side chain increases the unsymmetry of the cation and thus melting point is decreased. With long side chains molecular weight starts to dominate and melting point starts to increase

with increasing chain lengths. Branching, functional groups on the side chain or other substituents on the imidazolium ring increase the melting point.

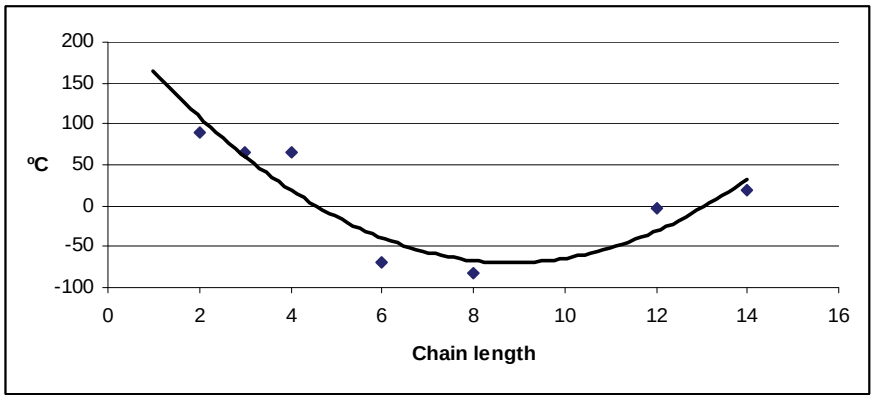


Fig. 1. The effect of increasing chain length on melting point on 1-alkyl-3-methylimidazolium chlorides.

3.3.2 Pyridinium cations

Pyridinium cations have not gained the popularity of imidazolium cations and thus the physical data is quite limited (see Table 2).

The charge density in a pyridinium cation is quite low, but it has a higher symmetry than the imidazolium cation and higher melting ionic liquid results with the same alkyl-tail (Table 1 entries 1, 11, 22 compared to Table 2, entries 1, 3, 6).

Table 2. The physical data of ethyl ([EPy]), butyl ([BPy]) and hexylpyridinium-based (HPy]) ionic liquids.

Entry	Cation	Anion	Melting point (°C)	Degradation temperature (°C)	Viscosity at 20 °C (cP)
1	[EPy]	[Cl]	116-118 (217)		
2	[EPy]	[Br]	117-121[a]		
3	[BPy]	[Cl]	130-131 (217)		
4	[BPy]	[Br]	105 (54)	237 (54)	
5	[BPy]	[BF_4]	15 (226)		
6	[HPy]	[Br]	46[b]	238 (54)	
7	[HPy]	[NTf_2]	0 (54)	392 (54)	80 (54) at 25 °C

[a]Acros Organics, [b]Merck Chemical Company

It is possible to modify the aromatic ring of pyridine in pyridinium-based ionic liquids (see Fig. 4). Pyridinium cation properties are different when different substituents are used on the aromatic ring (R^2 to R^6 varies). Usually the substituents on the ring can be anywhere and it has the same effect on the physical properties. Substituents lower the melting point because they increase the asymmetry on the cation. Although one must bear in mind that the increasing molecular weight increases the melting point after a certain weight has been achieved. (100)

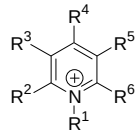


Fig. 4. The pyridinium cation ($R^1 = R^2 = R^3 = R^4 = R^5 = R^6$ = H, or alkyl chain).

3.4 Other aromatic heterocyclic cations

There has been some interest in aromatic heterocyclic cations other than imidazolium and pyridinium, but mostly the others have been just a curiosity and have not gained any interest as actual solvent. The lack of interest for other cations has been due to the high production costs without actual benefits compared to imidazolium or pyridinium analogues. Other aromatic heterocycles used as cation include pyridazinium (269), pyrazinium (90), tetrazolium (321), triazolium (205, 206, 322) (usually with fluorous tail) and benzotriazolium (77) (see Fig. 5).

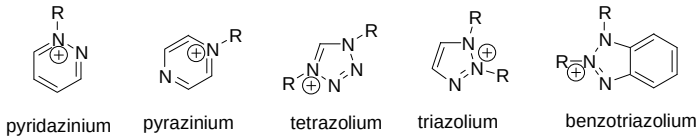


Fig. 5. Structures of aromatic heterocyclic cations (R = H or Alkyl chain).

3.5 Quaternary ammonium cations

Quaternary ammonium cations are widely used in phase transfer catalysts (59), gemini surfactants (202), surfactants (72) and some of them as ionic liquids. Usually in simple alkyl ammonium cations the charge is concentrated on the nitrogen atom. The stabilizing effect from alkyl chains is low compared to aromatic systems in aromatic heterocyclic cations. High charge density usually leads to high melting salts and therefore simple, especially symmetric, alkyl ammoniums have high melting points (See Table 3). Alkyl ammonium cations which have been used as a cation in ILs have different alkyl chains attached to central nitrogen and the counter anion is big and unsymmetric.

Table 3. Physical data of some acyclic quaternary ammonium-based salts.

Entry	Cation	Anion	Melting point (°C)
Symmetrical cations			
1	$N_{1,1,1,1}$	[Br]	>300 (306)
2	$N_{2,2,2,2}$	[Br]	284 (306)
3	$N_{4,4,4,4}$	[Br]	124-128 (306)
4	$N_{6,6,6,6}$	[Br]	99-100 (306)
5	$N_{8,8,8,8}$	[Br]	95-98 (306)
Unsymmetrical			
6	$N_{1,1,1,6}$	[Br]	176 (4)
7	$N_{1,1,12,12}$	[Br]	164 (4)
8	$N_{2,2,2,6}$	[Br]	115 (4)
9	$N_{8,6,6,3}$	[Br]	liquid (306)
10	$N_{8,6,5,1}$	[Br]	liquid (306)
11	$N_{8,8,2,2}$	[Br]	62 (306)
Unsymmetrical with big anion			
12	$N_{2,2,2,2}$	$[NTf_2]$	109 (281)
13	$N_{4,4,4,4}$	$[NTf_2]$	96 (281)
14	$N_{1,1,1,6}$	$[NTf_2]$	-74 (281) T_g
15	$N_{4,4,4,4}$	[DCA]	-62 (187)
16	$N_{8,6,6,3}$	$[ClO_4]$	liquid (306)
17	$N_{6,5,5,4}$	$[ClO_4]$	83 (101)

$N_{2,2,2,2}$ = tetraehtylammonium cation, suffix numbers presents the number of carbons in alkyl chain attached to the ammonium

A major drawback is associated with quaternary ammonium cations. The cation undergoes Hoffman elimination when used in basic conditions (Fig. 6). This is a problem if the reaction requires high temperatures.

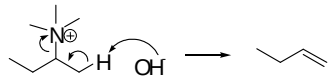


Fig. 6. Hoffman elimination of quaternary ammonium cation.

One special type of cation must be differentiated from the other ammonium cations, 2-(trimethylamino)ethane (choline), which has been used as a nutrient in poultry farming and already produced on a multi ton scale. Since choline is already used by nature it is completely biocompatible and if it is released back to nature choline do not cause hazard. Choline also provides a hydroxyl group which can be easily modified and whose physical properties can be easily tuned.

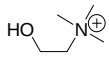


Fig. 7. Structure of choline cation.

Quaternary ammonium cations can also have a cyclic alkyl chain, where nitrogen is a part of the ring system. Pyrrolidine, 1,4-diaza-bicyclo[2.2.2]octane (dabco), morpholine and piperidine are used as cyclic amines for precursors to ionic liquids. (147, 187, 188, 299, 329, 333)

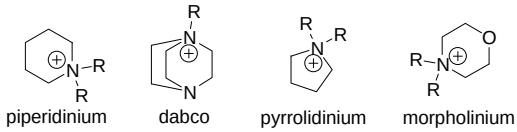


Fig. 8. Structures of heterocyclic cations (R = H or alkyl chain).

Guanidinium is a cation type which is sometimes used in ionic liquids. Tetra-alkyl dimethylguanidines produce low melting ILs (glass transition temperatures below -55 °C). (196)

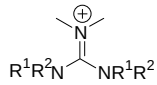


Fig. 9. Guanidinium cation ($R^1 = R^2$ = H or Alkyl chain).

Cyclic guanidines have also been used as cations, but usually their melting points are higher than in acyclic guanidiniums. (89)

3.6 Quaternary phosphonium cations

Quaternary phosphonium cations have been used in phase transfer catalysts just as their ammonium analogs.

The charge density on quaternary phosphonium cations is lower than in ammonium analogs, because phosphorous is bigger. The higher atomic mass of phosphorous compared to nitrogen increases melting points of ILs made from phosphonium cations (see Table 3 entries 2 and 5 compared to Table 4 entries 1 and 2).

The viscosities of quaternary phosphonium salts tend to be high, because long alkyl chains are needed to lower the melting point. Long alkyl chains wrap around

each other with Van der Waal's forces and shear force is needed to break the internal structure.

Table 4. Physical properties of some quaternary phosphonium-based salts.

Entry	Cation	Anion	Melting point (°C)	Viscosity 20 °C (cP)
Symmetrical cations				
1	$P_{2,2,2,2}$	[Br]	>300 (60)	
2	$P_{8,8,8,8}$	[Br]	45 (30)	
3	$P_{4,4,4,4}$	Cl	67 (30)	
Unsymmetrical				
6	$P_{4,4,4,14}$	[Cl]	60 (30)	
7	$P_{8,8,8,14}$	[Cl]	liquid (60)	
8	$P_{6,6,6,14}$	[Cl]	-56 (60) T_g	2469 (30)
Big anions				
12	$P_{4,4,4,4}$	[NTf_2]	65 (60) T_g	
13	$P_{6,6,6,14}$	[NTf_2]	-76 (60) T_g	450 (60)
14	$P_{6,6,6,14}$	[BF_4]	26 (30)	784 (25 °C) (127)

$P_{2,2,2,2}$ = tetraehtylphosphonium cation, suffix numbers presents the number of carbons in alkyl chain attached to the phosphorous

A base resistant ionic liquid based on a phosphazenium cation have been used in rare cases. Such ILs have a half-life of 477 h in 50 % NaOH/chlorobenzene solution. The structure of the phosphazenium cation is based on phosphorous and nitrogen, which are decorated with alkyl chains (see Fig. 10). (259) Unfortunately these types of salts tend to have high melting points (because of high molecular weight), but this problem could be overcome by a suitable anion.

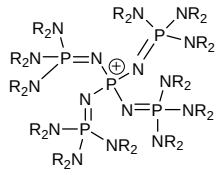


Fig. 10. Structure of phosphazenium cation.

3.7 Tertiary sulfonium cations

Tertiary sulfonium cations have been mostly a curiosity, since they are not stable toward heat or acids or bases, but in some cases they might have the properties needed for certain applications (high conductivity (198) for example).

3.8 General preparation methods for ionic liquids

The universal method of preparing ionic liquids is the alkylation of a suitable heteroatom containing organic molecule to form the cation. After the alkylation the anion is changed to one desired. The chemistry has been quite simple, which makes it economic, but usually long reaction times are needed to complete the alkylation step. If anion needs to be changed an equimolar amount of salt is produced as a by-product. As a conclusion the preparation of ionic liquids is time-consuming and thus expensive.

Alkyl halides are most common alkylating agents used, because they are readily available in all size and shapes and they are inexpensive. If halide-free ionic liquids are needed it is possible to use other alkylating agents. The alkylating agents used includes alkyl sulfonates (306), alkyl triflates (306), alkyl phosphates (102) and alkyl sulfates (293). Alkyl sulfonates and triflates are such good leaving groups that quaternarization reactions can be carried out at ambient temperatures. When sulfonates or triflates are used water must be excluded from the reaction to prevent hydrolysis.

Michael addition has also been used as a quaternarization reaction. In the first step amine or phosphine is mixed with acid which forms the anion and in the second step the permanent cation is formed. The alkylating agent is an α,β-unsaturated carbonyl compound. (304)

3.8.1 Protic ionic liquids

Protic ionic liquids are the easiest to prepare, just mix an acid and a base carefully together and an ionic liquid forms. Amines have been the most common bases which are used in protic ILs. (6, 26) *N*,*N*-dimethylformamide derivatives have been used, with the advantage being that they are produced already on a multiton scale, so scaling up is not a problem. (120) When amides are used as precursors in protonated ionic liquids it must be remembered that protonated amides usually have high pK_a. High pK_a of protonated amides limits the acid which can be used to strong acids which actually can protonate amides. If the difference in pK_a values is not sufficient, the ionic liquid will not form. A wide variety of heterocyclic amines can also be utilized as a base. (115)

3.8.2 Aromatic heterocyclic cations

The first aromatic heterocyclic cation used in an ionic liquid was ethylpyridinium with aluminum chloride anion. (123) Alkylpyridinium chlorides are made by the alkylation of pyridine (Fig. 11) and then aluminum trichloride is added until the desired mole fraction is gained.

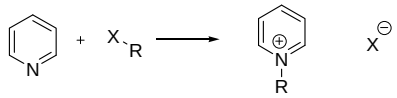


Fig. 11. Formation of alkylpyridinium salt by alkylation (R = alkyl chain and X = halide).

Imidazolium cations can be manufactured in the same way as the pyridinium cations, when 1-alkylimidazole is used as a starting material. A wide variety of alkyl halides can be utilized as alkylating agents.

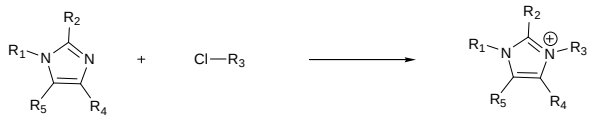


Fig. 12. Formation of 1,3-dialkylimidazolium salt by alkylation ($R_1 = R_3$ = alkyl chain, $R_2 = R_4 = R_5$ = H or alkyl chain, X = halide).

Table 5 lists various possibilities for manufacturing different imidazolium or pyridinium salts from alkyl halides. Table 5 shows that a many different heterocyclic aromatic cations have been manufactured. They have been utilized in various different applications and most of them are actually functional ionic liquids.

An interesting application of aromatic heterocyclic cations is the Wang-resin-type structure which was anchored to the imidazolium cation (Table 5, entry 5). The best parts of two worlds have been combined in a solid support in liquid phase. The solid support allows for easy removal of reagents and products and the liquid phase gave good mass transport properties. (11) The same idea was behind PEG-type cations (80) (Table 5, entry 7), which have been modified further with isothiocyanate derivatives. (108)

There are also representatives from the high class of organic synthesis, chiral cations (Table 5, entry 16 and 18). Chiral IL have been used as a chiral reaction medium and the desired chirality could be induced to the product. (185, 236)

Chiral crown-ether type structures have also been introduced to cations for molecular recognition studies (Table 5, entry 6). (126)

ILs have been used as a replacement of toxic and harmful high density fluids. The density and viscosity of ILs was generally better than the fluids used today and as a bonus they are practically non-volatile. (325)

Imidazolium cations have been prepared from fructose. After synthesis the end product has a hydroxyethyl tail on the imidazolium ring (see Fig. 13). This was a new way of producing imidazolium cations from a biorenewable source. (111) The ethanol group also makes possible the anchoring of IL onto surfaces with suitable spacers which was used as homogenous support materials. (110)

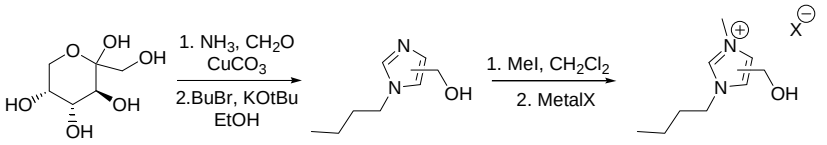
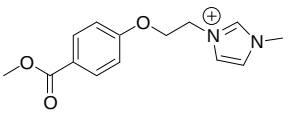
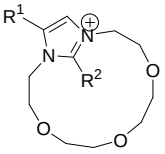
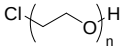
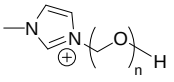
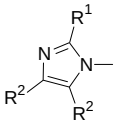
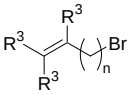
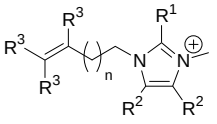
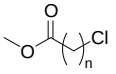
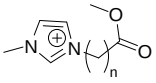
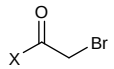
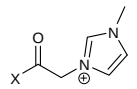
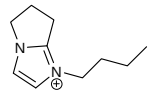
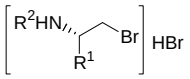
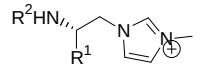
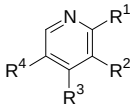
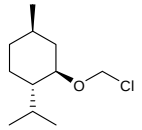
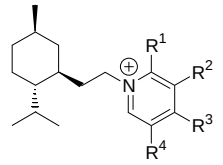


Fig. 13. Preparation of imidazolium based ionic liquid from fructose (X = I, OTs, OTf, $[NTf_2]$, $N(CN)_2$, OAc, CO_2CF_3). (111)

The biodegradability of ionic liquids is one of the key questions if ILs are to be called “green solvents”. It is known that dialkyl imidazoles are poorly biodegradable. (93) Fortunately there are studies going on focusing on readily biodegradable ILs. Some of the structural features which make cations biodegradable have been discovered. It has been noted that functionalization of the side chains attached to imidazolium ring enhance biodegradability (Table 5, entry 13).

Table 5. Alkyl halides used in cation formation on imidazolium cation.

Entry	Amine	Alkyl halide	Cation	Yield (%)
1	1-Methylimidazole	Alkyl Halide	1,3-Dialkylimidazolium	85-100 (312)
2	1-Methylimidazole	2,2,2-Trifluoroethyl iodide	1-Dethyl-3-(2,2,2-trifluoroethyl)imidazolium	20 (267)
3	1-Methylimidazole	1,1,1-Trifluoro-3-iodopropane	1-Dethyl-3-(3,3,3-trifluoropropyl)imidazolium	90 (267)
4	Sodium imidazolate	1,1,1-Trifluoro-3-halidepropane	1,3-Di(3,3,3-trifluoropropyl)imidazolium	80 (267, 268)
5	Sodium imidazolate	Methyl 4-(2-chloroethoxy)benzoate and MeI		80 (11)
6	2,4-Dialkyl sodium imidazolate	1,13-Dichloro-4,7,10-trioxatridecane		81 (126)
7	1-Methylimidazole			80 (80)
		n=1,2 or 3	n = 1,2 or 3	
8				70-90 (325)
	$R_1 = R_2$= H, [Br] or I	R = H, [Br] or F n = 1 or 2		
9	1-Methylimidazole	Allyl bromide	1-Allyl-3-methylimidazolium	92 (331)
10	1-Methylimidazole	Chloroethanol	1-(Ethanol)-3-methylimidazolium	82 (33)
11	Imidazole	Chloromethyl alkyl ethers alkyl chain lengths from 2 to 12	1,3-Di(alkylmethylether)imidazolium	<80 (237)
12	1-Methylimidazole			97+ (75)
		n = 1 or 3		

Entry	Amine	Alkyl halide	Cation	Yield (%)
13	1-Methylimidazole	 X = Alcohol (1 to 8 carbon chain)or amine		92+ (93)
14	1-Butylimidazole	1-Chloro-4-iodopropane		40 (46)
15	1-Methylimidazole	1-(Bromomethyl)-4-(dodecacyloxy)benzene	1-methyl-3-((1-methyl-4-dodecyloxy)benzene)-imidazole	88 (66)
16	1-methylimidazole	 R_1 = Me, *i*-Pr, *i*-Bu or 2-Bu		<92 (185)
17	Pyridine	Alkyl chloride	Alkyl pyridinium chloride	46 to 83 (217)
18	 R^1= H or Me R^2 = H, Me, OH, $CONH_2$ or $N(Me)_2$ R^3 = H, Me, Et, *Tert*-Bu, $N(CH_3)_2$ R^4 = H or OH			98 (236)
19	Imidazole	Alkyl alcohol	Alkylimidazolium	18-94 (145)

There are a couple of drawbacks associated with imidazolium cations. The first and probably the most fatal is sensitivity toward basic reaction conditions. The carbon between nitrogen on imidazolium has an acidic proton attached and in basic conditions imidazolium deprotonates and the cation is changed or decomposed. (7, 9) The alkyl chain attached to the carbon between the nitrogens has been used to improve its stability toward basic reaction conditions. Another problem with imidazoliums is their poor biodegradability, which can be sometimes improved with a suitable functional group on the side chain.

Other aromatic heterocyclic cations than imidazolium and pyridinium have been used. Usually these cations have been just a curiosity compared to imidazoliums, probably due to the discovery order and ease of preparation of imidazolium cations. As mentioned before (Chapter 3.4) other aromatic heterocyclic cations used include pyrazinium (90), pyridazinium (269), tetrazolium (321), triazolium (205, 206, 322) (usually with fluorous alkyltail) and benzotriazolium (77). All these cations have been prepared by alkylation with alkyl halide (usually iodide, sometimes bromide).

3.8.3 Quaternary ammonium cations

Acyclic cations have been used as phase transfer catalysts for a long time and there is quite much of knowledge about the manufacture cations (or more precisely manufacturing quaternary ammonium salts) and their environmental effects. When quaternary ammonium cations are used as ionic liquid usually long chain salts are needed to obtain the desired melting points. Long chain salts form glasses and they usually are highly viscous which might be one of the reasons why they are not so widely used in ionic liquid applications. Another problem is that the degradation temperatures are low compared to imidazolium derivatives.

The preparation of quaternary ammonium salts uses the same methodology which has been used with aromatic heterocyclic cations (or perhaps it is other way around). Acyclic and alicyclic quaternary ammonium cations are manufactured by the same procedures.

There is one special way of preparing acyclic quaternary ammonium IL which cannot be used for aromatic heterocyclic cations. Trialkylamide and aromatic alkyl halide was used as a starting material (see Fig. 14). (36, 37, 38, 252) The overall yields of the reaction were low (from 24 to 62 %), but compared to the alkyl halide ammonium route it was easier to control the substituents and purification of the end product have been easier.

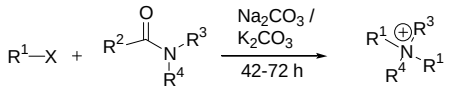


Fig. 14. Reaction of trialkyl amide and alkyl halide and alkaline carbonate to produce quaternary amines (R^1 = alkyl or substituted alkyl, R^2 = H or alkyl, R^3 = R^4 = alkyl)

A special case of acyclic ammonium cation is guanidinium, which is one of the strongest organic bases because of its resonance stabilized form of cation. Since

guanidinium is a strong base it makes good cations for ionic liquids (charge density is quite low, because of stabilization). Cations have been made with a straight alkylation with alkyl halides.

3.8.4 Quaternary phosphonium cations

A quaternary phosphonium cation has been made by similar methods to ammonium cations, but since phosphines are more nucleophilic than amines, reaction times are usually shorter. Phosphonium salts have not been widely used in ionic liquid applications and this gives the advantage that there is room for immaterial claims. (30)

3.8.5 Chiral ionic liquids

Chiral ionic liquids present the most complex application area of ionic liquids. Chirality in solvent is hard to achieve with simple molecular solvents, but chirality is an issue with complex liquids. There are two review articles which discuss chirality in the cations and the anions in the ionic liquid. (21, 64) In addition one review article discusses chiral reactions in ILs. (20) It is speculated that a high molecular order might have a beneficial effect on asymmetric induction in ILs compared to the traditional solvent systems. There was no real evidence to support that chirality in solvent would induce asymmetry in reactions. (20)

If an ionic liquid has a free hydroxy group it is possible to lock the reactant in certain conformation around the IL. The free hydroxy would act as a chiral catalyst which is built into the solvent. (289)

The first reported chiral ionic liquid used lactate as anion. This still remains one of the few examples where chirality is induced in an anion. (70)

Amino acids have been used as chiral anions in ionic liquids. (82, 83) Dialkyl imidazoliums have been used as cations, mainly in 1-ethyl-3-methyl imidazolium. All these dialkyl imidazolium amino acids have glass transition temperatures lower than 6 °C. If phosphonium cations were used instead of dialkyl imidazoliums better thermal stability (typically over 250 °C) and lower viscosity could be achieved. (134) (*S*)-10-Camphorsulfonate and (*R*)-1,1´-binaphthylphosphate have also been used as chiral anions, but the thermal properties were weaker than amino acid derivatives. (189) All of these ionic

liquids have been prepared by the anion exchange of hydroxyl anion to appropriate alkali salt of chiral anion.

There is a wide selection of chiral ionic liquids which use chiral cations. Imidazolium derivatives have been the most widely used (see Table 6). Usually a chiral center is introduced close to the quaternary nitrogen. Chiral imidazolium derivatives have been used as a reaction medium in Diels-Alder reactions (Table 6, entry 9), Michael-addition (Table 6, entry 11), but no significant improvement in enantioselectivity was found.

Chirality has been introduced to the ring structure, with dihydroimidazoles cations, (Table 6, entry 2). These types of cations were used in chiral resolution and NMR studies. (51)

Thiazolium (178) and oxazolium (191, 303) cations have been used as chiral cations. Chirality was easily generated from their synthetic precursor amino acids. Thiazolium and oxazolium derivative ring systems were chiral (see Fig. 15). The anions which were used were the usual [PF_6], [BF_4] or [NTf_2]. Thiazolium cations could withstand basic reaction conditions better than imidazolium derivatives, but degradation temperatures were low compared to imidazolium.

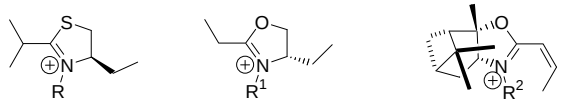
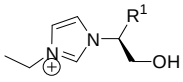
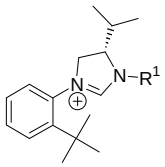
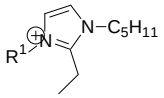
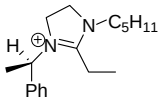
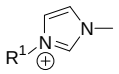
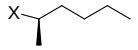
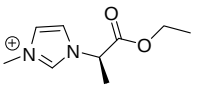
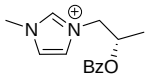
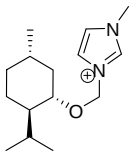
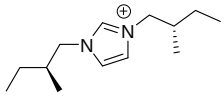
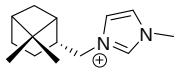
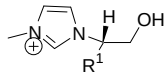
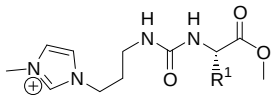
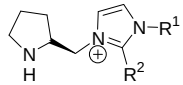
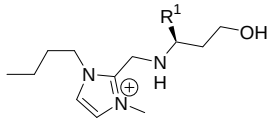


Fig. 15. Thiazolium and oxazolium cation (R = n-Bu or n-dodecane, R^1 = Pentyl or methyl, R^2 = Propyl).

Table 6. Structures of chiral imidazolium cations and specific rotation (if given).

Entry	Cation	R^1	Anions ($[\alpha]_D^{20}$)	Ref.
1		Methyl	[Br] (+3.7°)[a]	(18)
		Isopropyl	[Br] (-10°)[a]	
		2-Methylpropyl	[Br]	
		Benzyl	$[BF_4]$ (+9.2°)[a]	
2		CD_3	$[PF_6]$	(51)
		C_8H_{17}	$[PF_6]$	
		$(CH_2)_8OH$	$[NTf_2]$	
		$(CH_2)_3OH$	$[PF_6]$	
		$(CH_2)_8OH$	$[PF_6]$	
3			[Br] (+17°)	(96)
			$[NTf_2]$ (+17°)	
			[Br] (-25°)	
			$[BF_4]$ (-25°)	
4			[Br] (-16°)	
			$[BF_4]$ (-10°)	
			$[NTf_2]$ (-7°)	
5			[I]	(145)
			[I]	
6			[Otf]	(132)
			$[PF_6]$	
			$[NTf_2]$	
			$[N(SO_2C_2F_5)_2]$	
			$[N(SO_2C_4F_9)Tf]$	
7			$[PF_6]$ (+30.5°)	(300)
			$[BF_4]$ (+19.9°)	
8			$[NTf_2]$ (+54.6°)	(65)

Both (+) and (-) isomer

Entry	Cation	R^1	Anions ($[\alpha]_D^{20}$)			Ref.
9			[Br] (+19°)			(119)
10			OTs			(189)
11		Methyl	[Cl] (+4.1)	$[BF_4]$ (+3.4)	$[PF_6]$ (+6.0)	(231)
		Isopropyl	[Cl] (+3.5°)	$[BF_4]$ (+4.4°)	$[PF_6]$ (+4.2°)	
		$CH_2CH(CH_3)_2$	[Cl] (+5.5°)	$[BF_4]$ (+7.9°)	$[PF_6]$ (+5.3°)	
12		Isopropyl	$[BF_4]$ (-8.2°)	$[PF_6]$ (-8.3°)	$[NTf_2]$(-6.7°)	(224)
		$CH_3C(CH_3)_2$	$[BF_4]$ (-13.3°	$[PF_6]$ (-10.2°)	$[NTf_2]$(-10.8°)	
		$PhCH_2$	$[BF_4]$ (-1.3°)	$[PF_6]$ (+3.2°)	$[NTf_2]$(+0.8°)	
13		Butyl	[Br]	$[BF_4]$	$[PF_6]$	(186)
		CH_2CH_2OH		[Br]		
		CH_2CH_2OH		[Br] ($R_2 = CH_3$)		
14		Propyl	$[BF_4]$ (-2.4°)	$[PF_6]$ (-2.4°)	$[NTf_2]$ (-1.5°)	(225)
		$CH_3CH(CH_2)_2$	$[BF_4]$ (-7.5°)	$[PF_6]$ (-6.0°)	$[NTf_2]$ (-5.0°)	
		$CH_3CH(CH_2)_2$	$[BF_4]$(+6.2°)	$[PF_6]$ (+6.2°)	$[NTf_2]$ (+5.2°)	
		Butyl	$[BF_4]$ (-7.8°)	$[PF_6]$ (-6.9°)	$[NTf_2]$ (-5.5°)	
		$PhCH_2$	$[BF_4]$ (-18.2°)	$[PF_6]$ (-29.40°)	$[NTf_2]$ (-15.9°)	

Some chiral pyridinium cations have also been used as a cation in chiral ILs. Asymmetry in pyridinium salts has been in the alkyl-chain attached to nitrogen (Menthyl group Fig. 16). (236) Chiral pyridinium derivatives could be constructed so that pyridium is part of the bigger ring system (see Fig. 16).

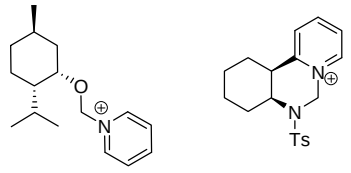


Fig. 16. Pyridinium cations, with chirality induced on *N*-substituent and pyridinium cation as a part of fused ring system.

Probably the easiest choice for making chiral ionic liquids is to protonate amino acid's amino group. Strong acids must be used in order to fully protonate the amino group. At least proline, alanine and phenylalanine have been used, with a wide variety of different acids. (286, 287)

Methyl ephedrine has been quite popular chiral cation. Its preparation has been investigated in the search of a specific microwave effect. (289) When methyl ephedrine was used as a solvent in a Baylis-Hillman reaction, chirality has actually transferred to the reactants. The reason for asymmetric induction of methyl ephedrine, was due to the hydroxyl group, which could bind reagents into the desired configuration (see Fig. 17). (233)

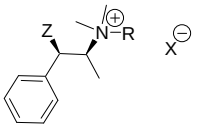


Fig. 17. Structure of Methyl ephedrine (Z = OH or OAc, R = alkyl group, X = OTf or [PF_6])

The menthyl group has been used to induce chirality in quaternary ammonium salts. Different alkyl chain lengths on *N*-alkyl group have been used to tune the melting point of the salt. Much effort was used to characterize their physical properties. (235)

3.9 Preparation of ionic liquid with microwaves

Surprisingly few articles have been published on the microwave heating in the manufacturing of ionic liquids. Usually, a quaternarization step in the cation production takes from several hours to days to complete with the conventional heating. Usually, refluxing conditions are needed for the quaternarization step in order to achieve reasonable reaction rates.

The first article where microwave heating was used in the ionic liquid production used normal household microwave oven. A quaternarization reaction was carried out in an open reaction vessel. The yields were 81 to 94% in about two minute's reaction time. Pulsed heating was used with 5 to 30 s pulses for temperature control. Temperatures were usually between 70 to 100 °C (measurement was carried out immediately after heating was stopped). The alkylating agent used was 1-bromo- or iodobutane and methylimidazole was the

amine. Typically the same alkylation in “normal” conditions takes about 24 hours (1440 min). (301, 302)

Chloroaluminate ionic liquids have been synthesized with microwave heating, using household microwave oven. Chloroaluminates must be handled in a dry atmosphere because the aluminum trichloride precursor is very hygroscopic. Aluminum trichloride dried as the ionic liquid was formed when the microwave heating was used. This gave a simplified method of preparing chloroaluminate ionic liquids. (215)

The results are usually hard to repeat, when an unmodified household microwave oven is used in heating. Household microwave ovens have scattered microwave fields inside the oven because standing waves are created. Standing waves produce microwave power maxima somewhere inside the oven. The place of the maximum power depends on cavity dimensions and tuning of the cavity. Tuning of the cavity changes every time a microwave absorbing matter is placed inside. A water bath can be used to modify the microwave power in the reaction vessel. Using a water bath gave more repeatable results with unmodified household microwave ovens. (167) Later when advanced microwave systems were used repeatable results could be obtained and a wide selection of cations has been made. (58)

Microwave heating was used to accelerate the ion exchange reaction. [Br], [Cl], and [I] were changed to [BF_4] by using microwave heating. Reaction times were minutes instead of hours. An unmodified household microwave oven was used so temperature measurements were imprecise and might have affected the results. (214)

(-)-*N*-Methylephedrine (Fig. 17) was alkylated with various alkylbromides using microwave heating. Reaction times were usually 10 to 120 min. Using conventional heating takes up to 24 h or more to complete the reaction. The microwave reactor used was a single-mode reactor. This is one of the first examples which use a single-mode microwave reactor in the production of chiral cations. This group has also used microwaves to accelerate the anion exchange. (289)

Dialkyl imidazolium tetrachloroindates have been prepared with household microwave oven. The reaction times used were 30 to 75 s. The reaction time was not sufficient to allow all $InCl_3$ to react. The desired ionic liquid was not formed, instead an indeterminate mixture of [BMIM][Cl] and $InCl_3$ was produced. (148)

3.10 Purity of ionic liquids

Purity of ionic liquids is one of the major issues in ionic liquid chemistry. Impurities in ILs might change their physical properties considerably. Impurities cause variability in the measured physical data (melting point, viscosity, surface tension, etc.). For example the melting point for 1,2-dimethyl-3-propylimidazolium chloride varies from 58-66 °C (312) to 138 °C (220) in the literature.

Impurities might also affect the performance of IL. Different impurities have different effects. Sometimes it is good to have impurities in solvents in order to get desired results. Water is the most common impurity and ion exchange could leave anionic impurities in the ILs.

3.10.1 Water impurities in ionic liquids

All ionic liquids are hygroscopic and ILs take water from the air. The amount of water in IL depends mostly on anion. Strong hydrogen bonding anions tend to absorb more water than non-hydrogen bonding anions ([BMIM][Cl] is water miscible and [BMIM][NTf_2] is water immiscible). Also the hydrophobicity of the cation affects water absorption. Longer alkyl chains in cation usually results in lower water absorption. The rate at which ILs absorb water depends on hydrophobicity, viscosity and humidity. (12) Water is usually absorbed between the anions as a free HOH unit and not in self-associated form. (42)

The hygroscopic property of hydrophilic ILs is easy to understand, but the hygroscopic nature of hydrophobic ILs is often overlooked. For example [BMIM][NTf_2] contains 1.4 mass% (27) of water and [BMIM][PF_6] 1.8 mass% (260) of water when saturated even though both are water immiscible ILs.

3.10.2 Impurities from anion change

Almost all ionic liquid cations have been made by alkylating suitable precursors with an alkylating agent (see Fig. 18). For most ionic liquids it is necessary to change the anion after the cation has been made. Usually it has been hard to complete the anion change and as a result some of the anion from the alkylation step remains as an impurity in the new ionic liquid.

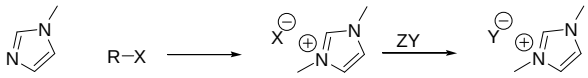


Fig. 18. Preparation of IL cation and following anion change.

Chloride impurities have been found when the alkylation step is carried out with alkyl halides. Chloride impurities are quite hard to detect, especially low amounts, and removing them is hard. Chloride-ions have been detected by a chloride selective electrode, ICP-MS (200), ion chromatography and to some extend by ESI-MS (158). Probably the most sensitive detecting method is ion chromatography. Chloride impurities affect viscosity and density and can destroy the catalyst.

Sodium or silver impurities can also exist when Na or Ag salts are used in anion exchange. There are no published results on cationic impurity effects, but it is good to be aware that cations can remain from exchange reactions as impurities. (260)

Water immiscible ionic liquids can usually be purified from ionic impurites by repeated washing with water. Water miscible ILs are much harder to purify of ionic impurities. Usually precipitation from a suitable organic solvent can be used, but it is not very effective because of the phase transfer catalyst nature of ILs.

3.11 Use of ionic liquids as a catalytic solvent

The main use of ionic liquids is as solvents in chemical reactions. The unique solvent properties and tunability makes them an appealing choice of solvent. Sometimes a catalytic effect has been detected when a molecular solvent is changed to the ionic liquid. Catalysts can be fabricated as part of an ionic liquid (chloroaluminates) or catalytic properties result from cation-anion relation.

Sometimes it is hard to prove if the ionic liquid is responsible for catalysis. Traces of IL decomposing products could act as catalysts, especially when [PF_6] salts are used as solvents. [PF_6] decomposes to HF and [PF_4] when it comes into contact with water and heated. (283)

A classical case of IL catalysis is to use 1-ethyl-3-methylimidazolium tetrachloroaluminate as a solvent in the Friedel-Crafts reaction (see Fig. 19). Two fold excess of aluminum trichloride compared to [EMIM] gave the best conversions. The catalyst had a structure of $[Al_2Cl_7]^-$. The product was isolated

from the IL with water. The ionic liquid was usually decomposed during product isolation due to the moisture sensitivity of aluminum trichloride. (28)

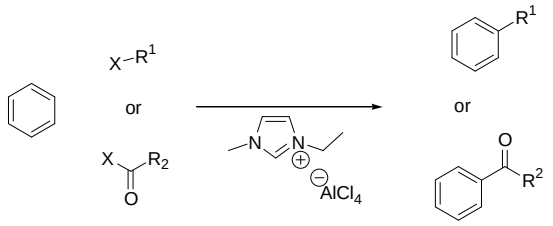


Fig. 19. Friedel-Crafts alkylation and acylation reaction in 1-ethyl-3-methylimidazolium tetrachloroaluminate (R= alkyl chain.)

Triethylammonium nitrate, the first ionic liquid discovered, has been used in the Diels-Alder reaction (see Fig. 20). Enhanced *endo* selectivity and increased reaction rates were observed compared to conventional solvents. Finally, it was concluded that water as a solvent gave better results. Nitrate salts are explosive, so extreme caution must be exercised. (128)

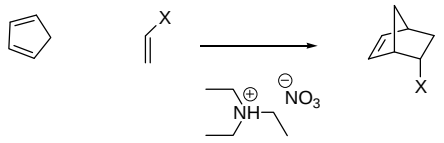


Fig. 20. Diels-Alder reaction in ethylammonium nitrate (X = CO_2Me, or COMe).

Imidazolium salts with bromide or trifluoroacetate anion have been used as Lewis acid catalysts in various Diels-Alder reactions. Electron withdrawing groups attached to the imidazolium ring increased the Lewis acidity. (119) Other cations (ethylpyridinium (316), butylpyridinium (173)) and anions ($[AlCl_4]$ (173), $[BF_4]$ (76), ClO_4 (76), CF_3SO_3 (76), NO_2 (76)) have also been used and good results have been obtained. The Diels-Alder reaction between methylacrylate and cyclopentadiene has been used as a measure of solvent polarity, since polar solvent tends to favor *endo* product. (76)

Phosphonium tosylates have been used as catalytic ionic liquids in the hydroformulation of hex-1-ene (see Fig. 21). Ruthenium catalyzed reaction was compared to the reaction in the neat ionic liquid. It was found that the catalyst had only a negligible effect on the yield. So ionic liquids have a remarkable catalytic effect on hydroformulation reactions. (138)

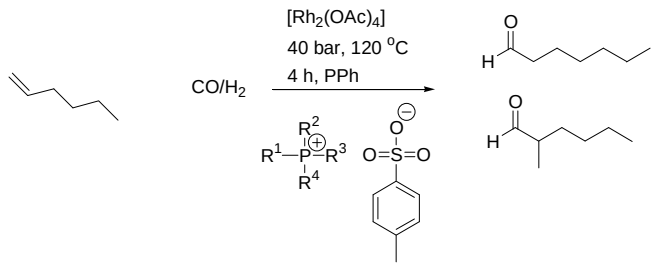


Fig. 21. Hydroformulation of hex-1-ene in phosphonium tosylate ($R^1 = R^2 = R^3 = R^4$ = Ph, Et or Bu).

The high halide concentration of [BMIM] salts has been used to convert alcohols to alkyl halides. Mild conditions and simple Brønsted acid was used. (246) The long side chain in imidazolium helps to dissolve fatty alcohols and diols in imidazolium salts and thus they were converted to alkyl halides (see Fig. 22). (221, 222)

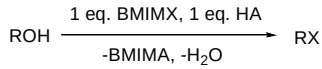


Fig. 22. Conversion of alkyl alcohols into alkyl halides in 1-butyl-3-methylimidazolium salt, assisted by Brønsted acid (HA).

Nucleophilicity of halides is increased in [BMIM] salts. The increased nucleophilicity has been used to cleave ethers. Brønsted acids were used as proton source. (29)

The nucleophilicity of water increases significantly in ionic liquids. Increased nucleophilicity has been used in the hydroxylating of alkyl halides in various [BMIM] salts ($[BF_4]$, [OAc], [OTf], $[PF_6]$, $[SbF_6]$, $[NTf_2]$). The nucleophilicity of alcohols was also increased but not as much as that of water. Ionic liquids was recycled several times without a loss of activity. (142, 309)

It can be seen from previous chapters that alkyl halides could only be made in dry ionic liquids. If water was present in IL it competes with the halides and leads to by-products. Also, the increased nucleophilicity of water might be a problem when nucleophilic reactions are carried out with IL as a solvent.

Acidic [BMIM][HSO_4] and [BMIM][H_2PO_4] have been used in tetrahydropyranation of a wide variety alcohols (see Fig. 23). The acidity was due to the latent acidity of [HSO_4] or [H_2PO_4] anion. (67)

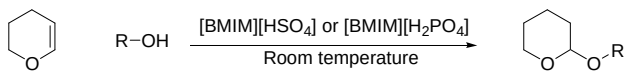


Fig. 23. Tetrahydropyranation of alcohols in acidic ionic liquid (R =Alkyl or aryl).

2,3-Unsaturated glucopyranosides undergo Ferrier rearrangement in [BMIM][Cl]-$FeCl_3$ (see Fig. 24). High anomeric selectivity was observed. The method was applicable to various different alcohols. (290)

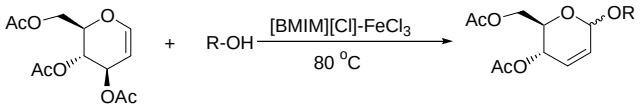


Fig. 24. Ferrier rearrangement catalyzed by [BMIM][Cl]-$FeCl_3$ (R = Alkylchain).

Microwave heating has rarely been used with ionic liquids, possibly since both are relatively new subjects in research (both less than 100 years old). Microwave heating and ionic liquids have been utilized in the attaching of tetrahydropyrano-protecting group onto alcohols. [BMIM][$InCl_4$] was used as a solvent and a variety of different alcohols were tested. Usually reaction times were 5 to 10 min and yields 77 to 88%. (148)

[BMIM][$InCl_4$] has been used as a catalytic reaction medium in reactions between activated olefins with cyclic acyliminium ions (see Fig. 25). The ionic liquid acted as a Lewis acid and the reactions proceeded at room temperature for 24 h to gave 65 to 79% yields of product. (239)

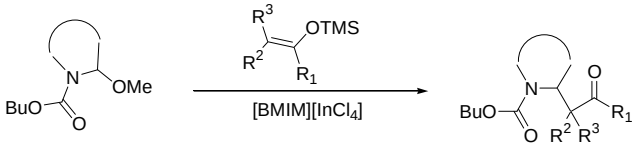


Fig. 25. Reaction of activated olefin with acyliminium ion (R^1 = R^2 = R^3 = H, Methyl, phenyl, or methoxy and ring = 5 or 6 member).

The use of ionic liquid accelerated the reaction rate of the fluorination reaction of mesyl esters with metal fluorides (see Fig. 26). The reaction has been carried out in various [BMIM] salts ([BF_4], [OAc], [OTf], [PF_6], [SbF_6], [NTf_2]). [BMIM][PF_6] gave the best yields, but it might decompose during the reaction releasing HF which might act as an actual fluorination catalyst. (143, 144)

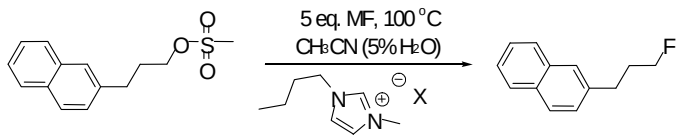


Fig. 26. Fluorination of mesyl ester with metal fluoride (M = Li, Na, K, Rb, Cs, Ca or Ag and X = [BF_4], [OAc], [OTf], [PF_6], [SbF_6], [NTf_2]).

The electrochemical nitration of aromatic compounds benefits from the use of ionic liquid as a reaction medium. NH_4NO_3/TFAA, isoamyl nitrate/$BF_3{\cdot}Et_2O$, isoamyl nitrate/TfOH, $Cu(NO_3)$/TFAA, and $AgNO_3/Tf_2O$ have been used as a nitration system (see Fig. 27). When an ionic liquid was used, it was possible to avoid to use large quantities of strong acids, which had to be neutralized after the reaction. (159) Ferric nitrates have also been used as additional catalysts for the nitration. (241) Cations must be selected wisely in order to nitrate the substrate and not the solvent. If imidazolium derivatives were used as cations, they got nitrated instead of the aromatic substrate. Preferably a quaternary ammonium cation should be used. (163)

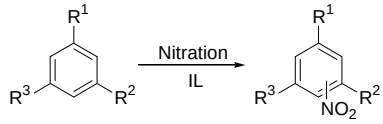


Fig. 27. Nitration of aromatic in ILs (R^1 = R^2 = R^3 = H, Me, OMe, Br, Cl, F, OH, *Tert*-Bu or CF_3).

Ionic liquids have been used as a dehydrator, in the synthesis of *tert*-butyl ethers under mild conditions. The reaction has been carried out without acid catalysts (see Fig. 28). Dialkylimidazoliums were used as cations with [BF_4], [Cl] or [PF_6] anion. Interestingly with [PF_6] or [Cl] anions, the reaction did not proceed at all. The same was true when butylpyridinium [BF_4] was used as the solvent. (263)

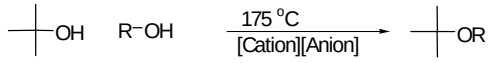


Fig. 28. Synthesis of tert-butylethers (Cation = [EMIM], [BMIM], DMIM, CMIM or [BPy] and Anion = [BF_4], [Cl] or [PF_6]).

1-Methyl-3-pentylimidazolium bromide has been used to catalyze the Michael addition of thiols to conjugated alkenes (see Fig. 29). The reactions were carried

out at room temperature and reaction times were 0.5 to 2 h. This method was versatile and ionic liquids could be recycled without significant loss of activity. (244) Also heterocyclic nucleophiles (318) and azide (195) have been used in this type of addition.

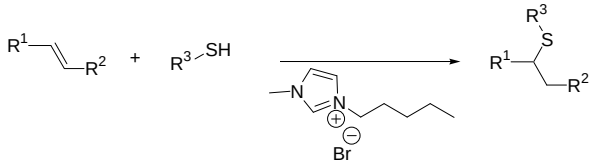


Fig. 29. Michael addition of thiols to conjugated alkenes.

[BMIM][PF_6] has been used in the regioselective ring opening of epoxides with trimethylsilylchloride (see Fig. 30). It was thought that the high Lewis acidity of IL was responsible for the high regioselectivity. No regioselectivity was found when $NaPF_6$ was used in CH_2Cl_2. [BMIM][PF_6] could be recycled without a loss of activity. (320)

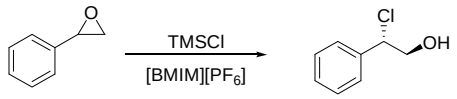


Fig. 30. Regioselective ring opening of 2-phenyloxirane with trimethylsilylchloride in [BMIM][PF_6]

Cyclic guanidinium derivative (see Fig. 31) has been used as a catalytic IL in the selective oxidation of benzyl alcohols to benzaldehyde with NaOCl. The ionic liquid increased the yields compared to phase transfer catalyst conditions. Selectivity toward carbonyl product was increased by over 90 %. The IL was recycled in the reaction several times without a loss of activity. (317)

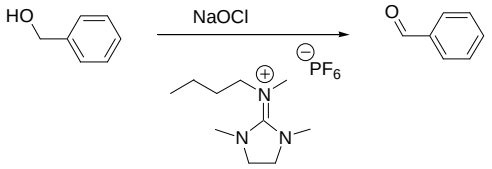


Fig. 31. Oxidation of benzyl alcohol to benzaldehyde in cyclic pentaalkylguanidium hexafluorophosphate.

Preparing dihalides from unsaturated alkenes benefits from the use of ionic liquids (see Fig. 32). Various [BMIM] based ionic liuquids have been studied. [BMIM][NTf_2] usually gave the best rates of conversion. Trihalides were used as a halide source. (47) Also, hydrogen fluoride could be used as halide source. (327)

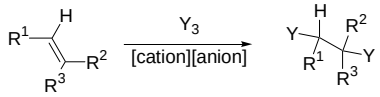


Fig. 32. The preparation of dihalides from alkenes in ionic liquids (Cation = [BMIM], [EMIM], [BDMIM] or [BPy], Anion = [NTf_2] or [PF_6], $R^1 = R^2 = R^3$ =H, Propyl, Phenyl, COOEt, Ethyl or Methyl, Y = ICl_2, Br_3 $F(HF)_{2.3}$).

As can be seen above ionic liquids have some effect on the outcome of the reaction by catalyzing different reactions. Different catalytic properties of an IL can be used in choosing the best IL for particular reaction. This concept has been proven to work and from the same starting materials different products was generated simply by changing the IL (see Fig. 33). (69)

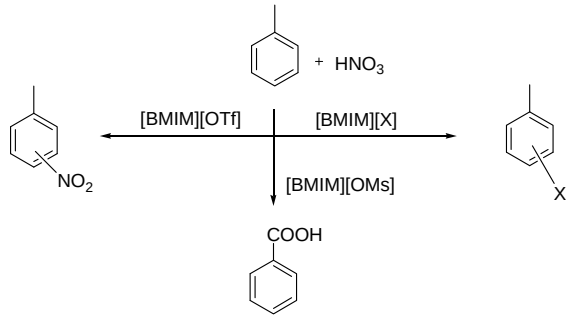


Fig. 33. Illustration of different product just by changing to new IL.

The Fischer indole synthesis has been carried out in choline chloride zinc dichloride melts (see Fig. 34). This has been used as a replacement for the hot phosphoric acid which has traditionally been used. Various different indoles have been synthesized. Only one equivalent of solvent compared to the starting materials was used. The product was isolated by sublimation from the IL. (210)

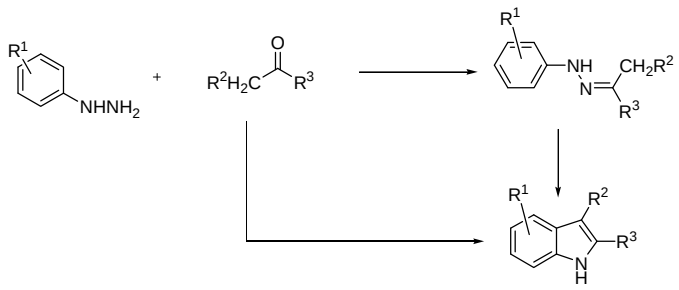


Fig. 34. Fischer indole synthesis in choline zinc dichloride (R^1 = H, Cl or Me, R^2=H or Me, R^3 = Ethyl or Propyl).

Ionic liquids with basic cations could be used in basic solvent/catalysts systems. The problem associated with the basic anions is that they tend to be aggressive toward the cations in IL. Every now and then there have been claims that new ILs with hydroxyl anion have been prepared. Usually the hydroxyl anion is so aggressive that it tears most of the cations apart just by the nucleophilic attack on electrophilic carbon next to positively charged heteroatoms. In the case of imidazolium, basic anions take acidic hydrogen from the imidazolium ring and turn the imidazolium ring into a carbene. Despite all this there are papers which claim that aldol condensation (5), Michael addition (243), Knovenagel condensation (245) and Markovnikov addition (319) have been preformed in hydroxyl ionic liquids.

It has been noted earlier in this chapter that ILs enhance the nucleophilic substitution rate of reaction and selectivity. The same was noted when symmetrical alkyl carbonates were prepared (see Fig. 35). Some problems might be associated with the basic character of the metal carbonates used but they were not observed. [BMIM][PF_6] was used as solvent and K_2CO_3 and Cs_2CO_3 were the best carbonates to be used in alkylation. Cyclic carbonate was manufactured by adding carbon dioxide to glycidyl ethers. (232)

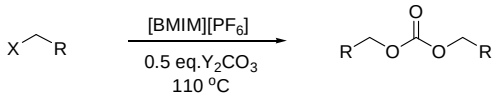


Fig. 35. Preparing of dialkyl carbonates from metal carbonate and substituted alkyls (R = Phenylethyl-, Ethoxybenzene, Butyl, methylbenzene, Benzyl-4-phenyl-, Undecane, X= Cl, Br, OMs, pTsO, Y = Ba, Ag, Cs, Ca, Na, NaH.).

A bipyridinium cation has been used in a copper catalyzed cross-coupling reaction between 4-iodo-1-alkylbenzene and perfluoroalkyl or pentafluoro phenyl compounds (see Fig. 36). Increased reactivity was detected and the IL could be recycled. (315)

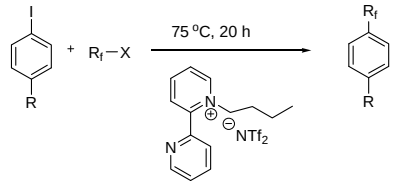


Fig. 36. Copper catalyzed cross coupling of aryl iodines and perluoro alkyls or aryls (R = H, Me or NO_2, X = I or Br, R_f = $CF_3(CF_2)_3$, $CF_3(CF_2)_5$ or C_6F_5).

Potonated guanidine based ionic liquids have been used as a solvent and a ligand in a palladium catalyzed Heck reaction (see Fig. 37). This way the reaction could be carried out without additional base and without additional palladium ligands and IL/palladium is rycyclable. (179)

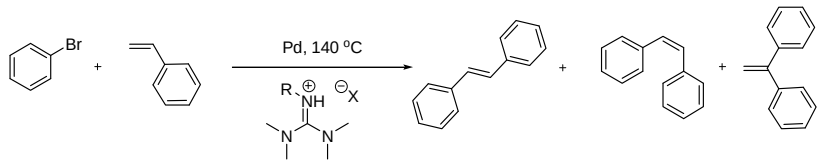


Fig. 37. Palladium catalyzed Heck reaction in guanidinium ionic liquid (R = H or Bu, X = OAc or $[PF_6]$,).

Protonated guanidium ILs have also been used in aldol reactions as a catalytic solvent (see Fig. 38). It was thought that the catalysis proceeded via an enamine intermediate, which attacks the aldehyde compound. Tetramethylguanidinium acetate gave the best results. A wide variety of different aldehydes and carbonyl compounds was studied. (334)

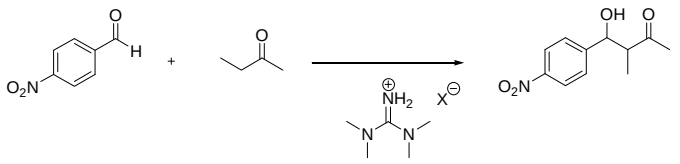


Fig. 38. Aldol condensation of 2-butanone and 4-nitro-phenylaldehyde in guanidinium ionic liquid (X = lactate, acetate, trifluoroacetate, propionate, butyrate or isobutyrate).

Trialkylimidazoliums have been used as a solvent in Grignard reaction (see Fig. 39) because the alkylation of the imidazolium ring gave better stability of imidazolium in basic reaction conditions. The 2-propyl group was used in the imidazolium ring and it provided sufficient protection against the Grignard reactant. Without modification it was virtually impossible to use imidazolium ionic liquids under required conditions. With modification ILs could be recycled (10 times at least). (109)

[BMIM][$FeCl_4$] have been used as a solvent for an aryl Grignard reaction. The recycling of IL was also studied and it was found that the IL could be recycled 4 times. (25)

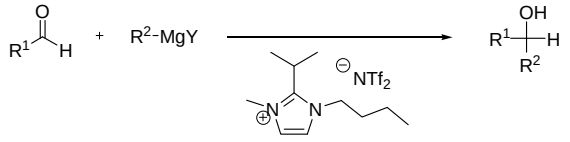


Fig. 39. Grignard reaction in imidazolium ionic liquid (R_1 = 4-metoxyphenyl, benzyl or styrene, R^2 = Methyl, Vinyl or Phenyl).

2-Oxazolines have been efficiently synthesized by using [BMIM][$InCl_x$] ionic liquids as a solvent and a catalyst (see Fig. 40). $InCl_x$ was the best Lewis acid catalyst from Bi, Cu and Zn and [BMIM] was the best cation (pentyl and hexyl). (135)

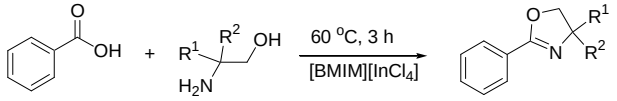


Fig. 40. Preparation of 2-oxazolines in [BMIM][$InCl_4$] R^1 = H, Me or Et, R^2 = H or Me).

Nanoparticles from gold have been synthesized in *N*-methyl-*N*-(2-hydroxyethyl) morpholine [BF_4] (see Fig. 41). The hydroxyl group in hydroxyethyl oxidized when gold reduced from oxidation state 2 to 0. The size and uniformity of the nanoparticles depended on the cation used. (146)

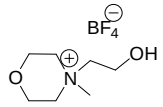


Fig. 41. *N*-methyl-*N*-(2-hydroxyethyl)-morpholine [BF_4].

3.12 Use of ionic liquids as a catalyst anchor

The purpose of this chapter is to give an overview of the applications where ionic liquids have been used as anchors for metal catalysts. It is by no means a comprehensive overview of the transition metal catalyzed reaction in ionic liquids but rather illustrates the versatility of the catalyst applications in ionic liquids.

The solvent properties of ionic liquids have been used to make new solutions to the old chemistry. Ionic liquids have been used to capture metal catalysts in the IL phase. Catalysts could easily be recovered and reused with ionic liquid. It has been crucial in most metal catalyzed applications that precious catalysts can be recovered and reused after each catalytic cycle. In some applications e.g. food industry creeping of the catalysts to the product could spoil the end product. (305, 306)

Selective oxidation of organic compound by atmospheric oxygen is a challenge to the catalyst designer. Especially those catalysts which are anchored and efficient have been hard to manufacture. (262) Dissolving catalysts in the ionic liquid is one possibility to achieve stable, effective and recyclable catalysts.

A chiral Jacobsen's catalyst (see Fig. 42) has been used to oxidize alkenes to epoxides. The catalyst was dissolved in [BMIM][PF_6]. Catalyst activity was improved and recycling could be done by simple extraction of the product.The reaction time was from 2 to 4 hours with yields from 72 to 86%. The achieved enantiomeric excesses were high, varying from 84 to 96%. NaOCl was used as an oxidant. (273) The same catalyst was used in the biomimetic electrochemical oxidation of olefins to epoxides, where molecular oxygen was used as an oxidant. (86)

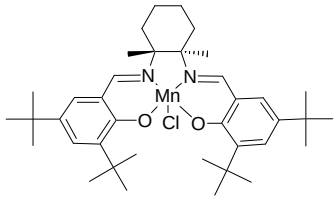


Fig. 42. Structure of the chiral Jacobsen catalyst.

Epoxides have been prepared using peroxides as an oxidant (see Fig. 43). *tert*-Butylhydroperoxide has been employed with molybdenum complexes in preparing epoxides from *cis*-cyclo-octene. Mo-complexes were water sensitive. The IL usually contained water and the catalyst was decomposed during the oxidation reaction. The decomposition of the oxidant and the reaction between epoxide and the ionic liquid led to low overall yields when [BMIM][PF_6] or [BMIM][BF_4] was used as solvent. [BMIM][NTf_2] gave good yields (100% after 4 h) if dried carefully before use. IL and the catalyst coud be recycled. (155)

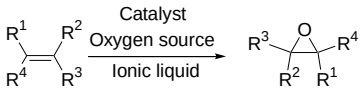


Fig. 43. Oxidation of alkene to epoxide (R^1 = R^2 = R^3 = R^4 = H, alkyl or aryl)

The oxidation of benzene to phenol has low selectivity because phenol is easier to oxidize than benzene. Low selectivity leads to multiple by-products. Fenton reagent (Fe^{2+}-H_2O_2) have been traditionally used as oxidation catalyst. (297) The reaction consumed an equimolar amount of the catalyst and over oxidation was hard to prevent. Metal dodecanesulfate complexes catalyzed the hydrogen peroxide oxidation of benzene to phenol in ionic liquid (see Fig. 44). To avoid over oxidation a two phase catalyst system was used. A water immiscible IL was used to shield the starting material and product. Hydrogen peroxide was present in the water layer and only a small amount was dissolved in IL, where the catalytic oxidation took place. After the oxidation phenol was extracted in the water phase. Selectivity toward phenol was excellent (76 to 91%) with all catalyst systems studied. With the iron catalyst, conversion of benzene was about 50% and the catalyst could be recycled at least 5 times without a loss of reactivity. (234)

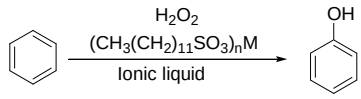


Fig. 44. Oxidation of benzene to phenol with hydrogen peroxide and metal dodecanesulfonate.

Methyltrioxorhenium (MTO) is an efficient catalyst for the oxidation of hydrocarbons (see Fig. 45), but it has one drawback. MTO has high solubility in molecular solvents. High solubility in turn made product recovery from ionic liquid challenging. Product extraction usually led to contamination of the product due to the high solubility of MTO. In order to use MTO catalysts efficiently polymer bound MTO complexes have been used with ionic liquids. Attaching the catalyst to polymer reduces its solubility in molecular solvents and thus makes the product recovery from IL easy. Polymers based on polyvinyl pyridine with different cross-linking have been used to immobilize MTO complexes into the ionic liquid. Triphenylmethane and benzhydrol were oxidized to benzophenone and 1-phenylethanol was oxidized to phenylethanone. Triphenylmethane conversions were usually around 50% and yields around 90% with a 48 h reaction time at 45 °C. Benzhydrol and 1-phenylethanol conversions were around 90% and yields around 85% after 24 h. Hydrogen peroxide was used as an oxidant. Usually, yields were slightly lower when polymer bound catalysts were used. The polymer bound catalyst and the IL was recycled without catalyst leaching. Usually [BMIM][PF_6] gave better results than [BMIM][NTf_2]. (24)

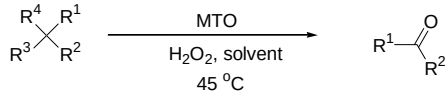


Fig. 45. Methyltrioxorhenium (MTO) catalyzed oxidation (R^1 = R^2 = R^3 = R^4 = Phenyl, OH, H or alkyl chain.)

The Diels-Alder reaction gives high yields in ionic liquids (see chapter 3.11 Use of ionic liquids as a catalytic solvent). Yields could be further improved with suitable catalysts. An additional benefit of using ionic liquid is that the catalyst recovery and reuse is usually simple. $Sc(OTf)_3$ has been used as a catalyst in the Diels-Alder reaction of 1,4-naphtoquinone with 2,3-dimethyl-1,3-diene (Fig. 46). The reaction was carried out at 20 °C for 2 hours. Yields were 99 %, with $Sc(OTf)_3$ as a catalyst and [BMIM][PF_6] as a solvent. Quantitative yields were

obtained with [BMIM][SbF_6] and [BMIM][OTf] as a solvent. Also a variety of diene and dienophiles reacted in good yields with [BMIM][PF_6] as a solvent and $Sc(OTf)_3$ as catalyst. The ILs and the catalyst could be used at least 11 times without a loss of effect. (274)

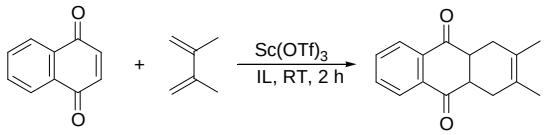


Fig. 46. Scandium triflate catalyzed Diels-Alder reaction.

Chiral catalysts have been used in enantioselctive Diels-Alder reactions. A chiral cationic palladium-phophinooxazoline-catalyst was used in the Diels-Alder reaction between cyclopentadiene and acryloyl-1,3-oxazolidin-2-one (see Fig. 47). Various [BMIM] based ILs were studied as solvents and catalyst anchors. [BMIM][BF_4] was the optimal solvent, with best reactivity and enantioselectivity. Yields were around 90% and the *endo* to *exo* ratio of product was usually 96 to 4. The enantiomeric excess (ee) of the *endo* product was typically over 90%. The ee values decreased with recycling of the catalyst. (285)

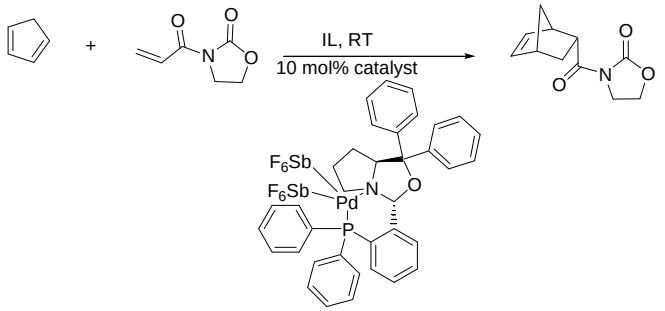


Fig. 47. Diels-Alder reaction catalyzed by palladium-phosphinooxazoline-catalyst.

Sometimes imidazolium cations get involved in reactions by releasing the acidic hydrogen. This leads to imidazolium carbenes. The carbene formation phenomenon was detected when new palladium phosphine complexes were made in imidazolium ILs. The palladium formed mixed ligand complexes where one phosphine ligand was replaced by imidazolium ligand. Such complexes were tightly bound in the IL phase and thus could be effectively recycled. Carbene

formation might be significant especially if basic reaction conditions are used (e.g. in Suzuki coupling). (197)

Ionic liquids have been attached to a solid support so that solid particles were covered with a liquid IL layer. The catalyst could be dissolved and anchored to the ionic liquid layer. A solid supported homogenous catalytic layer resulted. The solid supported ionic liquids catalyst layer combined the ease of purification of a heterogeneous catalyst with the fast mass transfer of a homogenous catalyst. This approach has been used in the hydroformulation of 1-hexene with a rhodium catalyst (see Fig. 48). The rhodium catalyst was prepared by dissolving the ligand (tri(*m*-sulfonyl)triphenylphosphine trisodium salt or (tri(*m*-sulfonyl)triphenylphosphine tris(1-butyl-3-methylimidazole) and rhodium to the ionic liquid phase. The catalyst in [BMIM][PF_6] was not as efficient (yield 70% in 3 h) as the homogenous catalysis in toluene (yield 90% in 2 h), but the recovery of the product was easy, since the product was insoluble in the ionic liquid. (201)

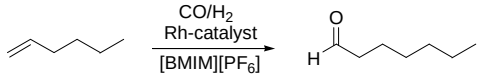


Fig. 48. Hydroformulation of 1-hexene to heptanal with rhodium catalyst.

The palladium catalyzed Heck-reaction of aryl iodides and bromides proceeded in good regioselectivity when [BMIM][BF_4] was used as a solvent. Usually aryl triflates were needed in order for the reaction rates to be reasonable. The Heck-reaction proceeded smoothly when IL was used as a solvent (see Fig. 49). Yields were 80 to 95% with a 24 h reaction time. A wide variety of different substrates were tested. (207) Modified pyrazoyl-ligands have been studied without using additional phosphine. Conversions were 100% when pyrazoyl ligands were used, but yields were not mentioned. (298)

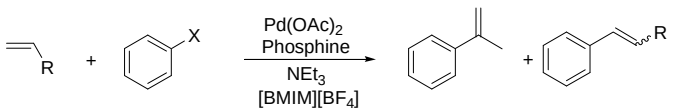


Fig. 49. Palladium catalyzed Heck-reaction (R = electron withdrawing group, X = I or Br).

Catalytic palladium nanoparticles have been prepared in tetrabutylammonium bromide ([TBA][Br]). The nanoparticles formed spontaneously just by adding

$Pd(OAc)_2$ or palladium di(3-Methyl-2,3-dihydro-benzothiazole) iodine to the IL.The nanoparticles were used as a catalyst in the Heck-type reaction where β-aryl cinnamic esters were synthesized. A wide variety of different substrates was used and yields were generally high from 82 to 95 %. The melting point of [TBA][Br] is about 100 °C which caused the reaction temperature to be 130 °C. (41)

Friedel-Crafts chemistry has been traditionally “catalyzed” by equimolar amounts of Lewis acids. (228) Most Lewis acids used are water sensitive and they have usually been destroyed during reaction workup. Recently, ionic liquids have been utilized successfully in the Friedel-Crafts chemistry. Ionic liquids boost the catalytic effect of transition metal Lewis acids. Bismuth derivatives have been used to catalyze Friedel-Crafts acylation in $[EMIM][NTf_2]$ ionic liquid. Other ILs were also tested, but all except $[BMIM][NTf_2]$ gave low yields of product. Most of the tested substrates gave 100% conversion in 2.5 hours when the reaction was carried out at 150 °C. Yields varied from 75 to 91%. A catalyst loading of 1% was used. The catalyst could be recycled at least three times without loss of efficiency. (99) Enantioselectivity could be achieved if a titanium or copper complex is used with binol ligands. They have been used in reactions between aromatic amines and ethylglyoxylates in pyridinium based ILs. (192)

Catalytic asymmetric hydrogenation has been widely studied in ionic liquids. Especially, attention has been on the catalyst anchoring in homogenous environments. At first the catalyst was simply dissolved in IL and it was found that leaching of the catalyst was low. Later, the ligands in the catalyst were modified so that they would bind in the IL phase more strongly. Imidazolium moiety could be added to ligand which reduces the leaching from imidazolium based ionic liquids. Extraction was used in product separation or sometimes the product was insoluble in IL and precipitated. Using IL as a solvent, conversion and enantioselectivity was enhanced compared to molecular solvents. The latest trend in the catalytic asymmetric hydrogenation has been to use nanoparticle catalysis in ionic liquids. (22, 35, 45, 131, 139, 174, 209, 219, 264)

Usually zinc catalyzed reductions need harsh reagents like NH_3, conc. HCl and aq. NaOH, with quite high temperatures. Zinc catalyzed reductions in IL on the other hand could be performed in relatively mild reaction conditions. The reduction of aromatic nitro and azo compounds with zinc and ammonium salt has been studied in ionic liquids (see Fig. 50). When ammonium chloride or ammonium formate was used as a reduction agent, no overoxidation of the aniline

product was seen. Yields were generally around 80 to 90%. Ionic liquids could be recycled at least 3 times without a loss of activity. (141)

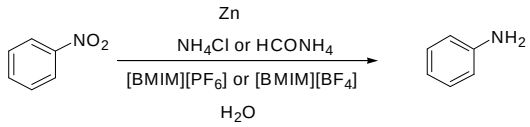


Fig. 50. Reduction of aromatic nitro compounds.

Organometallic reactions in ionic liquids have quite a few applications, probably because of the basic or strongly nucleophilic character of organometallic compounds. However, organozinc reactions have been carried out in butylpyridinium based ionic liquids (see Fig. 51). The formation of the organozinc reactant required that IL contains chloride or bromide impurities. Alkyl zinc reactants were first formed from alkyl halide and metallic zinc. The prepared alkyl zinc reagent was added to the aldehyde to produce the secondary alcohols. Different aldehydes were studied. Yields were around 90% for all alcohols at 50 °C with a 12 h reaction time. (169)

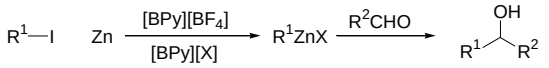


Fig. 51. Formation of Alkyl Zinc reagent and reduction of aldehyde to alcohol (R^1 = R^2 = alkyl chain or aromatic ring).

The Grignard reaction is another organometallic reaction which has been studied in pure [BPy][BF_4]. If impure IL was used the reaction did not proceed at all. Benzaldehyde was coupled with ethylmagnesium iodide. Pyridine was used as an additive to reduce the possible Lewis acid formation from Mg and halide. The optimal range for pyridinine was 1.3:1 (Ethyliodide : pyridine) or 2:1. The reaction time was usually about 12 h and yields varied from 22 to 83%. Other substrates were also studied. It is interesting to note that Grignard reagents change their reactivity in [BPy][BF_4] compared to molecular solvents. (168)

The next application of ionic liquids falls loosely in category of catalyst anchoring, but it is interesting to note the solvent power of ionic liquids. Ionic liquids based on [NTf_2] anion were used to dissolve aluminum trichloride to form highly acidic reaction medium. The formed ionic liquid was different than [cation][$AlCl_x$] liquids. They tend to dissolve much more aluminum trichloride than [cation][$AlCl_x$] ILs. [cation][NTf_2]-$AlCl_3$ was used in carbonylation of

toluene (see Fig. 52). The aluminum trichloride was destroyed by hydrolysis after the carbonylation reaction the IL could be recycled and reused. (34)

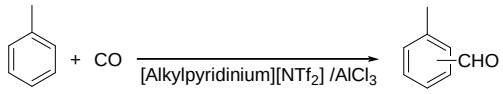


Fig. 52. Carbonylation of toluene in highly acidic [alkylpyridinium][NTf_2]/$AlCl_3$ mixtures.

The carbonylative Sonogashira coupling of aryl iodides, phenylacetylene and CO has been studied using microflow technology with [BMIM][PF_6] (see Fig. 53). The palladium catalyst was dissolved in the ionic liquid. CO pressures of 3 to 5 atm was used. The microflow system allowed efficient mixing of gas and liquid. The yields varied from 72 to 92% with the microflow system, while the batch reactor gave only 14 to 65% yields. (240)

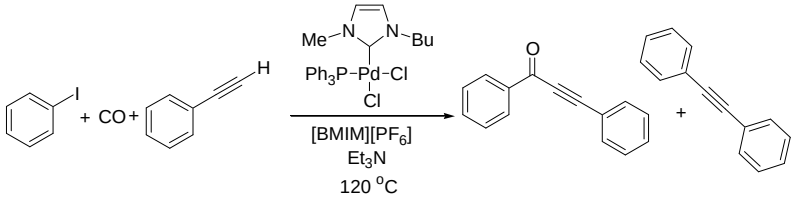


Fig. 53. Palladium catalyzed Sonogashira coupling of aryl iodide, phenylacetylene and CO in microflow system.

The osmium catalyzed asymmetric dihydroxylation of alkenes has been a useful reaction to make enatiomerically pure vicinal diols (see Fig. 54). The high toxicity of osmium and high cost of asymmetric ligand have been a main challenge. A recyclable system is essential for this type of chemistry. Osmium have been efficiently anchored to [dialkylimidazolium][PF_6] salts. Better yields (35 to 92%) and enantiomeric excesses (71 to 97%) were obtained in IL compared to molecular solvents. Leaching of osmium to product was usually 3-6%. The system could be recycled 9 times with a 5% yield of reduction. Even if complex ligand was used on osmium enantiomeric excess was not improved. (31, 32, 272, 324)

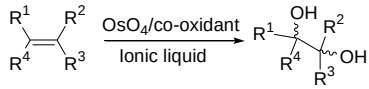


Fig. 54. Osmium catalyzed dihydroxylation of alkenes in ionic liquid ($R^1 = R^2 = R^3 = R^4$ = H, alkyl or aryl).

The synthesis of various 5-methylene-1,3-oxazolin-2-ones has been carried out in IL using Cu(I) salt as catalysts (see Fig. 55). Mild conditions could be used with ILs. The yields in [BMIM][BF_4] was around 90% with a 15 h reaction time. The CO_2 pressure was 2.5 MPa and reaction temperature 100 °C. The ionic liquid and catalyst could be recycled at least 4 times without significant loss of reactivity. (104)

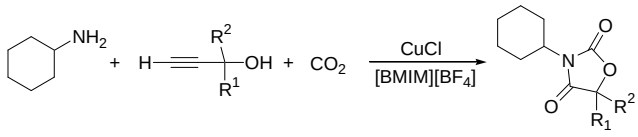


Fig. 55. Synthesis of 5-methylene-1,3-oxazolin-2-one from propargylic alcohols, Amines and CO_2 ($R^1 = R^2$ = alkyl or aryl chain or ring).

Odorless sulphur chemistry is desired by people who work with ill-smelling sulphur compounds. The sulphur compounds were anchored in an ionic liquid backbone. A Swern oxidation catalyst was manufactured (see Fig. 56). The ionic liquid with Swern oxidation catalysts was recyclable and sulfoxide could be regenerated. (113)

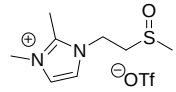


Fig. 56. Recyclable odourless sulphur catalyst for Swern oxidation.

The catalyzed hydrosilylation of olefins is an industrially interesting process (see Fig. 57). Hydrosilylation has been improved by using biphasic conditions with ionic liquids. Usually catalyst recycling has not been used in industrial hydrosilylation processes because only ppm levels of catalyst are needed compared to the end product. The catalyst was easily recycled, when biphasic conditions were used. The catalyst was anchored to the IL phase and the silyl product was precipitated. A variety of pyridinium and imidazolium based ILs

were tested. [3-methyl-1-ethylpyridinium][NTf_2] gave the best conversion with K_2PtCl_4 (around 98%) and $Pt(PPh_3)_4$ catalyst (around 90%) at 90 °C in 3 hours. K_2PtCl_4 and $Pt(PPh_3)_2Cl_2$ catalysts could be recycled 10 times without a significant loss in stability. (95)

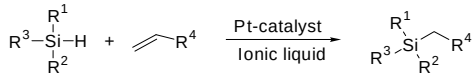


Fig. 57. Catalyzed hydrosilylation of olefin in ionic liquid (R^1= R^2 = R^3 = R^4 = Alkyl, aryl or ether) .

Ionic liquids have been used as a solvent in the metal nanoparticle catalysis. There is a new review article of the subject, so they have been mostly omitted from this study to avoid writing the same articles several times. (203)

4 Selected reactions using ionic liquids and microwave activation

The purpose of this chapter is to give context for the experimental part of this thesis. Up to this point the focus has been more introductory than reaction specific and now the focus is shifted toward to the reactions studied in this thesis.

4.1 Esterifications

The esterification reaction may be the most common chemical reaction in the living world. Since the early stages of microwave chemistry esterification reactions have been one of the most studied reaction. (184) In many cases the reaction rates of esterification have been higher under microwave heating than in traditional conditions. A combination of microwaves and ionic liquids in esterification has been rare even though numerous articles have been published about esterification with microwave heating or with ionic liquids.

4.1.1 Esterifications of simple alcohols

There are books (112, 136, 184) and review articles (136, 164, 165, 180, 227) concerning microwave chemistry which cover the most important literature about esterification reactions up to the year 2001.

There is an article which presents a new idea about performing microwave chemistry. The microwave reactor used was not commercially available, but it has some features which might attract even industrial attention. It was a single mode loop reactor where the reactants were first mixed and then led through a microwave chamber. The loop reactor also had catalyst particles embedded in the microwave chamber. The reactor could be run in a continuous mode. The heating mode (traditional versus microwave) did not affect the results. It is possible to introduce higher temperature gradients between solid catalyst (hotter) and reactant (cooler) with microwaves.The reaction studied with this microwave system was esterification of propionic acid with ethanol. The best conversion of ethanol to ethylpropionate was observed when equimolar amount of starting materials were used. (292)

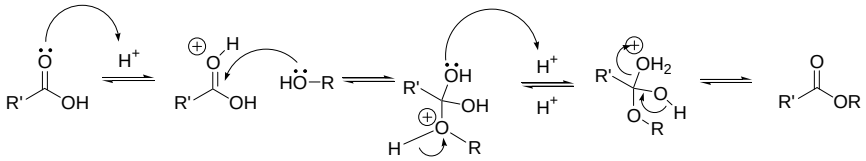


Fig. 58. Reaction mechanism for the esterification reaction.

Esterification reactions (see Fig. 58) have been studied in [BPy][Cl]*$AlCl_3$. The ionic liquid formed was water stable, when the molar ratio of $AlCl_3$ was less than one. In water stable IL alcohols could be used without destroying $AlCl_3$. The molar ratio of 1:2 $AlCl_3$ to [BPy][Cl] was used. The alcohol had to be added to the reaction mixture first followed by carboxylic acid. The reactions were also carried out with a sulfuric acid catalyst as a comparison to the IL. The usual reaction time was 2 h and temperature 80 °C for acetic acid esterification (see Table 7). A minor by-product in IL for benzyl alcohol esterification was benzyl chloride. The by-product in the sulfuric acid catalyzed reaction was phenylmethyl ether. The IL could be recycled at least three times without a significant loss of yield (Table 7, entries 3-5). Glycerol was let to react with acetic acid. The products were different acetins (monoacetins (monoacetin-1 and monoacetin-2), diacetins (diacetins-1,3 and diacetins-1,2) and triacetin) with high conversions of 99 to 100%. Low temperatures seemed to favor mono and diacetin products while higher temperatures seemed to produce all acetins in almost the same selectivity. The products could be simply decanted from the reaction mixture, because they were insoluble in the IL. (61)

Table 7. The effect of reaction conditions on the esterification of acetic or 1,9-nonanedioic acid with alcohols. Reaction time was 2 h.

Entry	Alcohol	Acid	Molar ratio	Temp. (°C)	IL		H_2SO_4	
					Conversion (%)	Selectivity (%)	Coversion (%)	Selectivity (%)
1	*Iso*-Propyl	Acetic	1/1	68	71	98	66	98
2	*Iso*-pentyl	Acetic	1/1	80	87	98	71	97
3	Benzyl	Acetic	1/1	80	79	97	71	94
4[a]	Benzyl	Acetic	1/1	80	65	97	-	-
5[b]	Benzyl	Acetic	1/1	80	67	98	-	-
6	*Iso*-octanol	1,9-Nonanedienoic	2/1	100	80	99	56	98

[a] 1st recycle of IL [b]2nd recycle of IL

A variety of 1,3-dialkylimidazolium salts with acidic anions have been used as catalytic solvents for esterification. Acidic [BMIM][H_2PO_4], [HMIM][HSO_4], 1-methyl-3-(methylsulfonyl)imidazolium [PF_6] ([MMSIM][PF_6]), 1-Methyl-3-(ethylsulfonyl)-imidazolium [PF_6] ([MESIM][PF_6]) and 1-(ethoxyethanol)-3-methylimidazolium[HSO_4] ([MEEIM][HSO_4]) have been used. Besides being a catalytic solvent, IL was immiscible in the produced esters. Separation of the products could be done by decanting. The esterification reactions were ran at 80 °C for an appropriate time (see Table 8). The esterification of *neo*-pentanol and hexanol with acetic acid was tested for comparison with the suphuric acid catalyst. The reaction times were shorter in the sulfuric acid catalyzed reaction, compared to the acidic IL. Usually the reaction time was 1 h in the sulfuric acid catalyzed reaction. The conversion of the acid to ester with pentanol was about 82% and with hexanol 62%. Some of the alcohols reacted to ethers in sulfuric acid. (79)

Table 8. Esterification conditions of various alcohols and acids in acidic anion containing ILs.

Entry	Acid	Alcohol	IL	Ratio Acid /alcohol/IL	Time (h)	Conversion (acid) (%)	Yield (%)[b]
1	Acetic acid	*Neo*-pentanol	[BMIM][HSO_4]	1/1/1	2.5	95	99
2	Acetic acid	*Neo*-pentanol	[BMIM][HSO_4]	1/1/3	0.5	99	99
3	Methoxy acetic acid	*Neo*-pentanol	[BMIM][HSO_4]	1/1/3	14	41	86
4	Methylmalonic acid	*Neo*-pentanol	[BMIM][HSO_4]	1/2/3	18	50[a]	99
5	Acetic acid	Decanol	[BMIM][HSO_4]	1/1/3	16	82	94
6	Acetic acid	*Neo*-pentanol	[BMIM][H_2PO_4]	1/1/1	14	41	89
7	Acetic acid	*Neo*-pentanol	[BMIM][H_2PO_4]	1/1/3	20	43	94
8	Acetic acid	*Neo*-pentanol	[HMIM][HSO_4]	1/1/3	15	77	92
9	Acetic acid	Hexanol	[HMIM][HSO_4]	1/1/3	14	55	83
10	Acetic acid	Heptanol	[HMIM][HSO_4]	1/1/3	14	50	91
11	Acetic acid	Decanol	[HMIM][HSO_4]	1/1/3	14	50	80
12	Acetic acid	*Neo*-pentanol	[MEEIM][HSO_4]	1/1/3	1	90	91
13	Methylmalonic acid	*Neo*-pentanol	[MEEIM][HSO_4]	1/2/3	18	50[a]	99
14	Acetic acid	Heptanol	[MEEIM][HSO_4]	1/1/3	14	47	84
15	Acetic acid	Decanol	[MEEIM][HSO_4]	1/1/3	16	43	84
16	Acetic acid	*Neo*-pentanol	[MMSIM][PF_6]	1/1/1	12	67	94
17	Acetic acid	*Neo*-pentanol	[MMSIM][PF_6]	1/1/3	15	89	98
18	Methoxy acetic acid	*Neo*-pentanol	[MMSIM][PF_6]	1/1/3	16	57	99
19	Methylmalonic acid	*Neo*-pentanol	[MMSIM][PF_6]	1/2/3	16	57[a]	99
20	Acetic acid	Heptanol	[MMSIM][PF_6]	1/1/3	18	65	93
21	Acetic acid	*Neo*-pentanol	[MESIM][PF_6]	1/1/3	14	88	99
22	Methylmalonic acid	*Neo*-pentanol	[MESIM][PF_6]	1/2/3	4	84[a]	99
23	Methoxy acetic acid	*Neo*-pentanol	[MESIM][PF_6]	1/1/3	14	92	99

[a]Conversion to diester, [b]Yield after decantation

Strong acids have been widely used as catalysts in the esterification reaction. Liquid strong acids are volatile notorious liquids. Solid acids have been used as a replacement of liquids acids, but mass transport usually limits the catalysis effect. In trying to create safe and environmentally friendly substituents for liquid acids zwitter ionic liquids have been invented. 1-Methyl-3-(4-butylsulfonyl)imidazolium trifluoromethane sulfonate and *P,P,P*-triphenyl-*P*-

(propylsulfonate)phosphine *p*-toluenesulfonate (see Fig. 59) have been used as catalytic solvents in esterification. They contain Brønsted acid functionality in their ionic liquid core. The esterification reaction between hexanoic acid and octanol gave 82% yield in 48 h at 22 °C. The esterification of acetic acid with ethanol gave 96% yield in 45 min at 175 °C. The product could be decanted when *P,P,P*-triphenyl-*P*-(propylsulfonate)phosphine *p*-toluenesulfonate was used as a solvent. The ionic liquids could be recycled at least 5 times without loss of reactivity. (52)

Fig. 59. Structure of *P,P,P*-Triphenyl-*P*-(propylsulfonyl)phosphine *p*-toluenesulfonate and 1-methyl-3-(4-butylsulfonyl)imidazolium trifluoromethane sulfonate (R = 4-methylphenyl or trifluoromethane)

Other zwitterionic cations have been 1-(4-butylsulfonyl)-3-methylimidazolium [HSO_4], (4-butylsulfonyl)pyridinium [HSO_4] and *N,N,N*-trimethyl(4-butylsulfonyl)ammonium [HSO_4] (see Fig. 60). The catalytic activity of ionic liquids was studied in the esterification of ethanol with acetic acid to ethyl acetate. 1-(4-Butylsulfonyl)-3-methylimidazolium [HSO_4] gave the best results and was chosen for thorough testing with other acids and alcohols (see Table 9). [105]

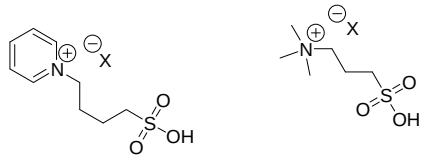


Fig. 60. Structure of [(4-butylsulfonyl)pyridinium] and [*N,N,N*-trimethyl(4-butylsulfonyl)ammonium] cation (X = [HSO_4])

Table 9. Esterification of various acids and alcohols in 1-(4-butylsulfonyl)-3-methylimidazolium [HSO_4] at 80 °C. Molar ratio of acid/alcohol was 1:1.

Entry	Acid	Alcohol	Time (h)	Conversion (%)[a]	Selectivity (%)[a]
1	*n*-Caproic acid	1-Butanol	4	92	100
2	*n*-Caproic acid	*Iso*-Amyl alcohol	4	90	100
3	*n*-Decanoic acid	1-Butanol	4	91	100
4	*n*-Decanoic acid	1-Octanol	4	91	100
5	Benzoic acid	1-Butanol	16	90	100
6	Benzoic acid	Benzyl alcohol	16	83	100
7	Methylmalonic acid	1-Butanol	10	85[b]	100
8	Oxalic acid	1-Butanol	10	87[b]	100

[a] Based on GC [b] No monoesterification was detected by GC, and molar ratio of alcohol/acid was 2/1.

Simple protonated 1-methylimidazolium [BF_4] salts have been used as esterification catalysts. The reaction conditions were similar to those in previous studies. The products were immiscible with the IL so they could be separated easily. The esterification reaction was carried out at 110 °C and the ratio of an acid to alcohol was 1:1 for mono and 1:2 for diacids (see Table 10). Selectivity toward the ester was high and no by-products were produced. The IL could be recycled by simple drying in vacuum. (335)

Table 10. 1-Methylimidazolium [BF_4] catalyzed esterifications of various acids and alcohols at 110 °C.

Entry	Acid	Alcohol	Time (h)	Conversion (%)
1	Acetic acid	1-butanol	2	97
2	Acetic acid	1-Octanol	2	>99
3	*n*-Decanoic acid	1-Butanol	3	96
4	*n*-Decanoic acid	1-Octanol	3	97
5	*n*-Decanoic acid	Methanol	5	97
6	Stearic acid	1-Butanol	3	>99
7	Stearic acid	1-Octanol	3	>99
8	Stearic acid	Methanol	6	>99
9	Undecanoic acid	1-Butanol	3	>99
10	Undecylenic acid	1-Butanol	3	>99
11	Lactic acid	1-Butanol	2	>99
12	But-2-enoic acid	Methanol	6	93
13	Oxalic acid	Ethanol	4	>99
14	Oxalic acid	1-Octanol	4	>99
15	Benzoic acid	1-Butanol	10	80
16	3-hydroxybenzoic acid	1-Butanol	10	93

Hydrogen sulphate anion is acidic and can be used to catalyze the esterification reaction. [BMIM][HSO_4] and [BPy][HSO_4] ionic liquids have been used in the esterification of propanoic acid and *neo*-pentanol. The conversions were poor (24 h, 80 °C, 57 and 70% respectively). The reaction rate increased considerably (30 min, 80 °C, 62%) when 15% sulfuric acid was added to [BMIM][HSO_4]. The addition of sulfuric acid decreased the solubility of the product and thus separation of the product was eased. Yields could be further increased by the use of microwave heating (see Table 11). (14)

Table 11. [BMIM][HSO_4] catalyzed esterification of various acids with *neo*-pentanol under microwave heating at 80 °C (ratio alcohol : acid:IL was 1:1:3).

Entry	Acid	Time (h)	Yield (%)
1	Propanoic acid	1.5	95
2	Cyclohexanecarboxylic acid	2.5	90
3	Butyl-4-enoic acid	3.5	89
4	Phenylacetic acid	4.5	40

1,3-Dibutylimidazolium bromide has been utilized as a solvent in the esterification reactions. Sonication has been used as a reaction promoter. Several different alcohols were acetylated with acetic anhydride with short reaction times

and excellent yields of acetylated product. The reaction temperature was 30 °C and the reactions were run until completion. Also other 1,3-dibutylimidazolium based ionic liquids were studied ([Cl], [ClO_4], [BF_4], [PF_6]), but they did not give such good yields as 1,3-dibutylimidazolium [Br] (see Table 12). (97)

Table 12. Acetylation of alcohols under sonication in 1,3-dibutylimidazolium [Br].

Entry	Alcohol	Time (min)		Isolated yield (%)	
		Sonication	Silent	Sonication	Silent
1	Benzyl alcohol	5	60	95	91
2	2-Phenylethanol	5	60	94	93
3	1-Phenylethanol	5	55	92	90
4	2-Phenylethenol	5	20	93	90
5	Cyclohexanol	10	60	95	80
6	2-Isopropyl-5-methyl-cyclohexanol	30	180	90	50
7	D-(+)-Glucose	10	120	91	74
8	D-(+)-Mannitol	30	120	80	72
9	Etyleneglycol	30	180	95	90
10	Hexanol	65	600	65	61
11	Octanol	60	600	62	59

Fatty alcohols have been efficiently esterificated in 1-methyl-3-octylimidazolium [BF_4] with a *p*-toluenesulfonic acid catalyst. The esterification reactions were carried out at 80 °C for 1 hour. The reactions gave excellent yields of esters (see Table 13). Esterifications were also tried with microwave heating. The microwave apparatus was common household microwave oven, but still results were good. (223)

Table 13. Esterification of carboxylic acids with various alcohols in 1-methyl-3-octylimidazolium [BF_4]. Reaction time was 1 h at 80 °C.

Entry	Acid	Alcohol	Isolated yield (%)
1	α-Bromoacetic acid	Octanol	90
2		Dodecanol	98
3		Tetradecanol	93
4		Ocatadecanol	97
5	Propionic acid	Octanol	82
6		Dodecanol	81
7		Tetradecanol	98
8		Ocatadecanol	90
9	Lauric acid	Butanol	65
10		Hexanol	90
11		Octanol	96
12		Decanol	94
13	Benzoic acid	Hexanol	90
14		Octanol	96
15		Dodecanol	85

Esterification of acids can be done with trialkyl orthoacetates (see Fig. 61). Orthoacetates were good reagents for anhydrous esterifications, because they only produce the desired ester and alkyl ester from acetate. A wide variety of carboxylic acids were esterified with ethyl- or methyl orthoacetates. The solvent for the reaction was [BMIM][PF_6] and temperature 80 °C. Usually 2 equivalents of orthoacetate were used (see Table 14). (328)

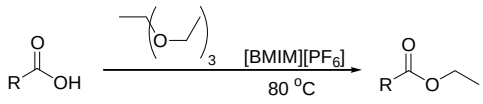
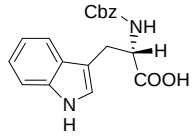
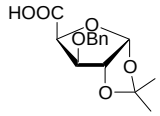


Fig. 61. Esterification using orthoacetate.

Table 14. Esterification of various carboxylic acids with ethyl orthoacetates in [BMIM][PF_6] at 80 °C.

Entry	Acid	Time (h)	Yield (%)
1	2,6-Dichlorobenzoic acid	2	94
2	3,4,5-Trimethoxybenzoic acid	4.5	98
3	Pyrazine-2-carboxylic acid	3	93
4	2,4,6-Trimethylbenzoic acid	1.5	96
5	2,4,6-Tri-isopropylbenzoic acid	3	97
6	Triphenyl acetic acid	3	96
7	Phenyl-propynoic acid	0.5	99
8	Benzoylamino-acetic acid	3	96
9	Octadec-9-enoic acid	4	90
10		12	96[a]
11		2	92
12	Phthalic acid	2[b]	99
13	Fumaric acid	2.5[b,c]	90
14	Maleic acid	7[b,c]	75

[a] Optically pure [b]3 eq. of acetate was used [c]Temperature 100 °C

4.1.2 Esterifications of carbohydrates

Acetylation of alcohols and carbohydrates (see for example Fig. 62) is an important reaction in protecting group chemistry, especially in carbohydrate chemistry. (53) Pyridine is conventionally used as a solvent and a catalyst in carbohydrate chemistry. It has limited use as a solvent with more complex polymeric carbohydrates, because carbohydrate solubility is low to pyridine. (140)

Cellulose fatty acid esters have been prepared in a homogenous phase in LiCl/*N*,*N*-dimethylacetamide (LiCl/DMAc) solvent. The reactions were carried out using microwave heating. Typically, reaction times varied from 30 min to two days for the reaction to be completed. Cellulose was first dissolved in

LiCl/DMAc. The catalyst *N*,*N*-dimethyl-4-aminopyridine (DMAP) was added. lauroyl chloride was used as an esterification reactant. The amount of lauroyl chloride varied between 2.4 to 14 equivalents per glucose units of cellulose. Amounts of DMAP used per lauroyl chloride were 0.05 to 0.5 equivalents. In order to avoid cellulose degeneration microwave heating conditions were optimized. The best conditions were when 300 W of microwave power for 1 min was applied. The highest yields were gained when 0.5 equivalents of DMAP was used. The amount of DMAP had negligible effect on the degree of substitution (DS) of the product. The DS of the product was proportional to the amount of lauroyl chloride used. DS was 0.7 with 2.4 equivalent and 2.6 with 14 equivalents of lauroyl chloride. (255)

Dialkylimidazolium[DCA] have been used as catalyst and solvent in the acetylation of α-D-glucose (see Fig. 62). The solubility of α-D-glucose was at least 10 wt-% to the IL but lower for more complex carbohydrates. Acetylation reactions have been carried out using acetic anhydride as an acetylation reagent and without additional catalysts. Usually, at the beginning of the reaction a part of the substrate remained undissolved, but as the reaction proceeded all was dissolved. The effects of different catalysts and concentrations of solutions were studied (NaOAc, pyridine, triethylamine). The catalysts did not improve the yields, even if elevated temperatures were used. The acetylation of α-D-glucose was also attempted in [BMIM][NTf_2], but product was not formed. (78)

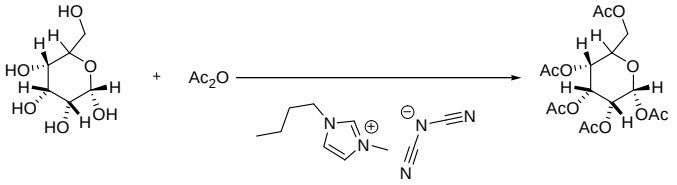


Fig. 62. Acetylation of Glucose in [BMIM][DCA].

Table 15. Acetylation of various alcohols in [DCA] based ionic liquids at room temperature.

Entry	Substrate	Solvent	Amount of Ac_2O (eq.)	Time (h)	Yield (%)
1	α-D-Glucose	[BMIM][DCA]	5	0.2	89
2	α-D-Glucose	[BMIM][DCA]	5	0.1	98[a]
3	β-Me-Glucose	[BMIM][DCA]	4.5	0.2	92
4	*N*-Acetylneuraminic acid	[EMIM][DCA]	5	24	72
5	Sucrose	[BMIM][DCA]	8	24	93
6	Raffinose	[EMIM][DCA]	11	24	90
7	2-Naphtol	[EMIM][DCA]	1	24	85
8	*t*-Butanol	[EMIM][DCA]	1	24	88
9	Cyclohexanol	[EMIM][DCA]	1	0.5	90

[a]At 50 °C

The solubility of carbohydrates in various [BMIM]-salts has been studied and only [BMIM][DCA] showed high solubility. Carbohydrates had low solubility in [BMIM]-salts with $[BF_4]$, $[PF_6]$, $[CF_3SO_3]$ and $[NTf_2]$-anions. Polar side chains such as methoxymethylether or ethoxymethylether have been employed in imidazolium to increase the solubility of carbohydrates. The ether side chains decreased glucose solubility but increased sucrose solubility. The solubility of sucrose was increased the most by methoxymethylether sidechain. Enzyme catalyzed esterification was studied in 1-methoxymethyl- or 1-ethoxymethyl-3-methyl-imidazolium [DCA] ionic liquids. *Candida antarctica* lipase was used as a catalyst in the esterification reaction between dodecanoic acid and sucrose. (183)

The first reported acetylation of cellulose in an IL was published in 2004. 1-Allyl-3-methylimidazolium chloride ([AMIM][Cl]) was used as a solvent and acetic anhydride as acetylation reagent. Cellulose was dissolving pulp with the degree of polymerization (DP) about 650. The acetylation was carried out in low concentration of cellulose in [AMIM][Cl], so that the viscosity of the reaction medium would be low enough. The reaction temperature was usually 80 °C and no stirring was used. The degree of substitution depended on the reaction time so that DS of 2.21 was obtained in 4 hours and 2.49 in 8 hours. Increasing the reaction time to a 23 h gave almost the same DS than an 8 h (see Table 16). The IL was completely recyclable after distillation of the volatile components. (314)

Table 16. Acetylation of cellulose in [AMIM][Cl] with different reaction times and temperatures.

Entry	Wt-% of cellulose in IL	Molar ratio[b]	Temperature (°C)	Time (h)	DS
1	4	5	80	0.25	0.94
2	4	5	80	0.5	1.39
3	4	5	80	1	1.61
4	4	5	80	2	1.80
5	4	5	80	3	1.86
6	4	5	80	4	2.21
7	4	5	80	8	2.49
8	4	5	80	23	2.74
9	4	4	80	4	2.15
10	4	6.5	80	4	2.43
11	4	8	80	4	2.38
12[a]	3	3	100	3	1.99
13[a]	3	4	100	3	2.09
14[a]	3	5	100	3	2.3

[a]Stirred [b]Acetic anhydride/anhydroglucose unit

The acetylation of different celluloses has been studied in [BMIM][Cl], 3-methyl-*N*-butylpyridium chloride ([B-3-MPy][Cl]) and benzyldimethyl(tetradecyl)ammonium chloride ([BDTAC][Cl]). Celluloses used in the study were microcrystalline cellulose (DP was 286), spruce sulfite pulp (DP was 593) and cotton linters (DP was 1200). The high DP decreases the solubility of cellulose in an IL. Cellulose had highest solubility in [BMIM][Cl] (from 10 to 18%) and [B-3-MPy][Cl] (from 12 to 39%). Solubility was poor in [BDTAC][Cl] (from 5 to 1%). Depolymerization was not detected for lower DP polymers and for higher DP polymer only slight depolymerization was detected in [BMIM][Cl] and [BDTAC][Cl]. Severe depolymerization was detected in [B-3-MPy][Cl]. Acetic anhydride and acetyl chloride were used as acetylation reagents. Pyridine was studied as a catalyst, but when it was used with acetyl chloride the DP of cellulose was degraded. (19, 114)

Table 17. Acetylation of microcrystalline cellulose, spruce sulfite pulp and cotton linters in [BMIM][Cl] at 80 °C with acetic anhydride and acetyl chloride.

Entry[a]	Acetylation reagent	Molar ratio	Time (h)	DS
A1	Acetic anhydride	5	2	2.72
A2	Acetic anhydride	3[d]	2	2.56
A3	Acetic anhydride	5[d]	2	2.94
A4	Acetic anhydride	10[d]	2	3.0
A5	Acetyl chloride	5[d]	2	2.93
A6	Acetyl chloride	3	2	2.81
A7	Acetyl chloride	5	2	3.0
A8	Acetyl chloride	10	2	3.0
A9	Acetyl chloride	5	0.25	2.93
A10	Acetyl chloride	5	0.5	3.0
B1	Acetyl chloride	3	2	3.0
B2	Acetyl chloride	5	2	3.0
C1	Acetyl chloride	3	2	2.85
C2	Acetyl chloride	5	2	3.0

[a]Cellulose types: A = Microcrystalline, B = Spruce sulfite pulp, C = Cotton linters [b] Molar ratio of AGU to acetylation reagent [c]Determined by ^{1}H NMR [d]Pyridine 2.5 eq.

Similar systems have been used for the preparation of cellulose fatty acid esters. A wide variety of different ionic liquids was studied as reaction media. The cellulose was dissolved in [alkylMIM][Cl]. Lauryl chloride was used as an esterification reagent and microcrystalline cellulose (DP was 600) was used as a reagent. The DS correlated with the amount of lauroyl chloride used, with higher loading giving higher DS. [BMIM][Cl] gave the best DS for esterification. The reactions were carried out at 80 °C for 2 h (see Table 18). (19)

Table 18. Esterification of cellulose with lauroyl chloride in [BMIM][Cl] for 2 h at 80 °C.

Entry	Solvent	Molar ratio[a]	DS[b]
1	[BMIM][Cl]	1	0.34
2	[BMIM][Cl]	3	1.54
3	[BMIM][Cl]	5	1.44
4	[BMIM][Cl]	3	0.77
5	[BDMIM][Cl]	3	0.36
6	[AdMIM][Br]	3	0.12

[a]Mol AGU per mol of lauroyl chloride [b]Determined by ^{1}H NMR after perpropionylation

The modification of bacterial cellulose is one of the most difficult challenges in cellulose chemistry. Bacterial celluloses have higher DPs than plant celluloses and it can be as high as 10000. Bacterial cellulose is free of hemicelluloses and

also their fibrils are finer than in plant celluloses. Before the use of ionic liquids, bacterial celluloses were hard to dissolve to any solvent. A bacterial cellulose with a DP of 6500 was easily dissolved in [BMIM][Cl] at 80 °C. The acetylation was carried out at 80 °C for 2 h, by using acetic anhydride as an acetylating reagent. The DS depends on the ratio of acetic anhydride to glucose unit of cellulose. Complete acetylation was achieved when 10 equivalents of the anhydride per glucose were used. A similar reaction with phenyl isocyanate produced carbamic acid esters (see Table 19). (258)

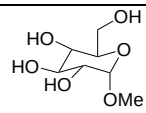
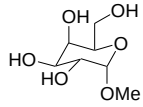
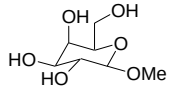
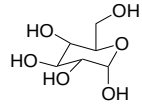
Table 19. Homogenous acetylation and carbanilation of bacterial cellulose in [BMIM][Cl]. Reaction time was 2 h and temperature 80 °C.

Entry	Reagent	Molar ratio[a]	DS[b]
1	Acetic anhydride	1	0.69
2	Acetic anhydride	2	1.66
3	Acetic anhydride	3	2.25
4	Acetic anhydride	5	2.5
5	Acetic anhydride	10	3.0
6	Phenyl isocyanate	1	0.29
7	Phenyl isocyanate	3	0.82
8	Phenyl isocyanate	5	1.75
9	Phenyl isocyanate	10	2.25
10	Phenyl isocyanate	10	3.0[c]

[a]Mol reagent per mol of anhydroglucose repeating unit [b]Determined by ^{1}H NMR after perpropionylation
[c]Reaction time 4 h

Choline chloride/zinc dichloride deep eutectic liquid has been used as a catalytic solvent for the acetylation of carbohydrates and cellulose. The cellulose was only slightly soluble (<3 wt-%) in the liquid. Four different glucose derivatives and also some other choline based ionic liquids were tested (see Table 20). Only fully acetylated product was detected, even if low amounts of acetic anhydride was used (Table 20, entry 8). Cellulose was also acetylated in choline chloride/zinc dichloride. The amount of acetic anhydride controlled the DS cellulose of the acetylation. (2)

Table 20. Choline based ionic liquid catalyzed acetylations of different glucose derivatives at 90 °C. Reaction time was 3 h.

Entry	Substrate	Solvent	Acetic anhydride (eq.)	Yield (%)[a]
1		$[ChCl][ZnCl_2]_2$	5	78
2		$[ChCl][ZnCl_2]_2$	6	81
3		$[ChCl][ZnCl_2]_2$	5	78
4		$[ChCl][ZnCl_2]_2$	5	79[b]
5	See entry 1	$[AcChCl][ZnCl_2]_2$	5	66
6	See entry 1	$[ChCl][SnCl_2]_2$	5	68
7	See entry 1	$[ChCl][Urea]_2$	5	<5
8	See entry 1	$[ChCl][ZnCl_2]_2$	1	96[c]

[a]Isolated yield [b]3:1 mixture of α:β anomers [c]Yield based on Ac_2O

Sugarcane bagasse is produced from sugar plants after sugar juice is removed. It is a product with little use, but it could be used as a new feedstock. After drying the sugarcane bagasse contains 52.4% of cellulose and hemisellulosic sugars. The major component of the hemisellulosic sugars was glucose (55.7%). Minor components were xylose (25.8%), arabinose (12.8%), galactose (3.2%) and mannose (1.2%). The preparation of cellulosesuccinate from sugarcane bagasse was investigated. The succinylation was carried out for crude cellulose in [BMIM][Cl] diluted with DMSO (DMSO was used to lower the viscosity of the solution). Succinic anhydride was used as an esterification reagent. Usually succinate reacted to monoesters. The DS of the succinylation followed the amount of succinic anhydride used per glucose unit of cellulose. The reaction times were short around 1 h. Increasing the time to 2 h produced same DS product (see Table 21). (182)

Table 21. Succinylation of sugarcane bagasse in [BMIM][Cl]/DMSO system. Concentration of cellulose was 2.35 wt-%.

Entry	Succinic anhydride[a]	Time (min)	Temperature (°C)	DS
1	4	60	85	0.071
2	4	60	90	0.087
3	4	60	95	0.11
4	4	60	100	0.18
5	4	60	105	0.22
6	4	5	100	0.037
7	4	15	100	0.049
8	4	30	100	0.14
9	4	70	100	0.20
10	4	90	100	0.24
11	4	120	100	0.26
12	1	30	100	0.038
13	2	30	100	0.049
14	3	30	100	0.062
15	6	30	100	0.21
16	9	30	100	0.31
17	12	30	100	0.53

[a]Equivalent of succinic anhydride compared to cellulose glucose units.

Native barley starch has been acetylated with acetic anhydride, propyl anhydride or maleic anhydride in [BMIM][Cl]. Different degrees of substitutions from a DS of 1 to 3 have been observed. [BMIM][Cl] was used as a solvent and a 10 wt-% solution from starch was made. The esterification was carried out at 80 °C and the reaction time was 2 h. The DS depended on the amount of esterification reagent. (212)

4.2 Etherifications

The focus on the etherification part of the literature survey is on recent research on the classical Williamson ether synthesis (see Fig. 63) and on the reaction of epoxides with oxygen nucleophiles. The microwave and ionic liquid assisted synthesis and synthesis of ethers from starch and cellulose have been considered carefully because they will serve the purpose and application area of the experimental work. The literature for microwave assisted etherification has been covered up to 2003 in books, so it is unnecessary to through them again here. (112, 136, 184)

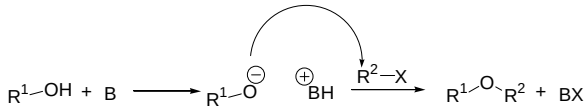


Fig. 63. Reaction mechanism for Williamson ether synthesis (R^1 = R^2 = Alkyl or aryl, B = base)

The preparation of methoxyethyl ethers from different aromatics have been studied under microwave heating. K_2CO_3 was used as a base and methanol was used as a solvent (see Fig. 64). Milder reaction conditions could be used for Br as a leaving group than for Cl (Fig. 64 and Table 22). The yields were generally better with Cl. The reaction was also studied in ethanol, but it gave lower yields, because of the lower solubility of K_2CO_3. (254)

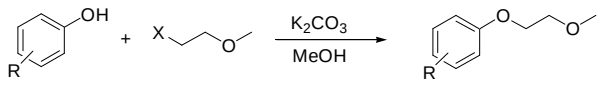


Fig. 64. The preparation of methoxyethyl ethers from different aromatics (R = CHO or CN).

Table 22. Microwave assisted etherification of phenols with methoxyethyl halides.

Entry	R	X = Br			X = Cl		
		T (°C)	Time (min)	Yield (%)	T (°C)	Time (min)	Yield (%)
1	4-CHO	100	15	45	140	30	65
2	3-CHO	100	15	78	140	30	74
3	2-CHO	100	15	81	140	30	76
4	4-CN	120	30	87	140	30	96
5	3-CN	120	30	89	140	30	73
6	2-CN	120	30	80	140	30	91

The alkylation of galactosides has been carried out using dibutylstannane as a catalyst under microwave heating. Usually, tin-mediated 3-O-alkylations take up to 16 h to complete. When microwave heating was used the reaction took 5 min for tin-acetal formation and 6 to 10 min for alkylation. High temperatures have to be used (150-170 °C) in order to achieve good yields (70 to 86 %) (see Fig. 65 and Table 23). (15)

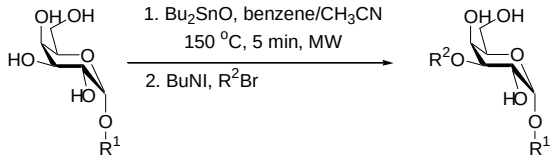


Fig. 65. Tin-mediated alkylation of galactosides (R^1 = sugar, R^2 see Table 23).

Table 23. Microwave assisted tin-mediated alkylations of galactosides.

Entry	R^2	Time (min)	T (°C)	Isolated yield (%)
1	Benzyl bromide	10	150	80
2	Benzyl bromide	6	170	84
3	Allyl bromide	6	170	86
4	(4-Bromomethyl-phenyl)-phenyl-methanone	10	150	75
5	1-(4-Azido-phenyl)-2-bromo-ethanone	20	110	45
6	Bromo-acetic acid tert-butyl ester	15	170	85

Cellulose ethers have been prepared in [BMIM][Cl]. Sodium chloroacetate was used as an alkylating agent and NaOH as a catalyst. Cellulose was first dissolved in [BMIM][Cl], to lower the viscosity of the reaction mixture it was diluted with DMSO. The yield of the product was 83 % and DS was 0.49 when 1:1 chlroacetate was used per glucose unit. The DS did not improve even if 3:1 chloroacetate was used. (114, 211)

A deep eutectic solvent chlorocholine chloride/urea has been used in the NaOH catalyzed cationization reaction of cellulose (see Fig. 66). Chlorocholine chloride forms a liquid similar to ionic liquids when it is mixed with urea. Chlorocholine chloride urea deep eutectic liquid acts as an alkylation reagent to form cationized cellulose. The cellulose was mixed with the deep eutectic liquid in 90 °C for 15 h and a DS of 0.22 was obtained. Several different temperatures (60 to 120 °C) were tested, but they gave lower DS. Note that the solvent was used as a reagent (3)

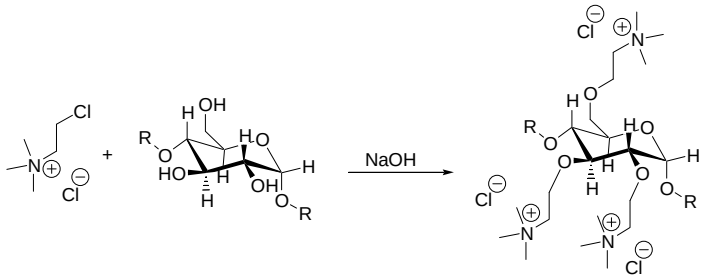


Fig. 66. Reaction of chlorocholine chloride with cellulose.

4.3 Ene reactions

The ene reaction is pericyclic reaction, where alkene π-bond and allylic C-H react in a four electron system to form a new C-C σ-bond with a shifting double bond (see Fig. 67). The allylic part acts similar to diene in the Diels-Alder reaction and is called an enophile. Ene reactions have higher activation energy than Diels-Alder reactions, because of higher activation energy of the σ-C-H bond than the C-C bond in the Diels-Alder reaction. Due to the high activation energy the reaction needs high temperature to proceed. Because of the demand for the elevated temperature and long reaction times the ene reaction has never reached the popularity of "easier" pericyclic reactions, such as the Diels-Alder reaction. High temperatures and long reaction times required by the ene reaction produces by-products, consumes vast amount of energy and requires high boiling solvents or high pressures with low boiling solvents. (117, 204, 230)

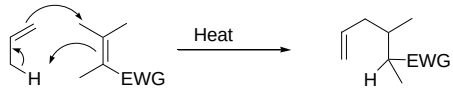


Fig. 67. Reaction mechanism for an ene reaction (EWG = electron withdrawing group). (43)

High temperatures required for the ene reaction were conveniently overcome by using microwave heating. The reaction times were also reduced considerably. There is a review article concerning the pressure effect on cycloaddition reaction which states that usually cycloaddition reactions benefit from using high pressure. (199) Even though pressures achieved in microwave reactors are low

compared to pressurized reactions, they might play some role in accelerating reaction rates in cycloaddition reactions.

There are only a few recent articles in the literature about the ene reaction between two carbon centers. This is probably due to the poor yields of ene reactions.

The ene reaction have been used in diasteroselective cyclizations. Theoretical calculations have shown that activated ene cyclizations favor *trans*-configuration and inactivated *cis*- configuration for steric reasons. In practical sense this gives an opportunity to design cyclizations, which yield correct stereoisomers. (208)

Enallenes have been used in carbocylizations, where allenic double bond acts as the ene (see Fig. 68). The reaction proceeded with high stereo- and regioselectivity. The ene reaction was competing with cycloaddition. Microwave heating and ionic liquids were tested in the ene reaction. The ratio of ene to Diels-Alder product was 83:17 in acetonitrile after 1 hour at 160 °C under microwave heating. The ratio in [BMIM][BF_4] was 80:20 after 15 h at 110 °C. The ratio in DMF was 90:10 after 24 h at 120 °C. (218)

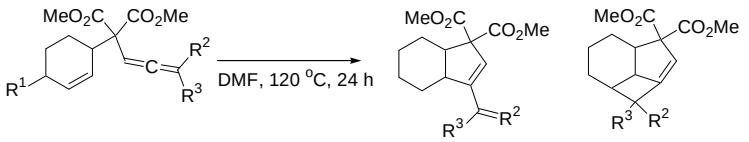


Fig. 68. Cyclizations of allenic double bond and enophile (R^1 = H, t-$BuCO_2$ or $PhCO_2$, R^2 = R^3 = H or Me (ring size could also change)).

4.4 Sulfonylation reactions

The sulfonylation reaction is analogous of the Friedel-Crafts acylation. In sulfonylation, sulfonyl chloride reacts with aromatic compounds to form sulfones. The same catalysts usually work in the sulfonylation reaction as in the Friedel-Crafts acylation. (130) It has been shown earlier in this thesis that Friedel-Crafts chemistry benefits from the use of ionic liquids.

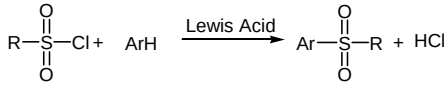


Fig. 69. Principle of sulfonylation reaction

In general, Lewis acid catalyzed sulfonylation proceeds via ionized sulfonyl compound when an excess of sulfonyl chloride is used (see Fig. 70). The rate-determining step of a sulfonylation reaction is the step where a Lewis acid captures chlorine from sulfonyl chloride. An aromatic compound then attacks upon the ionized sulfonyl group and forms the product. The aromatic group attacks practically as fast as the ionized sulfonyl group is formed (see Fig. 70).

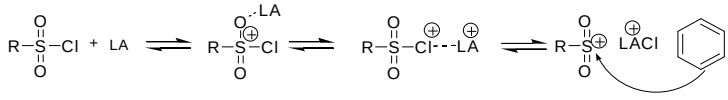


Fig. 70. Lewis acid assisted ionization of sulfonyl chloride and the attack upon an aromatic compound to ionized sulfonyl group (LA = Lewis acid R = Alkyl or Aryl group)

Ionization can also be incomplete and the complex between the Lewis acid and sulfonyl compound is formed. An aromatic compound attacks the complex and forms the sulfone (see Fig. 70). (288)

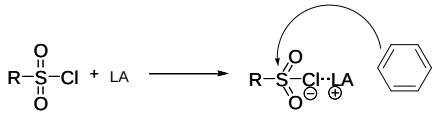


Fig. 71. Lewis acid complex of sulfonyl chloride and an aromatic compound attack on complex (LA = Lewis acid and R = aryl or alkyl group).

The ionization mechanism dominates if the sulfonylation is carried out in a polar solvent. Zero order kinetics is observed with reactive aromatics (e.g. mesitylene). Third order kinetics is observed with less reactive aromatics (e.g. benzene), since the rate determining step is the attack of aromatic compound upon the sulfonyl chloride-Lewis acid complex. (40)

A solvent affects the solvation of sulfonyl chloride-Lewis acid complexes and thus solvents that solvate the complex efficiently should be quite good solvents for Lewis acid catalyzed sulfonylation.

Traditional Lewis acid catalysts form stable complexes with sulfonyl chlorides and sulfone products. The complexes between the Lewis acid and sulfone could decrease catalyst activity.

Kinetics for aluminum trichloride catalyzed sulfonylation has been studied. Benzenesulfonyl chloride was used as a solvent and reagent. The

benzenesulfonylation of toluene showed second order kinetics. The benzenesulfonylation of chlorobenzene showed 3.5 order kinetics. (16)

The sodium periodate catalyzed sulfonylation of toluene with *p*-toluenesulfonyl chloride has been studied. The yield of the product was 82% in 5 h at 110 °C. (17) Sodium perchlorate has also been used as a catalyst and the catalytic activity was the same as with sodium periodate. (247)

Bismuth(III) derivatives in combination with triflic acid have been used as a sulfonylation catalyst. Bi(III)Cl in combination with triflic acid catalyzes the reaction between benzenesulfonyl chloride and toluene efficiently. Excellent yield was observed (95%) in 1.25 h at 110 °C. (248)

The catalytic effect of Bi(III)OTf on the benzenesulfonylation of toluene has been studied. The yields were the same as in the Bi(III)Cl/triflic acid catalyzed reaction. The catalytic activity of Bi(III)Cl/OTf comes from the ability of bismuth to exchange between Cl and the OTf groups. Released OTf generated benzenesulfonyl triflate group which was the active sulfonylating reagent (see Fig. 72). (92)

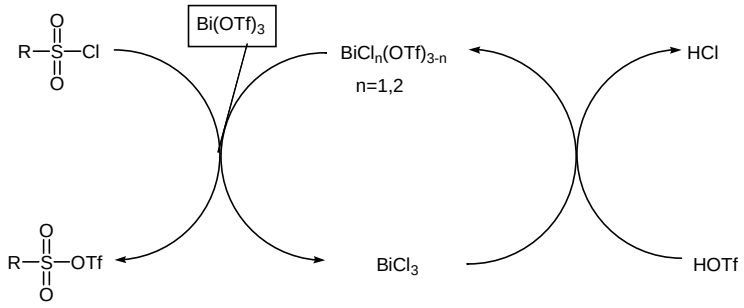


Fig. 72. Assumed reaction cycle for $BiCl_3$/triflic acid catalyzed sulfonylation.

In (III) has been used as a catalyst for sulfonylation. The catalyst system was the same as in the Bi(III) catalyzed reaction, but instead of Bi In was used in combination with triflic acid. Chlorobenzene can be sulfonylated with *p*-fluorobenzenesulfonyl chloride with an 80 % yield in 2 h at 70 °C. (266)

Cu(II)OTf and Sn(II)OTf have been used as sulfonylation catalysts, but their catalytic activity was poor in comparison to In or Bi compounds (99 % yield in 12 h at 110 °C). (193)

Microwave heating has been used to accelerate sulfonylation with a $FeCl_3$ catalyst. The reaction between toluene and benzenesulfonyl chloride produced the

sulfone product at 95 % yield in 5 min at 110 °C. Under microwave heating $FeCl_3$ was the best catalyst for the reaction, out of $AlCl_3$, $SmCl_3$, $Fe(OTf)_3$, $Bi(OTf)_3$, $Sc(OTf)_3$, which all gave lower yields. (216)

Ionic liquids have been used as catalytic solvents in sulfonylation reactions. Chloroaluminate ionic liquid ([BMIM][Cl]/$AlCl_3$) catalyzed sulfonylation of benzene with *p*-toluenesulfonyl chloride efficiently. The yield was 89 % in 5 h at 30 °C. (8) The results were better than any of the metal catalyzed reaction. Unfortunately the IL was destroyed in the process. Another catalytic IL used was [BMIM][Cl]-$FeCl_3$) and it was as active as the chloroaluminate system but more water stable. (49)

Iron has been attached to a montmorillonite (265) and bentonite (161) carrier and used as a catalyst in sulfonylation reactions. The yield of the benzenesulfonylation of toluene was 84% in 6 h at 110 °C when iron montmorillonite catalyst was used. Bentonite was a better carrier and a 74 % yield in 2 h at 110 °C was observed. Zinc attached to zeolites has also been used as a catalyst for sulfonylation, but the catalytic activity was poor in contrast to iron systems (43 % conversion, in 24 h at 110 °C). (68)

5 Application of ionic liquids and microwave activation in selected reactions

5.1 Project background

The aim of this thesis was to find the scopes and limitations of the microwave heating technique together with ionic liquids. This was done by choosing four different reactions where microwaves and ionic liquids were used. The reactions were chosen so that they would be interesting in academic and industrial point of view. Combining different reaction types it is also possible to have a broad view of techniques.

Microwave heating and ionic liquids were the “hot topics” in chemistry by the time this work was started. Both techniques were used and studied independently and combining microwaves and ionic liquids provided academic and industrially interesting new areas of research.

The main part of this work was done with the esterification of polyols. Kemira Oyj needed economically feasible ways of making polyol esters for their purposes. Collaboration with Kemira Espoo research center provided an industrial view for the research. Esterification is a simple and versatile way of changing the polarity of alcohol groups and it has been already thoroughly studied. Therefore it is hard to improve on esterifications. Fortunately, the microwave technique and ionic liquids provided a means of improving the esterifications.

The etherification of alcohols was challenging for ionic liquids because basic reaction conditions were required. Only little was known about using ionic liquids under basic conditions when project was started. Developing ionic liquids for basic conditions was one of the key issues in succeeding in etherification reactions. The ultimate goal would be to manufacture basic ionic liquids.

The ene reaction requires high temperatures to proceed at a reasonable rate. Using microwaves and ionic liquids, high temperatures could be reached easily compared to conventional heating. This part of the work was done in collaboration with the University of Helsinki Drug Discovery and Development Technology Centre

The aim in the sulfonylation reaction studies was to find out metal bistrilimide complex activity as a catalyst. Metal bistriflimide complexes could be generated simply by dissolving metal into an bistriflimide ionic liquid and used the formed ionic liquid as catalytic solvent. This part of the work was carried out

in QUILL at Queen's University Belfast. It provided a new way of thinking about ionic liquids.

5.2 Results and discussion

5.2.1 Esterification of aliphatic alcohols

Aliphatic polyalcohols provided a safe starting point for the modification of polyols. They are robust and relatively easy to work with. At this point the focus of the study was to get high reaction rates and find out the effect of microwave heating and ionic liquids as a reaction medium. The prerequisite for polyols was to be as small as possible with a maximum number of hydroxyl groups. Also price was an issue, since industrial applications was a factor. Three different polyols 2,2-bis(hydroxymethyl)-1,3-propanediol (pentaerythritol), 2-ethyl-2-hydroxymethyl-propane-1,3-diol [trismethanolpropane (TMP)] and 2,2-dimethyl-propane-1,3-diol were chosen as the main starting materials (see Fig. 73). The esterifications (acetylations see Fig. 74) were carried out mainly in a microwave reactor with glacial acetic acid as an acetylation regent. The effect of temperature, molar ratio, ionic liquid and sulfuric acid catalysts were determined.

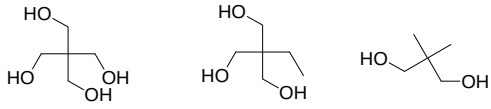


Fig. 73. Structure of polyols used in this work 2,2-bis(hydroxymethyl)-1,3-propanediol (pentaerythritol), 2-ethyl-2-hydroxymethyl-propane-1,3-diol (TMP) and 2,2-dimethyl-propane-1,3-diol.

The reactions were carried out in sealed microwave tubes. It was not the ideal reaction vessel because water formed during the esterification cannot be removed during the reaction. The reaction times with microwave heating were usually 10 min, because it was sufficient for the equilibrium to set at temperatures used under microwave heating. It takes a couple hours for equilibrium to set with conventional heating. The reactions were carried out without an additional solvent or if a solvent was used it was an ionic liquid. Acetic acid was chosen as an acetylation reagent because the only by-product from the reaction was water, which was an acceptable by-product. Another choice of acetylation reagent would have been acetic anhydride, but it was not chosen at this point because of the

acetic acid by-product would have been generated. Also, it was thought that yields would be high enough with the use of an excess of acetic acid together with microwave heating and ionic liquids.

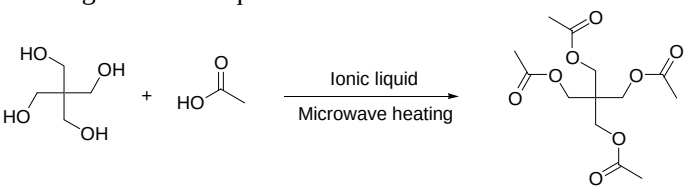


Fig. 74. Acetylation of pentaerythritol with acetic acid by microwave heating and ionic liquids.

In order to have a reference point the esterification of pentaerythritol and TMP were first carried out under normal reflux conditions where water was not removed and an oil bath was used in heating. A sulfuric acid catalyst was used (1 mol-%) and glacial acetic acid was used as an esterification reagent [8 equivalents for pentaerythritol (1 hydroxy group per 2 acids) and 6 equivalents for TMP (1 hydroxy group per 2 acids)]. The yields were 60% for pentaerythritol and only 34% for TMP in 4 hours at 117 °C. The initial temperature for the microwave reaction was chosen with the usual guidelines of microwave chemistry, which is to use a 30 °C to 50 °C higher temperature than in conventional heating. The reaction time was also chosen with same principles. Microwave heating at 150 °C did not give as good yield (41%) for pentaerythritol as conventional heating. For TMP microwave heating gave better yield (54%). The reaction times with microwave heating were only 10 minutes compared to 240 min required with conventional heating (See Table 24). (170)

Table 24. Acetylation of pentaerythritol and TMP with glacial acetic acid under conventional heating and microwave heating with H_2SO_4 catalyst. Molar ratio of hydroxy groups per acid was 1:2.

Entry	Alcohol	Temperature (°C)	Time (min)	Microwave heating	Yield of ester(%)
1	Pentaerythritol	117	240	No	60
2	TMP	117	240	No	34
5	Pentaerythritol	150	10	Yes	41
6	TMP	150	10	Yes	54

The effect of temperature was tested by increasing temperatures from 150 to 170 or 190 °C. Increasing the temperature from 150 °C to 170 or even to 190 °C gave

practically the same yields for pentaerythritol and TMP. Only 2,2-dimethyl-propane-1,3-diol gave better results at 150 °C than at 170 °C. The reason for the similar results obtained at 170 and 190 °C temperatures for pentaerythritol and TMP was due to the equilibrium in the sealed reaction vessel. After equilibrium was set no more products could be formed even if the temperature was increased (See Table 25). Equilibrium is probably reached faster at higher temperatures and even shorter reaction times might be used. For practical purposes a 10 minute reaction time is short enough, because most of the time was already taken by analysis of the product. Decreasing reaction time with higher reaction temperature was not reasonable because of higher energy consumption at higher temperature.

Also heating with cooling was tested because it might give better results due to the higher microwave power input. The esterification of pentaerythritol was carried out for 5 min and microwave power was set to 300 W. The cooling was done by blowing air outside the walls of the reaction vessel in the microwave chamber. The air flow to the microwave chamber could not be adjusted. Cooling with heating did not give good results. The yield of the ester was only 5 %. The results were probably due too efficient cooling, so the actual temperature was too low for the reaction to proceed. One problem with the cooling was that the microwave reactor used did not give reliable temperature measurements with cooling, because of the measurement method used. The microwave reactor measures IR radiation from the reaction vessel surface and when the reaction vessel is cooled IR radiation from the vessel surface gives unreliable results.

Table 25. Effect of temperature on sulfuric acid catalyzed acetylation of pentaerythritol, TMP and 2,2-dimethyl-propane-1,3-diol. Molar ratio of hydroxy groups to acetic acid was 1:2.

Entry	Alcohol	Temperature (°C)	Time (min)	Yield of ester (%)
1	2,2-dimethyl-propane-1,3-diol	150	10	72
2	2,2-dimethyl-propane-1,3-diol	170	10	56
3	TMP	150	10	54
4	TMP	170	10	50
5	TMP	190	10	52
6	Pentaerythritol	150	10	41
7	Pentaerythritol	190	10	45

The acetylation reactions were usually carried out with sulfuric acid as a catalyst. The reactions without the catalyst gave lower yields. High temperature could be used to some extent to compensate for the lack of catalyst. Since the catalyzed reaction gave so much better yields of products it was advisable to use the catalyst (see Table 26).

Table 26. Effect of catalyst on acetylation of TMP and pentaerythritol. Temperature was 150 °C and reaction time 10 min under microwave heating. Molar ratio of hydroxy groups to acetic acid was 1:2.

Entry	Alcohol	Catalyst	Yield of ester (%)
1	TMP		11
2	TMP	H_2SO_4	54
3	Pentaerythritol		3
4	Pentaerythritol	H_2SO_4	41

Ionic liquids were tested as reaction media, because they have been reported to increase reaction rates. It was initially thought that ILs might act as dehydrators and thus could increase the yields of the esterification. Ionic liquids did not work as was intended and the yields were actually lower when ILs were used. It might be that at this point of the study the choice of ILs was not the most appropriate one. However, the choices were based on the available information at that the time. [BMIM][PF_6] was chosen because it is water immiscible and water might separate from the ionic liquid. The separation of water from the reaction mixture would shift the equilibrium toward product esters. [BMIM][DCA] was chosen because it was reported to catalyze esterification reactions. (78) Even though esterificatios have been made in [BMIM][DCA], the IL decomposed during the reaction. At this point it was simply concluded that [BMIM][DCA] could not be heated to this extent and was not investigated further. [BMIM][SCN] was thought to act as a nucleophilic catalyst for the reaction, where [SCN] would coordinate to hydroxy group and pull its hydrogen loose and thus increase hydroxyl group nucleophilicity. Unfortunately [BMIM][SCN] was also decomposed during the esterification (see Table 27).

Table 27. Effect of an ionic liquid on the acetylation of TMP and pentaerythritol. Reaction time was 10 min under microwave heating. Molar ratio of hydroxy groups to acetic acid was 1:2.

Entry	Alcohol	Temperature (°C)	Solvent	Yield of ester (%)
1	TMP	150	[BMIM][DCA][a]	0
2	TMP	150	[BMIM][SCN][a]	10
3	TMP	190	[BMIM][PF_6]	32
4	Pentaerythritol	150	[BMIM][DCA][a]	0
5	Pentaerythritol	150	[BMIM][SCN][a]	2
6	Pentaerythritol	190	[BMIM][PF_6]	31
7	Pentaerythritol	150	[BMIM][PF_6]	34

[a]Decomposed

The effect of the molar ratio of the reactants was studied. Esterifications were carried out under standard conditions (150 °C for 10 min, with microwave heating). The best ratio which gave the highest yields of the product was 2 equivalents acetic acids per hydroxy group of an alcohol (15 equivalents of acetic acid with TMP and 20 equivalents with pentaerythritol). Even 5 equivalent of acetic acids per alcohol hydroxy group did not improve the yield of the ester. This was somewhat surprising, since excess of the acid in a sealed reaction vessel should shift the equilibrium point toward products. One explanation might be the pressure in the reaction vessel. When a 2 fold excess of the acid was used the pressure dropped toward the end of the reaction, but with a 5 fold excess pressure in the reaction vessel stayed practically the same. Even the high temperatures under microwave heating did not affect the yield when a low molar ratio of the alcohol to the acid was used (see Table 28).

Table 28. Effect of molar ratio of acetic acid to alcohol in suphuric acid catalyzed acetylation of pentaerythritol, TMP and 2,2-dimethyl-propane-1,3-diol. Reaction time was 10 min under microwave heating.

Entry	Alcohol	Temperature (°C)	Molar ratio	Yield of ester (%)
1	Pentaerythritol	150	8	41
2	TMP	150	6	54
3	Pentaerythritol	150	20	22
4	TMP	150	15	41
5	Pentaerythritol	150	4	24
6	Pentaerythritol	190	4	22
7	Pentaerythritol	190	8	27
8	2,2-dimethyl-propane-1,3-diol	150	20	21
9	2,2-dimethyl-propane-1,3-diol	150	4	72

Usually, the boiling points of the products were so high that GC-MS analysis for the degree of substitution was impossible. The degrees of substitution were studied with thin layer chromatography (TLC). A methanol ethyl acetate mixture (various ratios) was used as a mobile phase for TLC. The plates were visualized first with UV and then coloring with an anisaldehyde or phosphomolybdic acid (PMA) solution. The coloring solutions were sprayed onto the plates and after it was dry the plates were heated to visualize the products. After visualization the products were extracted from the plates and analyzed by mass spectrometry. It would be reasonable to assume that some partially esterificated products would form because the reaction was not complete. Reactions with each starting alcohols produced two different products. A fully acetylated product was the main product. The other identified product was with one free hydroxy group on alcohol. Other products were not found. This esterification method seems to suit only for the production of fully acetylated products while obtaining partially acetylated products is hard.

5.2.2 Esterification of carbohydrates

In searching for a low molecular weight polyol, carbohydrates gave a good option for high hydroxy loading polyols. Environmetally, carbohydrates were an easy choice because they are the most widely spread hydroxy group containing organic molecules on earth, so nature has adopted them as a food source. It is safe to say

that carbohydrates are the most environmentally friendly substrates which can be found. Carbohydrates also have different hydroxy groups in the same molecule and thus esterification could be studied in detail. Complex polymeric carbohydrates have been hard to dissolve in conventional solvents. Ionic liquids dissolve polymeric carbohydrates and would be a new reaction medium for modification of them.

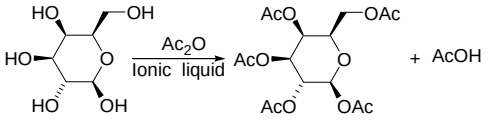


Fig. 75. Esterification of D-glucose with acetic anhydride.

The study of carbohydrate esterification was started from the acetylations of D-glucose (see Fig. 75). D-Glucose is one of the simplest of the carbohydrates and provided a relatively easy analysis of the products compared to polymeric carbohydrates. D-Glucose was also expected to react similarly to the more complex carbohydrates and thus provide a good model for the reactions. Initially, sulfuric acid catalyzed acetylation was tested with acetic acid as the esterification reagent. The reaction was carried out at 150 °C with microwave heating for 10 min, which were similar conditions to the polyol esterification. After the reaction crystallization of the acetylated product from the reaction mixture was unsuccesful. The D-glucose decomposed during the reaction and esterification did not proceed. It was concluded that milder reaction conditions and a stronger acetylation reagent were needed. Since acetic anhydride is used in number of sugar acetylation it was chosen as an acetylation reagent for further studies.

Carbohydrates have been reported to dissolve in [BMIM][DCA] and [BMIM][DCA] also catalyze the *O*-acetylation of alcohols. (78) It was the obvious choice as the first ionic liquid for acetylation reactions. In our experience D-glucose had too low solubility to a dry [BMIM][DCA] for our purposes. The solubility difference might be explained by the different degrees of purity of [BMIM][DCA]. It is very hard to get pure [DCA] salts from [Cl] salts via metathesis because the cationic affinities of [DCA] and [Cl] are almost the same.

The catalytic activity of [BMIM][DCA] was found to be moderate at the concentrations used (Table 29). The aim was to use as short a reaction time as possible while heating was applied to the reaction mixture. The heating of [BMIM][DCA] to 80 °C in a microwave oven resulted the release of gas as before in the aliphatic alcohol case (the gas was thought to be hydrogen cyanide).

Thorough analysis by mass spectrometry revealed acetamide and diacetamide from the reaction mixture. They were degradation products of [DCA]. The decomposition of [BMIM][DCA] was further studied by heating [BMIM][DCA] with acetic acid. The same decomposition products were detected as from the D-glucose acetylation attempts. The reported catalytic activity of [BMIM][DCA] in a concentrated carbohydrate solution might have been initiated from the decomposition of dicyanamide anion. Due to the detected decomposition of [BMIM][DCA] and possible formation of hydrogen cyanide, [BMIM][DCA] was not used in further studies.

Table 29. Esterification of D-Glucose with acetic anhydride in [BMIM][DCA] under microwave heating.

Entry	Temperature (°C)	Time (min)	Molar ratio[a]	Microwave	Yield (%)
1	RT	1440	5	N	55
2	60	5	5.5	Y	0
3	80	10	5.5	Y	0

[a]Molar ratio of acetic anhydride to alcohol

[BMIM][Cl] was the next choice of ionic liquid for the acetylation reaction. It dissolves complex carbohydrates, even cellulose at high concentrations. (283) Whether [BMIM][Cl] would have catalytic properties was not know at the time. On the other hand it provided the possibility to dissolve and derivatize complex carbohydrates, which is unique even amongst ionic liquids. Before stargin to employ [BMIM][Cl] the decomposition was tested. A mixture of [BMIM][Cl] and acetic acid was heated to 120 °C for 2 h and fortunately no sign of decomposition was detected according to NMR or MS.

Acetylation of D-glucose with a low excess of acetic anhydride was first tested with microwave heating in [BMIM][Cl] at 70 °C for 30 min. The thought was that the ionic liquid would act as a catalytic solvent, and so a short reaction time and low excess of acetic anhydride was justified. The microwave heated reaction gave a low yield (see Table 30). The yield was determined as a pure isolated yield and enough of the product was required in order to determine yields reliably. At the time we only had 5 ml microwave reaction vessels and for practical purposes they were too small. Thus it was concluded that it was better to use an oil bath heating and bigger reaction vessels.

The acetylation of D-glucose without a catalyst in [BMIM][Cl], proceeded slowly at 90 °C, with 9 equivalents of acetic anhydride (roughly 2 acetic

anhydrides per hydroxyl group of D-glucose). The excess of anhydride was driven from the previous acetylations with acetic acid. The yield of D-glucose penta-acetate was 21% after 2 hours (Table 30, entry 6), 65% after 8 hours (entry 8). The yield at 80 °C was 63% after 24 h (entyr 4). The product was conveniently precipitated from [BMIM][Cl] with addition of water. Only acetylated product was precipitated, which was confirmed by NMR and MS analysis. The low yields at 90 °C could be explained by the poor crystallization of the product. NMR analysis from the reaction mixture showed higher yields, but pure isolated yields were low because of the poor crystallization of the product. After the reaction and product precipitation, [BMIM][Cl] was analyzed with NMR and mass spectrometry and found to be intact allowing recycling several times (at least three) (see Table 30).

Increasing the reaction temperature from 90 °C to 120 °C the yield of acetetylated product improved (from 21 to 71% in 2 h, Table 30, entry 6 and 10), but at the same time a brownish color appeared in the reaction mixture. The ionic liquid was analyzed with NMR and MS for residual starting materials, but they were not found. The color change was a sign of possible degradation of the IL and the recyclability was lower at higher temperatures. After the possible degradation of ionic liquid at 120 °C, further reactions were carried out at 90 °C.

Table 30. Esterification of D-Glucose with acetic anhydride to glucose penta-acetate in [BMIM][Cl].

Entry	Temperature (°C)	Time (h)	Molar ratio[a]	Yield (%)
1	70[b]	0.5	5,5	0
3	RT	18	10	~1
4	80	24	10	63
5	80	24	10	80[c,e]
6	90	2	9	21[d]
7	90	4	9	18[d]
8	90	8	9	65
9	90	8	9	32[d]
10	120	2	9	71

[a]Molar ratio of acetic anhydride to alcohol [b]Microwave heating [c]Conversion [d]Inappropriate crystallization [e]Recycled

In order to improve the yield of the acetylation of D-glucose the effect of different basic, acidic and Lewis acid catalysts were studied. Sodium acetate has been commonly used as a catalyst in acetylations. (84) Acetylations require 170 mol-% loadings of sodium acetate and accordingly the term catalyst might not be

appropriate. Sodium acetate catalyzed acetylations in [BMIM][Cl] gave 87% yield of D-glucose penta-acetate at 90 °C in 2 h with acetic anhydride (Table 31, entry 1). However, basic catalyst affected [BMIM][Cl] resulting black coloring of employed ionic liquid. The yield dropped to 27% when the recycled ionic liquid was used as a solvent in the esterification (Table 31, entry 2). Some impurities seemed to build up in the ionic liquid. Sodium acetate cannot be used as a catalyst in [BMIM][Cl] if recyclability is an issue. The reason for ionic liquid degradation was probably the acid base reaction between 1-butyl-3-methylimidazolium and sodium acetate.

Because of the good catalytic activity of NaOAc in [BMIM][Cl], less base sensitive ionic liquid was tested. An acidic proton in the carbon between nitrogens in the imidazole ring is subject to deprotonation by basic reagents. It is known that when the methyl group is attached to the carbon between nitrogens in imidazole it has improved tolerance toward basic reaction conditions. (229, 305, 306, 308) The sodium acetate catalyzed acetylation of D-glucose in 1-butyl-2,3-dimethylimidazolium chloride [BDMIM][Cl] yielded 75% of D-glucose penta-acetate after 2 h at 90 °C with conventional heating. However, a reuse of [BDMIM][Cl] resulted in a somewhat brownish reaction mixture with a remarkably decreased yield of penta-acetate. Even if [BDMIM][Cl] tolerates basic reaction conditions better than [BMIM][Cl], it is not completely recyclable. Also the observed drop in the yield after recycling was somewhat surprising. It was thought that probably sodium acetate leached from the reaction mixture when precipitation of the product was carried out.

Imidazole has been used as an esterification catalyst. (116) Methylimidazolium-based ionic liquids are made from 1-methylimidazole. It was thought that methylimidazole could be used as a basic catalyst with [BMIM][Cl]. Unfortunately, 1-methylimidazole seemed to be a poor catalyst for the acetylation reaction. The yield after 2 hours at 90 °C was low. The product also contained 1-methylimidazole as an impurity. Despite of being a poor catalyst 1-methylimidazole was also leaching into the product. [BMIM][Cl] was getting darker after the reaction, which is an indication of degradation of the IL and makes recycling of the solvent impossible in the long run (Table 31, entry 3).

Table 31. Catalyzed acetylation of D-glucose with acetic anhydride to glucose penta-acetate in ionic liquids under conventional heating.

Entry	Temperature (°C)	Time (h)	Solvent	Catalyst	Molar ratio[a]	Yield (%)
1	90	2	[BMIM][Cl]	NaOAc	9	87
2	90	2	[BMIM][Cl][a]	NaOAc	9	27
3	90	2	[BDMIM][Cl]	NaOAc	9	75
4	90	2	[BDMIM][Cl]	NaOAc	9	26
5	90	2	[BMIM][Cl]	1-Methylimidazole	9	1[a]

[a]Inappropriate crystallization

After screening of the basic catalysts it was evident that even slightly basic catalysts cannot be used with [BMIM][Cl]. Suphuric acid were chosen as a catalyst since [BMIM][Cl] is stable under acidic conditions. The esterification reaction was first tested with microwave heating and only 5.5 equivalent of acetic anhydride. The product was not formed after 30 min at 70 °C. The reaction was then carried out with traditional heating at 90 °C for 2 h, but no product was formed. Intrestingly, sulfuric acid was an efficient inhibitor of acetylations in [BMIM][Cl]. The solvent was completely recyclable, along with all the starting D-glucose (Table 32, entry 1 and 2). It was considered that perhaps sulfuric acid is not acidic enough in [BMIM][Cl] to catalyze the acetylations and a stronger acid is needed.

Next emphasis was toward triflic acid catalysed acetylations. It is more acidic than sulfuric acid, so it was thought that it might catalyze the acetylations in [BMIM][Cl]. Triflic acid was proven to be too acidic for D-glucose. The reaction was carried out at 90 °C for 2 h, with conventional heating. Ionic liquid survived the reaction conditions, but the D-glucose was turned brown. The boiling point (162 °C) of triflic acid was too low and some triflic acid was lost during the acetic acid distillation (Table 32, entry 3).

The catalytic activity of some Lewis acids was also studied. $ZnCl_2$ is an effective Lewis acid catalyst for acetylations in conventional solvents. (84) The catalytic activity of $ZnCl_2$ was only moderate in [BMIM][Cl]. The yield of glucose penta-acetate was 54% after 2 h at 90 °C (Compared to ref. 311 yield is just little lower). Unfortunately, the $ZnCl_2$ in [BMIM][Cl] was not completely recyclable because it was partially precipitated along with the product. The acetylations required the addition of the catalyst every reaction cycle and the product might be contaminated with small amount of $ZnCl_2$ (Table 32, entry 4).

Triflate salts have been commonly used as Lewis acid catalysts. LiOTf, (137) $Cu(OTf)_2$ (253, 284) and $Ce(OTf)_3$ (56) have been used to catalyze the acetylation reaction of various alcohols. They were tested in D-glucose acetylation with acetic anhydride. The reactions were carried out at 90 °C for 2 h, with conventional heating. The catalytic activity of LiOTf, $Cu(OTf)_2$ and $Ce(OTf)_3$ in [BMIM][Cl] was moderate at best. The yield of acetate was low. $Ce(OTf)_3$ did not work as a catalyst. $Cu(OTf)_2$ gave only low yields of 13%, and after recycling 17%. The best Lewis acid catalyst was LiOTf which yielded 26% of the acetylated product. $Cu(OTf)_2$ could be recycled even though it was water sensitive. The same was assumed to be true for other triflate salts as well. The recycling and drying of the IL returned the catalytic activity of metal triflate (Table 32).

Table 32. Catalyzed acetylation of D-glucose with acetic anhydride to glucose penta-acetate in [BMIM][Cl] under conventional heating.

Entry	Temperature (°C)	Time (h)	Catalyst	Molar ratio[a]	Yield
1	70	0,5[b]	H_2SO_4	5,5	0
2	90	2	H_2SO_4	9	0
3	90	2	HOTf	9	0
4	90	2	$ZnCl_2$	9	54
5	90	2	LiOTf	9	26[c]
6	90	2	$Cu(OTf)_2$	9	13
7	90	2	$Cu(OTf)_2$	9	17 [d]
8	90	2	$Ce(OTf)_3$	9	0

[a]Molar ratio of acetic anhydride to alcohol [c]Inappropriate crystallization [b]Microwave heating [d]Solvent Recycled

Non-catalyzed sonochemical acetylations of alcohols have been successfully performed in 1,3-dibutylimidazolium bromide [BBIM][Br]. (97) It was though that acetylations might proceed in [BMIM][Br], since it is almost the same than [BBMIM][Br]. The acetylation of D-glucose was slow in [BMIM][Br] with conventional heating. After 2 hours at 90 °C the reaction had not proceeded. Acetic anhydride was used as an acetylation reagent with 9 fold excess.

Since traditional Lewis acids in [BMIM][Cl] were not very efficient catalysts for the acetylation of D-glucose new ionic liquids with anions derived from Lewis acids were tested as reaction media. It is know that when Lewis acidic metal chlorides (such as $AlCl_3$) are dissolved in dialkylimidazolium chlorides Lewis acidic, neutral or Lewis basic ionic liquids are formed. (306) Neutral or Lewis acidic ILs could catalyze the acetylation similar as Lewis acids in conventional

solvents. As the first step neutral ionic liquids were prepared. Four new ionic liquids with different Lewis acid anions were prepared and tested in the acetylation reaction. The ILs prepared were [BMIM][$SnCl_4$], [BMIM][$ZnCl_3$] and [BMIM][$InCl_4$], which were made by adding the corresponding Lewis acid to [BMIM][Cl] (e.g. add $FeCl_3$ to [BMIM][Cl] and [BMIM][$FeCl_4$] was formed). The solubility of D-glucose was poor in the Lewis acidic ILs. Also the viscosities were high. High viscous reaction mixtures were hard to stir properly and the esterification reagent was difficult to spread evenly in the reaction mixture. The acetylation in [BMIM][$InCl_4$] and [BMIM][$ZnCl_3$] gave reasonably good yields of the acetylated product, 70 and 86% respectively. [BMIM][$FeCl_4$] and [BMIM][$SnCl_4$] both caused the D-glucose to turn into a black tar at the reaction condition (2 h at 90 °C). The leaching of metals to the product was low (under the detection limit of ICP-MS analysis). [BMIM][$SnCl_4$], [BMIM][$ZnCl_3$] and [BMIM][$InCl_4$] could be recycled and reused in the reaction (see Table 33).

Table 33. Acetylation of D-glucose with acetic anhydride to glucose penta-acetate in Lewis acidic ionic liquids under conventional heating.

Entry	Temperature (°C)	Time (h)	Solvent	Molar ratio[a]	Yield (%)
1	90	2	[BMIM][$FeCl_4$]	9	0
2	90	2	[BMIM][$InCl_4$]	9	70
3	90	2	[BMIM][$SnCl_4$]	9	0
4	90	2	[BMIM][$ZnCl_3$]	9	86

[a]Molar ratio of acetic anhydride to alcohol

Interestingly, with all the D-glucose acetylations carried out in this study the isolated product was always penta-acetate, even if the overall yield was low. It seems that there was some activating force in the ionic liquids which promotes full acetylation once acetylation is initiated.

Acetylated disaccharides could be used as paper sizing and coating chemicals (213), so it was interesting to see if they could be prepared efficiently with ionic liquids. The solubility of D-cellobiose was studied to various ionic liquids ([BMIM][DCA], [BMIM][Cl], [BMIM][BF_4] and [BMIM][CF_3CO_2]) but only [BMIM][Cl] was able to dissolve D-cellobiose. Dissolution was tested by adding 1 wt% of cellobiose to the ionic liquid and stirring first at room temperature for 2 h and then the solution was heated to 80 °C for 2 h ([BMIM][Cl] had to be heated to 80 °C from the beginning because of its high melting point). Similar behavior was expected for other disaccharides but was not studied further.

The acetylation of disaccharides D-lactose, D-maltose and D-cellobiose were studied in [BMIM][Cl], with acetic acid as an acetylation reagent. The reaction was carried out by dissolving saccharides into a dry[BMIM][Cl] and after dissolving acetic anhydride was added to the solution by stirring. The reaction time was 20 h at 90 °C. It was found that disaccharides reacted slower than D-glucose and a high excess of acetic anhydride was needed in order for the reaction to proceed (see Table 34). As was the case with D-glucose acetylation, only fully acetylated ester was collected, even though the yields were poor.

Sometimes it is important to be able to control the degree of substitution in acetylations (in paper coating for example). It was attempted to acetylate lactose to different acetylation degrees. The reaction was carried out so that acetic anhydride was added in portions. First, only 1 equivalent of acetic anhydride was added and the reaction was carried out for 2 h at 90 °C, the formed acetic acid was distilled and a sample was taken. The reaction was repeated 7 more times to obtain a fully acetylated product. The samples were analyzed with HPLC and NMR. Only fully acetylated product was found. The yield of fully acetylated product increased for every sample.

Table 34. Acetylation of lactose, maltose, cellobiose and starch in [BMIM][Cl] at 80 °C.

Entry	Carbohydrate	Time (h)	Molar ratio[a]	Yield octa-acete (%)
1	Lactose	20	24	12
2	Maltose	20	24	17
3	Cellobiose	20	8.6	0

[a]Molar ratio of acetic anhydride to disaccharide

To test the most complex carbohydrates, cellulose and starch were dissolved and acetylated in [BMIM][Cl]. The acetylated starch (E1421) has been used in the food industry for a long time as a thickening agent. Acetylated starch has a better tolerance of temperature and wider pH range compared to untreated starch. Acetylated starch could be used as drug delivery bed for modern peptide or protein based drugs. (295) Acetylated starch or cellulose could be used as a paper coating for enhanced printing quality. High DS cellulose acetate has been used as fiber in textile industry, also cine films have been made from it. (1, 152, 177) Before acetylations dissolution and degradation tests were performed for cellulose and starch. It was known at the time that cellulose will dissolve in [BMIM][Cl] but because of the high melting point of [BMIM][Cl] other ionic liquids were tested. The solubility was detected by visual detection and the cellulose was considered dissolved when a homogenous clear solution was observed.

[BMIM][Cl] was the only solvent of all the tested ionic liquids which dissolves cellulose in high concentrations (at least 25 mol% of cellulose in [BMIM][Cl]). Interestingly, the mixture of [BMIM][Cl]/[BMIM][DCA] did not dissolve cellulose. If cellulose was first dissolved in [BMIM][Cl] and [BMIM][DCA] was added, the cellulose remained dissolved until about 20 mol% of [BMIM][DCA] was added to the [BMIM][Cl]. [BMIM][CF_3CO_2] caused degradation of the cellulose chains (see Table 35).

Table 35. Dissolution tests of cellulose in various ionic liquids.

Entry	Solvent	Temperature (°C)	Time (min)	Dissolution
1	[BMIM][Cl]	80	30	Yes[a]
2	[BMIM][[DCA]	60[b]	30	Partly
3	[BMIM][SCN]	60[b]	30	Partly
4	[BMIM][CH_3SO_3]	120[b]	30	No
4	[BMIM][CF_3CO_2]	140[b]	30	No
5	[BMIM][Cl]/ [BMIM][[DCA]	RT	60	Partly
6	[TBA][Cl]	90	3 days	No
7	[Choline][Cl]/Urea	80	3 days	No

[a]Various different concentrations from 1 to 25 wt% were prepared. [b]Microwave heating

The esterification of starch or cellulose was studied in [BMIM][Cl] since it was only solvent which dissolved them. The carbohydrate was first dissolved in dry [BMIM][Cl] and acetic anhydride was used as an acetylation agent. The reaction mixture was heated to 80 °C with microwaves for 30 min. Three equivalents of acetic anhydride per D-glucose unit of carbohydrate were used. Similar acetylations were carried out for cellulose and starch. The results of the esterification were somewhat imprecise because the means of analysis of complex carbohydrates were limited. It was obvious from the analysis that acetylation reaction proceeded, but the achieved DS could not be detected with repeatable results (hydrolysis and titration gave unreliable results). The solubility to acetone or water of cellulose or starch was not changed (151), which indicates that DS might be lower than 0.5. Titration and IR studies gave a DS of about 1, which might have been affected by the contamination of acetic acid from the acetylation reaction.

Conclusions on esterification

According to this study ionic liquids can be used as a solvent in the acetylation of carbohydrates. Catalysts and unreacted starting materials could be recycled for the first time, without laborious and expensive work out. It was possible to remove the acetic acid by-product easily as pure acid and produce fully acetylated carbohydrates. Water could be used as precipitation agent for the acetylated product and with the removal of water, ionic liquids, catalysts and unreacted starting materials could be recycled to into the next reaction cycle.

It was possible to recycle the ionic liquid when an acid catalyst was used. When basic catalysts are used the recycling needed ILs other than imidazolium-based ionic liquids. Ionic liquids made from [BMIM][Cl] and metal chloride Lewis acids could be used as a catalytic solvent for monosaccharides although carbohydrates have low solubility in them.

The use of an ionic liquid as a solvent gave several advantages to the acetylation reaction. The initial thought of ionic liquid being used as a catalytic solvent was not realized but other features were found which justify the use of ionic liquid. It was a common practice from the beginning of the project to use the low volatility of ionic liquids and products as an advantage in separation and purification of the product. The acetic acid produced in the acetylation with acetic anhydride could be easily removed by vacuum distillation without distilling the solvent or product. After removing the acetic acid the product was precipitated with water. On a larger scale it is important to be able to distill the produced acetic acid without water because it is not economically or environmentally feasible to concentrate water-diluted solutions of acetic acid.

Combining all common practices used in the acetylation it was possible to develop a new process scheme for alcohol esterification with different acid anhydrides. The process could be completely closed with only the starting materials going in and product coming out. This would be a perfect process scheme from a green chemistry point of view (Fig. 76).

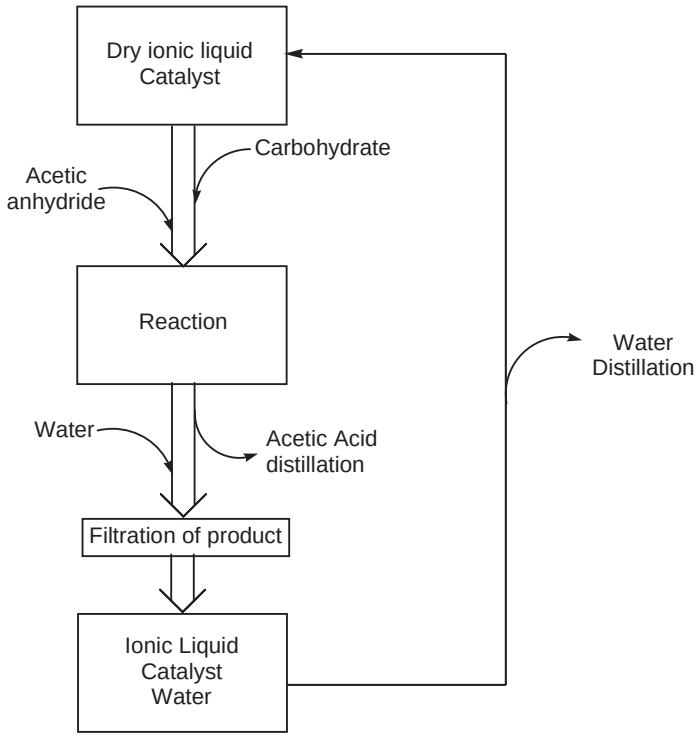


Fig. 76. New process scheme for esterification of carbohydrates in ionic liquids.

The biggest challenges for the new acetylation process were the yields of the acetylation reactions and precipitation of the product. They must be improved for the process to gain industrial interest. The sodium acetate catalyzed acetylations had the potential reaction rate for competing with existing processes. Finding a suitable ionic liquid for the sodium acetate catalyst or finding a catalyst suitable for present ionic liquids will be the challenge in the future. The poor crystallization of acetylated product was a problem in [BMIM][Cl] mediated acetylations. The temperature of the crystallization was the most crucial factor for success. Even a small deviation from the optimum temperature and the product precipitated as goo. Sometimes even the yield achived is affected by this undesirable phenomenon.

5.2.3 Etherification reactions

The ether group is chemically more stable than the ester group. Also the polarity of the hydroxyl group can be masked better with the ether group than with the ester group.

The etherification reaction is usually carried out under basic conditions. Basic conditions were not used extensively with ionic liquids when this study was started.

The carboxymethyl and quaternary ammonium groups attached to starch have been used in the paper industry for increasing fiber wet strength. Since a new process for acetylation was realized, etherification could be improved with ionic liquids as well. Also, using cellulose instead of starch could be realized with ionic liquids.

The experience gained so far had shown that [BMIM][Cl] was the only choice to use in carbohydrate chemistry. Any other commonly used ionic liquids could not dissolve the carbohydrates at reasonable levels. It was published that [BMIM]-salts were successfully used with bases such as KOH and NaOH. (306) These pieces of information provided the starting point for studying etherifications in ionic liquid.

It can be seen from Table 36, Table 37 and Table 38 that none of the tested etherifications worked properly. All the etherifications in ionic liquid produced dark brown/black tar like product, which turned out to be degradation products from the carbohydrate and ionic liquid. All attempts of base catalyzed etherification lead to degraded ionic liquid, even in the case where [BDMIM][Cl] was used as IL. The reason for the IL degradation was the deprotonation of imidazolium ring. Probably the hydrogen attached to carbon between the nitrogens in imidazolium ring leaves first and then the others will detach. This phenomenon has been proven later. (7)

After finding degradation products from the IL, base stability was tested and it was found out that a gentle heating of [BMIM][Cl] with NaOH leads to severe degradation of the imidazolium ring. However if imidazolium is dissolved in water the mild basic conditions could be used (83).

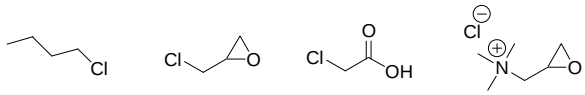


Fig. 77. Structures of etherification reagents used (chlorobutane, epichlorohydrin, chloroacetic acid, trimethyloxiraneylmethylammonium chloride)

Etherification of D-glucose with chlorobutane (see Fig. 77) was tried in water to get an overview of the reaction. Tetrabutylammonium[HSO_4] was used as a phase transfer catalyst. NaOH was used as a base catalyst to remove a proton from the carbohydrate hydroxy group. Different temperatures were tested; 120 °C for 30 min and room temperature for 3 days, but both resulted in degradation of D-glucose unit (see Table 36, entries 1 and 2).

The etherification of D-gluose in water was tested with epichlorohydrin (see Fig. 77) as alkylating agent. The reaction was first carried out at 0 °C for 20 h, with tetrabutylammonium[HSO_4] as a phase transfer a catalyst and NaOH as a catalyst. The low temperature was chosen because of the degradation of the D-glucose unit observed before. The reaction seemed to work with at the first try according to ESI-MS. The amount of the product was very low and the yield could not be determined (Table 37, entry 3). The rection temperature was raised to 100 °C and the reaction time was increased to 40 h. At higher temperatures D-glucose was severely degraded and no product could be detected (Table 36, entry 4).

Acetonitrile has been used widely as a solvent in carbohydrate chemistry and etherification with epichlorohydrin was tried in it. It was also thought that basic NaOH causes the degradation of the D-glucose unit, so the etherification reaction was tested without additional catalyst. The hydroxy groups in D-glucose should be nucleophilic enough to cause the epoxy ring in epichlorohydrin to react. The D-glucose did not dissolve completely in acetonitrile, so the reaction was a two phase reaction where D-glucose was swelled in acetonitrile and the reagent was dissolved in it. The etherification was carried out by refluxing acetonitrile at 81 °C for 20 h. After the desired time the reaction mixture was quenched with water and extracted with dichloromethane. The product was not formed and all the starting D-glucose could be regenerated from the water layer. Probably the hydroxyl groups in D-glucose were too hindred for the reaction to occur (Table 36, entry 5).

Sometimes reactions without additional solvents give good yields with microwave heating. The etherification of D-glucose was tested with microwave heating, where epichlorohydrin acted as a solvent. The reaction time was 30 min and temperature 120 °C. The reaction mixture was quenched with water and extracted with dichloromethane, but no products were found. Probably the hydroxyl groups were too hindred here as well because epichlorohydrin is such a poor solvent for D-glucose (Table 36, entry 6).

Since reactions with epichlorohydrin gave such unwanted results, a completely new system was tested. The solvent was changed to ethanol. The etherification agent was changed to sodium chloroacetate in order to see if the carboxymethyl group could actually be attached to the glucose unit. NaOH was already proven to be poor catalyst with D-glucose so it was changed to sodium imidazole. The D-glucose was dissolved in dry [BMIM][Cl] where the sodium chloroacetate and sodium imidazole were added. The reaction mixture was heated to 80 °C for 7 h. The reaction mixture was analyzed with ESI-MS. It could be seen from the MS-spectrum that some product might have been formed, but the amounts were so low that isolation was impossible. The major by-product from the reaction was substituted imidazole, which was a result of the reaction between sodium imidazole and chloroacetic acid (Table 36, entry 7).

Table 36. Etherification of D-glucose in different reaction conditions.

Entry	Solvent	Reagent	Base	T (°C)	Time (h)	Yield (%)
1	Water	Chlorobutane	NaOH	120	0.5[a]	-
2	Water	Chlorobutane	NaOH	RT	3 days	-
3	Water	Epichlorohydrin	NaOH	0	20	Some
4	Water	Epichlorohydrin	NaOH	100	40	-
5	Acetonitrile	Epichlorohydrin	-	81	20	-
6	-	Epichlorohydrin	-	120	0.5[a]	-
7	Ethanol	Sodium chloroacetate	Sodium imidazole	80	7	-

[a]Microwave heating

Since the etherification reactions with conventional solvents were disappointing, a new reaction medium was tested. It was known that D-glucose is highly soluble in [BMIM][Cl] and epichlorohydrin was also soluble. It was thought that the etherification would proceed in [BMIM][Cl] without an additional catalyst, since D-glucose hydroxyl groups should be available. It was also proved that the basic catalyst cannot be used. D-Glucose was first dissolved in dry [BMIM][Cl] and

then epichlorohydrin was added. The reaction was carried out at 80 °C for 20 h. After the desired time, the reaction mixture was quenched with water and extracted with dichloromethane. No product was found and most of the D-glucose could be recovered from the water phase with black ionic liquid. Epichlorohydrin might have reacted with [BMIM][Cl] and caused the color change of the ionic liquid (Table 37, entry 1).

Epoxides should react with alcohols, with acid catalysts as well as with base catalysts. An acid catalyst should change the end product by changing the chemoselectivity of the epoxide ring. Since chemoselectivity would not be an issue here, also acid catalysts were tested. D-Glucose was first dissolved in dry [BMIM][Cl] where sulfuric acid was added as a catalyst followed by addition of epichlorohydrin. The reaction was carried out at 80 °C for 20 h and the workout was the same as before. No product was found with the acid catalyst. The color of the ionic liquid was black after the reaction. This was a further evidence that epichlorohydrin reacts with ionic liquids since now the reaction mixture was acidic during the whole reaction (Table 37, entry 2).

It was assumed that probably the proton between the nitrogens in the [BMIM]-ring reacted with epichlorohydrin. So the etherification was tested in [BDMIM][Cl]. The reaction was carried out as before with [BMIM][Cl] (Table 37, entry 3). After the reaction, the ionic liquid had turned black. The ionic liquid was carefully analyzed with ESI-MS and NMR in order to find the reasons for the color change. It was also assumed that epichlorohydrin reacted with [BDMIM]-cation. No evidence for this was found, however, it seemed from the spectra that the ionic liquid was intact. The color change was so intense, that even if the IL seemed to be intact it was concluded that epichlorohydrin could not be used with imidazolium based ionic liquids.

Because etherifications with epichlorohydrin lead to black ionic liquid and quite poor results with conventional solvents, a new epoxide reagent was tested. Trimethyloxiraneylmethylammonium chloride (see Fig. 77) was chosen as the etherification reagent. It has been used in the preparation of cationized starch for the paper industry, so it was a good candidate to test. If the reaction would work it would give a new method for making high volume products. First, the trimethyloxiraneylmethylammonium chloride was dissolved in [BMIM][Cl] and the mixture was dried in vacuum at 70 °C for 24 h. D-Glucose was then added and the reaction was carried out at 80 °C for 20 h. The product separation was problematic, since the ionic product had to be separated from the ionic liquid. According to ESI-MS, a hint of product where one hydroxy group of D-glucose

reacted was found. Product separation was tested with solid phase extraction with a strong cation exchange column, which binds imidazolium and unfortunately the product as well. The extraction column was changed to weaker cation exchanger, but it did not bind either the imidazolium or the product. It was also attempted to precipitate the product with CH_2Cl_2, but the amount of the product was probably too low for precipitation to succeed. So one product was formed, but it was virtually impossible to get it out from the reaction mixture (Table 37, entry 4).

Table 37. Etherification of D-glucose in ionic liquids with different etherification reagents at 80 °C for 20 h.

Entry	Ionic liquid	Reagent	Catalyst	Yield (%)
1	[BMIM][Cl]	Epichlorohydrin	-	-
2	[BMIM][Cl]	Epichlorohydrin	H_2SO_4	-
3	[BDMIM][Cl]	Epichlorohydrin	-	-
4	[BMIM][Cl]	Trimethyl-oxiranylmethyl-ammonium chloride	-	-

Cellulose ethers have been prepared in *N*,*N*-dimethylacetamide/LiCl mixture where cellulose has been dissolved and etherification has been done with sodium chloroacetate catalyzed by NaOH. This produces cellulose ethers with non-uniform substitution patterns. (152) It was thought that perhaps etherifications in ionic liquid would produce uniform substitutions because of better solubility of cellulose in ionic liquids.

After realizing that the recycling of [BMIM][Cl] in base catalyzed etherification was impossible, base catalyzed etherifications were tested for cellulose and starch, just to see the results. Carboxymethyl cellulose was prepared with a heterogeneous mixture of cellulose, NaOH and sodium monochloroacetate dissolved in a suitable alcohol. This method consumes vast amout of sodium chloroacetate in the reaction where sodium chloroacetate reacts with the alcohol catalyzed by NaOH.

The carboxymethylation (see Fig. 78) of cellulose was tried with various different temperatures and times. The reaction was carried out by dissolving cellulose in dry [BMIM][Cl] and sodium monochloroacetate and NaOH was added. The reaction mixture was first heated in an oil bath 1 h at 80 °C and after that the reaction mixture was heated with microwaves for 1 h at 80 °C. Cellulose was precipitated from the reaction mixture with addition of water. The analysis was done with IR, but no product was formed (Table 38 entry 1). Because etherification did not proceed at 80 °C, the reaction temperature was increased to

100 °C and heating was done with microwaves only. After 2 h at 100 °C the cellulose was precipitated with water and analyzed. IR indicated that some acetic acid groups were attached to the cellulose chains, but the degree of substitution could not be detected (Table 38 entry 2).

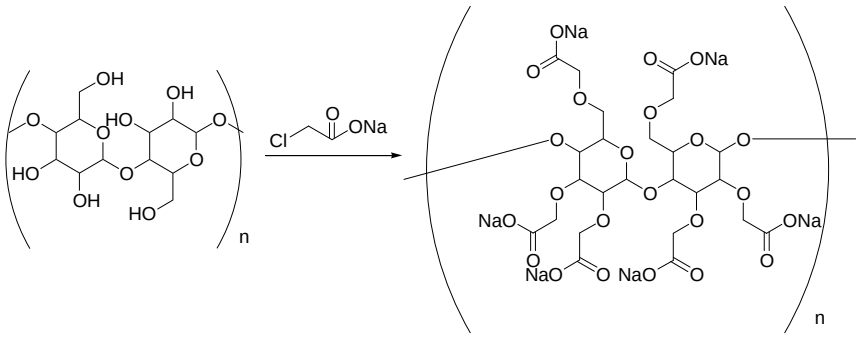


Fig. 78. Carboxymethylation of cellulose.

Since promising results were gained, the reaction time was increased from 2 to 15 h. The temperature was lowered to 55 °C because it was thought that the cellulose chains would degrade at high temperatures over such a long time. After product separation and analysis it could be seen that product was formed (Table 38, entry 3). Because of the low DS the temperature was increased to 110 °C and the reaction time was continued to 20 h. Still the DS of the acetic acid groups was very low (Table 38, entry 4).

Similar reactions were carried out for starch. Starch was known to degrade at high temperatures in ILs (212), so 80 °C was the practical maximum temperature. The reaction was done similarly as with cellulose, where starch was first dissolved in dry [BMIM][Cl] and NaOH and mono chloroacetic acid was added. The results for starch were similar with those for cellulose. Some acetic acid groups were attached to the chain, but the DS was very low (Table 38, entry 5).

The common fact for all cellulose and starch etherifications was that [BMIM][Cl] was severely degraded during the reaction. It was evident that base catalysis could not be used, even though it has been claimed in literature. All isolated ILs were black and some even had precipitate in them. Purification by filtering and charcoal mixing somewhat reduced the color, but recyclability was not satisfactry.

Table 38. Etherification of Cellulose and starch with chloroacetic acid catalyzed by NaOH in [BMIM][Cl].

Entry	Carbohydrate	T (°C)	Time (h)	Yield (%)
1	Cellulose	80	1 + 1[a]	-
2	Cellulose	100	2[a]	Some
3	Cellulose	55	15	Some
4	Cellulose	110	20	Some
5	Starch	80	20	Some

[a]Microwave heating

Conclusions on etherification of carbohydrates

Looking back in the results it can be concluded that the base catalyzed etherification reaction is a huge challenge in ionic liquid chemistry. Basic reaction conditions cannot be used with [BMIM]-cation, which seems to be the only usable cation with carbohydrates. This result was not a complete surprise at this point of the study, since basic catalysts gave bad results in the recycling of [BMIM] in acetylation reactions as well. The single use of [BMIM][Cl] in carbohydrate etherification gave poor yields of products.

The most unexpected reaction was the reaction of epichlorohydrin with [BMIM]-cation. It is not clear why epoxide reacts with [BMIM]-cation so eagerly, probably because [BMIM]-cation has an acidic proton. After proton release imidazolium could form carbene, which can react with epoxide. These products were sought out, but the reaction mixtures were so complex that proving the reaction path was virtually impossible.

5.2.4 Ene reactions

The ene reaction of allylbenzene and N-methylmaleimide (Fig. 79) has potential use for the cross-linking of polymers, in particular between a cyanate ester resin and a bismaleimide. (55)

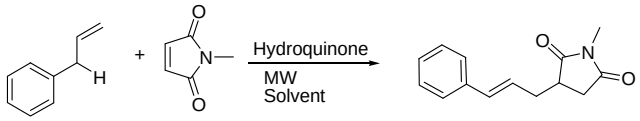


Fig. 79. Ene reaction between allylbenzene and *N*-methylmaleimide.

The ene reaction studies were a combined study with the University of Helsinki Drug Discovery and Development Technology Centre (DDTC). They needed reaction conditions for the ene reaction with reasonable yield and reaction times. Microwave heating and ionic liquids were tested in the ene reaction. The reaction was carried out in DDTC with conventional heating and in 1,2,4-trichlorobezene with 4% yield. It was imperative to increase the yield of the reaction before it could be used further. The ene reaction needs lot of energy to proceed, so microwaves were an obvious choice for improving the yield. Pericyclic reactions usually give better yields with polar solvents, so the effect of ionic liquids was tested.

First microwave assisted ene reaction was performed in 1,2,4-trichlorobenzene at 200°C. Equal amounts of allylbenzene and N-methylmaleimide were used and 0.1 mol% of hydroquinone was used to prevent side reactions. After 15 min the yield of 1-methyl-3-(3-phenyl-allyl)-pyrrolidine-2,5-dione was low and practically no product was formed. The temperature was raised to 250 °C and after 15 min the yield was 7%. The product was a mixture of *cis*- and *trans*-products. Increasing the reaction time to 60 min at 250 °C increased the yield to 20%. After 60 min all *N*-methylmaleimide was consumed, so a longer reaction time has no effect on the yield (Table 39). Yields were determined from a gas chromatography by comparing the allylbezene peak area to the product peak areas. Products were also isolated and the yield was confirmed with the pure isolated product.

Table 39. Reactions of equimolar amount of allylbenzene and *N*-methylmaleimide in 1,2,4-trichorobenzene with 0.1 mol% of hydroquinone. Microwave heating was used. The product was 1-methyl-3-(3-phenyl-allyl)-pyrrolidine-2,5-dione.

Entry	T (°C)	Time (min)	Yield[a] (%)
1	200	15	< 1%
2	250	15	7%
3	250	60	20%
4	250	120	20%

[a]Calculated from GC mixture of Cis – and Trans-product

A small amount of ionic liquid in nonpolar solvent has been reported to help the microwave heating of such a solvent (171). Toluene, for example, could be heated to 250 °C when IL is added to it. Without ionic liquid toluene heats slowly and it is hard to achieve temperatures higher than 150-170 °C with microwave heating. [BMIM][PF_6] was chosen for a doping IL because it has been reported to be

stable up to 300°C. So far the ene reaction was only carried out in 1,2,4-tricholobenzene, so it was concluded that toluene doped with the IL would create similar reaction conditions. In toluene doped with [BMIM][PF_6] (3 mass% of [BMIM][PF_6] in toluene) the reaction was carried out at 200 °C for 25 min, but the yield was low only <1%. The reaction temperature was increased to 250 °C for 30 min, which increased the yield to 5%. Increasing the reaction time to 60 min slightly increased the yield to 7%. Hydroquinone under these conditions did not have any effect on the yield.

A polar reaction medium usually gives better yields in Diels-Alder reactions. (73) Since the ene reaction is also a pericyclic reaction it was concluded that a polar reaction medium might give good results. The use of microwave heating was another reason to use ionic liquids as a solvent, because ILs heat efficiently with microwaves and high temperatures were needed. The ene reaction in [BMIM][PF_6] at 250 °C produced 10% of the product in 60 min, but purifying the reaction mixture was quite tedious and some degradation of the IL was observed. [BMIM][NTf_2] was the next choice as a solvent, since it is more stable than [BMIM][PF_6] at high temperatures. The yield was 21% after 60 min at 250 °C. Degradation of IL was not observed, but the purification of the product from the IL was hard.

It was reported that the ene reaction in ethanol at 220 °C gave 40% yield in 8 hours. (162) The maximum pressure used in the microwave reactor was 21 bar, where ethanol could only be heated to 180 °C. The yield of the ene reaction in ethanol at 180 °C was only 2% in 49 min (Table 41, entry 1). The reaction time was 49 min, because after that time the magnetron in the microwave reactor was too hot and caused the reactor to shut down.

1- and 2-propanols were tested as solvents because of the pressure limitation of the microwave reactor. The temperatures achieved at 21 bar pressure were 190 °C with 2-propanol and with 210 °C 1-propanol. The yields were very low <1% with both alcohols and almost all staring materials could be recovered. The low yields might be due to a combination of too low temperatures and the less polar reaction medium compared to ethanol (Table 40, entries 2 and 3).

Ethylene glycol was the next alcoholic solvent tested in the ene reaction. It is polar and has a high boiling point which would make it an almost ideal solvent. A good yield of 24% was achieved in 49 min reaction time at 220 °C (Table 40, entry 4). When the temperature was raised to 250 °C the yield increased 46 % in 60 min (Table 40, entry 5). After 60 min all maleimide was consumed in a side reaction. In order to prevent the side reaction the maleimide was added in

portions. Yields were similar even if the maleimide was added all at once or in different portions (Table 40, entries 6 and 7).

Table 40. Reactions of equimolar amount of allylbenzene and *N*-methylmaleimide in different alcohols. Microwave heating was used. The product wa 1-methyl-3-(3-phenyl-allyl)-pyrrolidine-2,5-dione

Entry	Hydroquinone	Solvent	T (°C)	Time (min)	Yield[c] (%)
1	0.1 mol-%	Ethanol	180	49	2%
2	-	1-Propanol	210	49	< 1%
3	-	2-Propanol	190	49	< 1%
4	0.1 mol-%	Ethylene Glycol	220	49	26%
5	0.1 mol-%	Ethylene Glycol	250	60	46%
6[a]	0.1 mol-%	Ethylene Glycol	250	60	46 %
7[b]	0.1 mol-%	Ethylene Glycol	250	60	41%

[a]Maleimide added in 2 equal portions with 30 min heating after each addition. [b]Maleimide added in 3 equal portions with 20 min heating after each addition. [c]Calculated from GC mixture of Cis – and Trans-product

Since all tested solvents added more variables to the ene reaction, the reaction was decided to be carried out without an additional solvent. The high concentration of reactants might increase the contacts and thus improve the yields. The results were practically the same as in the reactions with ethylene glycol. The purification of the product was quite simple and straight forward because there were no additional solvents to get rid of at the end of the reaction. The reaction was first carried out at 220 °C and the yield was 26%. The temperature was then increased back to 250 °C and yield was improved to 55% in 60 min (Table 41, entries 1 and 2). The reaction was tested with an excess of allylbenzene (300 mol%), but heating was not efficient with microwaves and only low yields were observed. Maleimide had to be added in three portions with 20 min of heating after each portion to get the best results. By adding maleimide in portions side reactions could be avoided to some extent. A lack of side reactions might be due to the high concentration of allylbenzene in the reaction mixture, so at the beginning the desired reaction dominates and the side reactions only happen after the allylbenzene is consumed from the reaction mixture. This was clearly the best way of performing the reaction, because purification of product was easiest and no solvent waste occured.

Table 41. Reactions of equimolar amount of allylbenzene and *N*-methylmaleimide without additional solvent. Microwave heating was used. The product was 1-methyl-3-(3-phenyl-allyl)-pyrrolidine-2,5-dione

Entry	Hydroquinone	T (°C)	Time (min)	Yield[c] (%)
1	0.1 mol-%	220	60	26%
2[a]	0.1 mol-%	250	60	43%
3[b]	0.1 mol-%	250	60	55%

[a]Maleimide added in 2 equal portions with 30 min heating after each addition. [b]Maleimide added in 3 equal portions with 20 min heating after each addition. [c]Calculated from GC mixture of Cis – and Trans-product

Conclusions on Ene-reaction

The ene reaction requires high temperatures to progress at a reasonable rate. Using microwave heating such high temperatures could be reached easily. The ene reaction between allylbenzene and *N*-methylmaleide could be performed with high yield in short time with microwave heating. The microwave reactor used limits the pressures to 21 bar and thus simple alcohols could not be heated to temperatures where the ene reaction would proceed. The ionic liquid or polar high boiling alcohols might be used as reaction media, but yields were lower than without additional solvent. If the reaction is carried out without additional solvents high pressures would not be generated during high temperature reaction. The reaction is best made without additional solvents. The best yields were obtained when *N*-methylmaleimide was added to allylbenzene gradually.

5.2.5 Sulfonylation reactions

Sulfonylation reactions were studied in QUILL in Queen's University in Belfast. It was part of a bigger project where the bistriflimide catalyst was studied in Friedel-Crafts chemistry. Sulfonylation is a variation of Friedel-Crafts acylation and it was interesting to see if the same catalyst would work in acylation and sulfonylation reactions. Also, new catalysts were made and tested in the reaction. The reason why these reactions were included in this thesis was that they give new perspectives on the use of ionic liquids. This was the first time, when the reactivity and solvent properties of ionic liquids were used in the manufacture of active catalysts and the same solutions were used in reactions.

The sulfonylation of toluene with benzenesulfonylchloride was the model reaction which was used to test all the prepared catalysts for their activity. The same reaction was also used in the microwave heating test.

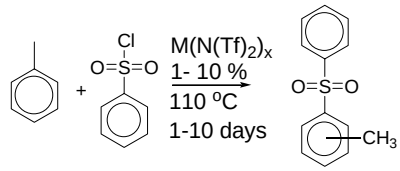


Fig. 80. Sulfonylation of toluene catalyzed by metal bistriflimide.

It was expected that zero order kinetics would dominate in bistriflimide catalyzed sulfonylations. Zero order kinetics suggests a complete ionization of sulfonyl chloride, where metalbistriflamide would capture Cl from the sulfonyl chloride. The rate determining step would then be the attack of the aromatic compound to the sulfonyl species (see Fig. 81).

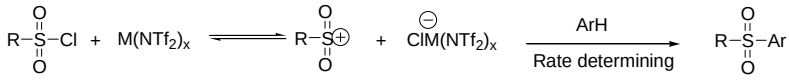


Fig. 81. Expected mechanism of metalbistriflamide catalyzed sulfonylation of aromatics.

Magnesium complexes have not usually been used as a Lewis acid catalyst but with bistriflimide ligand even Mg could be used as a Lewis acid catalyst. Mg-bistriflimide did not work very well for the sulfonylation of toluene with benzenesulfonylchloride, but catalytic effect can be observed (reaction did not proceed at all without the catalyst). The reactions were generally carried out without additional solvent in refluxing toluene. 1.5 Equivalent of toluene was used compared to sulfonyl chloride because of the slow evaporation of toluene. The catalyst loading was usually 1 mol%, because it was thought to be a practical amount of a catalyst to be used on a larger scale. At the beginning of the reaction, the starting materials and catalysts were measured to a dry reaction vessel. The reaction was carried out under flow of dry nitrogen. The reaction times were very long up to 10 days. The yields of phenyl-4-tolylsulfone were low, generally <1%. Interestingly, the scale of the reaction did affect the yields; bigger scale seemed to give lower yields. High catalyst loading (10 mol%) did not improve the yield with $Mg(NTf_2)$ catalyzed reactions. Microwave heating decreased the reaction time

from days to hours. The by-product HCl increases the pressure in the sealed microwave reactor and limits the reaction (see Table 42).

Table 42. $Mg([NTf_2])_2$ catalyzed sulfonylation of toluene with benzenesulfonyl chloride to phenyl-4-tolylsulfone. Catalyst loading is indicated as mol-% of sulfonylchloride, T = 110 °C.

Entry	Reaction time (days)	Catalyst (mol%)	Toluene (mmol)	Benzenesulfonylchloride (mmol)	Solvent	Yield (%)
1	6	1	7.5	5	-	1
3	7	1	23.6	15.7	-	<1
4	2 hours[a]	1	23.6	15.7	-	0.7
5	6	1	31.4	15.7	-	0.3
6	5	10	28.2	18.8	-	<1
7	4	10	24.1	16.1	-	<1
8	10	1	7.5	5	[BMIM][NTf_2]	6

[a]microwave heating

Transition metals have been used extensively as catalytic metals in Friedel-Crafts chemistry. (271) Some transition metal bistriflimide complexes were tested in the sulfonylation of toluene with bezenesulfonyl chloride. The reactions were carried out similarly to the Mg catalyzed reaction where 1.5 equivalent of toluene was used compared to sulfonyl chloride and 1 mol% of catalyst. The reactions were carried out without an additional solvent, because the catalytic effect of different metals needed to be compared without solvent effects. Cobalt and nickel complexes were poor catalysts. Cobalt gave at best a 47% yield of sulfonylated product after 11 days and nickel only gave a 15% yield after 7 days. Copper bistriflimide was a better catalyst than cobalt or nickel, but still the reaction times were long (8 days), but yields were good 91%. Yttrium bistriflimide was a crossover catalyst. It gave a good yield of 88%, but reaction times were still quite long (6 days). Indium and iron bistriflimide complexes were excellent catalysts for sulfonylation; both gave quantitative yields in just 24 h. The structure of the catalyst remained unsolved, namely the amount of oxygen attached to the catalyst was hard to find out (see Table 43).

Table 43. Sulfonylation of toluene with benzenesulfonyl chloride to phenyl-4-tolylsulfone catalyzed by 1 mol% of metal bistriflimide complex.

Entry	Reaction time (days)	Catalyst	Toluene (mmol)	Benzenesulfonyl chloride (mmol)	Yield (%)
1	3	$Co(NTf)_2$	31.4	15.7	<1
2	11	$Co(NTf_2)_2$	24,1	15,7	47
3	7	$Ni(NTf_2)_2$	31,4	15,7	15
4	8	$Cu(NTf_2)_3$	31,4	15,7	91
5	6	$Y(NTf_2)_3$	24,1	15,7	88
6	6	$HNTf_2$	31.4	15.7	5
7	1	$In_xO_y(NTf_2)_z$	31.4	15.7	100
8	1	$Fe_xO_y(NTf_2)_z$	31.4	15.7	100

Lanthanoids could be an interesting group of metals, especially with the bistriflimide ligand, because of the size of lanthanoid. A series of lanthanoids were tested as catalysts in the benzenensulfonylation of toluene. The sulfonylation reactions were carried out similarly as before. The first lanthanoids La, Ce and Pr were poor catalysts with low yields and long reaction times were detected (13, 11 and 9 days with 46, 10 and 32% yields respectively). Nd was better with a 66% yield in 11 days. Gd was a poor catalyst with only about a 4% yield in 11 days and also Gd bistriflimide induced a side reaction which consumed benzenesulfonyl chloride. $Yb(NTf_2)_4$ was a good catalyst for the sulfonylation reaction. It gave quantitative yields in just two days, so it was almost as good as indium or iron (See Table 44).

Table 44. Sulfonylation of toluene with benzenesulfonyl chloride to phenyl-4-tolylsulfone catalyzed by 1 mol% of lanthanoid bistriflimide complex.

Entry	Reaction time (days)	Catalyst	Toluene (mmol)	Benzenesulfonyl chloride (mmol)	Yield (%)
1	13	$La(NTf_2)_3$	31,4	15,7	46
2	11	$Ce(NTf_2)_3$	24,1	15,7	10
3	9	$Pr(NTf_2)_3$	24,1	15,7	32
4	11	$Nd(NTf_2)_3$	23,6	15,7	66
5	11	$Gd(NTf_2)_3$	24,1	15,7	~4 %
6	2	$Yb(NTf_2)_4$	31,4	15,7	100

An interesting catalyst can be manufactured from heavy metals. Bismuth triflates have been used as Friedel-Crafts catalyst (99), so it was thought that it might work in sulfonylation catalyst as a bistriflimide complex. The bismuth complex was proven to be an efficient catalyst for sulfonylation. First, the sulfonylation

was carried out for three days with a quantitative yield. The reaction time could be reduced to 24 h with a quantitative yield. The structure of the bismuth complex could not be determined because of poor crystallization of the complex. Also, the amount of oxygen in complex was hard to determine. Interestingly, when $Bi(NTf_2)_X$ catalyzed sulfonylation was carried out in [BMIM][NTf_2] the yields were poor, only 13% in two days. The catalyst is probably changed in [BMIM][NTf_2] to a complex with more [NTf_2]-ligands and this might explain the poor results observed (see Table 45).

Table 45. Sulfonylation of toluene with benzenesulfonyl chloride to phenyl-4-tolylsulfone catalyzed by 1 mol% of Bi-bistrilimide-complex.

Entry	Reaction time (Days)	Toluene (mmol)	Benzenesuofonyl chloride (mmol)	Solvent	Yield (%)
1	3	31,4	15,7	-	100
2	1	31,4	15,7	-	100
3	2	31,4	15,7	[BMIM][NTf_2]	13

The kinetics of the benzenesulfonylation of toluene were studied in order to find out more details about how the catalyst works. The reaction was carried out similarly as before, where toluene acted as a solvent and a reactant and was used 1.5 equivalents compared to benzenesulfonyl chloride. 1 Mol% of the catalyst was used compared to benzenesulfonyl chloride. The reaction temperature was 110 °C. A series of samples were taken from the reaction mixture and analyzed with GC. Sulfonylation follows roughly zero order kinetics, so yields increase linearly with time (See Fig. 82). Toward the end of the reaction the amount of toluene becomes a limiting factor and thus the reaction rate drops. The reaction will go on to completion with the same rate if a higher excess of toluene is used.

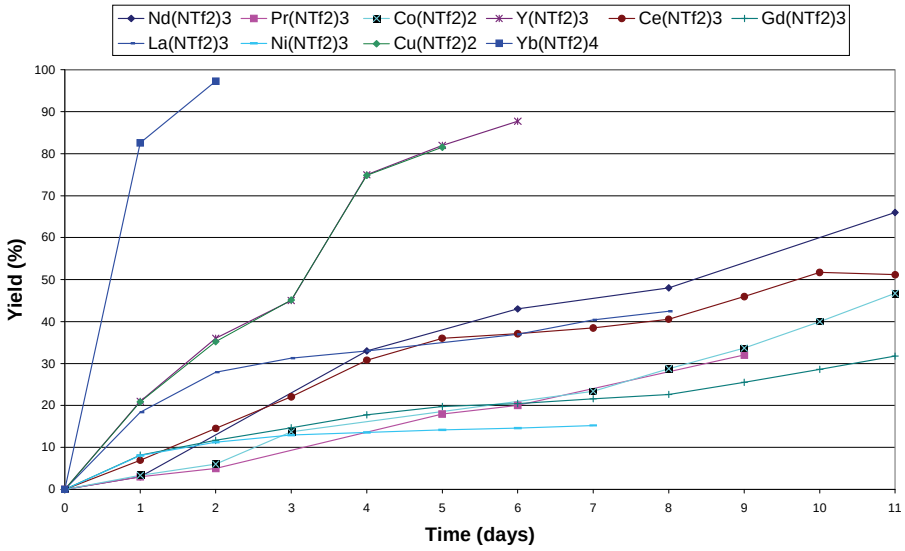


Fig. 82. Metal bistriflimide catalyzed sulfonylation of toluene with benzenesulfonyl chloride to phenyl-4-tolylsulfone.

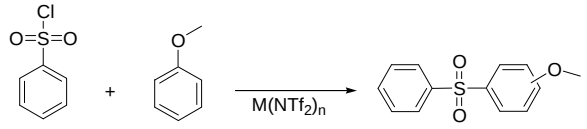


Fig. 83. The Benzenesulfonylation of anisole to methoxyphenylphenylsulfone catalyzed by metaltriflimide complex.

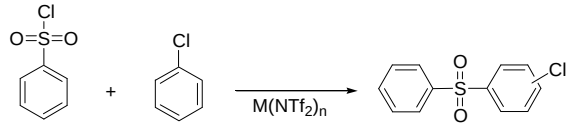


Fig. 84. The Benzenesulfonylation of chlorobenzene to chlorophenylphenylsulfone catalyzed by metaltriflimide complex.

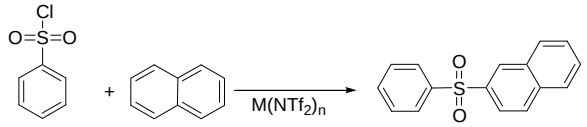


Fig. 85. The Benzenesulfonylation of naphtalene to naftoylphenylsulfone catalyzed by metaltriflimide complex.

The benzenesulfonylation of different aromatics was tested with Co, Nd, Bi and Yb bistriflimide complexes, in order to find out their catalytic effect. Anisole was chosen because it is an electron releasing and activating group on the aromatic ring (see Fig. 83). Chlorobenzene on the other hand is electron withdrawing and it deactivates the aromatic ring (see Fig. 84). Naphthalene is a bigger aromatic system(see Fig. 85). These aromatics gave a nice overview of the electronic effects on the aromatic ring. The reactions were carried out at 110 °C for three days each to get comparable results for toluene sulfonylations. In some cases *p*-toluenesulfonyl chloride was used instead of benzenesulfonyl chloride. Some differences of the results might be explained by the different aromatic sulfonyl compounds which have different reactivities (see Table 47). The electronic effects on the aromatic ring act as expected. Thus chlorobenzene reacts slowly with all catalysts and the difference in the catalytic performance between metal complexes was small (yields <1, 19, 21 and <1% respectively). Anisole had the next best yields of sulfonylated products 4, 41, 81 and 61%. The Bi complex shows a much higher reaction rate than other bistriflimide complexes. The same is true for naphthalene as well, which reacts with good yields on all catalysts (13, 81, 100 and 83%). The similar reaction rates observed with catalysts with chlorobenzene probably results from the low reactivity of chlorobenzene. Even if the complex produces ionized sulfonyl compound (Yb and Bi) the limiting step of the reaction is the formation of the product. When the aromatic is changed to a more reactive aromatic the limiting step is the formation of an ionized sulfonyl compound (See Table 46).

Table 46. Sulfonylation of anisole, chlorobenzene and naphtalene with benzene- or *p*-toluenesulfonyl chloride to corresponding sulfone at 110 °C for 3 days.

Entry	Catalyst	Aromatic	Yield (%)
1	$Co(NTf_2)_2$	Chlorobenzene	<1[a]
2	$Co(NTf_2)_2$	Anisole	4[a]
3	$Co(NTf_2)_2$	Naphthalene	13[a]
4	$Nd(NTf_2)_3$	Chlorobenzene	19
5	$Nd(NTf_2)_3$	Anisole	41
6	$Nd(NTf_2)_3$	Naphtalene	81
7	$Bi_xO_y(NTf_2)_z$	Chlorobenzene	21
8	$Bi_xO_y(NTf_2)_z$	Anisole	81
9	$Bi_xO_y(NTf_2)_z$	Naphtalene	100
10	$Yb(NTf_2)_4$	Chlorobenzene	<1[a]
11	$Yb(NTf_2)_4$	Anisole	61
12	$Yb(NTf_2)_4$	Naphthalene	83[a]

[a] *p*-toluenesulfonyl chloride

Different reactivities have been visualized in Fig. 86. Naphthalene was the most active, but interestingly toluene was more active than anisole under the same conditions. The activities of benzene and chlorobenzene could be boosted if higher temperatures would be used.

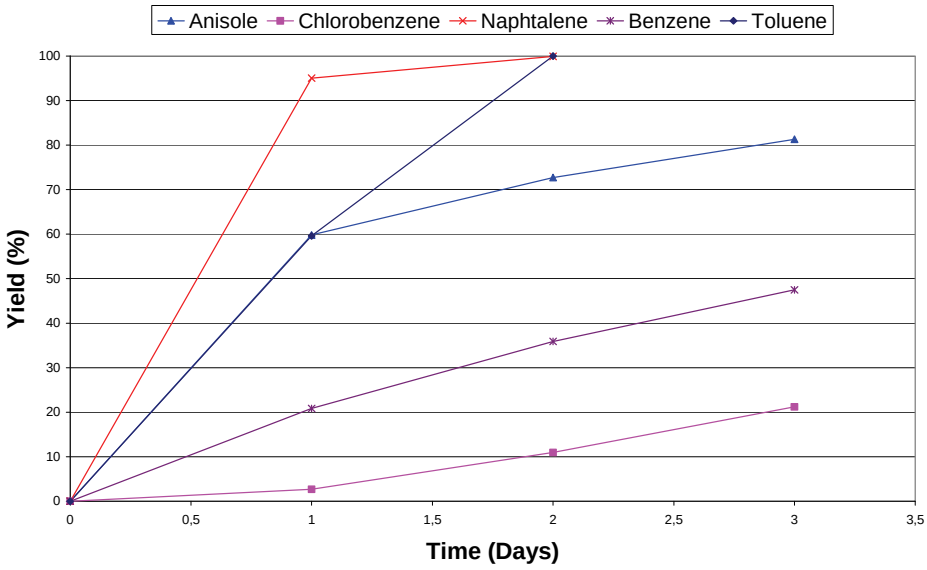


Fig. 86. Sulfonylation of different aromatic compounds, with benzenesulfonyl chloride catalyzed to corresponding sulfone by $Bi(NTf_2)3$.

Different sulfonyl chlorides were tested in sulfonylation to find out if there were differences in reactivity. The first tested sulfonyl chloride was *p*-toluenesulfonyl chloride, which was thought to have almost the same reactivity as benzenesulfonyl chloride. It was speculated that *p*-toluenesulfonyl chloride might probably act just slightly better because of the methyl group on the aromatic ring. The sulfonylation reaction was carried out as before, with toluene as a solvent and a reactant and 1 mol% of metal bistriflimide complex as a catalyst. When a cobat bistriflimide complex was used as a catalyst the reaction rates were similar, probably because Co is such a poor catalyst anyway. With Nd bistriflimide as the catalyst *p*-toluenesulfonyl chloride was more active than benzenesulfonyl chloride and with Yb the opposite reactivity was detected. The reason for the observed reactivity remained unclear, since with the Nd complex the reactivity difference was high favoring *p*-toluenesulfonyl chloride while Yb seems to favor benzenesulfonyl chloride (see Table 47).

Table 47. Sulfonylation of toluene with 1 mol% of *p*-toluenesulfonyl chloride or with benzene sulfonyl chloride to sulfone, reaction time was 3 days and temperature 110 °C.

Entry	Catalyst	Yield (%)	
		p-Toluenesulfonyl chloride	Benezenesulfonyl chloride
1	$Co(NTf_2)_2$	<1	<1
2	$Nd(NTf_2)_3$	33	<1
3	$Yb(NTf_2)_4$	48	100
4	$Bi_xO_y(NTf_2)_z$	100	100

p-Toluenesulfonyl chloride was tested in the sulfonylation of benzene to see if the sulfonylation would proceed at lower temperatures than 110 °C. The reactions were carried out in refluxing benzene, which acted as a solvent and reactant. The amount of benzene was 1.5 equivalent compared to *p*-toluenesulfonyl chloride. The catalyst was used at 1 mol% compared to sulfonyl chloride. The reaction time was chosen to be 3 days, which was sufficient for the best catalyst to have complete conversion of sulfonyl chloride to the product. The weaker catalysts (Co, Nd Yb) had poor conversions; the product could be identified with GC-MS but isolation of the product was practically impossible. When Bi bistriflimide was used as the catalyst the product yield was 47% in 3 days at 80 °C. The activation at lower temperature was not sufficient for sulfonylation to proceed at a reasonable rate.

Table 48. Sulfonylation of benzene with 1 mol% of *p*-toluenesulfonyl chloride to 4-methylphenyl phenylsulfone reaction time was 3 days and temperature 80 °C.

Entry	Catalyst	Aromatic	Yield (%)
1	$Co(NTf_2)_2$	Benzene	<1
2	$Nd(NTf_2)_3$	Benzene	<1
3	$Yb(NTf_2)_4$	Benzene	<1
4	$Bi_xO_y(NTf_2)_z$	Benzene	47

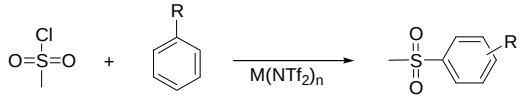


Fig. 87. Methanesulfonylation of different aromtics to produce methylphenyl sulfones catalyzed by metal triflimide complexes.

Methanesulfonyl chloride showed different activity than the aromatic sulfonyl chlorides. The difference was probably due to the less stable sulfonyl cation (see

Fig. 81 and Fig. 87). The reaction seems to need aromatic stabilation in order to proceed at reasonable reaction rates. The reactions were carried out as sulfonylations with benzenesulfonyl chloride, where the aromatic compound was the solvent and reactant and it was used 1.5 equivalents compared to sulfonyl chloride. 1 Mol% of catalyst was used. Only with the Bi-complex did sulfonylation proceed between toluene and methanesulfonyl chloride at a reasonable rate, while the other catalysts (Co, Nd, Yb) gave low yields of product. Even naphtalene, which was easy to sufonylate, reacted very slowly with methanesulfonyl chloride. Complete sulfonylation of toluene was observed only after 7 days at 110 °C with the Bi-complex. Higher catalyst loading gave better results and even chlorobenzene can be sulfonylated in 3 days with a 43% yield, when 7% of Bi-catalyst is used (see Table 49).

Table 49. Sulfonylation of aromatics with methanesulfonyl chloride catalyzed by 1 mol% of metalbistriflimide complexes. Reaction time was three days and temperature 110 °C.

Entry	Reaction time (days)	Catalyst	Aromatic	Yield (%)
1	3	$Co(NTf_2)_2$	Toluene	<1
2	3	$Co(NTf_2)_2$	Chlorobenzene	<1
3	3	$Co(NTf_2)_2$	Naphthalene	<1
4	3	$Co(NTf_2)_2$	Anisole	<1
5	3	$Nd(NTf_2)_3$	Toluene	<1
6	3	$Nd(NTf_2)_3$	Chlorobenzene	<1
7	3	$Nd(NTf_2)_3$	Anisole	<1
8	3	$Nd(NTf_2)_3$	Naphthalene	<1
9	7	$Bi_xO_y(NTf_2)_z$	Toluene	99
10	3	$Bi_xO_y(NTf_2)_z$	Chlorobenzene	<1
11	3	$Bi_xO_y(NTf_2)_z$	Anisole	<1
12	3	$Bi_xO_y(NTf_2)_z$	Toluene	25
13	3	$Yb(_lTf_2)_4$	Chlorobenzene	<1
14	3	$Bi_xO_y(NTf_2)_z$ (7%)	Chlorobenzene	43
15	3	$Bi_xO_y(NTf_2)_z$ (4%)	Anisole	20
16	3	$Bi_xO_y(NTf_2)_z$	Naphthalene	66

The effect of catalyst loading was studied with less well working catalysts, Co, Nd and Yb, to see if they would be active enough to catalyze sulfonylation in higher concentrations. The reactions were carried out as before, except that the amount of catalyst was varied. When the amount of Co-bistriflimide complex was increased to 10 mol% the yield of sulfonylated product was 42% after 3 days at

110 °C. The increase was significant when compared to 1 mol%, which only had traces of the product. With 10 mol% of Co, even chlorobenzene (yield 26%) and anisole (yield 28%) could be sulfonylated. The Nd-complex reacted similarly with a 1 or 4 mol% loading. Probably a higher loading might show differences. The Yb-bistriflimide complex has similar reactivity with toluene and anisole, but with chlorobenzene higher yield was observed with 10 mol% catalyst loading compared to 1 mol% of catalyst. The difference might be explained by the higher amount of cationic sulfonyl compound (see Fig. 81). When more than 1 mol% of catalyst was used, better results were observed (see Table 50).

Table 50. Effect of catalyst loading on sulfonylation of aromatic hydrocarbons with Benzenesulfonyl chloride to corresponding sulfone. Reaction time was three days and temperature was 110 °C.

Entry	Catalyst	Mol% catalyst	Aromatic	Yield	
				Higher mol% catalyst	1 mol% catalyst
1	$Co(NTf_2)_2$	10	Toluene	42	<1
2	$Co(NTf_2)_2$	10	Chlorobenzene	26	<1
3	$Co(NTf_2)_2$	10	Anisole	28	4
4	$Nd(NTf_2)_3$	4	Chlorobenzene	16	19
5	$Nd(NTf_2)_3$	4	Anisole	46	41
6	$Yb(NTf_2)_4$	5	Toluene	100	100
7	$Yb(NTf_2)_4$	10	Chlorobenzene	66	<1
8	$Yb(NTf_2)_4$	8	Anisole	71	61

The applicability of the metalbistriflamide catalyst was tried in the sulfonylation between *p*-toluene sulfonic acid and toluene. The amount of catalyst was 6 mol%, the reaction was very slow and in 6 days only trace amount of the product was found. With a higher catalyst loading the reaction might proceed faster. Reason for the low reaction rate was probably coordination of the sulfonic acid group to the metal center.

Conclusions on sulfonylation

The best catalysts for the sulfonylation of toluene with benzenensulfonyl chloride were $Bi_xO_y(NTf_2)_z$, $Yb(NTf_2)_3$, $In_xO_y(NTf_2)_z$ and $Fe_xO_y(NTf_2)_z$. The reactions were completed in less than 24 h with these catalysts.

The reaction followed zero order kinetics. The mechanism reveals that either catalyst-sulfonyl chloride complex or ionized sulfonyl species reacts with the aromatic compound.

The catalyst could be formed with the reaction of metal carbonate with $HNTf_2$ or simply by dissolving the metal to [BMIM][[NTf_2]], where the catalyst forms. Sometimes ionic liquid accelerates the sulfonylations, but with some catalysts the reaction was inhibited by the use of IL. Microwaves could be used to accelerate the reaction but ventilated reaction vessels were mandatory.

6 Conclusion

It was shown that ionic liquids could be used as solvents in the acid catalyzed esterification of polyols and carbohydrates with good yields. The yields were usually similar or better compared to the reaction in conventional solvents. The main difference between ionic liquids and conventional solvents was that produced acetic acid by-product could be separated before the actual product precipitation and the product was precipitated with simply adding water to the reaction mixture. This order of the product separation avoids the production of water diluted solutions of the acid. The acetic acid could be recycled back to the anhydride. The overall process has high atom economy since all acetic anhydride could be used. In addition, ionic liquids, catalysts and unreacted starting materials could be recycled. Using this methodology it was possible to design a new process scheme for the acetylation to be used on an industrial scale with a high efficiency. Microwave heating could be used to accelerate the esterification. It was shown that at least simple alcohols can be esterificated in minutes compared to several hours with conventional heating.

The etherification reaction was proven to be more problematic, since a base catalyst and epoxides could not be used with [BMIM]-cation. It might be possible to use different cations in the etherification reaction, possibly one which has a basic functionality built in the cation core.

The ene reaction was a success with microwave heating. Ionic liquids did not play a major role in the ene reaction, since it was most successfully carried out without additional solvent. The ene reaction showed that microwave heating gave a great advantage with energy intensive reactions.

The sulfonylation reaction catalyzed by metal bistriflimide catalysts has shown for the first time that ionic liquid reactivity and solvent ability could be used to manufacture a new kind of reaction medium. The catalysts were manufactured so that they could be prepared easily in ionic liquids containing [NTf_2]-anion. One structure of bistriflimide catalyst was found. New efficient catalysts could be manufactured, although their actual structure could not be solved. The bistriflimide catalyst could be recycled without a loss of efficiency and if the reactions were performed in ionic liquid the recycling is easy. The product was just precipitated and ionic liquids with the catalyst were dried. Microwave heating could be used to accelerate the reaction, but ventilated reaction vessels would be needed in order to use microwaves efficiently in sulfonylation reactions.

Overall, ionic liquid and microwave heating allow scientists to open new unexplored functionalizations of complex systems. At the same time the recycling of the solvent and catalyst are possible. This helps implement the green aspect from basic research to the multiton industrial process right from the beginning of the research. It is easier to design a green reaction from scratch than to try to implement green on an industrial scale process.

7 Experimental

7.1 General

All chemicals were research grade and were usually used as obtained from a supplier. Acetic anhydride was distilled under N_2 with a fractionating column. The reactions were carried out in round bottomed flasks under nitrogen atmosphere and mainly in oil bath. The microwave reactions were carried out in sealed microwave tubes. 1-Butyl-3-methylimidazolium bromide was purchased from Fluka and was used as such.

The microwave reactor was Emrys Creator from Biotage (personal Chemistry), where temperature, pressure and microwave power could be controlled. The reaction vessels used were 2-5 ml or 0.5-2 ml tubes. The maximum usable pressure was 21 bar, max usable temperature 250 °C and max microwave power 300 W. The reactor was a single mode reactor, where the microwave cavity was tuned for every sample, so that the absorption of microwaves was at the highest possible level.

NMR spectra were recorded with a Brucker DPX-200 spectrometer. The solvents used were $CDCl_3$ or D_2O. All spectra were calibrated to TMS (internal standard in $CDCl_3$) or solvent residual peak (D_2O) and chemical shifts are reported in ppm on the δ scale calculated from internal standard or from the solvent residual peak.

GC chromatograms were recorded with a Perkin Elmer AutosystemXL, with FID detector. GC-MS-spectra (EI) were recorded with a HP 6890 with quadrupole detector HP 5973 MSD. The columns used were selected to be suitable in all cases, usually low polarity columns were used (for example BPX-5, 30 m, 0.25 mm internal diameter and 0.25 μm film thickness from Supelco). ESI-MS-spectrums were recorded with a Micromass LCT mass Spectrometer.

7.2 Preparation of ionic liquids

7.2.1 1-Butyl-3-methylimidazolium chloride

1-Chlorobutane (159.5 g, 1.72 mol) in a 500 ml flask was mixed with 1-methylimidazole (103.0 g, 1.25 mol) and refluxed until all methylimidazole had reacted (24-48 h). The reaction was followed by electrospray mass spectrometry

and ^{1}H NMR. A crude product was recrystallized from ethyl acetate acetonitrile mixture. Yield of white [BMIM][Cl] was 174.8 g, 1.0 mol, 80 %. [BMIM][Cl]: ^{1}H NMR (200 MHz, CDCl3): δ 0.96 (3H, t, J_{HH} = 7.3 Hz), 1.41 (2H, m), 1.89 (2H, m), 4.13 (3H, s), 4.34 (2H, t, J_{HH} = 7.3 Hz), 7.47 (1H, t, J_{HH} = 1.8 Hz), 7.62 (1H, t, J_{HH} = 1,8 Hz), 10.67 (1H, s). MS(ESI^{+}) [*m/z* (rel. int. (%))]: 139 ([BMIM]). MS(ESI^{-}) [*m/z* (rel. int. (%))]: 210 ([Cl][BMIM][Cl]).

7.2.2 1-Butyl-3-methylimidazolium dicyanamide

[BMIM][Cl] (4.50 g, 25.8 mmol) was dissolved in CH_2Cl_2, and sodium dicyanamide (1.9 g, 25.3 mmol) was added. The reaction mixture was stirred at room temperature ca. 48 h. The reaction mixture was filtered through Kielselguhr. Solvent was evaporated with a rotary evaporator and the product was dried under high vacuum at 70 °C for 24 h.Yield of [BMIM][DCA] was 5.2 g, 24.3 mmol, 96 %. MS(ESI^{+}) [*m/z* (rel. int. (%))]: 139 ([BMIM]), 344 ([BMIM][DCA][BMIM]). MS(ESI^{-}) [*m/z* (rel. int. (%))]: 66 (DCA), 271 ([DCA][BMIM][DCA]).

7.2.3 1-Butyl-3-methylimidazolium hexafluorophosphate

[BMIM][Cl] (4.50 g, 25.8 mmol) was dissolved in CH_2Cl_2, and sodium hexafluorophosphate (4.33 g, 25.8 mmol) was added. The reaction mixture was stirred at room temperature ca. 48 h. The reaction mixture was filtered through Kielselguhr. Solvent was evaporated with a rotary evaporator and the product was dried under high vacuum at 70 °C for 24 h. Yield of [BMIM][PF_6] was 7.0 g, 24.8 mmol, 93 %. MS(ESI^{+}) [*m/z* (rel. int. (%))]: 139 [BMIM]. MS(ESI^{-}) [*m/z* (rel. int. (%))]: 145 [PF_6].

7.2.4 1-Butyl-3-methylimidazolium thiocyanate

[BMIM][Cl] (4.50 g, 25.8 mmol) was dissolved in CH_2Cl_2, and sodium thiocyanate (2.43 g, 30 mmol) was added. The reaction mixture was stirred at room temperature ca. 48 h. The reaction mixture was filtered through Kielselguhr. Solvent was evaporated with a rotary evaporator and the product was dried under high vacuum at 70 °C for 24 h. Yield of [BMIM][SCN] was 4.8 g, 24.5 mmol, 94 %. MS(ESI^{+}) [*m/z* (rel. int. (%))]: 139 (100) [BMIM]. MS(ESI^{-}) [*m/z* (rel. int. (%))]: 81 (100) (SCN).

7.2.5 1-Butyl-3-methylimidazolium stannyl trichloride

Stannyl trichloride (4.281 g, 40.6 mmol) was carefully added to [BMIM][Cl] (5.617 g, 32.2 mmol). Colorless liquid started to form immediately. The reaction mixture was dried under high vacuum at 70 °C for 24 h.

7.2.6 1-Butyl-3-methylimidazolium zinc dichloride

Zinc dichloride (4.281 g, 40.6 mmol) was carefully added to [BMIM][Cl] (5.617 g, 32.2 mmol). Colorless low viscosity liquid started to form slowly. The reaction mixture was dried under high vacuum at 70 °C for 24 h.

7.2.7 1-Butyl-3-methylimidazolium indium trichloride

Indiumtrichloride (6.174 g, 25.3 mmol) was carefully added to [BMIM][Cl] (4.413 g, 25.3 mmol). Colorless liquid started to form slowly and the reaction mixture had to be heated before all indiumchloride was dissolved. The reaction mixture was dried under high vacuum at 70 °C for 24 h.

7.2.8 1-Butyl-3-methylimidazolium iron trichloride

Iron trichloride (5.269 g, 29.7 mmol) was very carefully added to [BMIM][Cl] (5.186 g, 32.7 mmol). The reaction vessel was cooled in a water bath. Brown liquid formed rapidly after addition of $FeCl_3$. The reaction mixture was dried under high vacuum at 70 °C for 24 h.

7.2.9 1-Butyl-3-methylimidazolium tetrafluoroborate

[BMIM][Cl] (10.0 g, 57.3 mmol) was dissolved in CH_2Cl_2, and sodium tetrafluoroborate (6.91 g, 63.0 mmol) was added. The reaction mixture was stirred at room temperature ca. 48 h. The reaction mixture was filtered through Kielselguhr. Solvent was evaporated with a rotary evaporator and the product was dried under high vacuum at 70 °C for 24 h. Yield of [BMIM][BF_4] was 11.9 g, 52.7 mmol, 92 %. MS(ESI^+) [*m/z* (rel. int. (%))]: 139 [BMIM]. MS(ESI^-) [*m/z* (rel. int. (%))]: 110 (BF_4).

7.2.10 1-Butyl-3-methylimidazolium trifluoroacetate

[BMIM][Cl] (5.00 g, 28.7 mmol) was dissolved in CH_2Cl_2, and silver trifluoroacetate (6.63 g, 30.0 mmol) was added. The reaction mixture was stirred at room temperature ca. 48 h. The reaction mixture was filtered through Kielselguhr. Solvent was evaporated with a rotary evaporator and the product was dried under high vacuum at 70 °C for 24 h. Yield of [BMIM][CF_3CO_2] was 6.9 g, 27.3 mmol 95 %. MS(ESI^+) [*m/z* (rel. int. (%))]: 139 [BMIM]. MS(ESI^-) [*m/z* (rel. int. (%))]: 113 (CF_3CO_2).

7.2.11 1-Butyl-3-methylimidazolium methanesulfonate

[BMIM][Cl] (5.00 g, 28.7 mmol) was dissolved in CH_2Cl_2, and sodium methanesulfonate (3.54 g, 30.0 mmol) was added. The reaction mixture was stirred at room temperature ca. 48 h. The reaction mixture was filtered through Kielselguhr. Solvent was evaporated with a rotary evaporator and the product was dried under high vacuum at 70 °C for 24 h. Yield of [BMIM][CH_3SO_3] was 6.4 g, 27.3 mmol, 95 %. MS(ESI^+) [*m/z* (rel. int. (%))]: 139 [BMIM]. MS(ESI^-) [*m/z* (rel. int. (%))]: 95 (CH_3SO_3).

7.2.12 1-Butyl-3-methylimidazolium bistriflimide

[BMIM][Cl] (4.50 g, 25.8 mmol) and lithium bistriflimide (7.43 g, 25.8 mmol) was dissolved in water separately and mixed. The reaction mixture was stirred at room temperature ca. 48 h and [BMIM][NTf_2] formed a separate layer. The product was washed with water and the product was dried under high vacuum at 70 °C for 24 h. Yield of [BMIM][NTf_2] was 10.4 g, 24.7 mmol, 96 %. MS(ESI^+) [*m/z* (rel. int. (%))]: 139 (100) ([BMIM]). MS(ESI^-) [*m/z* (rel. int. (%))]: 281 (100) ([NTf_2]).

7.2.13 1-Butyl-2,3-dimethylimidazolium chloride

1-Chlorobutane (9.70 g, 104.4 mmol) in a 250 ml flask was mixed with 1,2-dimethylimidazole (9.5 g, 99.5 mmol). The reaction mixture was refluxed until all 1,2-dimethylimidazole had reacted (24-48 h). The reaction was followed with ESI-MS and NMR. The product was recrystallized from ethyl acetate acetonitrile mixture. Yield of [BDMIM][Cl] was 12.2 g, 79.6 mmol, 80 %. [BDMIM]Cl: ^1H

NMR (200 MHz, CDCl3): δ 0.96 (3H, t), 1.37 (2H, m), 1.81 (2H, m), 2.84 (3H, s), 4.07 (3H, s), 4.26 (2H, t), 7.61 (1H, d), 7.89 (1H, d). MS(ESI^+) [*m/z* (rel. int. (%))]: 153 ([BDMIM]). MS(ESI^-) [*m/z* (rel. int. (%))]: 223 ([Cl][BDMIM][Cl]), 411 ([Cl][BDMIM][Cl][BDMIM][Cl])

7.3 Dissolution of cellulose in ionic liquds

Choline chloride/urea melt was first prepared by adding 1 equivalent of urea to choline chloride. Cellulose (1 wt%) was added and the mixture was dried under high vacuum at 80 °C. The mixture was stirred for 3 days, but cellulose was not dissolved. The mixture was allowed to stand for 1 month, but cellulose remained undissolved.

Cellulose (1 wt%) was added to tetrabutylammonium chloride and the mixture was dried under high vacuum at 100 °C for 24 h. Mixture was stirred for 3 days, but cellulose did not dissolve. The mixture was allowed to stand for 1 month, but cellulose remained undissolved.

7.4 Esterifications

7.4.1 Esterification of pentaerythritol with acetic acid

Pentaerythritol (1.00 g, 7.4 mmol) was weighted in two neck round bottom flask, where glacial acetic acid (3.56 g, 59.4 mmol) was added. Then H_2SO_4 (7.2 mg, 0.074 mmol) was added as a catalyst. The reaction mixture was refluxed for 4 hours. CH_2Cl_2 (20 ml) was added to the reaction mixture and the mixture was extracted with saturated $NaHCO_3$ (4 *12 ml). The organic phase was then washed with water (10 ml) and then dried with $MgSO_4$. After drying, CH_2Cl_2 was evaporated and the product was collected and analyzed. Yield of acetic acid 3-acetoxy-2,2-bis-acetoxymethyl-propyl ester was 1.35 g, 4.4 mmol, 60%. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.13 (12H, s, $CH_2OC(O)R$), 3.53 (d, J_{HH} = 6.72 Hz, CH_2OH), 2.56 (t, J_{HH} = 6.78 Hz, CH_2OH), 2.09 (12H, s, $CH_3C(O)OR$).

7.4.2 Esterification of TMP with acetic acid

TMP (1.00 g, 7.5 mmol) was weighted in two neck round bottom flask, where glacial acetic acid (3.67 g, 61.1 mmol) was added. Then H_2SO_4 (7.3 mg, 0.075

mmol) was added as a catalyst. The reaction mixture was refluxed for 4 hours. CH_2Cl_2 (20 ml) was added to the reaction mixture and mixture was extracted with saturated $NaHCO_3$ (4 *15 ml). The organic phase was then washed with water (10 ml) and then dried with $MgSO_4$. After drying, CH_2Cl_2 was evaporated and the product was collected and analyzed. Yield of Acetic acid 2,2-bis-acetoxymethyl-butyl ester was 0.66 g, 2.5 mmol, 34%. ^{1}H-NMR (200 MHz, CDCl3): δ 4.03 (9H, s, $CH_2OC(O)R$), 3.44 (d, J_{HH} = 6.45 Hz, CH_2OH), 2.47 (t, J_{HH} = 6.54 Hz, CH_2OH), 2.09 (9H, s, $CH_3C(O)OR$), 1.49 (2H, q, J_{HH} = 7.64Hz, CH_2CH_3), 0.89 (3H, t, J_{HH} = 7.44Hz, CH_2CH_3).

7.4.3 Esterification of pentaerythritol with acetic acid in microwave reactor

Pentaerythritol (0.885 g, 6.6 mmol) was weighted in the microwave vessel, where glacial acetic acid (3.147 g, 52.4 mmol) was added. Then H_2SO_4 (6.4 mg, 0.066 mmol) was added as a catalyst. The reaction mixture was heated to desired temperature for desired time. Purification and analysis were the same than for the reaction with conventional heating.

7.4.4 Esterification of TMP with acetic acid in microwave reactor

TMP (1.160 g, 8.6 mmol) was weighted in the microwave vessel, where glacial acetic acid (3.147 g, 52.4 mmol) was added. Then H_2SO_4 (8.4 mg, 0.086 mmol) was added as a catalyst. The reaction mixture was heated to the desired temperature for the desired time. Purification and analysis were the same as for the reaction with conventional heating.

7.4.5 Esterification of 2,2-dimethyl-propane-1,3-diol with acetic acid in microwave reactor

2,2-dimethyl-propane-1,3-diol (1.325 g, 12.7 mmol) was weighted in the microwave vessel, where glacial acetic acid (3.147 g, 52.4 mmol) was added. Then H_2SO_4 (12.4 mg, 0.127 mmol) was added as a catalyst. The reaction mixture was heated to the desired temperature for the desired time. Isolation and analysis were the same as for pentaerythritol and TMP. ^{1}H-NMR (200 MHz, CDCl3): δ 3.94 (6H, s, $CH_2OC(O)R$), 3.31 (d, J_{HH} = 6.60Hz, CH_2OH), 2.14 (6H, s, $CH_3C(O)OR$), 1.64 (1H, s, H_2O), 0.97 (6H, s, CH_3Cq).

7.4.6 TLC analysis

TMP and 2,2-dimethyl-propane-1,3-diol could be visualized with anisaldehyde coloring solution, which was prepared as follows: 5 ml (5.595 g, 41.1 mmol) of anisaldehyde was mixed with 1 ml ((1.05 g, 17.5 mmmol) of glacial acetic acid. 5 ml (9.15 g, 93.3 mmol) of conc. H_2SO_4 was added to 90 ml of EtOH. This colouring solution was sensitive to light. Pentaerythritol needed phosphomolybdic acid coloring solution in order to visualize product from the TLC plates. 5 g of phosphomolybdic acid hydrate (PMA) was dissolved in 200 ml of ethanol. 3 ml H_3PO_4 85% and 10 ml H_2SO_4 was added to the solution.

The product was dissolved in methanol for concentrations of about 1%. When products were liquids the 0.1 ml was dissolved in 10 ml of methanol. If the product was solid about 10 mg was dissolved in 10 ml of methanol.

The eluent in TLC was methanol ethyl acetate mixture with varying ratios. The best eluent for pentaerythritol was methanol : ethyl acetate (10:90), for TMP methanol : ethyl acetate (25:75) and for 2,2-dimethyl-propane-1,3-diol plain ethyl acetete. After developing the TLC plate, they were visualized first with UV-light and then sprayed with the coloring solution. After the coloring solution was dried the plates were heated gently to visualize the products.

7.4.7 Typical procedure for the acetylation of D-glucose.

An ionic liquid (10 g) was dried in a round bottom flask at 80 °C under high vacuum for 24 to 48 hours prior the use. A catalyst followed by anhydrous D-glucose (1.00 g, 5.55 mmol) was dissolved in IL and finally freshly distilled acetic anhydride (5.10 g, 50 mmol) was added. The reaction mixture was heated to a desired temperature in an oil bath. After the desired reaction time the produced acetic acid and unreacted acetic anhydride were distilled in vacuum. Addition of water (30 ml) into the distillation residue precipitated glucose penta-acetate product from the ionic liquid. The product was filtered and most of the water in the filtrate was removed in a rotary evaporator. Finally, the ionic liquid containing the catalyst and unreacted starting material was dried at 80 °C under high vacuum for 24 to 48 hours for the next reaction batch. Analysis ^{1}H NMR (200 MHz, CDCl3): δ 2.03 (3H, s), 2,04 (6H, s), 2,09 (3H, s), 2,12 (3H, s), 3,84 (1H, m), 4,08 (0,5H, d) 4,14 (0,5H, d), 4,26 (0,5H, d), 4,34 (0,5H, d), 5,2 (2H, m), 5,72 (1H, d).

7.4.8 Acetylation of D-glucose catalyzed by sodium acetate.

An ionic liquid (10 g) was dried in a reaction flask at 80 °C under high vacuum for 24 to 48 hours prior the use. Anhydrous sodium acetate (0.77 g, 9.0 mmol) and anhydrous D-glucose (1.00 g, 5.55 mmol) were added and finally a freshly distilled acetic anhydride (5.10 g, 50 mmol) was added to the reaction mixture. The reaction mixture was heated to 90 °C in oil bath and after 2 hours formed acetic acid and unreacted acetic anhydride was distilled. 30 ml of water was added to the reaction mixture which precipitated the product. The product was filtered and dried in dessicator. Finally, ionic liquid containig the catalyst and unreacted starting materials was dried at 80 °C under high vacuum for 24 to 48 hours for the next reaction batch.The yield of glucose penta-acetate was 1,861 g, 4.8 mmol, 87 %. The product was anaylzed by NMR.

7.4.9 Acetylation of D-Lactose

[BMIM][Cl] (8 g) was dried in a reaction flask at 80 °C under high vacuum for 24 hours prior the use. Anhydrous D-lactose (4.00 g, 11.7 mmol) was added and finally freshly distilled acetic anhydride (28.67 g, 281 mmol) was added to the reaction mixture. The reaction mixture was heated to 80 °C in an oil bath. After 20 hours the formed acetic acid and unreacted acetic anhydride were distilled. 30 ml of water was added to the reaction mixture to precipitate the product. Precipitation was not efficient from warm (about 40 °C) the reaction mixture. The mixture was cooled with ice bath to 0 °C, until product was precipitated (in about 2 hours). The product was re-cystallized from ethanol. The yield of lactose octa-acetate was 0.924 g, 1.3 mmol, 12%. Analysis ^{1}H NMR (200 MHz, CDCl3): δ 2.13 (24H, m, acetyl), 4.13 (6H, m), 4.49 (1H, d, J_{HH} = 13 Hz), 5.00 (3H, m), 5.40 (3H, m), 5.75 (0.5H, d, J_{HH} = 8.97 Hz), 6.28 (0.5H, d, J_{HH} = 3.59 Hz).

7.5 Etherification

7.5.1 Etherification of cellulose in ionic liquid

An ionic liquid (5 g) was dried in a reaction flask at 80 °C under high vacuum for 24 to 48 hours prior the use. Microcrystalline cellulose (40 mg, 0.24 mmol) was dissolved during drying. Sodium chloroacetate and NaOH powder were added to the reaction mixture. The reaction mixture was heated to 80 °C in an oil bath and

after desired reaction time 30 ml of EtOH was added to the reaction mixture which precipitated the product. The product was filtered and dried in dessicator. The degree of substitution of the product was detected by titration from acidified samples with NaOH solution with phenolphtalene as indicator and by IR analysis in Kemira. The DS was low.

7.5.2 Etherification of D-glucose with epichlorohydrin in water

NaOH (25 g, 625 mmol) in water, epichlorohydrin (11.0 ml, 138 mmol) and tetrabutylammonium[HSO_4] were mixed together and solution was cooled to 0 °C with ice bath. D-glucose (1.00 g, 5.55 mmol) was then added to the reaction mixture. After adding D-glucose the reaction mixture was allowed (2 hours) to warm to room temperature. After 3 days the water layer was extracted three times with 40 ml of CH_2Cl_2. After combining organic layers, they were washed with water until washings were neutral. Solvent was evaporated. The product was analyzed with NMR and ESI-MS.

7.5.3 Etherification of D-glucose with butylchloride in water

The reaction was performed similarly as etherificaiton with epichlorohyderin. D-glucose (0.500 g, 2.78 mmol), NaOH (aq) (2.78 g, 69.5 mmol), chlorobutane (14.46 ml, 138 mmol) and tetrabutylammonium[HSO_4] were mixed toghetter. The reaction mixture was heated 30 min at 120 °C with microwaves. After heating the water layer was extracted three times with 40 ml of CH_2Cl_2. The organic layer was washed with water until washings were neutral.Solvent was evaporated with a rotary evaporator. The product was analyzed with NMR and ESI-MS.

7.6 Ene Reaction

A typical experiment: allylbenzene (1.347 g, 11.4mmol), *N*-methylmaleimide (1.267 g, 11.4 mmol) and hydroquinone (0.117 g, 0.11 mmol) were added to the solvent (2 ml) in a microwave tube (0.5-2 ml tubes). The mixture was heated to the desired temperature (180 -250 °C) with microwaves.

The experiments without additional solvent: 3.8 mmol of each starting compound and 0.4 mmol of hydroquinone. The microwave tube was purged with argon before capping.

After the reaction a sample of a crude product was dissolved in CH_2Cl_2/MeOH mixture and analyzed by GC [Perkin-Elmer AutoSystem XL TM, column HP-1 (Hewlett-Packard), temperature program 60°C (2 min) - 12.5 °C/min – 250 °C – 45 °C/min – 275 °C (2 min)] and GC-MS [Varian Saturn, column Equity –1 (Supelco)]. Retention times were calibrated with pure products and starting materials.

Isolation of pure products: The reaction mixture was distilled under vacuum 0.13 mmHg to remove the solvent (1,2-dichlorobenzene). Distillation residue was dissolved in smallest possible amount of acetonitrile. Diethyl ether was added to the mixture to precipitate by-products. By-products were filtered. The product was further purified by flash chromatography using iso-octane : chloroform (1:3) mixture. The product was a mixture of *cis* and *trans*-isomers. Analysis ^{1}H NMR (200 MHz, CDCl3): δ 2.55 (2H, m), 2.90 (6H, m), 6.04 (0.5H, t, J_{HH} = 7.2 Hz), 6.13 (0.5H, t, J_{HH} = 7.2 Hz), 6.45 (0.5H, t, J_{HH} = 1.2 Hz), 6.53 (0.5H, t, J_{HH} = 1.2 Hz), 7.28 (5H, m).

7.7 Sulfonylation

7.7.1 Reaction of toluene with benzenesulfonyl chloride

The catalyst (0.157mmol) was weighted to a dry 10 ml round bottom flask, where toluene (2.89 g, 31.4 mmol) and benzenesulfonylchloride (2.77 g, 15.7 mmol) were added. The reaction mixture was heated to 110 °C, and ran to completion or until all toluene was evaporated from the reaction vessel (this took up to 11 days). The reaction was followed with NMR and GC. The relative concentrations have been determined from ^{1}H NMR spectrum, from the peaks 8.1 ppm of benzenesulfonylchloride and 8.21 ppm of the product. With these two peaks relative concentrations can be easily determined. GC was also used to confirm the relative concentrations of starting materials to product phenyl tolylsulfone. Analysis ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.35, 2.39, 2.45 (3 H, methyl), 7.21 (4 H, multiplet), 7.60 (2 H, multiplet), 7.88 (2 H, multiplet), 8,21 (1 H, duplet of duplets). GC-MS (EI) [*m/z* (rel. int. (%))]: 232 (45), 214 (55), 197 (20), 167 (50), 166 (100), 165 (50), 153 (15), 152 (20), 137 (40), 125 (15), 89 (30), 77 (45), 65 (45), 63 (15), 51 (25), 39 (15).

7.7.2 Reaction of toluene with p*-toluenesulfonyl chloride*

The catalyst (0.157mmol) was weighted to a dry 10 ml round bottom flask, where toluene (2.89 g, 31.4 mmol) and *p*-toluenesulfonylchloride (2.77 g, 15.7 mmol) were added. The reaction mixture was heated to 110 °C, and ran for 3 days. The reaction was followed with GC. Analysis GC-MS (EI) [*m/z* (rel. int. (%))]: 246 (45), 140 (10), 139 (100), 107 (15), 91 (25), 77 (10), 65 (20).

7.7.3 Reaction of toluene with methanesulfonyl chloride

The catalyst (0.157mmol) was weighted to a dry10 ml round bottom flask, where toluene (2.89 g, 31,4 mmol) and methanesulfonylchloride (1.80 g, 15,7 mmol) were added. The reaction mixture was heated to 110 °C, and ran for 8 days. The reaction was followed with GC. Analysis ^{1}H-NMR (300 MHz, CDCl3) δ: 2.42 (3 H, methyl), 3.72 (3 H, methyl), 7.85 (2 H, multiplet), 8,10 (2 H, multiplet). GC-MS (EI) [*m/z* (rel. int. (%))]: 170 (70), 155 (20), 109 (10), 107 (35), 91 (100), 90 (25), 89 (20), 79 (10), 77 (15), 65 (30), 63 (15), 39 (15).

7.7.4 Reaction of anisole with benzenesulfonyl chloride

The catalyst (0.157mmol) was weighted to a dry10 ml round bottom flask, where anisole (3.39 g, 31,4 mmol) and benzenesulfonyl chloride (2.77 g, 15,7 mmol) were added. The reaction mixture was heated to 110 °C, and ran for 3 days. The reaction was followed with GC. Analysis GC-MS (EI) [*m/z* (rel. int. (%))]: 248 (80), 155 (40), 123 (100), 107 (15), 92 (15), 77 (35), 64 (15), 51 (15).

7.7.5 Reaction of anisole with p*-toluenesulfonyl chloride*

The catalyst (0.157mmol) was weighted to a dry10 ml round bottom flask, where anisole (3.39 g, 31.4 mmol) and *p*-toluenesulfonylchloride (2.99 g, 15.7 mmol) were added. The reaction mixture was heated to 110 °C, and ran for 3 days. The reaction was followed with GC. GC-MS (EI) [*m/z* (rel. int. (%))]: 262 (70), 227(10), 165 (15), 152 (17), 139 (20), 125 (17), 105 (100), 92 (15), 91 (17), 77 (33), 65 (23).

7.7.6 Reaction of anisole with methanesulfonyl chloride

The catalyst (0.157mmol) was weighted to a dry10 ml round bottom flask, where anisole (3.39g, 31.4 mmol) and methanesulfonylchloride (1.80 g, 15.7 mmol) were added. The reaction mixture was heated to 110 °C, and ran for 3 days. The reaction was followed with GC.

7.7.7 Reaction of naphthalene with benzenesulfonyl chloride

The catalyst (0.157mmol) was weighted to a dry10 ml round bottom flask, where naphthalene (4.02 g, 31.4 mmol) and benzenesulfonylchloride (2.77 g, 15.7 mmol) were added. The reaction mixture was heated to 110 °C, and ran for 3 days. The reaction was followed with GC. Analysis GC-MS (EI) [*m/z* (rel. int. (%))]: 269 (15), 268 (100), 204 (20), 203 (85), 202 (30), 143 (60), 127 (50), 115 (85), 101 (15), 77 (30), 51 (15).

7.7.8 Reaction of naphthalene with p*-toluenesulfonyl chloride*

The catalyst (0.157mmol) was weighted to a dry10 ml round bottom flask, where naphthalene (4.02 g, 31.4 mmol) and *p*-toluenesulfonylchloride (2.99 g, 15.7 mmol) were added. The reaction mixture was heated to 110 °C, and ran for 3 days. The reaction was followed with GC. Analysis GC-MS (EI) [*m/z* (rel. int. (%))]: 282 (100), 202 (15), 175 (40), 147 (15), 143 (17), 139 (75), 127 (40), 115 (50), 91 (15), 77 (17), 65 (15).

7.7.9 Reaction of naphtalene with methanesulfonyl chloride

The catalyst (0.157mmol) was weighted to a dry10 ml round bottom flask, where naftalene (4.02 g, 31.4 mmol) and methanesulfonylchloride (1.80 g, 15.7 mmol) were added. The reaction mixture was heated to 110 °C, and ran for 3 days. The reaction was followed with GC.

7.7.10 Reaction of chlorobenzene with benzenesulfonyl chloride

The catalyst (0.157mmol) was weighted to a dry10 ml round bottom flask, where chlorobenzene (3.53 g, 31.4 mmol) and benzenesulfonylchloride (2.77 g, 15.7 mmol) were added. The reaction mixture was heated to 110 °C, and ran for 3

days. The reaction was followed with GC. GC-MS (EI) [*m/z* (rel. int. (%))]: 254 (20), 252 (40), 161 (20), 159 (45), 125 (100), 111 (15), 97 (10), 77 (35), 75 (20), 51 (25).

7.7.11 Reaction of chlorobenzene with p*-toluenesulfonyl chloride*

The catalyst (0.157mmol) was weighted to a dry10 ml round bottom flask, where chlorobenzene (3.53 g, 31.4 mmol) and *p*-toluenesulfonylchloride (2.99 g, 15.7 mmol) were added. The reaction mixture was heated to 110 °C, and ran for 3 days. The reaction was followed with GC.

7.7.12 Reaction of chlorobenzene with methanesulfonyl chloride

The catalyst (0.157mmol) was weighted to a dry10 ml round bottom flask, where chlorobenzene (3.53 g, 31.4 mmol) and methanesulfonylchloride (1.80 g, 15.7 mmol) were added. The reaction mixture was heated to 110 °C, and ran for 3 days. The reaction was followed with GC.

7.7.13 Reaction of benzene with p*-toluenesulfonyl chloride*

The catalyst (0.157mmol) was weighted to a dry10 ml round bottom flask, where benzene (2.42 g, 31.4 mmol) and *p*-toluenesulfonylchloride (2.99 g, 15.7 mmol) were added. The reaction mixture was heated to 110 °C, and ran for 3 days. The reaction was followed with GC. GC-MS (EI) [*m/z* (rel. int. (%))]: 232 (100), 139 (95), 126 (15), 125 (70), 107 (75), 97 (15), 91 (40), 79 (17), 77 (40), 65 (30), 51 (20).

7.7.14 Reaction of benzene with methanesulfonyl chloride

The catalyst (0.157mmol) was weighted to a dry10 ml round bottom flask, where benzene (2.42 g, 31.4 mmol) and methanesulfonylchloride (1.80 g, 15.7 mmol) were added. The reaction mixture was heated to 110 °C, and ran for 3 days. The reaction was followed with GC.

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