Ionic Liquids and Microwaves in Promotion of Organic Synthesis

Friedel-Crafts reaction, Deuterolabelling and O-Demethylation

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ACADEMIC DISSERTATION

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ABSTRACT

The use of ionic liquids in chemical research has gained considerable interest and activity in recent years. Due to their unique and varied physicochemical properties, in comparison to molecular solvents, the potential applications for ionic liquids are enormous. The use of microwave irradiation, as a powerful dielectric heating technique, in synthetic organic chemistry has been known since 1986. Since then, it has gained significant recognition for its research and application in both academia and industry. The use of either ionic liquids or microwave irradiation in synthetic organic chemistry has been known to afford improved, alternative or complimentary selectivities, in comparison to traditional processes. In this study, the use of ionic liquids as solvents, co-solvents and catalytic media was explored in Friedel-Crafts, deuterolabelling and *O*-demethylation reactions.

Alternative methods for the production of a variety of aromatic ketones using the Friedel-Crafts acylation methodology were investigated using ionic liquid–catalyst or ionic liquid–acidic additive systems. The disclosed methods, i.e. metal bistriflamides and chloroindate ionic liquids systems, possessed good catalytic activity in the synthesis of typical benzophenones. These catalytic systems were also recyclable. Microwave irradiation was found to be useful in the synthesis of various polyhydroxydeoxybenzoins and arylpropanones as synthetic precursors to naturally occurring or potentially bioactive compounds. Under optimized condition, the reaction occurred in only four minutes using systems such as [bmim][NTf_2]/$HNTf_2$ and [bmim][BF_4]/$BF_3{\cdot}OEt_2$.

Naturally occurring polyphenols, such as isoflavones, can possess various types of biological or pharmacological activity. In particular, some are noted for their beneficial effects on human health. Isotopically labelled analogues of polyphenols are valuable as analytical standards in the quantification of these compounds from biological matrices. A new strategy for deuterolabelling of polyphenols was developed using ionic liquids as co-solvents and 35% DCl/D_2O, as a cheap deuterium source, under microwave irradiation. Under these conditions, perdeuterated compounds were achieved in short reaction times, in high isotopic purity and in excellent yields.

An *O*-demethylation reaction was developed, using an ionic liquid reaction medium with BBr_3 for the deprotection of a variety methyl protected polyphenolic compounds, such as isoflavons and lignans. This deprotection procedure was found to be very practical as the reaction occurred under mild reaction conditions and in short reaction times. The isolation and purification steps were particularly straightforward and high yielding, in comparison to traditional methods.

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Helsinki, January 2009

Ullastiina Hakala

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals (I-V). Roman numeral VI refers to unpublished results relevant to the synthesis of new ionic liquids.

I. Earle, M. J., Hakala, U., McAuley, B. J., Nieuwenhuyzen, M., Ramani, A. and Seddon, K. R. Metal bis{(trifluoromethyl)sulfonyl}amide complexes: highly efficient Friedel-Crafts acylation catalyst. *Chem. Comm.* **2004**, *12*, 1368-1372.

II. Earle, M. J., Hakala, U., Hardacre, C., Kärkkäinen, J., McAuley, B. J., Rooney, D. W., Seddon, K. R., Thompson, J. M. and Wähälä, K. Chloroindate(III) ionic liquids: recyclable media for Friedel-Crafts acylation reactions. *Chem. Comm.* **2005**, *7*, 903-905.

III. Hakala, U. and Wähälä, K. Microwave-promoted synthesis of polyhydroxydeoxybenzoins in ionic liquids. *Tetrahedron Lett.* **2006**, *47*, 8375-8378.

IV. Hakala U. and Wähälä, K. Expedient deuterolabeling of polyphenols in ionic liquids-DCl/D_2O under microwave irradiation. *J. Org. Chem.* **2007**, *72*, 5817-5819.

V. Hakala, U., Hakola, H., Bruon, S. and Wähälä K. Expedient cleavage of aromatic alkyl ethers with BBr_3 in ionic liquid. Submitted.

VI. Preparation of halide-free ionic liquids from sulfonate esters.

GENERAL ABBREVIATIONS

Bn	benzyl
Bz	benzoyl
n-Bu	*n*-butyl
DCM	dichloromethane
DMA	dimethylacetamide
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DPPP	1,3-bis(diphenylphosphino) propane
Et	ethyl
EtOAc	ethyl acetate
HA	Brønsted acid
HMPTA	hexamethylphosphorotriamide
HPLC	high performance liquid chromatography
IL	ionic liquid
IR	infrared radiation
ISM	industrial scientific and medical frequencies
Me	methyl
MeOH	methanol
MSA	methane sulfonic acid
MW	microwave
NMP	*N*-methylpyrrolidone
Ph	phenyl
PTSA	*para*-toluene sulfonic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TPPTS	triphenylphosphine trisulfonate, sodium salt
TSIL	task-specific ionic liquid
US	ultrasound

IONIC LIQUID ABBREVIATIONS

CATIONS:

[bmim]	1-butyl-3-methylimidazolium
[bpy]	butylpyridinium
[emim]	1-ethyl-3-methylimidazolium
[omim]	1-octyl-3-methylimidazolium
[pmim]	1-pentyl-3-methylimidazolium
[*i*Prmim]	1-isopropyl-3-methylimidazolium

ANIONS:

[Al_2Cl_7]	heptachloroaluminate
[BF_4]	tetrafluoroborate
Br	bromide
[CF_3SO_3]	trifluoromethylsulfonate
Cl	chloride
[ClO_4]	perchlorate
[$FeCl_4$]	tetrachloroferrate
[HSO_4]	hydrogen sulfate
I	iodide
[$InCl_4$]	tetrachloroindate
[NO_3]	nitrate
[NTf_2]	bis(trifluoromethanesulfonyl)imide
[meebs]	*p*-(2-(2-methoxyethoxy)ethoxy) benzenesulfonate
[OMe]	methylsulfonate, mesylate
[OTf]	4-methylbenzenesulfonate, tosylate
[PF_6]	hexafluorophosphate

1. INTRODUCTION

The principles of Green Chemistry have been introduced to eliminate or reduce the use or generation of hazardous materials in chemical processes. One of the key areas of green chemistry is the replacement of hazardous solvents with environmentally benign ones or the elimination of solvents altogether.[1,2,3] Although a solvent-free alternative process is the best solution, a solvent is often vital to a successful chemical reaction. Finding an ideal "green" solvent for an organic reaction is not easy. However, some alternatives for traditional solvents, for example fluorous solvents and supercritical fluids, have already been identified.[4,5]

Lately, ionic liquids (ILs) have gained much attention as "designer solvents" for a diversity of chemical applications (Figure 1). The reason for this interest is the enormous selection of weakly bonding anion and cation combinations, which make up this special class of low melting salts. It has been calculated that there are some 10^{18} possible single ILs, and the number of ILs increases still further when binary and tertiary ILs are included.[6]

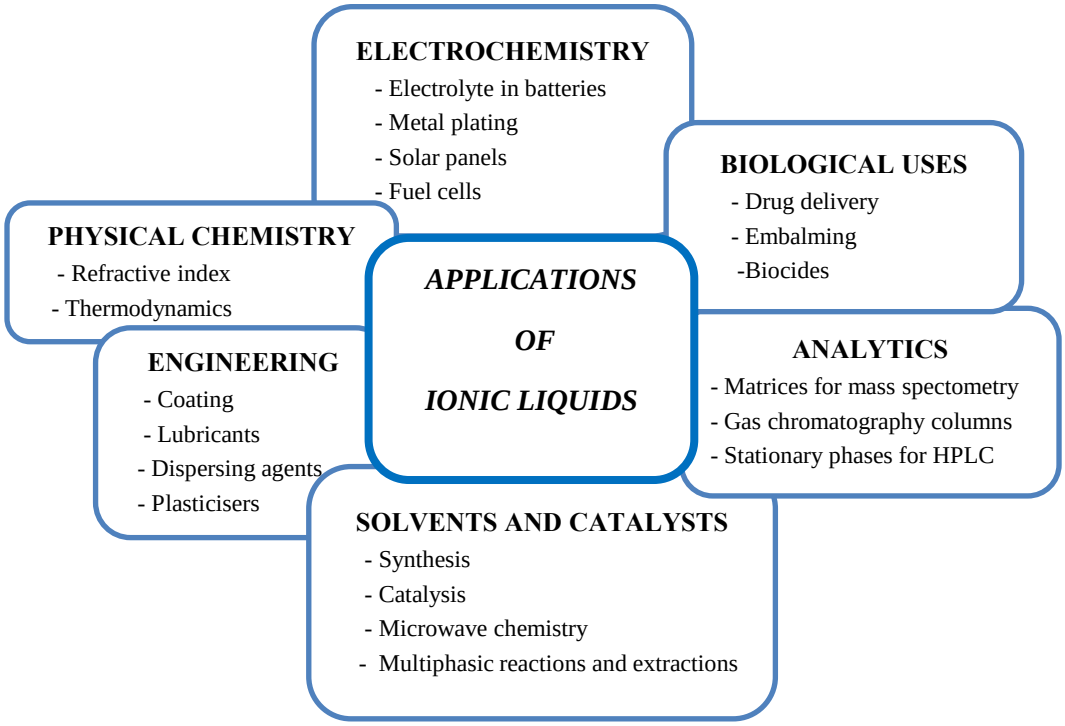


Figure 1. Present and potential applications of ionic liquids. Figure is modified from ref. 6.

Many synthetic processes require heating in order to proceed in moderate reaction times. Still, reaction times of several hours or even days to drive a reaction to completion are not uncommon. In laboratory scale, organic reactions are traditionally accelerated with the aid of an external heat source, such as an oil bath or a hot plate. These heating methods rely on the thermal conductivity of different materials as the energy drifts from the heating source to the reaction mixture. As a result, the temperature of the reaction vessel is often higher than that of

the reaction mixture, making the method both slow and inefficient. Heat created by microwave (MW) irradiation produces efficient internal heating by direct coupling of microwave energy with polar or ionic molecules that are present in the reaction mixture and, not surprisingly, MW irradiation has proven to be an excellent alternative to traditional heating methods.[7]

This study was undertaken to develop new and more environmentally benign methods for the synthesis of selected aromatics and biologically active polyphenolic compounds. Ionic liquids were used as primary reaction solvents or co-solvents, and microwave irradiation was applied where appropriate as an alternative heating source to reduce reaction times. In addition, a selection of new ionic liquids was prepared from sulfonate esters in a halogen-free route.

The literature review that follows focuses on the applications of ionic liquids in organic synthesis under microwave irradiation. As of less importance to this work, the preparation of ionic liquids under MW conditions is excluded. Recent advances in Friedel-Crafts reactions are included. Figure 2 gives an idea of the vast literature dealing with ionic liquids and microwave synthesis showing the number of publications on ionic liquids and microwave synthesis separately and together between 1990 and 2007. As can be seen, despite the enormous amount of research that has been done on ionic liquids (red) and microwave synthesis (green), studies where these two methods have been combined (blue) are relatively few.

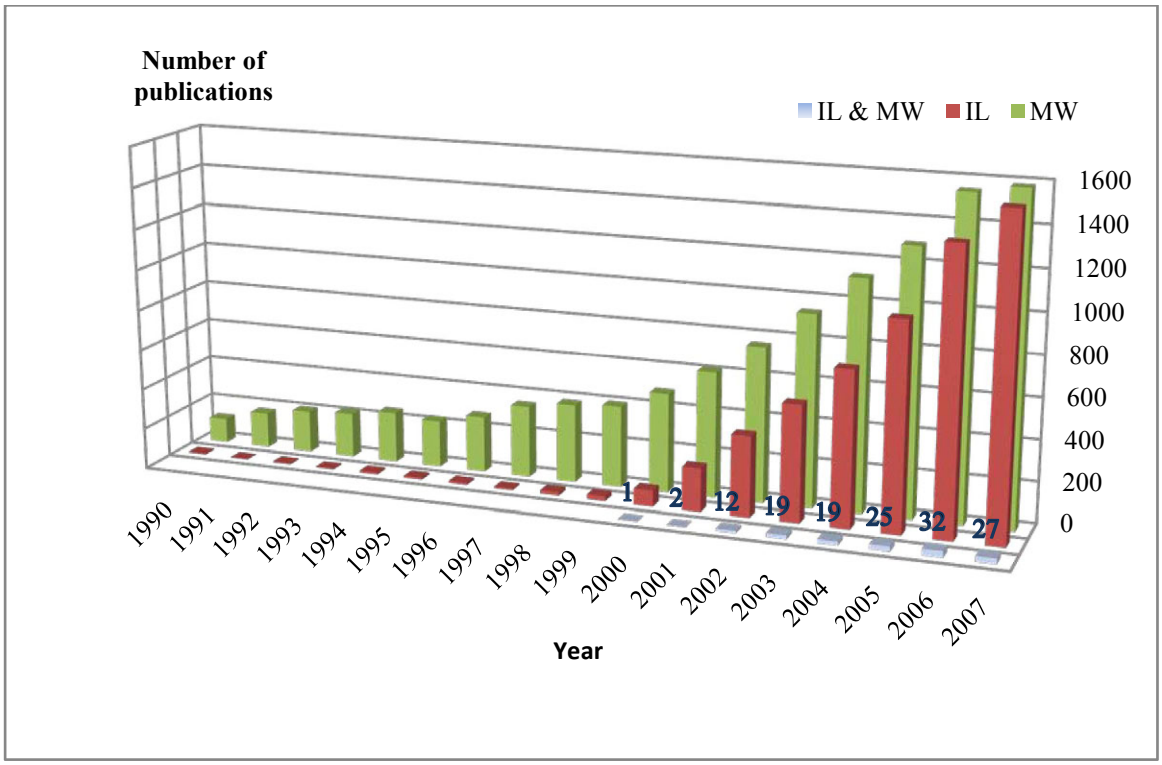


Figure 2. Number of publications on ionic liquids, microwave synthesis, and ionic liquids used in conjunction with microwave synthesis by year, 1990-2007. This figure was prepared with use of the

SciFinder Scholar Explore Literature search on 10 April 2008. The IL search was done by using the research topic phrase "ionic liquids", limited by Publication year (1990-2007), Document type (journal, patent, review) and Language (English). The 7359 references obtained were analyzed by publication year. The same limitations were used the MW search, which was done by using the phrase "microwave synthesis". The 12102 references obtained were analyzed by the publication year. The IL&MW search was done by refining the obtained IL references by research topic "microwave". Again, the results were analyzed by year.

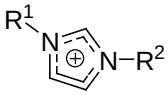
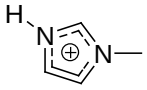
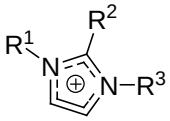
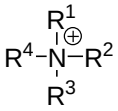
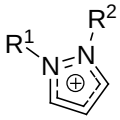
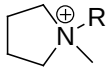
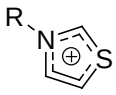
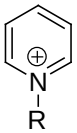
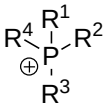
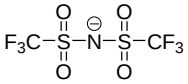
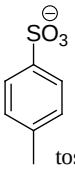
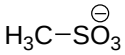
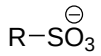
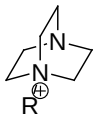
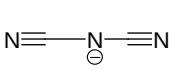
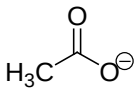
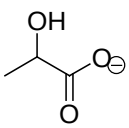
1.1 Ionic Liquids

Ionic liquids have been attracting the attention of the scientific community since the early 1990s. A number of comprehensive reviews concerning the physicochemical properties of ILs and their applications in synthesis and catalysis have been published, [8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24], the most recent in 2008.[8-13] Only a brief summary of ionic liquids is presented here.

Ionic liquids are defined as salts that are in a liquid form at or below 100 °C. This temperature limit is merely a convenient marker, as it separates ILs from high-temperature molten salts.[25] The main reason for low melting points of ILs compared with those of simple inorganic salts (m.p. of NaCl is 800 °C) is the size difference between the ions and a molecular structure characterized by high degree of asymmetry. The lack of symmetry inflicts the ion – ion packing by decreasing the Coulombic attraction between the ions.[26]

The structure and nomenclature of the most common cations and anions in ILs are shown in Table 1. Typically, the cations are imidazolium, ammonium, pyridinium, pyrrolidinium, phosphonium and sulfonium derivatives. The anions may be of inorganic or organic origin. Common inorganic anions are halide, tetrachloroaluminate (also tetrachloroferrate and tetrachloroindate), tetrafluoroborate, hexafluorophosphate and bis(trifluoromethylsulfonyl)imide, and common organic anions are derivatives of sulfate or sulfonate esters, trifluoroacetate, lactate, acetate or dicyanamide.[6,8,27] Substituents (the R-group) on the cation are usually alkyl chains, but can contain any of a variety of functional groups, such as fluoroalkyl, alkenyl, methoxy or hydroxyl. Functionalized ILs are often designed for a particular use, e.g. for specific reactions, extractions or separations, and are then referred to as "task specific ionic liquids" (TSILs).[28] Table 1 shows the cations and anions organized according to their relative acidity and basicity. So far, the acidity and basicity of ions has received little attention in IL research; further study can be expected, because the IL family is expanding rapidly, particularly Lewis basic ILs.[29]

Table 1. Structures and nomenclature of the most common cations and anions in ILs, and their acid/base properties. [6,27]

CATION	ANION	
 *N*,*N*-dialkyl-imidazolium *Protonated cations, e.g.*  methylimidazolium	*Brønsted amphoteric* $H_2PO_4^-$ HSO_4^- dihydrogen phosphate, hydrogen sulfate *Lewis* $AlCl_4^-$ $FeCl_4^-$ $InCl_4^-$ tetrachloroaluminate, -ferrate and -indate	**ACIDIC**
R ≠ H,  *N*,*N*,*N*-trialkyl-imidazolium  tetraalkyl-ammonium  1,2-dialkyl-pyrazolium  *N*-alkylmethyl-pyrrolidinium  *N*-alkyl-thiazolium  *N*-alkyl-pyridinium  trialkyl-sulfonium  tetraalkyl-phosphonium	 hexafluoro-phosphate  bis(trifluoromethyl-sulfonyl)imide  tetrafluoro-borate  tosylate  mesylate  sulfonate  nitrate Cl^- chloride Br^- bromide	**NEUTRAL**
 1-alkyl-4-aza-1-azoniabicyclo-[2.2.2]octane [$C_n$dabco]	 dicyanamide  acetate  lactate	**BASIC**
R^1, R^2, R^3, R^4= alkyl, aryl, alkylacid, -ketone, -ester, -ether etc., including chiral.		

The most striking feature of ionic liquids is that their physicochemical properties can be modified by changing the cation, anion or substituents (R-groups); in other words, ILs can be tailored to the needs of the reaction. The water miscibility of IL can be controlled by changing the anion or the R-group of the cation. Thus, increasing the alkyl chain length in the R group increases the hydrophobicity of the cation and, thereby, the hydrophobicity of IL. Lewis acidity or basicity can be controlled through the selection and amount of the chosen anion. For example, the Lewis acidity of [bmim][$AlCl_4$] can be adjusted by the amount of $AlCl_3$ added. The easy of modification is an invaluable feature of ionic liquids in where they can be used not only as reaction solvents but also as catalysts or catalytic solvents.[15]

The beginning of IL preparation and the birth of the entire field is usually dated to 1914, when ethylammonium nitrate ([$EtNH_3$][NO_3], mp 13-14 °C) was prepared by neutralization of ethylamine with concentrated nitric acid. The discovery did not attract much scientific interest and these new materials went largely unrecognized almost the 1970s when organic chloroaluminates (first-generation ILs, Figure 3) were investigated more closely. The first organic reaction performed in IL reaction medium was in the mid-1980s. In the 1990s, Wilkes and Zaworotko reported the preparation of new combinations of cations and anions forming air- and moisture stable ionic liquids (second-generation ILs, Figure 3). Since then, a wide range of ILs have been developed including TSILs (third-generation ILs, Figure 3), which were introduced by Davis[28] in 2004.[6,8]

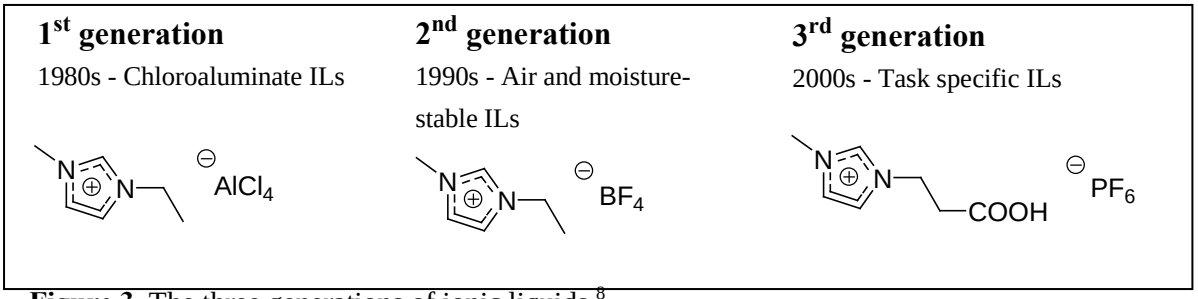


Figure 3. The three generations of ionic liquids.[8]

The synthesis of ILs most often proceeds in two steps: formation of the cation and anion exchange. Typical synthesis paths for the preparation of ionic liquids are shown in Figure 4, where the preparation of imidazolium based ILs is shown as an example. The cation formation step is described as a quaternization reaction, and it is this that gives the compound its ionic nature. In general, the starting material, imidazolium (or amine, pyrimidine, etc.), is alkylated with an appropriate alkylhalide (RX), and in halogen based ILs only this step is required. The quaternization reaction can also be carried out by protonation with Brønsted

acid. The anion exchange reactions fall into two categories: a halide salt is treated with a Lewis acid, which forms a Lewis acidic IL, or the exchange reaction is performed by anion metathesis.[27] The quaternization reaction with alkylhalides may leave traces of halide ion in the ionic liquid. Although for many purposes this may not be a problem, halide ions can also interfere with metal catalysts, cause corrosion problems in chemical plants, and interfere with measurements of physical property of ionic liquids.[30] It is also possible to synthesise ILs via a "halogen-free" route, where an alkyl alkylsulfonate, usually alkyl methylsulfonate (mesylate)[31] or alkyl toluenesulfonate (tosylate),[32] is used for the quaternization reaction.

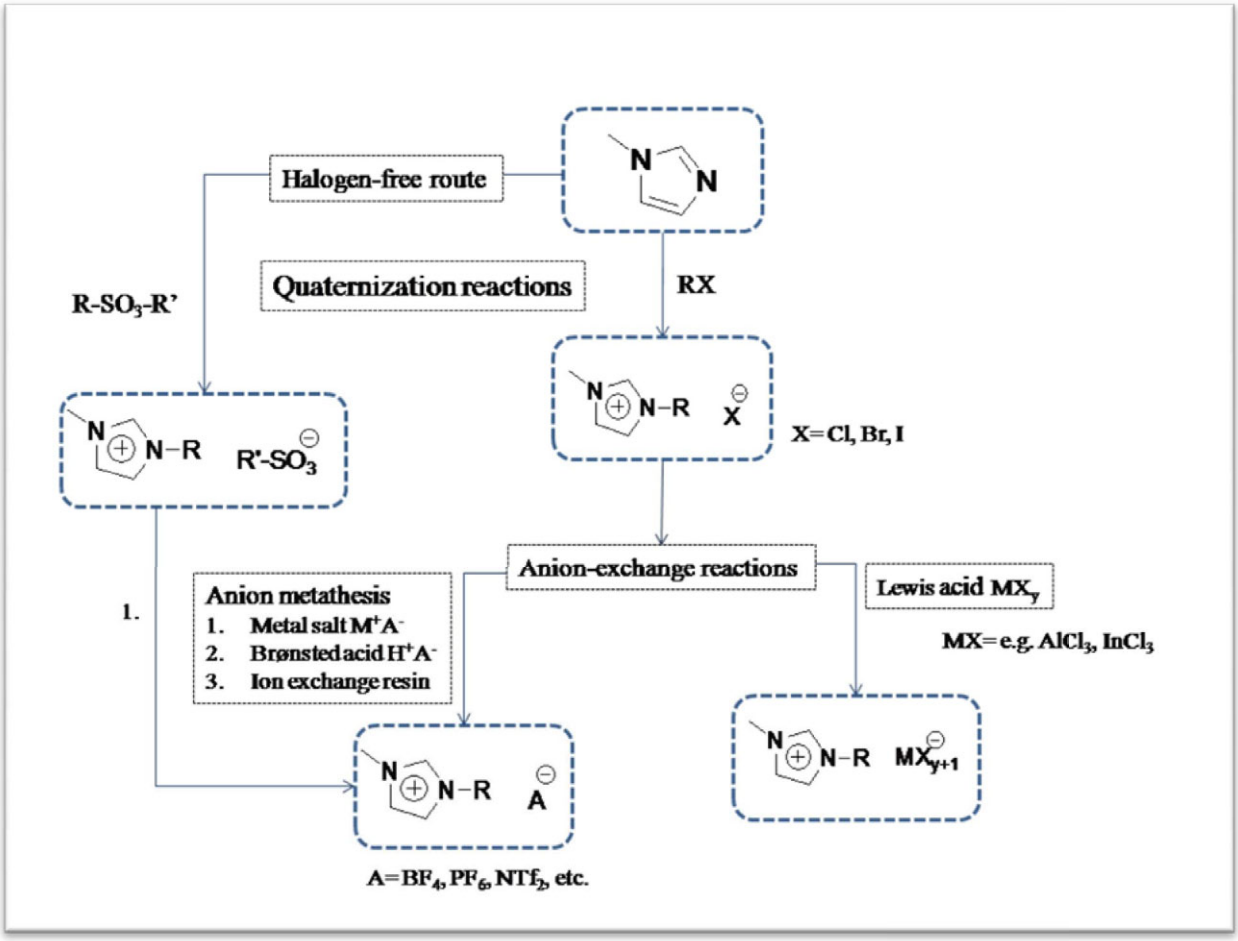


Figure 4. Synthesis routes for the preparation of methylimidazolium based ionic liquids.[27]

Most of the ionic liquids that are well established in organic synthesis are methylimidazolium based. Notable are ILs where 1-butyl- or 1-ethyl-3-methylimidazolium ([bmim] or [emim]) cation is joined with a neutral anion such as tetrafluoroborate [BF_4], hexafluorophosphate [PF_6] or bis(trifluoromethanesulfonyl)imide [NTf_2]. Several suppliers also provide a wide range of other ionic liquids, including ammonium, pyridinium and pyrrolidium based ILs. Merck supplies an extensive selection of ILs, and it also provides a useful IL website (http://ildb.merck.de/ionicliquids/en/startpage.htm), with a wealth of valuable information including melting points and solubility data.

1.2 Microwave heating

Microwave heating relies on the ability of molecules or substances to absorb and transmit microwave irradiation. MW irradiation is electromagnetic irradiation in the frequency range of 0.3 to 300 GHz. To avoid interference with telecommunications and mobile phone frequencies, heating applications must use ISM bands (Industrial Scientific and Medical frequencies) which are 27.12 MHz, 915 MHz or 2.45 GHz. All domestic "kitchen" microwave ovens and laboratory microwave reactors operate at a frequency of 2.45 GHz. The microwave photon corresponding to this particular frequency has energy close to 0.0016 eV. This amount of energy is too low to break chemical bonds and MWs cannot, therefore induce chemical reactions.[33]

The origin of "microwave dielectric heating" is the electric component of an electromagnetic field, which creates heat by two main mechanisms: dipolar polarization and ionic conduction. When a sample is irradiated at microwave frequencies, the dipoles or ions of the sample mixture align and realign in the applied oscillating and alternating electric field. Through molecular friction and dielectric loss, energy is lost in the process in the form of heat. The ability of the sample to align itself with the given frequency (of the applied field) is directly related to the amount of heat generated. No heating occurs if the dipole or ion does not have enough time to realign with the field or if it reorients too fast. The assigned frequency of 2.45 GHz, used in all commercial MW ovens and reactors, is such as to allow dipoles or ions to align in the field but not to follow the alternating field completely. The ability of a specific material or solvent to convert microwave energy into heat at a given frequency and temperature is determined by the loss factor tangent (tan δ), which is expressed as the ratio of the dielectric loss (ε´´) to the dielectric constant (ε´). A reaction medium, usually the solvent, with a high tan δ is required for good absorption and effective heating. In general, solvents can be classified according to how well they absorb microwaves: viz. high (tan δ > 0.5), medium (tan δ 0.1-0.5) and low MW absorbing (tan δ < 0.1). Representative examples of traditional solvents, with their tan δ values are collected in Table 2.[34]

Table 2. Tan δ of common solvents from high to low MW absorbing ability.[34]

Solvent	tan δ	MW absorbing ability
ethylene glycol	1.350	HIGH
ethanol	0.941	
DMSO	0.825	
methanol	0.659	
butanol	0.571	
NMP	0.275	MEDIUM
acetic acid	0.174	
DMF	0.161	
1,2-dichloroethane	0.127	

water	0.123	
acetonitrile	0.062	
ethyl acetate	0.059	
acetone	0.054	
THF	0.047	LOW
dichloromethane	0.042	
toluene	0.040	
hexane	0.020	

Currently, the loss factor tangent values of ILs are not specified in the literature, although the dielectric constant (ε) is given in some reports of polarity studies.[8,35] Although ILs are usually understood as medium MW absorbing compounds, this has not been scientifically confirmed with the tan δ value. However, the most frequently used ILs, e.g., [bmim][BF_4] and [bmim][PF_6], possess ideal solvent properties for microwave promoted reactions. In addition to the good thermal and chemical stability mentioned above, ILs also feature polar and ionic character enabling them to interact through thus both MW energy transfer mechanisms (dipolar polarization and ionic conduction).[36]

The use of microwave irradiation as an alternative heating technique in synthetic chemistry was first described by the groups of Gedye[37] and Giguere[38] in 1986. Its widespread acceptance, in both, academia and industry, is evidenced by the large number of published reports[39, 40, 41, 42, 43, 44, 45, 46, 47] and books.[48,49] Initially, domestic, sometimes modified, kitchen microwave ovens were the only available technology. This equipment suffers from lack of reaction controllability and reproducibility.[50] Much valuable pioneering work was nevertheless done with these ovens. Microwave reactors specifically designed for synthetic applications e.g. CEM Discover and Biotage Initiator, have been taken into use, with the result that reaction conditions can be more controlled. These reactors feature a built-in system for direct temperature measurement of the reaction mixture, operating through an external infrared (IR) sensor, magnetic stirrers, and software that enables on-line temperature and pressure control by regulation the microwave power output. The latest upgrade in commercial available MW reactors is an internal fibre-optic probe temperature measurement system (CEM Discover), which enables more accurate internal measurement of the reaction temperature than the IR sensor system.[51] This fibre-optic technology became available in our laboratory only recently and was used briefly in study **V**.

2. USE OF IONIC LIQUIDS IN ORGANIC SYNTHESIS UNDER MICROWAVE CONDITIONS

The first report of an organic synthesis being carried out in a microwave-irradiated ionic liquid reaction medium was that of Bazureau and co-workers[52] in 2000. Their report was quickly followed by a number of studies and four reviews.[53, 54, 55, 56] All organic reactions to date utilizing ILs under microwave irradiation are collected in Table 14 (in sect 2.5) at the end of this chapter. Selected reactions are discussed in the following according to the various uses of ionic liquids:

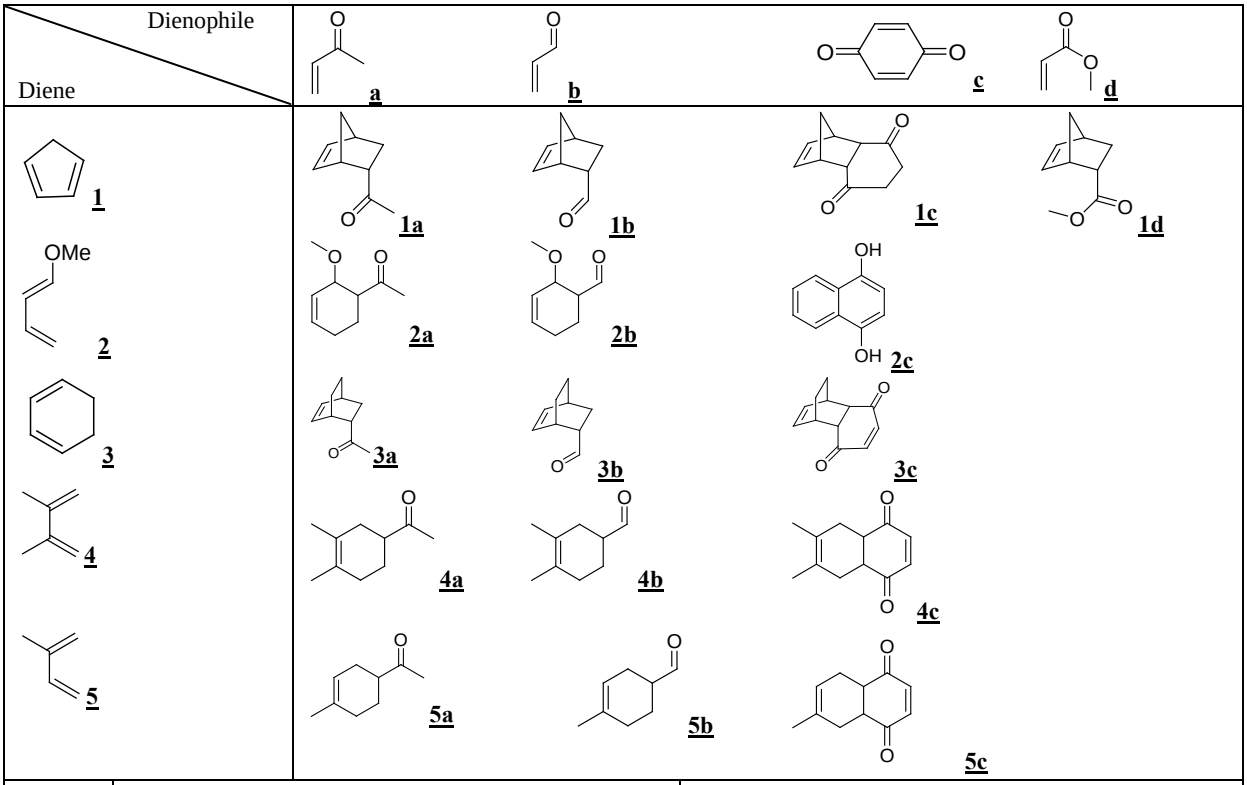
- as solvents and co-solvents
- as reagents/catalysts and solvents
- as catalysts
- as heating aids
- soluble supports

2.1 Use of ionic liquids as solvents and co-solvents

2.1.1 Cycloaddition reactions

Diels-Alder reactions have been performed successfully in room temperature ionic liquids (RTILs) such as [bmim][BF_4], [bmim][ClO_4], [emim][CF_3SO_3], [emim][NO_3] and [emim][PF_6][57,58] and in combination with MW conditions.(52) [59,60,61] The extensive study of Yu and co-workers,[60] microwave assisted organotungsten Lewis acid catalysed Diels-Alder reactions were performed in IL, and for comparison in water. The results for selected dienes, dienophiles and Diels-Alder adducts are collected in Table 3.

Table 3. $[O=P(2\text{-py})_3W(CO)(NO)](BF_4)_2]$ catalysed Diels-Alder reactions in H_2O and $[bmim][PF_6]$.[60]



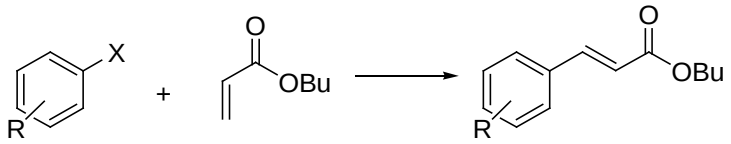
Diels-Alder adduct	Conventional heating at 50 °C						Microwave irradiation (T_{max} 50 °C)					
	H_2O			$[bmim][PF_6]$			H_2O			$[bmim][PF_6]$		
	Time (h)	**Yield (%)**	***endo/ exo***	**Time (h)**	**Yield (%)**	***endo/ exo***	**Time (s)**	**Yield (%)**	***endo/ exo***	**Time (s)**	**Yield (%)**	***endo/ exo***
1a	0.58	90	10:1	0.35	90	10:1	50	90	93:4	25	92	8:1
1b	0.67	92	19:2	0.42	88	8:1	50	87	8:1	25	85	8:1
1c	0.6	82	*endo*	0.5	80	*endo*	50	84	*endo*	30	81	*endo*
1d	3.5	96	3.7:1	3.5	97	4:1	60	97	7:2	60	96	4:1
2a	0.5	80	*endo-syn*	0.35	72	*endo-syn*	50	86	*endo-syn*	25	75	*endo-syn*
2b	0.35	85	*endo-syn*	0.25	72	*endo-syn*	50	88	*endo-syn*	25	78	*endo-syn*
2c	0.42	77		0.35	73		50	83		25	78	
3a				0.58	90	11:2				25	90	6:1
3b				0.58	76	5:1				25	77	6:1
3c				0.66	78	*endo*				30	80	*endo*
4a				1.1	80					30	80	
4b				1.1	87					30	88	
4c				0.58	78					30	80	
5a				1.7	78					35	83	
5b				1.7	85					35	88	
5c				2.5	70					40	75	

To summarize the results in Table 3, where starting materials were sufficiently polar, reaction times, yields and stereoselectivity were not markedly different under similar heating conditions when water and [bmim][PF_6] were used as the solvent (**1b** exception). As the use of water is limited by the low substrate solubility, [bmim][PF_6] served as the only feasible reaction medium for compounds **3**–**5.** In all cases (**1**–**5**), reaction times were reduced, from 21–150 minutes to 25–40 seconds, under microwave conditions. In addition, the recovery of the organotungsten catalyst was successful in [bmim][PF_6]. Little catalytic activity was lost and the catalyst could be recycled as many as ten times. By contrast, the recovery in water revealed 20% decay in catalytic activity after just six recyclings.

2.1.2 Heck reaction

Traditional solvents used in the Heck reaction, such as DMF, DMA and NMP, are known for their high solvation abilities towards Heck catalysts, i.e., palladium complexes. Today, these solvents are on the "environmental blacklist"[62], and new reaction protocols are avidly being sought.[63] Ionic liquids are known to dissolve a variety of Heck reagents and are becoming useful as alternative solvents.[64,65,66] Microwave promoted Heck reactions have been investigated in ILs by Vallin and co-workers in [bmim][PF_6][67] and by Xie and co-workers in [omim][BF_4].[68] Representative results from these two studies are collected in Table 4.

Table 4. Comparison of the Heck reaction in [bmim][PF_6][65] and [omim][BF_4][66] under microwave conditions.

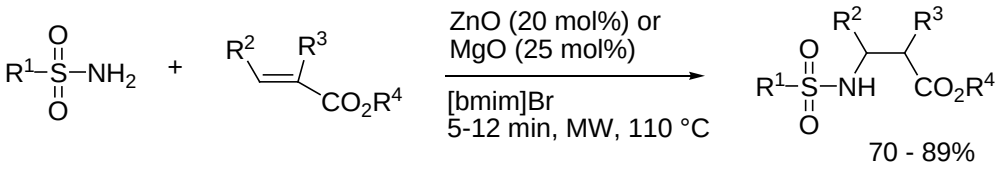


X	R	IL	Pd source	Ligand	Base	Time (min)	Temp (°C)	Yield (%)
Br	OMe	[bmim][PF_6]	$PdCl_2$	----	Et_3N	45	180	94
Br	OMe	[bmim][PF_6]	$PdCl_2$	P(*o*-tol)$_3$	Et_3N	45	180	99
Br	OMe	[bmim][PF_6]	Pd/C	----	Et_3N	45	180	29
Br	OMe	[omim][BF_4]	Pd/C	----	Bu_3N	1.5	not recorded	56
Br	H	[bmim][PF_6]	$PdCl_2$	P(*o*-tol)$_3$	Et_3N	20	220	87
Br	H	[omim][BF_4]	Pd/C	----	Bu_3N	1.5	not recorded	80
I	H	[bmim][PF_6]	$PdCl_2$	P(*o*-tol)$_3$	Et_3N	5	180	95
I	H	[omim][BF_4]	Pd/C	----	Bu_3N	1.5	not recorded	86

In the study of Vallin and co-workers, different palladium sources, e.g., $PdCl_2$, $Pd(OAc)_2$ and Pd/C, and common phosphine ligands, such as PPh_3, DPPP and P(*o*-tol)$_3$, were examined in [bmim][PF_6]. The best catalytic system was found to be $PdCl_2$ with ligand P(*o*-tol)$_3$; ordinary $Pd(OAc)_2$ gave much lower conversions. The IL [bmim][PF_6] was shown to be stable at high reaction temperatures as well as in the product isolation procedure (Kugelrohr distillation at 1–2 mm Hg and 170 °C), and the catalytic IL system was recycled five times. In the study of Xie *et al.*, reactions were carried out in [omim][BF_4] with Pd/C as catalyst and without a phosphine ligand. The reaction times were much shorter than those reported by Vallin and co-workers, no mention was made of reaction temperatures or the MW equipment that was used, and reproducing reactions with different MW equipment would probably prove difficult.

2.1.3 Aza-Michael addition

ILs have repeatedly provided high reaction accelerations in Michael addition and related reactions.[69,70,71,72,73,74,75,76,77] Recently, Zare and co-workers reported microwave-assisted aza-Michael addition of aromatic sulfonamides to various α,β-unsaturated esters.[78,79] The reactions were carried out in the presence of a catalytic amount of MgO[78] or ZnO[79] with [bmim]Br as the reaction solvent (Scheme 1).

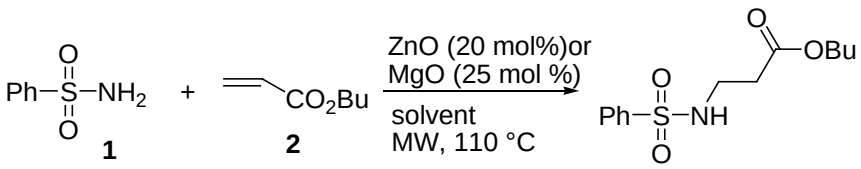


R^1= Ph, 4-MeC_6H_4 or 2-naphthyl
R^2= H or Me
R^3= H or Me
R^4= Et, *n*-Bu, Bn, CH_2CH_2Ph or $CH_2CH{=}CHPh$

Scheme 1. Aza-Michael addition of sulfonamides to α,β-unsaturated esters.[78,79]

In the studies of Zare and co-workers, both metal oxides showed good catalytic activity and the reactions were carried out successfully in 5–12 minutes, with yields varying between 70 and 89%. Both metal oxide–IL systems were still active towards the reaction after several recyclings. Under optimised reaction conditions, only minor quantities of diadduct products were formed. The authors showed that the reaction was as much as five times as fast in [bmim]Br as in conventional solvents under microwave conditions (Table 5).

Table 5. The effect of [bmim]Br as compared with conventional solvents in aza-Michael addition of benzenesulfonamide (**1**) to *n*-butyl acrylate (**2**) in the presence of ZnO[79] or MgO[78].

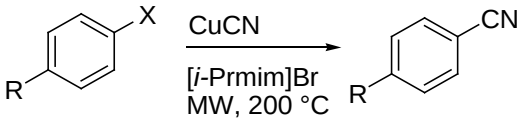


Solvent	Time (min)		Yield	
	ZnO	MgO	ZnO	MgO
[bmim]Br	5	5	86	89
DMSO	20	20	68	73
DMF	20	20	63	64
HMPTA	25	25	50	49
o-Xylene	25	25	44	26
none	---	---	37	23

2.1.4 Synthesis of nitriles from aryl halides

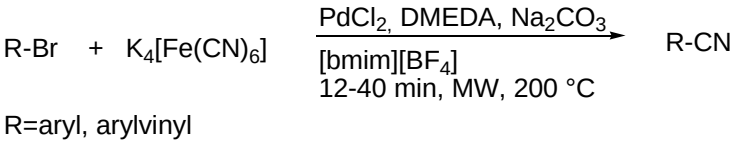
Aryl nitriles can be synthesised from the corresponding halides in IL reaction media using microwave promoted Rosenmund von Braun reaction (Table 6).[80] The reaction time was reduced from 24 hours in the conventional method to 3 or 10 minutes depending of the substrate. Under these reaction conditions, aryl iodide substrates gave the highest isolated yields (examples 1, 4 and 7), while aryl bromides required somewhat longer reaction times (examples 2, 5, 6, 8 and 9). Aryl chloride failed to react (example 3).

Table 6. Microwave promoted Rosenmund von Braun reaction with [*i*Prmim]Br as the solvent.[80]



Example	X	R	Time (min)	Yield (%)
1	I	Me	3	75
2	Br	Me	10	63
3	Cl	Me	10	0
4	I	OMe	3	65
5	Br	OMe	10	40
6	Br	Ac	10	64
7	I	NO_2	3	55 (at 150 °C)
8	Br	NO_2	10	16
9	4,4'-dibromobiphenyl		10	19

Another study of microwave accelerated synthesis of aryl nitriles in ILs was recently done by Liang and co-workers.[81] In their approach, the cyanation of aryl and arylvinyl bromides was carried out with potassium hexacyanoferrate(II), $K_4[Fe(CN)_6]$, catalysed by $PdCl_2$ in [bmim][BF_4] (Scheme 2). For aryl nitriles, the yields were 44–84% and arylvinyl nitriles between 31–74%. Interestingly, this method failed to convert 4-bromotoluene to the corresponding nitrile in 30 minutes at 200 °C, whereas in CuCN conditions the cyanation reaction was achieved in 10 minutes in 63% yield (Table 6, example 2). In the case of 4-bromoacetophenone, both methods gave reasonable yield of the corresponding nitrile (56% for the latter).



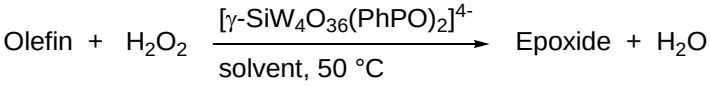
Scheme 2. Cyanation of aryl and arylvinyl bromides with $K_4[Fe(CN)_6]$.[81]

2.1.5 Epoxidation

Epoxidation reactions with hydrogen peroxide (H_2O_2) as oxidant have been studied widely in ILs, e.g., [bmim][BF_4] and [bmim][PF_6], under conventional heating methods.[82,83,84,85] Recently, Berardi and co-workers presented a microwave promoted small-scale epoxidation of olefins in [bmim][PF_6] or [bmim][NTf_2].[86] The purpose of the hydrophobic ILs was to act as solubiliser for the catalyst pair polyoxotungstate, $[\gamma\text{-}SiW_{10}O_{36}(PhPO)_2]^{4-}$–$H_2O_2$. For comparison, the reactions were also carried out under conventional heating. The results are

shown in Table 7. Results from an earlier study carried out with organic solvent acetonitrile (CH_3CN) are included in the table.[87]

Table 7. The catalytic epoxidation of olefins with H_2O_2 and $[\gamma\text{-}SiW_{10}O_{36}(PhPO)_2]^{4-}$ in $[bmim][NTf_2]$ or CH_3CN.[86,87]



Olefin	[bmim][NTf$_2$]				CH$_3$CN	
	Thermal (50 °C)		MW (57–60 °C)		MW (90–120 °C)	
	Time (h)	Epoxide Yield (%)	Time (min)	Epoxide Yield (%)	Time (min)	Epoxide Yield (%)
Cyclohexene	4	> 99	15	> 99	25	99
E-2-Octene	15	> 99	45	> 99		
1-Octene	40	75	180	54	50	79
1-Hexene	40	85	120	99	50	50
Z-2-Hexene	15	77	30	97		
E-2-Hexene	15	89	60	99		
Z-Stilbene	15	89	30 (58-73 °C)	44		

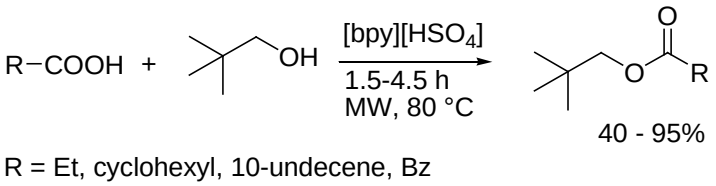
Yields of epoxides in the IL reaction media were mainly excellent, for both heating methods. Microwave heating was again superior to conventional heating, with reaction times 13–30 times shorter. Only 1-octene and *Z*-stilbene gave lower yields under MW conditions. 1-Octene was achieved in better yield with acetonitrile as the reaction solvent, though a higher reaction temperature was used. Green chemistry features could be considered to be present in this epoxidation method since the IL and catalyst were recycled at least four times without loss of activity.

2.2 Use of ionic liquids as reagents/catalysts and solvents

2.2.1 Fisher esterification reaction

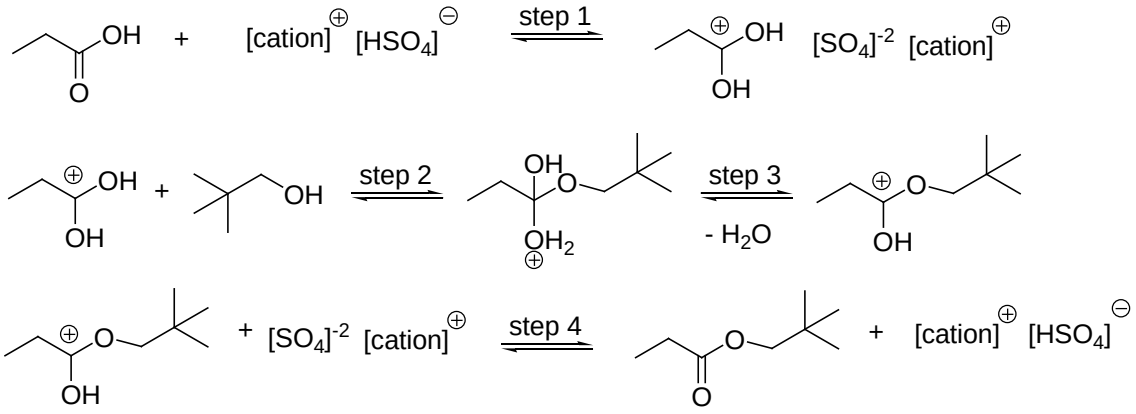
Task-specific ILs, particularly ILs with an acidic counteranion, have been applied successfully in esterification reactions as dual solvent–catalyst system. Bazureau and Arfan investigated the reaction between *neo*-pentanol and carboxylic acids to synthesise lipophilic

esters under microwave conditions (Scheme 3).[88] In their approach, [bpy][HSO_4] was used as both catalyst and solvent. Since the product ester was not soluble in [bpy][HSO_4], products could be isolated by simple decantation. This insolubility of the product also facilitated the shift of the reaction equilibrium to the product side, enabling better yields.



Scheme 3. Fisher esterification of acids with *neo*-pentanol in [bpy][HSO_4] under microwave irradiation at 80 °C.[88]

The authors also presented a plausible reaction mechanism for the esterification, a mechanism that follows Ingold's tetrahedral ($A_{AC}2$) mechanism[89] for ester formation (Scheme 4). The acidic counteranion of the IL initiates the reaction by donating a proton to the carboxylic acid, after which the reaction continues with nucleophilic attack of the alcohol and water abstraction (steps 2 and 3). In the final step, the acidic counteranion of the IL is regenerated by proton loss of the intermediate carbocation.



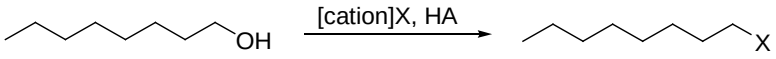
Scheme 4. The TSIL catalysed esterification reaction mechanism by Bazureau and Arfan.[88]

2.2.2 Halogenation reactions

Ionic liquids have been reported to operate as effective reagents and solvents in the synthesis of several types of long chain alkyl halides and alkyl dihalides from corresponding alcohols in the presence of an organic or inorganic acid.[90, 91, 92] Shorter reaction times were observed

when microwave irradiation was introduced to the method.[80,91,92] A good example of this new IL based technique is the halogenation reactions of *n*-octanol to corresponding octylchloride, octylbromide and octyliode. The results collected in Table 8 show that the particular IL–acid pair plays an important role in the reaction, together with the reaction temperature for this reaction. The best results seem to have been obtained with the organic acids *para*-toluenesulfonic acid (PTSA) and methane sulfonic acid (MSA). The different methods cannot properly be compared, particularly under MW conditions, since reaction conditions are not the same.

Table 8. The halogenation reactions of 1-octanol under MW and conventional heating conditions.



Product	[Cation]X	Energy source/ Reaction temperature	HA	Time	Yield	Ref.
C_8Cl	[bmim]Cl	r.t.	MSA	24 h	100 (GC)	91
	[bmim]Cl	r.t	H_2SO_4	19 h	50 (GC)	91
	[bmim]Cl	MW/ 200 °C	PTSA	3 min	32	80
	[bmim]Cl	MW/ 200 °C	H_2SO_4	3 min	49	80
C_8Br	[bmim]Br	r.t	H_2SO_4	5.5 h	90	91
	[omim]Br	oil bath/90 °C	PTSA	60 min	100 (GC)	92
	[*i*Pmim]Br	MW	PTSA	2 min	72 (GC)	92
	[*i*Pmim]Br	MW/ 200 °C	PTSA	3 min	95	80
	[*i*Pmim]Br	MW/200 °C	H_2SO_4	30 s	73	80
C_8I	[bmim]I	r.t	MSA	24 h	70	91
	[bmim]I	r.t	H_2SO_4	22 h	30	91
	[omim]I	oil bath/90 °C	PTSA	60 min	92 (GC)	92
	[*i*Pmim]I	MW	PTSA	2 min	51 (GC)	92
	[*i*Pmim]I	MW/200 °C	PTSA	30 s	81	80
	[*i*Pmim]I	MW/200 °C	H_2SO_4	1 min	38	80

Nguyen and co-workers regenerated [omim]Br and [omim]I by exchanging the tosylate (OTf) anion with the bromide and iodides of sodium salt (NaBr and NaI) (Figure 5). The authors affirmed that, after five runs, the conversion dropped by only 10%.

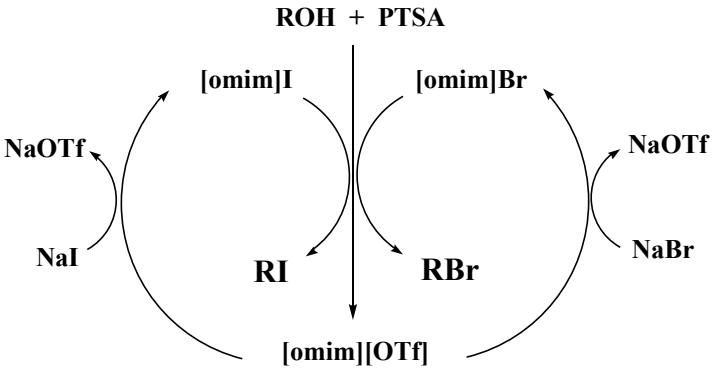


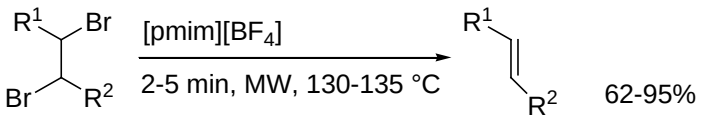
Figure 5. Recycling procedure of Nguyen and co-workers for conversion of the fatty alcohols into corresponding halides.[92]

2.2.3 *O*-Dealkylation reactions

O-Dealkylation of ethers, i.e., the removal of the alkyl group as a deprotection step to unmask a hydroxyl group, is a widely used reaction in the synthesis of polyfuctional molecules. There are a few reports of this reaction where ILs, including [Hmim]Br[93] and [bmim]Br/[bmim][BF_4][94], are used as reaction media in combination with a proton source (e.g., HBr) and [bmim][Al_2Cl_7][95,96] and with conventional heating methods. Microwave assisted dealkylation of alkyl aryl ethers in ILs [bmim]Br and [bpy]Br has been reported by Chauhan and Jain.[97] In their method, the reaction was performed without any Brønsted or Lewis acids in an unmodified microwave oven. An attempt was made to repeat this reaction in our laboratory (study **V)** and the results are discussed below (sect. 4.3)

2.2.4 Dehalogenation reactions

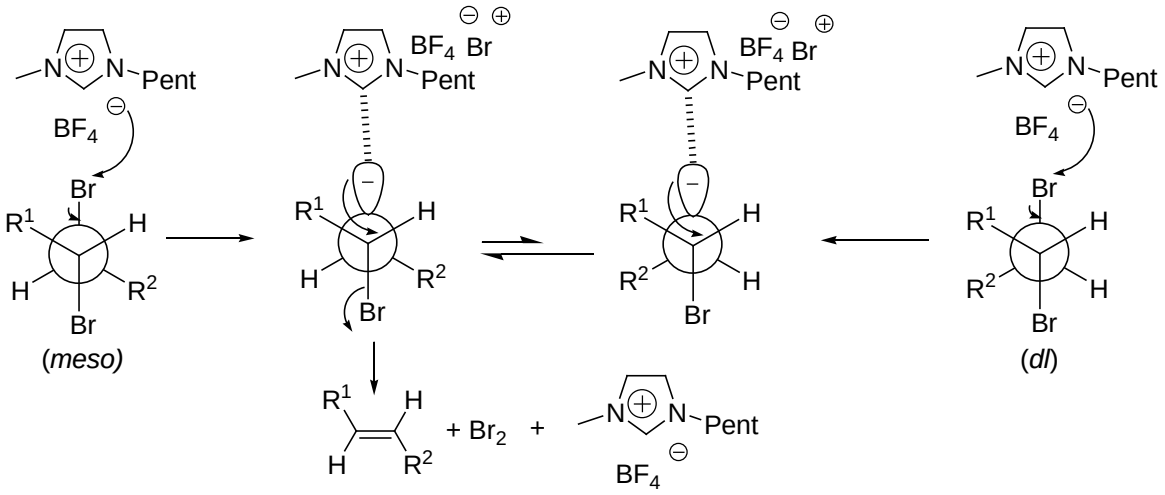
Conventionally, debromination can be achieved by using a metal, e.g., Zn, Mg[98] or In[99], in an organic solvent, such as THF or MeOH. Ranu and Jain have demonstrated that IL, [pmim][BF_4], can be used as an effective catalyst as well as reaction medium for the stereoselective debromination of a wide range of vicinal dibromides to the corresponding (*E*)-alkenes in a domestic microwave oven (Scheme 5). [100]



R^1, R^2 = alkyl, aryl, CN, CO_2Me, CO_2Et, COPh, NO_2

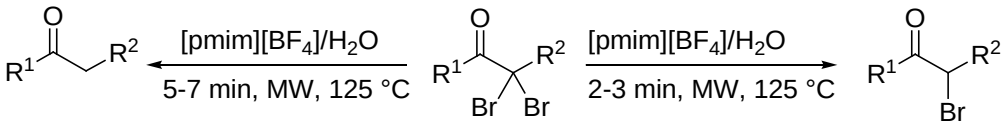
Scheme 5. Debromination of vicinal dibromides.[100]

According to the authors, the reaction did not occur at all under conventional heating conditions (r.t. or 90 °C for 12 hours), without IL under MW irradiation, nor with [pmim]Br as IL. The [pmim][BF_4] remained intact and could be reused several times. Thus, the ionic mechanism outlined in Scheme 6 was suggested for this reaction that is. Unfortunately the reaction was not tested with other ILs with different counter anions, such as [PF_6] or [NTf_2], which would have given valuable information both to confirm the reaction mechanism and to indicate the usefulness of other ILs.



Scheme 6. Suggested reaction mechanism for debromination of dibromoalkane by Ranu and Jana.[100]

In another application of [pmim][BF_4] for the debromination reaction,[101] α-bromoketones were selectively debrominated to either monobromo or debromoketones through control of the reaction time (Scheme 7). The use of [pmim][BF_4] was also found suitable for the dehalogenation of α-halo ketones and esters and of *vic*-bromoacetals.



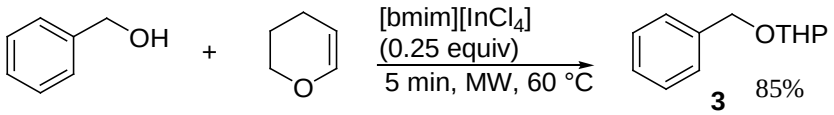
R^1 = Ar, OEt
R^2 = COPh, COMe, Me, H

Scheme 7. The debromination of α-bromoketones to monobromoketones or debromoketones.[101]

2.3 Use of ionic liquids as catalysts

2.3.1 Protection of alcohols as THP-ethers

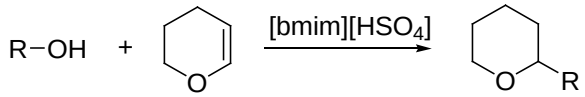
Lewis acidic [bmim][$InCl_4$] IL has been applied as catalyst in the microwave promoted solvent-free reaction of alcohols with tetrahydropyrane (THP).[102] An example reaction is presented in Scheme 8. The protected product, 2-(benzyloxy)-tetrahydro-2*H*-pyran (**3**), was obtained, in very good yield, with use of only 0.25 molar equiv of the IL catalyst. Furthermore, [bmim][$InCl_4$] maintained its catalytic activity well; even after five cycles the yield was 86%. However, the procedure was not effective under conventional heating (at 60 °C), where only 39% of the target compound **3** was obtained.

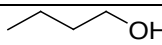
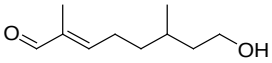
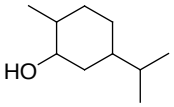
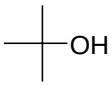
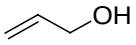
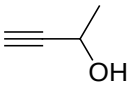
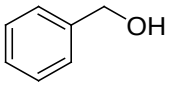
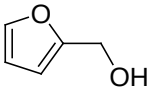
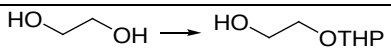
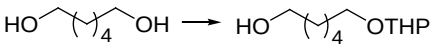


Scheme 8. The THP protection of phenylmethanol in the presence of Lewis acidic [bmim][$InCl_4$] IL.[102]

Another approach for the protection of alcohols as THP ethers has been presented by Singh and co workers. [103] In their study, Brønsted acidic [bmim][HSO_4] IL was used as a catalyst for the etherification of various primary, secondary and tertiary alcohols and diols. The reactions were studied in MW conditions, as well as in ultrasound and room temperature conditions (Table 9). All reactions gave good to excellent yields of the corresponding THP ether under MW irradiation. The recyclability of IL was tested for all methods. The authors observed the decomposition of the ionic liquid in experiments under microwave conditions, with only 50% yield of the THP ether in the first collection of IL. Under ultrasound conditions the yield was still 60% after six runs and under room temperature conditions 65% after nine runs.

Table 9. [bmim][HSO_4] catalysed tetrahydropyranylation of selected alcohols and diols under microwave (MW), ultrasound (US) and room temperature (r.t.) conditions.[103]

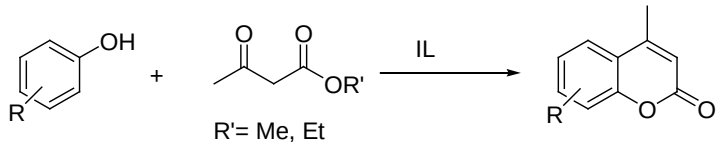


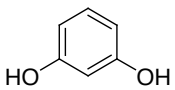
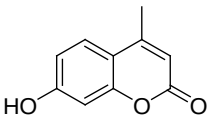
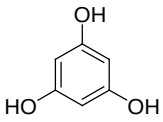
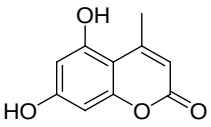
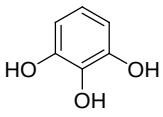
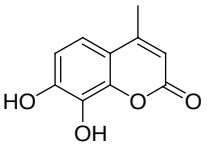
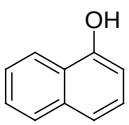
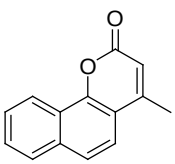
Substrate	MW		US		r.t.	
	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
	1.5	98	5	97	25	92
	1.5	84	5	82	45	80
	2	88	6	86	60	89
	2	75	6	71	60	62
	2	90	6	90	45	90
	2	76	6	74	60	71
	1.5	92	6	92	60	90
	1.5	89	5	90	45	90
Substrate → Product						
	2	86	5	85	60	84
	2	97	5	88	60	85

2.3.2 Pechmann reaction

The Pechmann reaction normally refers to an acid catalyzed condensation of phenols with β-ketoesters, and it is widely applied for the synthesis of coumarins. A large number of reagents have been exploited for this reaction, including sulfuric acid,[104] phosphorus pentoxide,[105] aluminium chloride,[106] and trifluoroacetic acid.[107] Nowadays, gentle and more environmentally friendly reagents ($SnCl_2$,[108] oxalic acid[109], alum ($KAl(SO_4)_2 \cdot H_2O$),[110] silica triflate,[111] and iodine[112]) are preferred for the reaction. A number of studies have also shown that ionic liquids, either neutral[113] or acidic[114,115,116], promote coumarin synthesis via Pechmann condensation. Singh *et al.* studied the combination of an IL and microwave irradiation for this reaction in a common household microwave oven.[117] The reaction was also performed under conventional heating conditions with Brønsted acidic [bmim][HSO_4] as the catalyst (Table 10). In all cases, microwave conditions gave better yields of coumarins in much decreased reaction times.

Table 10. Brønsted acidic IL [bmim][HSO_4] catalysed Pechmann reaction under microwave and conventional heating conditions.[117]



Example	Substrate	Product	IL=[bmim][HSO_4]			
			MW (140 W)[a]		Thermal (80 °C)	
			Time	Yield (%)	Time	Yield (%)
1			2 min	81	12 h	62
2			9 min	85	20 h	65
3			10 min	79	15 h	58
4			6 min	96	5 h	75

[a] The reaction temperature was not recorded.

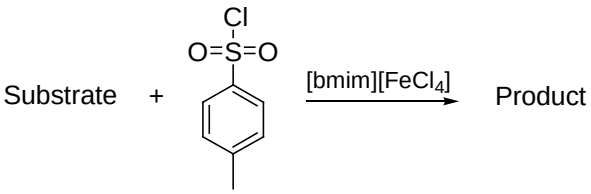
2.3.3 Friedel–Crafts reaction

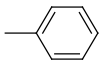
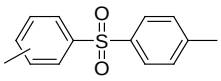
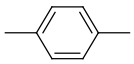
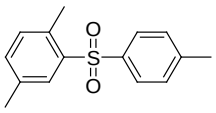
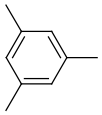
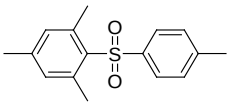
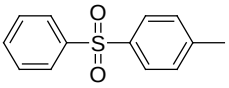
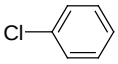
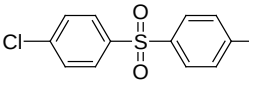
Friedel–Crafts (FC) reactions are familiar and powerful methods for C–C bond formation in organic synthesis and have been the subject of continuous investigation ever since the nineteenth century.[118,119,120,121] The FC acylation reaction has been extensively used in the synthesis of aromatic and cyclic ketones, which are important synthetic intermediates in the fine chemical and pharmaceutical industries. In a typical reaction, an acid chloride is used as the acylating reagent with a stoichiometric amount of Lewis acid at high temperature. In this procedure, large amounts of HCl are formed as a by-product, and problems can arise in regard to waste handling, as well as corrosion problems in the equipment being used.

Friedel-Crafts alkylation and acylation reactions were the first reactions in IL reaction media to be studied back in 1986,[122] when the first generation ILs, i.e., chloroaluminate ILs, were just being introduced in organic synthesis.[123,124,125,126] Even thought chloroaluminates are excellent media for many synthetic processes, they suffer from several disadvantages. For example, they are moisture sensitive and can be difficult to separate from products containing heteroatoms. Moreover, the recyclability of the catalytic system is lost at the end of a reaction since chloroaluminate ILs are commonly quenched with water and lost in the form of acidic aqueous waste.[127] To overcome these disadvantages, several new ILs for Friedel-Crafts reactions have been introduced in recent years, among them metal triflates,[128] bismuth(III) derivatives,[129] zeolites[130] and pyridium based ILs.[131] We have designed a highly efficient Friedel-Crafts acylation procedure using metal *bis*{(trifluoromethyl)sulfonyl}amide complexes as catalysts in solvent-free or IL reaction conditions[**I**] and a chloroindate (III) IL as the reaction catalyst.[**II**] These procedures are reported in studies **I** and **II**.

So far, there are only two reports of microwaves being used as a heating source to decrease the reaction time in Friedel-Crafts and related reactions.[132,] [**III**] Samant and co-workers investigated FC sulfonylation of benzene and its derivatives using Lewis acidic [bmim][$FeCl_4$].[132] Table 11 presents examples of the reaction compared under MW and conventional heating conditions.

Table 11. Selected examples of sulfonylation reactions of benzene and its derivatives using Lewis acidic [bmim][$FeCl_4$] IL as a catalyst (5–10 mol%) under MW and conventional heating.[132]



Example	Substrate	Product	MW			Conventional		
			Time (min)	Temp (°C)	Yield (%)	Time (h)	Temp. (°C)	Yield (%)
1			3	160	90 (11o:89p)	1	110	90 (33o:67p)
2			3	165	87	0.5	135	92
3			3	165	91	0.5	120	93
4			30	80	36	8.5	80	70
5			15	150	64	12	120	62

As can be seen from Table 11, the sulfonylation reaction could be successfully carried out in both heating setups, and even the less reactive chlorobenzene (example 5) gave reasonable yields of the corresponding sulfone product. In all cases, MW conditions were superior in terms of reaction times.

MW promoted Friedel-Crafts acylation reaction was studied by our group using ILs as reaction medium or catalyst or both, for the synthesis of polyhydroxydeoxybenzoins. With an acidic additive–IL system under MW conditions, the FC acylation reaction proceeded in just 4 minutes. The reactions are discussed in study **III** below.

2.4 Use of ionic liquids as a heating aid

Leadbeater and co-workers carried out an extensive study on the effect of ILs on heating of non-polar solvents under microwave irradiation.[59] Following an idea introduced by Ley *et al.* in 2001,[133] their findings indicated that solvents such as hexane, toluene, THF and dioxane can be heated far above their boiling points in sealed vessels containing a small amount of an ionic liquid (see Table 12). However, the authors also pointed out that ILs with halogen counteranion undergo major decomposition above 230 °C, forming the corresponding methyl halide and alkylimidazole and contaminating the solvent in question. In contrast, [bmim][PF_6] did not decompose at temperatures as high as 280 °C. Except for certain limitations at high reaction temperatures, therefore, halogen based ILs can be considered very useful in microwave heating of non- polar solvents.

Table 12. Selected examples of ILs (20–50 mg) and their effect on heating of non-polar solvents (2 ml) under microwave irradiation.[59]

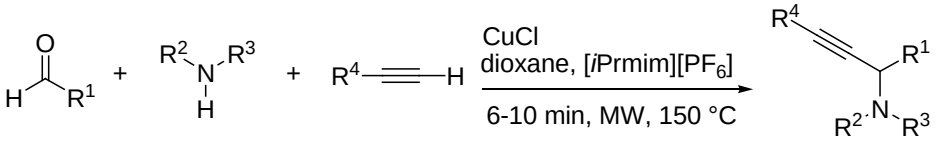
Solvent	IL added	Attained T (°C)	Time (s)	T without IL (°C)[a]	bp (°C)
Hexane	[bmim]I	217	10	46	69
	[iPrmim]Br	228	15		
	[bmim][PF_6]	279	20		
Toluene	[bmim]I	195	150	109	111
	[iPrmim]Br	234	130		
	[bmim][PF_6]	280	60		
THF	[bmim]I	268	70	112	66
	[iPrmim]Br	242	60		
	[bmim][PF_6]	231	60		
Dioxane	[bmim]I	264	90	76	101
	[iPrmim]Br	246	90		
	[bmim][PF_6]	149	100		

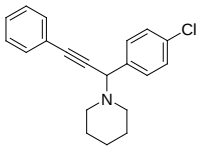
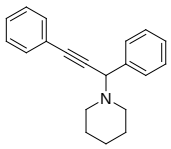
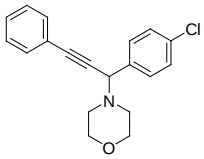
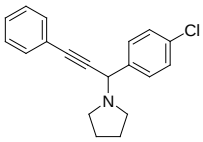
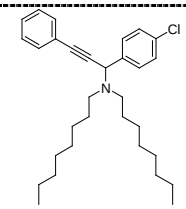
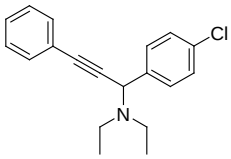
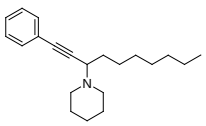
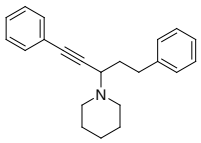
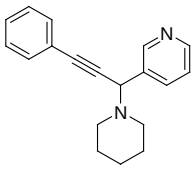
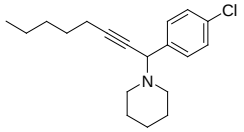
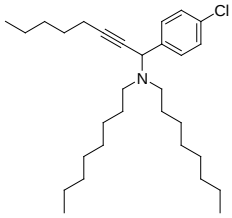
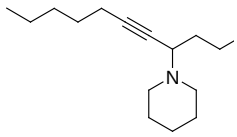
[a] Temperature attained during the same MW irradiation time.

Leadbeater's group also studied the three-component Mannich condensation of acetylenes, aldehydes and secondary amines using CuCl as activator of the acetylene component under MW conditions.[134] In this extensive research, the condensation reaction was carried out in three different reaction media, i.e., dioxane, dioxane together with a small quantity of ILs ([*i*Prmim][PF_6] or [bmim][PF_6]) and only with IL ([bmim][PF_6]). When dioxane alone was used as the solvent, the method produced only 40% of product **4** (see Table 13). When IL [*i*Prmim][PF_6] was combined with dioxane the reaction was highly improved, yielding 99%

of **4**. The use of [bmim][PF_6] with dioxane produced only 61% of the product, while the reaction using [bmim][PF_6] without dioxane failed altogether. The results for various substituted propargylamines where [*i*Prmim][PF_6] was used as a heating aid are collected in Table 13.

Table 13. Reaction conditions and results for the three-component Mannich-type reaction with dioxane and [*i*Prmim][PF_6].[132]



Products				
 (**4**) 99%	 97%	 96%	 82%	 79%
 43%	 91%	 85%	 65%	 67%
 49%	 75%			

2.5 Use of ionic liquids as a soluble support

Task specific ionic liquids (TSILs) have recently been introduced as soluble supports in liquid-phase organic synthesis (IoLiPOS) and represent a new strategy for combinatorial chemistry and high-throughput parallel synthesis.[135,136,137,138,139] The general concept of IoLiPOS, as formulated by Bazureau *et al.*, is illustrated in Figure 6.[140] The key benefit of this approach is the easy removal of excess reagents and by-products simply by washing the reaction mixture with appropriate solvent after each step.

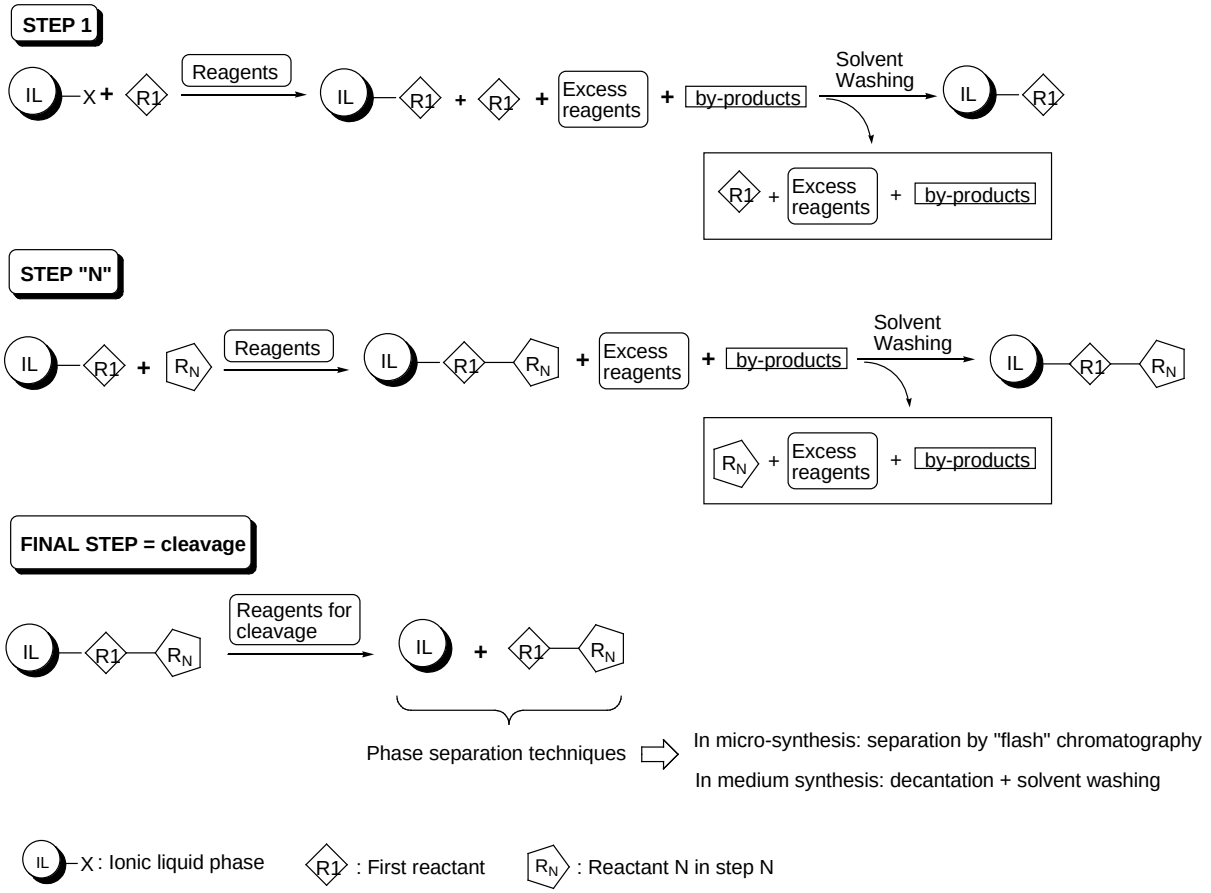
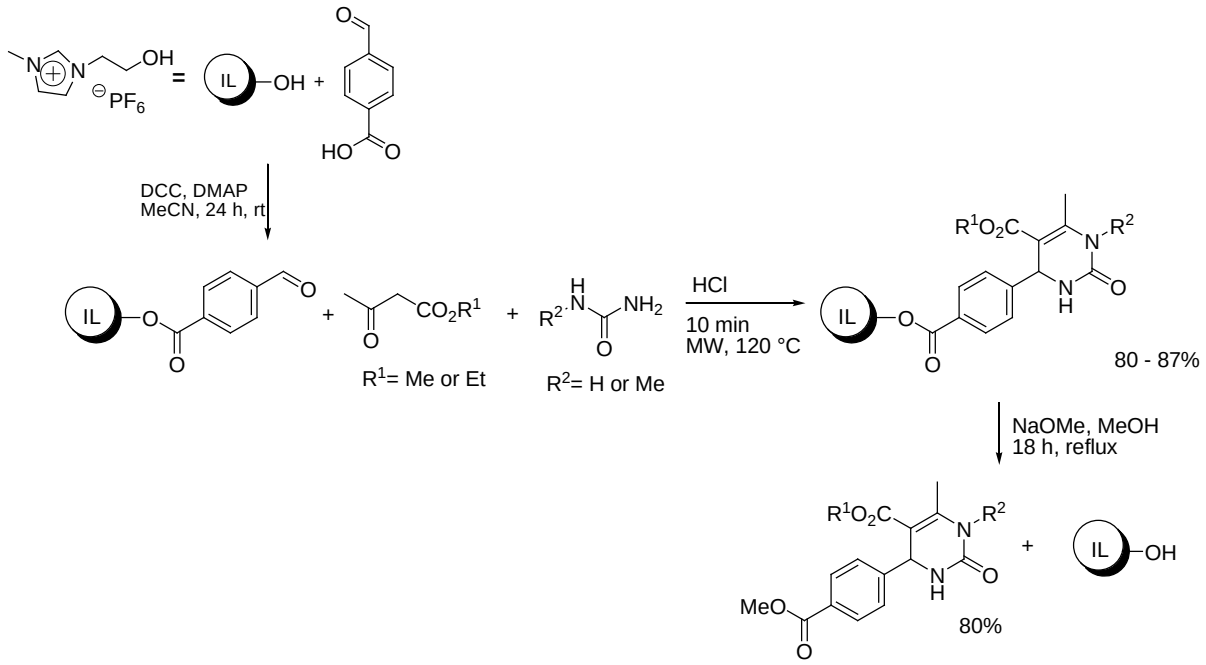


Figure 6. General concept of ionic liquid phase organic synthesis (IoLiPOS) as formylated by Bazureau and co-workers. [140]

Microwave irradiation has been included in this method in order to accelerate the reaction rate.[141,142] As an example of microwave assisted IoLiPOS, a one-pot three-component Biginelli 3,4-dihydropyrimidine (3,4-DHPM) synthesis is shown in Scheme 9.[136]



Scheme 9. Three-component, one-pot Biginelli synthesis with use of TSILs as soluble support.[140]

The term “one-pot” synthesis is justified in this case since one of the starting materials is first reacted with the IL in question (after which follows a separation procedure). Since only one molar equivalent of the low molecular weight IL phase is used, this IoLiPOS methodology offers the advantages of easy product isolation and high loading capacity of the ionic liquid phase.

2.6 *Summary of applications of ionic liquids in microwave promoted organic synthesis by reaction type*

As a supplement to section 2.1–2.5 above, Table 14 lists all uses that have been made of ionic liquids in microwave promoted organic synthesis, by reaction type.

Table 14. Summary of applications of ionic liquids to microwave promoted organic synthesis by reaction type. S: solvent, C: catalyst, R: reagent, CoS: co-solvent, SS: soluble support, HA: heating aid.

Reaction type	Reaction	Description	Purpose of IL	MW mode	Ref
Aliphatic nucleophilic substitution	Esterification	Esterification of carboxylic acids with C4-C18 alcohols	S	multi	143
		Esterification of carboxylic acids with *neo*-pentanol	C&S	mono	88
	Halogenation	Conversion of saturated and unsaturated alcohols to alkyl halides	R&S	mono	80
		Conversion of C8-C18 fatty alcohols to fatty halides	C&S	not specified	91
		Conversion of C6 –C16 1,ω-dialcohols to dihalides		multi	92
	Dealkylation	Dealkylation of alkyl aryl ethers	R&S	multi	97
	Tsuji-Trost reaction	Allylic substitution with various carbon and heteronucleophiles catalysed by $Pd(OAc)_2$/TPPTS	CoS	multi	144
	Acylation of amines by carboxylic acids	Synthesis of aromatic amides with coupling agent	S	mono	145
	N-Benzylation	*N*-Benzylation reaction of benzimidazole, carbazole etc. with dibenzyl carbonate as an alkylating reagent	CoS	mono	146
	Nucleophilic substitution	Nucleophilic substitution between ethoxymethylene isopropylidene malonate and thiophenol and anilines	S	not specified	147
Addition to carbon–carbon multiple bond	1,3-Dipolar cycloaddition	Cycloaddition reaction between imidate derived from diethyl aminomalonate and 2-ethoxybenzaldehyde	S	mono	52

	[4+2] Cycloaddition	Diels-Alder reaction involving 1,3-cyclopentadiene and numerous dienophiles	S	mono	61
		Organotungsten Lewis acid catalysed Diels-Alder reaction involving series of dienes and dienophiles	S	mono	60
	Transfer hydrogenation	Hydrogenation of homo or heteronuclear organic compounds using Pd/C as a catalyst and formate salts as a hydrogen source	S	multi	148
	Aza-Michael addition	Michael addition of sulfonamides to α,β-unsaturated esters catalysed by MgO	S	mono	78
		Michael addition of sulfonamides to α,β-unsaturated esters catalysed by ZnO	S	mono	79
	Olefin metathesis	Ring-closing metathesis with Grubbs catalyst	S	multi	149
	Hydro-alkoxy addition	Protection of alcohols as THP ethers using [bmim][$InCl_4$] as catalyst	C	mono	102
		Protection of alcohols as THP ethers using [bmim][HSO_4] as catalyst	C	multi	103
Addition to carbon–heteroatom multiple bond	Cyclization reactions	Cyclization reaction involving arylnitriles and dicyanodiamide to prepare 6-aryl-2,4-diamino-1,3,5-triazines	S	mono	150
		Cyclization reaction between IL bound acetoacetate and arylidenomalononitriles to prepare 4*H*-pyrans	SS	not specified	141
		Three component preparation of 2-thioxo tetrahydropyridin-4-(1*H*)-ones	SS	mono	142
		Three component preparation of 4*H*-pyran derivatives	C&S	mono	151
	Bigginelli synthesis	Synthesis of 3,4-dehydropyrimidines	SS	mono	140
	Mannich-type three-component reaction	Three component reaction involving aromatic or aliphatic aldehyde, cyclic or non-cyclic amine and aromatic or aliphatic alkyne	HA	mono	134
	[2+3] Cycloaddition	Cyclization reaction between arylnitriles and NaN_3 to form tetrazole	S	mono	152
	Hetero-Diels-Alder	Intramolecular Hetero-Diels-Alder reaction of alkenyl-tethered 2(1*H*)-pyrazinones	HA	mono	153
		Hetero-Diels-Alder reaction involving (*R*)-citronellal and aryl amines	C	multi	154
	Dehydrative cyclization	Intra-molecular conversion of substituted 1-(2-hydroxyphenyl)-3-phenyl-1,3-propene diones to the corresponding flavones	C&S	multi	155

	Pechmann reaction	Coumarins by condensation of phenols with β-ketoesters	C	multi	117
	Knoevenagel reaction	Synthesis of 5-arylidene barbituric acids and thiobarbituric acid derivatives	S	not specified	156
	Stetter reaction	Synthesis of chroman-4-ones by intramolecular addition of an activated aldehyde to an acceptor bearing activated double bond	S	mono	157
	Benzoin condensation	Solventless benzoin condensation with several imidazolium based ILs	C	mono	158
Elimination	Dehalogenation	Stereoselective debromination of a variety of structurally diverse vicinal-dibromides to the corresponding (*E*)-alkenes	C&S	multi	100
		Selective debromination of *gem*-*α*-dibromoketones, α-halo ketones and esters and stereoselective debromination–elimination of *vic*-bromo acetals.	C&S	mono	101
Free radical substitution	Heck reaction	Palladium catalysed arylation involving different arylhalides and butylacrylate in [bmim][PF_6]	S	mono	67
		Palladium catalysed arylation involving different arylhalides and butylacrylate in [omim][BF_4]	S	not specified	68
Aromatic electrophilic substitution	Friedel-Crafts reaction	Sulfonylation of benzene and its derivatives	C	mono	132
		Synthesis of polyhydroxydeoxydenzoins	S	mono	III
	Isotopic labelling	Deuterolabelling of polyphenols	CoS	mono	IV
	Iodination	Regioselective iodination of activated arenes	S	mono	159
Aromatic nucleophilic substitution	Rosenmund von Braun reaction	Conversion of series of aryl halides to nitriles	S	mono	80
	Cyano-de halogenation	Cyanation of aryl and arylvinyl bromides with $K_4[Fe(CN)_6]$	S	mono	81
Oxidation	Epoxidation	Catalytic epoxidation of *cis*-cyclooctene	S	mono	86
	Oxidation of alcohols	Oxidation of benzyl alcohols to the corresponding carbonyl compounds	C	multi	160
Rearregement	Beckmann rearrangement	Rearregement of ketoximes into amides	S	multi	161
Multistep synthesis	Pictet-Spengler	Three step synthesis of tetrahydro-β-carbolinediketopiperazines	CoS	mono	162

	Schotten-Baumann and intramolecular ester amidation				
Enzyme catalysis	Acylation	Lipase catalysed acylation of amino alcohols	CoS	mono	163

3. AIMS OF THE STUDY

The objective of the present study was to develop new synthetic methods for selected aromatic compounds using novel, highly solvating and recyclable ionic liquids. The effectiveness of microwave heating was investigated where appropriate.

The specific aims of the study were

1. To investigate the Friedel-Crafts acylation reaction in ionic liquids (**I, II**)

2. To develop a rapid method for the synthesis of polyhydroxydeoxybenzoins making use of ionic liquids (**III**)

3. To develop a more efficient deuterolabelling method for naturally occurring polyphenols (**IV**)

4. To improve a dealkylation method for poorly soluble aromatic alkyl ethers using BBr_3 in ionic reaction media (**V**)

5. To develop new ionic liquids using a halide-free method (**VI**)

4. RESULTS AND DISCUSSION

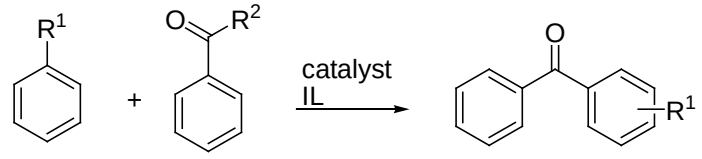
4.1 Friedel–Crafts acylation reactions

Friedel–Crafts acylation reactions are widely used in the pharmaceutical and fine chemical industries. The catalyst of choice for the reaction is conventionally a strong Lewis acid, such as aluminium(III) chloride. The downside of this reagent is that usually more than one molar equivalent of Lewis acid "catalyst" is needed, because once the ketone product is formed the carbonyl group strongly bonds to the Lewis acid and to some extent inactivates the Lewis acid.

With the goal of minimizing the amount of catalyst, bis{(trifluoromethyl)sulfonyl}amine ($HN(SO_2CF_3)_2$ or $HNTf_2$), metal bistriflamide complexes, i.e., $M\{N(SO_2CF_3)_2\}_n$, and chloroindate(III) were tested as catalysts for the synthesis of substituted benzophenones[I, II] and polyhydroxydeoxybenzoins[III] via Friedel–Crafts acylation reaction. Ionic liquids were present in the reaction media in most cases.

4.1.1 The study of different catalyst/IL -systems in benzoylation reaction [I, II]

The benzoylation reaction (Scheme 10) of several aromatics was investigated with use of metal bistriflamide complexes, as well as tin(IV) chloride, indium(III) chloride, zinc(II) chloride and bistriflamic acid (**I**) and chloroindate(III) ILs (**II**) as catalysts. Representative results are collected in Table 15.



R^1= Cl, F, OCH_3, CH_3
(or two CH_3 groups in xylene)
R^2= Cl, OH, PhCOO

Scheme 10. Benzoylation reaction of different aromatics.

Table 15. Representative results from studies **I** and **II** showing the usefulness of catalyst/IL systems in benzoylation.

Aromatic	Acylating agent	Catalyst	Solvent	Temp/ °C	Time/h	Yield/ %	Selectivity (o:m:p)
Ph-CH_3	**PhCOCl**						
Study I		1% $Co(NTf_2)_2$	solvent-free	110	3	99	
		5% $Zn(NTf_2)_2$	solvent-free	110	4	99	
		1%$Mn(NTf_2)_2$	solvent-free	110	5	99	
		1% $HNTf_2$	solvent-free	110	48	97	
		1% $SnCl_4$	[bmim][NTf_2]	110	2	97	
		1% $Co(NTf_2)_2$	[emim][NTf_2]	110	0.5	95	
Study II		12.5% $InCl_3$-[bmim]Cl	solvent-free	110	18	93	15.3:82
Ph-Cl	**PhCOCl**						
Study I		5% $Co(NTf_2)_2$	[bmim][NTf_2]	130	18	95	1:0:9
		5% $Zn(NTf_2)_2$	[bmim][NTf_2]	130	18	55	1:0:9
		15% $InCl_3$	[emim][NTf_2]	130	96	87	1:0:9
Study II		15% $InCl_3$-[bmim]Cl	solvent-free	120	69	78	11:2:87
Ph-OCH_3	**PhCOCl**						
Study I		10% $ZnCl_2$	[emim][NTf_2]	110	18	80	
Study II		12.5% $InCl_3$-[bmim]Cl	solvent-free	100	18	94	6:0:94
Ph-OCH_3	**$(PhCO)_2O$**						
Study II		5% $InCl_3$-[bmim]Cl	solvent-free	80	3	79	6:0:94
				80	48	97	2:0:98
				80	5^{th} recycle	62	6:0:94
***m*-Xylene**	**PhCOOH**						
Study I		10% $Zn(NTf_2)_2$	[bmim][NTf_2]	140	48	40	
		10% $Co(NTf_2)_2$	[bmim][NTf_2]	140	48	82	

In study **I**, the reaction of benzoyl chloride with toluene without solvent was selected as a model reaction to study the relative effectiveness of various metal(II) bistriflamide catalysts.[164] Metals investigated were magnesium(II), calcium(II), strontium(II), barium(II),

tin(II), manganese(II), cobalt(II), nickel(II), copper(II) and zinc(II). The bistriflamide salts of cobolt(II), zinc(II) and manganese(II) were found to give the highest conversions (monitored by GC) in moderate reaction times. The reaction was also carried out successfully with a number of metal(III) and metal(IV) bistriflamide salts (iron(III), indium(III) cerium(IV) as metals), but these materials are poorly characterized and their composition is not necessarily as claimed.[165,166] In subsequent reactions where ILs were used, the catalyst was generated *in situ* by taking a metal salt, e.g., a metal bistriflamide complex or $ZnCl_2$, and dissolving it in the ionic liquid. To this mixture, the acylating agent and the aromatic compound were added. The product separation could be carried out by direct vacuum distillation from the reaction vessel (Kugelrohr distillation) or solvent extraction. The direct vacuum distillation facilitated the recycling of the reaction medium since fresh starting materials could be added and the reaction could be directly repeated.

Study **II** investigated the suitability of chloroindate(III) ionic liquids as reaction catalysts in FC benzoylation reaction. Indium(III) species had previously been found useful as Lewis-acid catalysts in a variety of organic reactions.[167] The advantage of indium(III) chloride over aluminium(III) chloride is its hydrolytic stability and reduced oxophilicity. Combining the indium(III) chloride with an organic halide salt gives ionic liquids with good solvating ability and negligible vapour pressure, and a liquid that is both inherently Lewis-acidic and water stable. Chloroindate(III) ionic liquids were synthesised by mixing indium(III) chloride with an appropriate amount of [bmim]Cl at 80 °C, and the resulting IL was used without further treatment. In this study, the reaction of anisole with benzoic anhydride was used as a test reaction to find adequate Lewis-catalytic conditions for the reaction in question. Whit $InCl_3$ used in excess ($X(InCl_3)= 0.67$) the formed IL was effective enough to catalyse the benzoylation reaction in proportions of 5, 12.5 or 15 mol% with respect to the aromatics.

It should be noted that it is difficult to obtain good yields in truly catalytic Friedel–Crafts acylation reactions with aromatic compounds less reactive than benzene.[165] With the two methods described in studies **I** and **II**, good to excellent yields were obtained with these nonreactive compounds. In addition, both methods could be used in larger reaction scales and could therefore serve as good alternatives for FC acylation reactions in the pharmaceutical industry. Since many of the metal bistriflamide salts are not yet commercially available, chloroindate(III) ILs might be the better option at the moment. In both methods, however, the amount of the reaction solvent was minimized and the catalytic system was recyclable, making these types of Friedel-Crafts reactions closer to green and sustainable organic syntheses.

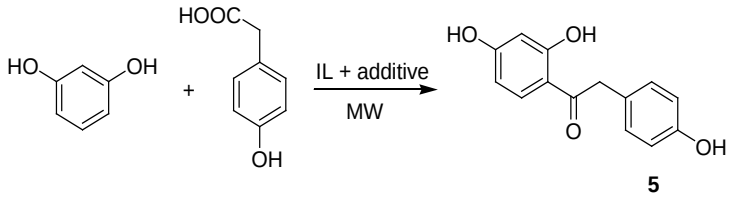
4.1.2 Synthesis of polyhydroxydeoxybenzoins and arylpropanones[III]

Polyhydroxydeoxybenzoins are mainly used as precursors for the synthesis of isoflavone phytoestrogens, among which daidzein and genistein are well known from the soya plant.[168] Phytoestrogens have attracted particular interest owing to their positive physiological effects on the female reproductive system, the cardiovascular system and the skeleton.[169,170] The physiological effects of phytoestrogens are believed to be exerted *via* the estrogen receptor (ER). Recently, certain polyhydroxydeoxybenzoins, in particular 2,4,4'-trihydroxydeoxybenzoin (**5**), were reported to possess selectivity and transcriptional bias towards ERβ, and can be considered to represent a promising new class of ERβ–biased phytoestrogens.[171]

In this work, ionic solvents were used to promote the synthesis of polyhydroxydeoxybenzoins under microwave conditions. Arylpropanones were included for comparison.

The synthesis of 2,4,4'-trihydroxydeoxybenzoin (**5**) (Table 16) was chosen as the model reaction to assess the activity of various IL/acidic additive systems. Chloroindate(III), $HNTf_2$ and $Co(NTf_2)_2$ were selected as additives for the reaction on the bases of the previous studies. Lewis acid $BF_3{\cdot}OEt_2$ was also tested since it is known to promote this particular FC reaction, (though it cannot be recovered after the isolation procedure).

Table 16. Comparison of different reaction media in the synthesis of 2,4',4'-trihydroxydeoxybenzoin, modified from **III**.



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Entry	Solvent/ additive (ratio)	T/°C	t/min	Yield/% (conversion by ^{1}H NMR)
1	[bmim]Cl–$InCl_3$ (0.6:2.0)	100	6	60 (67)
2	[bmim][NTf_2]/$HNTf_2$ (0.5:0.3)	90	4	73 (85)
3	[bmim][NTf_2]/$Co(NTf_2)_2$ (1.0:0.5)	90	4	20 (50)
4	[bmim][NTf_2]/ no catalyst (1.5)	120	30	20 (30)
5	[bmim]BF_4/$HNTf_2$ (1.0: 0.3)	120	4	30 (40)
6	[bmim]BF_4/$Co(NTf_2)_2$	90	5	39 (50)

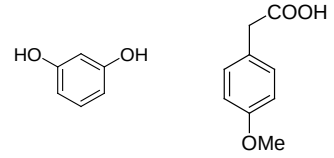
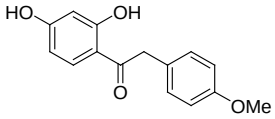
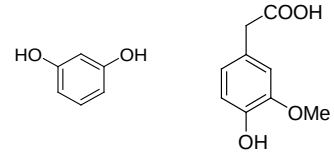
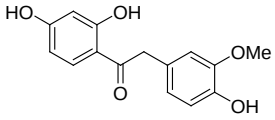
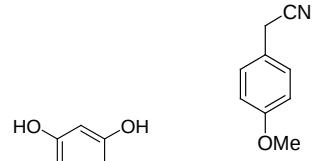
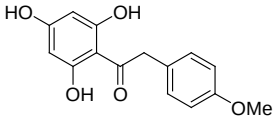
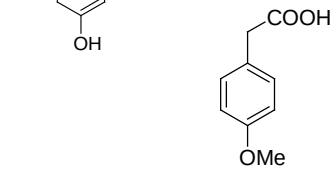
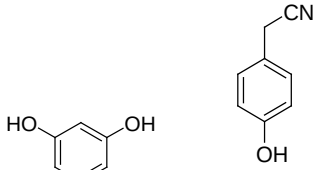
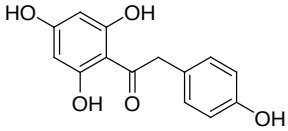
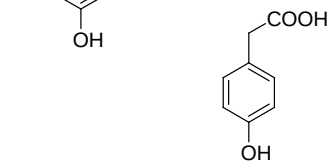
	(5.0:0.5)			
7	[bmim]BF_4/BF_3·OEt_2 (2.0:1.0)	100	4	88 (93)
8	[bmim]BF_4/no catalyst (2.0)	120	30	10 (20)
9	[bmim][NTf_2]/$HNTf_2$ (0.5:0.3)	100	120 oil bath	70 (85)

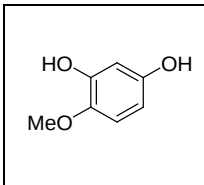
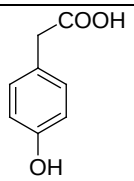
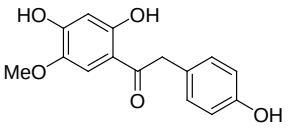
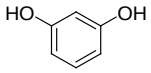
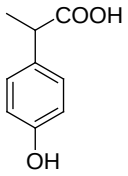
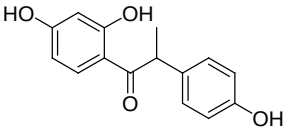
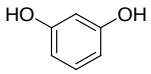
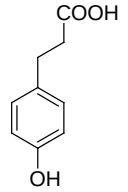
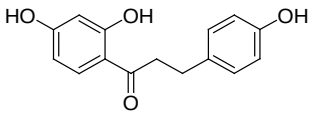
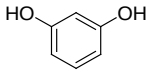
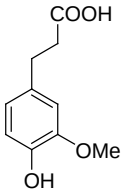
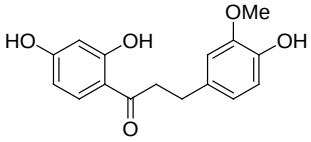
BF_3·OEt_2 in [bmim][BF_4] (Entry 7) provided the highest conversion and isolated yield, though complete reaction required the use of BF_3·OEt_2 in stoichiometric amount. Comparable yields were obtained with use of 0.3 molar equiv of the Brønsted acid $HNTf_2$ in [bmim][NTf_2] (Entry 2). The [bmim]Cl–$InCl_3$ system (Entry 1) appeared to be less active, perhaps because of the hydrophilic nature of the ionic liquid. However, isolation and purification of the compound from chloroindate(III) ionic liquid was straightforward: after the addition of water, only filtration, and no other purification method was required. In contrast to the results obtained in studies I and II, $Co(NTf_2)_2$ was not effective under these conditions, in either solvent, and it gave only marginally higher yields than reactions with no catalyst at all. Yields with no catalyst were 10-20%.

It was also found that the amount of IL could be reduced to as little as 0.5 molar equiv (higher ratios interfered with isolation procedures). With 1.0 molar equiv of [bmim][NTf_2] the isolated yield dropped to 46% due to the similar solubilities of the product and the IL. When the solvent was changed to [bmim][BF_4] (Entry 5), $HNTf_2$ reacted with the ionic liquid undergoing anion exchange and the result was a less acidic solution and thus reduced reaction rate.

The best performing systems, [bmim][NTf_2]/$HNTf_2$ and [bmim][BF_4]/BF_3·OEt_2, were applied to the synthesis of polyhydroxydeoxybenzoins and arylpropanones under optimised conditions for reaction of 4 minutes. The results are summarised in Table 17.

Table 17. Yields and structures of polyhydroxydeoxybenzoins and arylpropanones under optimized reaction conditions with MW irradiation and reaction time of 4 minutes.[III]

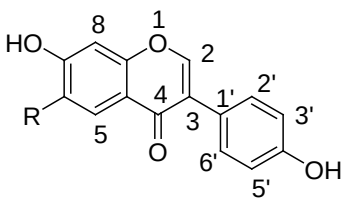
Starting materials	Product	Reaction media	Yield
		[bmim][NTf_2]/$HNTf_2$ 0.5:0.5	75
		[bmim][NTf_2]/$HNTf_2$ 0.5:0.5	70
		[bmim][NTf_2]/$HNTf_2$ 0.5:1.0	73
		[bmim][BF_4]/ $BF_3{\cdot}OEt_2$ 4:2	54
		[bmim][NTf_2]/$HNTf_2$ 0.5:1.0	65
		[bmim][BF_4]/ $BF_3{\cdot}OEt_2$ 4:2	67

			[bmim][BF_4]/ BF_3·OEt_2 4:2	85
			[bmim][NTf_2]/$HNTf_2$ 0.5:0.5	55
			[bmim][NTf_2]/$HNTf_2$ 0.5:0.5	60
			[bmim][BF_4]/ BF_3·OEt_2 2:1	88

4.2 Deuterolabelling[IV]

Many polyphenolic compounds (Figure 11) are biologically active and are widely found in plants and in food products. Their possible role in hormone-dependent diseases has been recently recognized. Isotopically labelled analogues for these compounds are needed, therefore, as internal standards for the quantitation from biological samples. (169)[172]

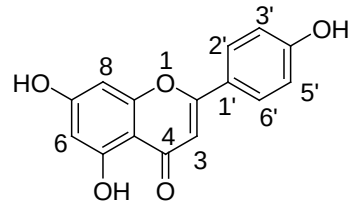
The purpose of the deuterolabelling work was to develop a rapid, low cost and more environmentally benign method for the labelling of naturally occurring polyphenols. The H/D exchange reaction was performed for selected naturally occurring polyphenolic compounds where ionic liquid [bmim]Cl, or [bmim]Br, was used as cosolvent in 35% DCl/D_2O, under MW irradiation.



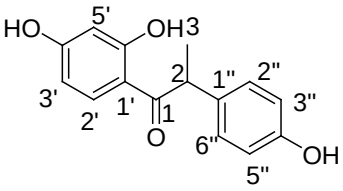
R = H, Daidzein **6**

R = OMe, Glycitein **7**

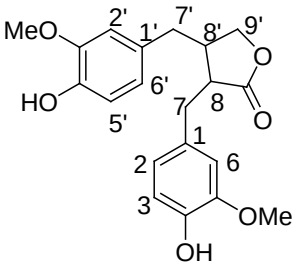
R = OH, 4',6,7-Trihydroxyisoflavone **8**



Apigenin **9**



O-Demethylangolensin **10**



Matairesinol **11**

Figure 11. Naturally occurring polyphenols.

Although synthetic methods for these labelled analogues of polyphenolic compounds are already available, very long reaction times are often required for high isotopic purity. Most deuterium-labelling procedures for polyphenols rely on electrophilic aromatic H/D exchange reactions catalyzed by acids or occasionally by bases. In previous studies, matairesinol-d_6, (**11**-d_6) has been prepared with $D_3PO_4{\cdot}BF_3$ in one day[173] or with D_3PO_4 in three days.[174] Similarly, daidzein-d_4 (**6**-d_4) has been produced in $D_3PO_4{\cdot}BF_3/D_2O$ in three days[175] and in CF_3COOD in nine days.[176] The production of daidzein-d_6 (**6**-d_6) required autoclave conditions for seven days in $D_3PO_4{\cdot}BF_3/D_2O$.[177] Recently, CF_3COOD was reported to allow deuteration of isoflavones in 15 hours under microwave irradiation.[178] Thus, although these methods mostly offer good yields and high isotopic purity, reaction times tend to be very long, partly because of the poor solubility of polyphenolics in water and other ordinary polar solvents. The purpose of the ionic liquid was to promote the dissolution of the polyphenolic compound into the acidic heavy water. Without IL as co-solvent, the exchange reaction did not proceed effectively and occurred in only 45% even in the more active aromatic sites of daidzen (e.g. H-3' and H-5'). The use of eight molar equivalents of [bmim]Cl was sufficient to solubilise the target compounds into 35% DCl/D_2O, and in most cases the exchange reaction took place in over 85% yield (Table 18). The importance of the reaction temperature was also shown, as the less active aromatic sites of daidzein (2' and 6') were deuterated when the reaction temperature was increased to 170 °C. The isolation procedure was also extremely straightforward, since most of the target compounds precipitated out from the DCl/D_2O – IL mixture at room temperature, and the product was simply filtered.

Table 18. Conditions and results for the deuteration of selected polyphenols from study **IV**.

Entry	Substrate	T/°C (P/W)	Total time/min.	i.p./% (yield/%)	Product
1	**6**	120 (40)	30	>85 (94)	[3',5',6,8-d_4]-daidzein
2	**6**	170 (70)	20	>90 (89)	[2',3',5',6,6',8,-d_6]-daidzein
3	**7**	120 (40)	30	>85 (95)	[3',5'5,8-d_4]-4',6,7-trihydroxyisoflavone
4	**7**	170 (70)	40	>78 (80)	[2',3',5,5',6',8-d_6]-4',6,7-trihydroxyisoflavone
5	**9**	120 (50)	20	>90 (93)	[2',3,3',5',6,8-d_5]-apigenin
6	**10**	120 (40)	15	>90 (90)	[2,3',3",5',5"-d_5]-*O* -demethylangolensin
7	**11**	70 (20)	40	>90 (91)	[2,2',3,5',6,6'-d_6]-matairesinol

To conclude, this study describes a fast, high-yielding and aryl ring selective acid catalyzed deuteration method for polyphenols in ILs using 35 % DCl/D_2O as a cheap deuterium source under MW irradiation. Our methodology is expected to be generally applicable and simple to carry out, with reaction times shortened from several days or 15 hour to 20-40 minutes.

4.3 O-Demethylation[v]

The *O*-demethylation of aromatic ethers is frequently required in the synthesis of multifunctional natural products, pharmaceuticals and fine chemicals. The Lewis acid BBr_3 is one of the most common *O*-demethylation reagents, allowing the reaction to occur under mild conditions. Strongly acidic or basic reaction conditions and reducing environments are thereby avoided.[179,180, 181] DCM and hexane are commonly used solvents in this methodology. However, solubility problems can emerge, particularly in the demethylation of flavones, isoflavonoids and coumarins, with long reaction times the frequent result.[182,183]

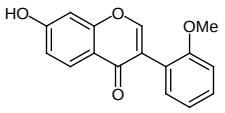
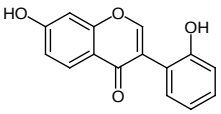
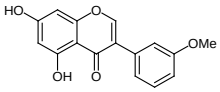
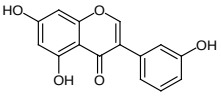
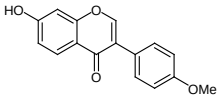
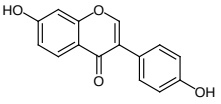
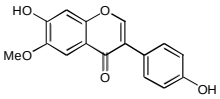
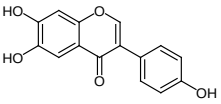
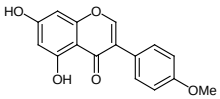
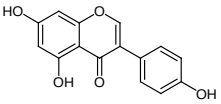
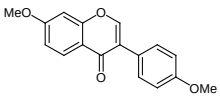
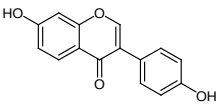
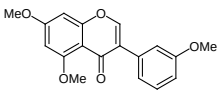
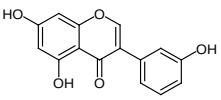
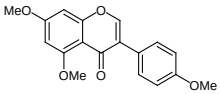
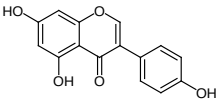
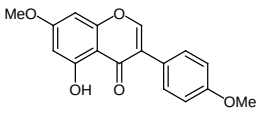
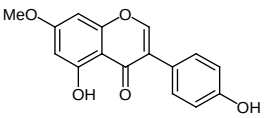
In an attempt to overcome the solubility problems, BBr_3 *O*-demethylation was investigated for several alkyl protected phenolic compounds with [bmim][BF_4], as primary solvent. ILs are reported to possess nucleophilicity in chemical reactions, especially those ILs with halogen counteranions.[23] Combining this type of IL with a proton source (HBr, TsOH or other Brønsted acids) gives an IL system that cleaves aromatic methyl ethers in varying yields.[93,94] However, long reaction times or high reaction temperatures, or both, are required. Lewis

acidic chloroaluminate ionic liquids, for their part, cleave aromatic methyl ethers in DCM.[95,96] While this method improves the substrate solubility in DCM, the reaction conditions require a high excess of chloroaluminate IL. Moreover, recyclability, one of the key benefits of an IL as reaction solvent, is lost in this method because of the work-up hydrolysis of the chloroaluminate IL. Finally, a microwave driven demethylation in a pyridinium bromide IL has been reported.[96] In this approach involving reaction at 100-110 °C in an unmodified microwave oven no Lewis or Brønsted acid was used because the demethylation was assumed to rely on bromine radical generation. The report did not make clear what kind of microwave oven was actually used. Since results obtained under unmodified MW heating are often unreliable, use of pyridinium bromide IL in the demethylation of anisole was tested in our laboratory microwave synthesizer (CEM Discover®) with use of two different methods. The first method is described as "Power Cycling", where MW irradiation of 20 W was used in power intervals to reach a reaction temperature of 110 °C (recorded with a fibre-optic sensor). The method resembles that used in an unmodified microwave oven so far as the reaction temperature is concerned. The original intention in the second method was to irritate the reaction media by as much as 350 W, but since the reaction temperature rose to 200 °C at just 150 W of initial power setup, the final choice was a maximum temperature of 200 °C and power input of 150 W. Both methods failed to promote the reaction, and no demethylation of anisole was observed at reaction temperature 110 °C or even 200 °C.

In our laboratory, compounds such as isoflavones, coumarins, lignans and long chain alkyl resorcinols have been difficult to demethylate, or the process has been time consuming when BBr_3 or HBr is used with conventional solvents. In the demethylation of 3*O*,3'*O*-dimethylenterolactone (Entry 14), for example, the reaction time in DCM was reduced from previously reported 18 hours[184] to one hour using IL. Most of the products precipitated after quenching with water, which simplified the isolation.

The results for the *O*-dealkylation of a variety of compounds are summarized in Table 19. As can be seen, the demethylation reaction of *O*-methylated isoflavones, isoflavan and flavone gave high yields of the corresponding polyphenols.

Table 19. BBr_3 *O*-demethylation of mono-, di- and trimethoxyaromatics from study **V**.

Entry	Substrate	BBr_3 (mol equiv)	Time (min)	Product	Yield (%)[c]
	ISOFLAVONES				
1		0.5	60[a] or 20[b]		75
2		0.5	30[b]		94
3		1.0	20[b]		85
4		0.5	20[b]		92
5		1.0	20[b]		75
6		3.5	160[b]		70
7		3.0	40[b]		94
8		3.0	80[b]		83
9		0.3	180[a]		75
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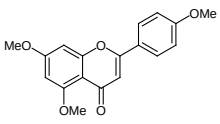
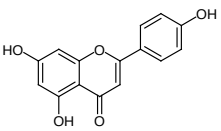
10		3.0	120[b]		75
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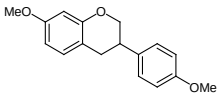
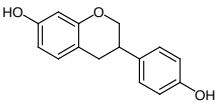
11		1.0	30[b]		85
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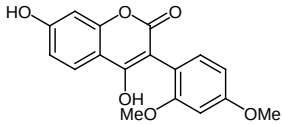
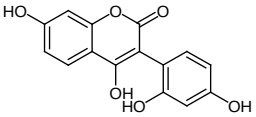
12		1.0	60[b]		51
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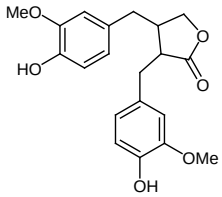
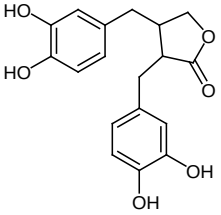
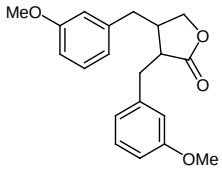
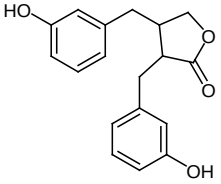
13		1.0	60[b]		80
14		1.0	60[b]		90
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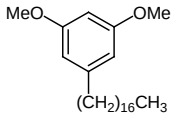
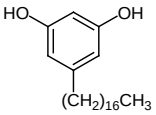
15		1.5	30[b]		85
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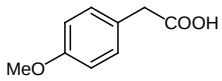
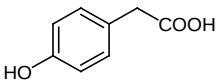
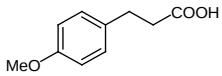
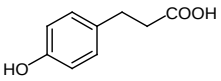
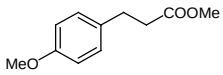
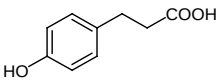
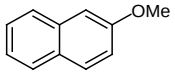
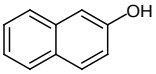
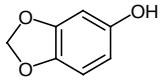
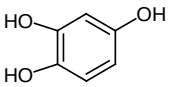
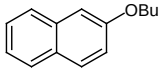
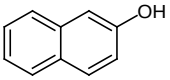
16		1.0	20[b]		58
17		1.5	20[b]		58
18		1.3	10[b]		85
19		0.5	20[b]		53 (73)[d]
20		1.0	60[a]		85
21		0.5	90[b]		55 (75)[d]

[a] reaction was carried out at room temperature, [b] reaction was carried out at 45-50 °C (pre heated oil-bath), [c] isolated pure product[d], an additional 20% of the product was collected by extraction with EtOAc

As a conclusion, from the experiments a mild and high yielding deprotection procedure for a series of alkylaromatics was established using a highly solvating ionic liquid reaction medium

with BBr_3. The procedure is straightforward with easy isolation and purification of the product. In previous experiments in our laboratory, HBr failed to *O*-demethylate 8-hydroxy-2'-methoxyisoflavone (structure presented in entry 1, Table 19). Also, in the BBr_3 demethylation reaction of C_{17}-alkylresorsiol, a black tar was formed with a conventional organic reaction solvent, and silica purification method was required. In addition, the new method benefits from recyclable reaction solvent, short reaction times at moderate or room temperature, and applicability for a variety of compounds.

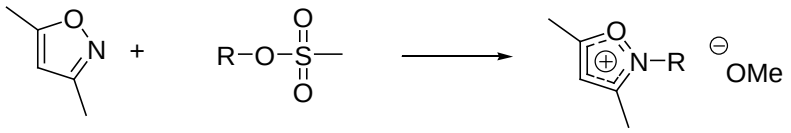
4.4 Synthesis of new ionic liquids in a halide-free route

Typically ionic liquids are made prepared by the reaction of haloalkanes with an ammonium or nitrogen heterocycle.[27] The resultant halide salt is then converted to a salt with the desired anion by a metathesis reaction. However, this reaction usually leaves traces of the halide ion in the ionic liquid.[30] Although for many purposes the impurities may not be a problem, halide ions can interfere with metal catalysts, lead to corrosion problems in chemical plants and interfere with the measurement of physical property of ionic liquids

4.4.1 Synthesis of 3,5-dimethylisoxazoles

Isoxazole ionic liquids have not been described in the literature previously, presumably because they are difficult to alkylate. They are significantly more difficult to alkylate than pyrazoles, and all attempts at using haloalkanes to convert 3,5-dimethylisoxazole to a 2-alkyl-3,5-dimethylisoxazolium halide ionic liquid resulted in very poor yields (< 15%). In this work, it was found that 3,5-dimethylisoxazolium ionic liquids could be prepared in moderate to good yields by using methanesulfonate esters as alkylation reagents.

Table 20. Yields of 3,5-dimethylisoxazolium mesylate ILs in the reaction of $(C_nH_{(2n+1)})$-O-SO_2CH_3 with 3,5-dimethylisoxazole. For identification of compounds **12-21**, see Experimental (sect. 6.1.)

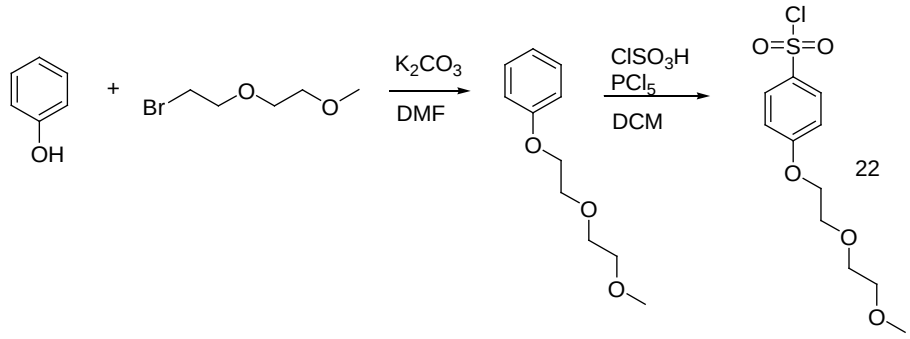


R= chain of 2-18 carbons

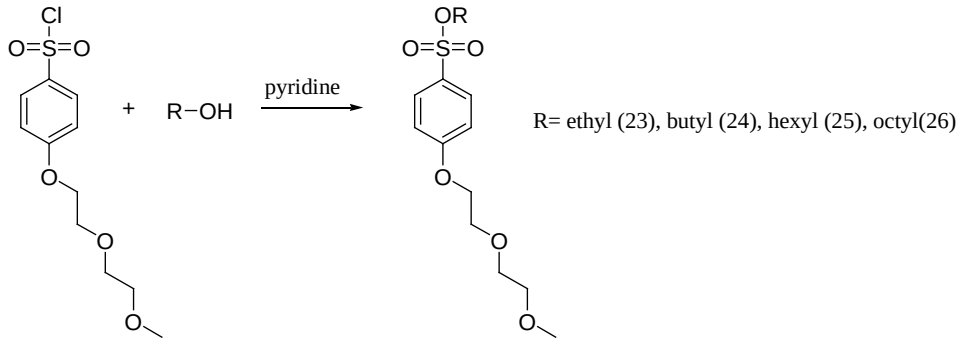
n	Temperature / °C	Time / h	% Yield	Compound
2	120	19	75	**12**
3	120	22	81	**13**
4	120	40	56	**14**
5	120	40	63	**15**
8	120	22	85	**16**
10	140	17	78	**17**
12	140	44	83	**18**
14	140	23	64	**19**
16	140	23	60	**20**
18	140	44	67	**21**

4.4.2 Synthesis of *p*-(2-(2-methoxyethoxy)ethoxy)benzenesulfonate ionic liquids

p-(2-(2-Methoxyethoxy)ethoxy)benzenesulfonate (meebs) ionic liquids were developed as new TSILs that could improve the effectiveness of $NaBH_4$ in certain reduction reactions. The idea was to synthesise a counteranion with an ether chain moiety, which could act in a similar manner to diglyme.[185] The starting point was to develop a synthetic procedure for *p*-(2-(2-methoxyethoxy)ethoxy)benzenesulfonyl chloride (**22**) (Scheme 11), which could be readily reacted with alcohols of different chain lengths to form the corresponding alkyl benzenesulfonate esters (Scheme 12).

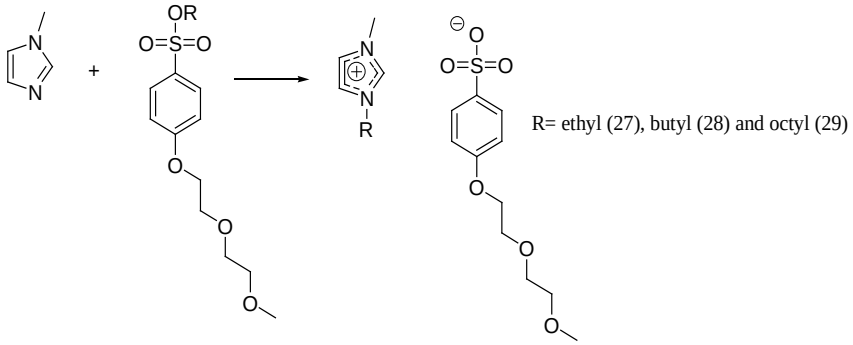


Scheme 11. Procedure for the synthesis of *p*-(2-(2-methoxyethoxy)ethoxy)benzenesulfonyl chloride (**22**)



Scheme 12. Procedure for the synthesis of alkyl *p*-(2-(2-methoxyethoxy)ethoxy)benzenesulfonate esters.

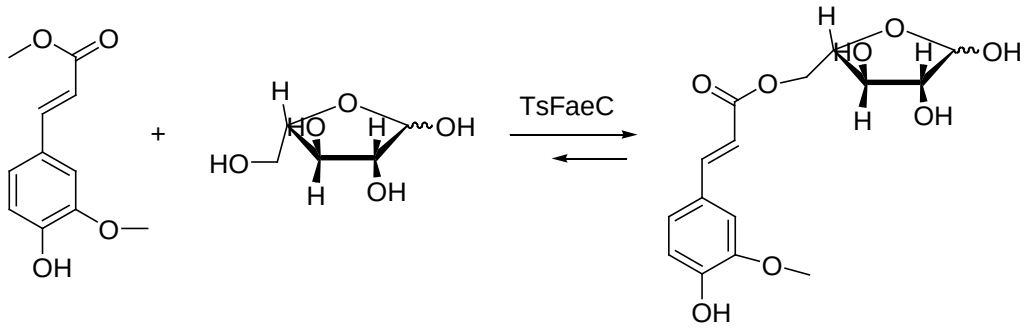
The quaternization reaction for the preparation of *p*-(2-(2-methoxyethoxy)ethoxy)benzenesulfonate (meebs) ionic liquids (Scheme 13) was carried out in the absence of reaction solvent at 45 °C. Several cation and anion combinations were synthesised, the cation being methylimidazole, pyridine or methyl pyrrolidine. Only [emim][meebs] (**27**), [bmim][meebs] (**28**) and [omim][meebs] (**29**) are described here as only these ILs have been fully characterized.



Scheme 13. Quaternization reaction for the preparation of *p*-(2-(2-methoxyethoxy)ethoxy)benzenesulfonate (meebs) ionic liquids.

Experiments investigating these TSILs, particularly [bmim][meebs], for their ability to improve $NaBH_4$ reductions are ongoing.

One of the new ionic liquids, [bmim][meebs], was used to study activity of feruloyl esterases for carbohydrate esterification. The test reaction was a reaction between methyl ferulate (MFA) and L-arabinose catalysed by type-C feruloyl esterase from *Talaromyces stipitatus* (TsFaeC) (Scheme 14). The synthetic activity of the esterase for the production of esterified carbohydrate was tested, unfortunately no esterified L-arabinose was detected, although, slight hydrolysis of MFA was observed. This result might indicate that to some extent the enzyme retain its hydrolytic activity in [bmim][meebs]. Other ILs (e.g. $[C_5O_2mim][PF_6]$ and $[C_5O_2mim][NTf_2]$) tested with this enzyme gave similarly poor results. However, a preliminary study of the solubility of L-arabinose indicated high solubility of this sugar when [bmim][meebs] was added as ionic liquid; 225 mg of the sugar was dissolved in 1 g of [bmim][meebs] (sugar was sonificated with IL at 60 °C for 2 hours and left stirring overnight at 50 °C; water content of IL < 100 ppm, KF titration).



Scheme 14. Transesterification reaction between methyl ester of cinnamic acid and L-arabinose catalysed by TsFaeC.

5. CONCLUSIONS

Substituted benzophenones were prepared to investigate Friedel-Crafts acylation reaction between various aromatics and an acylating agent where a metal bistriflamide complex, $HNTf_2$, a metal chloride or chloroindate(III) was used as catalyst in an ionic liquid or neat reaction environment. In many cases, excellent yields of the desired compounds were obtained, and the ionic reaction medium was recyclable. Future studies employing microwave irradiation to decrease the reaction time would be appropriate, since reaction times remained rather long when reactions were promoted with a conventional heating method (oil bath).

New microwave promoted methods were developed for the synthesis of several polyhydroxydeoxybenzoins and arylpropanones where ionic liquids [bmim][NTf_2] and [bmim][BF_4] were used as the reaction solvent. The reactions were promoted with acid additive $HNTf_2$, $BF_3{\cdot}OEt_2$ or chloroindate (III) IL. Under optimized conditions, $HNTf_2$ and $BF_3{\cdot}OEt_2$ in ionic reaction media gave good to excellent yields of the target compounds in just four minutes.

The development of new strategies for isotopic labelling of naturally occurring polyphenols is of great importance in the development of methods for the quantification of naturally occurring polyphenols in biological samples. When ionic liquid, [bmim]Cl or [bmim]Br, was added as a co-solvent, the use of deuteration reagent 35 % DCl in D_2O gave high isotopic purity of isoflavonoids and flavonoids. Furthermore, the reaction times under MW irradiation were exceptionally short as compared with those of previously reported methods.

The *O*-demethylation reaction of several methyl protected polyhydroxy aromatics was successfully carried out in [bmim][BF_4] with BBr_3 used as a mild demethylation reagent. The highly solvating ionic reaction media enabled the reaction to occur rapidly at moderate or room temperature.

New ionic liquids were synthesised with use of sulfonate esters as efficient *N*-alkylation reagents. In total, eleven 3,5-dimethylisoxazol mesylate ionic liquids and three alkyl imidazolium *p*-(2-(2-methoxyethoxy)ethoxy) benzene sulfonate ionic liquids were prepared and characterized. Of particular note, a new type of anion, *p*-(2-(2-methoxyethoxy)ethoxy) benzene sulfonate, was developed as a means to promote certain reduction reactions. This study is continuing.

6. EXPERIMENTAL

The experimental details of the research reported in publications **I-V** can be found in the respective publications. The experimental details for the unpublished work (study **VI**) are reported below.

6.1 General

Nuclear magnetic resonance (NMR) spectra of 3,5-dimethylisoxazolium ILs were obtained with a Bruker Advance DPX 300 MHz spectrometer using tetramethylsilane as an internal standard. Melting points were determined with A Perkin Elmer Pyris-1 power compensation differential scanning calorimeter (DSC). NMR spectra of compounds **23-29** were obtained with a Varian 300 MHz spectrometer using tetramethylsilane as an internal standard. Melting points were determined with Mettler 882e DSC. Thermal gravimetric analysis (TGA) was obtained with Mettler Toledo TGA/SDTA 851e. Electrospray ionization (ESI) mass spectral data were recorded with Mariner ESI-TOF. Water content was determined with Metrohn 756 KF Coulometer.

6.2 Synthesis of 3,5-dimethylisoxazole ionic liquids

General procedure

3,5-Dimethylisoxazole (dmio) and alkylmesylate (C_nOMs) were refluxed at 120–150 °C for 17–40 hours (Table 22). After reaction was completed (followed by ^{1}H NMR), the reaction mixture was cooled down to room temperature and excess of dmio was distilled off in a Kugelrohr apparatus.

Further purification was made to remove the black colour of the products, as follows: *N*-alkyl-3,5-dimethylisoxazolium methanesulfonate ([$C_n$dmio][OMs]) was dissolved in isopropanol and slowly flashed through charcoal under pressure in suitable column. This purification method was recently published.[186]

Table 22. Details for the synthesis of [$C_n$dmio][OMs]

	Starting materials			**Product**			
	m[g]	M[g/mol]	n[mmol]	**Reaction time / conversion[a]**	**M[$C_n$dmio][OMs]/** [g/mol]	**1st yield[b]**	**2nd yield[c]**
dmio	1.64	97.12	16.9	19 h / ~95 %	M[C_2dmio][OMs]/	75%	36%
C_2OMs	1.24	124.10	9.7		221.22	(black liquid)	(yellow liquid)
dmio	1.16	97.12	12.0	22 h / ~ 95 %	M[C_3dmio][OMs]/	81%	71%
C_3OMs	1.14	138.14	8.0		235.26	(black liquid)	(yellow liquid)
dmio	1.46	97.12	15.0	40 h / ~ 90 %	M[C_4dmio][OMs]/	56%	-
C_4OMs	1.80	152.2	11.8		249.32	(black liquid)	
dmio	1.46	97.12	15.0	40 h / ~ 93 %	M[C_5dmio][OMs]/	63%	60%
C_5OMs	1.66	166.27	10.0		263.40	(black liquid)	(yellow liquid)
dmio	1.46	97.12	15.0	22 h / ~ 95 %	M[C_8dmio][OMs]/	85%	20%
C_8OMs	3.14	208.32	15.0		305.44	(black liquid)	(yellow liquid)
dmio	0.78	97.12	8.0	17 h / ~ 90 %	M[C_{10}dmio][OMs]/	~78%	-
C_{10}OMs	1.18	236.37	5.0	140° C	333.49	+ side product	
dmio	0.39	97.12	4.0	44 h / ~ 95 %	M[C_{12}dmio][OMs]/	~83%	-
C_{12}OMs	0.66	264.43	2.5	150° C	361.34	+ side product	
dmio	0.78	97.12	8.0	23 h / ~ 95 %	M[C_{14}dmio][OMs]/	~64 %	-
C_{14}OMs	1.46	292.48	5.0	140° C	389.60	+ side product	
dmio	0.78	97.12	8.0	23 h / ~95 %	M[C_{16}dmio][OMs]/	~60 %	-
C_{16}OMs	1.60	320.53	5.0	140° C	417.65	+ side product	
dmio	0.78	97.12	8.0	44 h / ~95 %	M[C_{18}dmio][OMs]/	~67 %	-
C_{18}OMs	1.74	348.59	5.0		445.71	+ side product	

a: ^{1}H NMR spectra data were used to calculate conversions, b: yields after Kugelrohr distillation c: yields after charcoal purification

N-Ethyl-3,5-dimethylisoxazolium methanesulfonate **[C_2dmio][OMs] (12)**

^{1}H NMR ($CDCl_3$): δ 1.63 (3 H, t, H-2'), 2.69 (3 H, s, -OMs), 2.71 (3 H, s, 3-C**H_3**), 2.87 (3 H, s, 5-C**H_3**), 4.74 (2 H, m, H-1'), 7.18 (1 H, s, H-4) **^{13}C NMR** ($CDCl_3$): δ 12.82 (5-**C**H_3), 13.12 (3-**C**H_3), 13.39 (C-2'), 39.82 (-OMs), 48.36 (C-1'), 109.52 (C-4), 160.74 (C-3), 173.18 (C-5) **DSC**: liquid range –100° C - + 110° C

N-Propyl-3,5-dimethylisoxazolium methanesulfonate, **[C_3dmio][OMs] (13)**

^{1}H NMR ($CDCl_3$): δ 1.04 (3 H, t, H-3'), 1.96-2.09 (2 H, m, H-2'), 2.68 (-OMs), 2.74 (3 H, s, 3-C**H_3**), 2.80 (3 H, s, 5-C**H_3**), 4.64 (2 H, t, H-1'), 7.07 (1 H, s, H-4) **^{13}C NMR** ($CDCl_3$): δ 11.19 (5-**C**H_3), 12.87 (3-**C**H_3), 13.15 (C-3'), 21.77 (C-2'), 32.62 (-OMs), 54.26 (C-1'), 109.43 (C-4), 161.13 (C-3), 173.42 (C-5)

N-Butyl-3,5-dimethylisoxazolium methanesulfonate, **[C_4dmio][OMs] (14)**

^{1}H NMR ($CDCl_3$): δ 1.00 (3 H, t, H-4'), 1.36-1.49 (2 H, m, H-3'), 1.91-2.01 (2 H, m, H-2'), 2.69 (3 H, s, -OMs), 2.74 (3 H, s, 3-C**H_3**), 2.79 (3 H, s, 5-C**H_3**), 4.67 (3 H, t, H-1'), 7.11 (1 H, s, H-4) **^{13}C NMR** ($CDCl_3$): δ 12.70 (5-**C**H_3), 13.04 (3-**C**H_3), 13.64 (C-4'), 19.81 (C-3'), 30.00 (C-2'), 39.66 (-OMs), 52.54 (C-1'), 109.37 (C-4), 160.84 (C-3), 173.35 (C-5)

N-Pentyl-3,5-dimethylisoxazolium methanesulfonate, **[C_5dmio][OMs] (15)**

^{1}H NMR ($CDCl_3$): δ 0.95 (3 H, t, H-5'), 1.30-1.38 (4 H, m, H-4' H-3'), 1.98 (2 H, m, H-2'), 2.68 (3 H, s, -OMs), 2.77 (3 H, s, 3-C**H_3**), 2.78 (3 H, s, 5-C**H_3**), 4.60 (2 H, t, H-1'), 7.12 (1 H, s, H-4) **^{13}C NMR** ($CDCl_3$): δ 12.86 (5-**C**H_3), 13.15 (3-**C**H_3), 14.07 (C-5'), 22.32 (C-4'), 27.87 (C-2'), 28.65 (C-3'), 39.72 (-OMs), 52.88 (C-1'), 109.44 (C-4), 160.93 (C-3), 173.40 (C-5) The carbon-proton correlations were shown by 2D-spectrum. **DSC**: liquid range –100° C - + 110° C

N-Octyl-3,5-dimethylisoxazolium methanesulfonate, [**C_8dmio][OMs] (16)**

^{1}H NMR ($CDCl_3$): δ 0.90 (3 H, t, H-8'), 1.27-1.36 (10 H, m, H-3'- H-7'), 1.91-2.01 (2 H, m, H-2'), 2.66 (3 H, s, -OMs), 2.69 (3 H, s, 3-C**H_3**), 2.82 (3 H, s, 5-C**H_3**), 4.70 (2 H, t, H-1'), 7.20 (1 H, s, H-4) **^{13}C NMR** ($CDCl_3$): δ 12.80 (5-**C**H_3), 13.05 (3-**C**H_3), 14.26 (C-8'), 22.75 (C-7'), 25.73 (C-6'), 28.11 (C-5'), 29.06 (C-4'), 29.13 (C-2'), 31.83 (C-3'), 39.74 (-OMs), 52.85 (C-1'), 109.49 (C-4), 160.93 (C-3), 173.21 (C-5). **DSC**: melting point +31° C

N-Decyl-3,5-dimethylisoxazolium methanesulfonate, [**C_{10}dmio][OMs] (17)**

^{1}H NMR ($CDCl_3$): δ 0.88 (t, H-10'), 1.26-1.35 (m, H-3'-H-9'), 1.95-2.05 (m, H-2'), 2.67 (s, -OMs), 2.76 (s, 3-C**H$_3$**), 2.81 (s, 5-C**H$_3$**), 4.59 (t, H-1'), 6.91 (s, H-4). Side product is shown δ 1.56 (m) and 3.39 (t)

N-Dodecyl-3,5-dimethylisoxazolium methanesulfonate, [**C_{12}dmio][OMs] (18)**

^{1}H NMR ($CDCl_3$): δ 0.88 (t, H-12'), 1.26-1.35 (m, H-3'-H-11'), 1.93-1.97 (m, H-2'), 2.67 (s, -OMs), 2.75 (s, 3-C**H$_3$**), 2.82 (s, 5-C**H$_3$**), 4.58 (t, H-1'), 6.93 (s, H-4). Side product is shown δ 1.56 (m) and 3.39 (t)

N-Tetradecyl-3,5-dimethylisoxazolium methanesulfonate, [**C_{14}dmio][OMs] (19)**

^{1}H NMR ($CDCl_3$): δ 0.88 (t, H-14'), 1.25 (m, H-3'-H-13'), 1.93-1.99 (m, H-2'), 2.68 (s, -OMs), 2.75 (s, 3-C**H$_3$**), 2.84 (s, 5-C**H$_3$**), 4.58 (t, H-1'), 6.86 (s, H-4). Side product is shown δ 1.56 (m) and 3.39 (t)

N-Hexadecyl-3,5-dimethylisoxazolium methanesulfonate, [**C_{16}dmio][OMs] (20)**

^{1}H NMR ($CDCl_3$): δ 0.88 (t, H-16'), 1.25 (m, H-3'-H-15'), 1.93-1.98 (m, H-2'), 2.67 (s, -OMs), 2.76 (s, 3-C**H$_3$**), 2.81 (s, 5-C**H$_3$**), 4.60 (t, H-1'), 6.86 (s, H-4). Side product is shown δ 1.54 (m) and 3.39 (t)

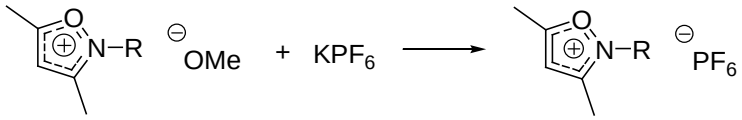
N-Octadecyl-3,5-dimethylisoxazolium methanesulfonate, [**C_{18}dmio][OMs] (21)**

^{1}H NMR ($CDCl_3$): δ 0.89 (t, H-18'), 1.25 (m, H-3'-H-17'), 1.92-1.99 (m, H-2'), 2.67 (s, -OMs), 2.77 (s, 3-C**H$_3$**), 2.84 (s, 5-C**H$_3$**), 4.57 (t, H-1'), 6.85 (s, H-4). Side product is shown δ 1.56 (m) and 3.39 (t)

Anion exchange of [$C_n$dmio][OMs] to [$C_n$dmio][PF_6]

[$C_n$dmio][OMs] (1.3-2.1 mmol) was dissolved in water (2 ml) and added to KPF_6/water solution (2.8-4.41 mmol in 3 ml of H_2O). After stirring for 20 minutes two phases were formed. The reaction mixture was extracted with dichloromethane, organic layers were collected and solvent was concentrated on a rotary evaporator. Results are presented in Table 23.

Table 23. Anion exchange of [$C_n$dmio][OMs] to [$C_n$dmio][PF_6]



Starting materials				Products	
	m[g]	M[g/mol]	n[mmol]	M[$C_n$dmio][PF_6]/ [g/mol]	Yield
[C_2dmio][OMs]	0.46	221.22	2.1	M[C_2dmio][PF_6]/	55%
KPF_6	0.77	184.07	4.2	271.12	(yellow liquid)
[C_5dmio][OMs]	0.56	263.40	2.1	M[C_5dmio][PF_6]/	83%
KPF_6	0.81	184.07	4.4	313.30	(yellow liquid)
[C_8dmio][OMs]	0.40	305.44	1.3	M[C_8dmio][PF_6]/	88%
KPF_6	0.52	184.07	2.8	355.34	(yellow liquid)

N-Ethyl-3,5-dimethylisoxazolium hexafluorophosphate **[C_2dmio][PF_6]**

^{1}H NMR (Methanol-D_4): δ 1.48 (3 H, t, H-2'), 2.52 (6 H, s, 3-CH_3, 5-CH_3), 4.56 (2 H, m, H-1'), 6.72 (1 H, s, H-4) **^{13}C NMR** (Methanol-D_4): δ 12.11 (5-CH_3), 12.62 (3-CH_3), 13.35 (C-2'), 48.88 (C-1'), 109.78 (C-4), 161.79 (C-3), 175.42 (C-5). **DSC**: + 54° C

N-Pentyl-3,5-dimethylisoxazolium hexafluorophosphate **[C_5dmio][PF_6]**

^{1}H NMR ($CDCl_3$): δ 0.91 (3 H, t, H-5'), 1.26-1.41 (4 H, m, H-4' H-3'), 1.91-2.04 (2 H, m, H-2'), 2.60 (6 H, s, 3-CH_3, 5-CH_3), 4.46 (2 H, t, H-1'), 6.76 (1 H, s, H-4) **^{13}C NMR** ($CDCl_3$): δ 11.93 (5-CH_3), 12.66 (3-CH_3), 14.00 (C-5'), 22.25 (C-4'), 27.62 (C-2'), 28.46 (C-3'), 52.37 (C-1'), 108.84 (C-4), 160.45 (C-3), 173.74 (C-5). **DSC**: liquid range –100° C - + 120° C

N-Octyl-3,5-dimethylisoxazolium hexafluorophosphate **[C_8dmio][PF_6]**

^{1}H NMR ($CDCl_3$): δ 0.80 (3 H, t, H-8'), 1.12-1.27 (10 H, m, H-3'- H-7'), 1.83-1.90 (2 H, m, H-2'), 2.53 (6 H, s, 3-CH_3, 5-CH_3), 4.36 (2 H, t, H-1'), 6.63 (1 H, s, H-4) **^{13}C NMR** ($CDCl_3$): δ 12.03 (5-CH_3), 12.74 (3-CH_3), 14.40 (C-8'), 22.91 (C-7'), 26.53 (C-6'), 28.00 (C-5'), 29.14 (C-4'), 29.25 (C-2'), 32.00 (C-3'), 52.42 (C-1'), 108.92 (C-4), 160.48 (C-3), 173.69 (C-5). **DSC**: melting point 24 ° C

6.3 Synthesis of p-(2-(2-methoxyethoxy)ethoxy)benzenesulfonate (meebs) ionic liquids

6.3.1 Synthesis of *p*-(2-(2-methoxyethoxy)ethoxy) benzenesulfonylchloride (**22**)

Phenol (0.39 mol) and K_2CO_3 (0.40 mol) were dissolved in DMF (550 ml). Bromo-2(2-methoxyethoxy)ethane (0.40 mol) was added slowly through a dropping funnel under vigorous stirring. The mixture was refluxed overnight. The reaction solution was poured into brine, and the product was extracted with ether. Combined extracts were washed with 1 M NaOH, saturated NH_4Cl and water and dried over $MgSO_4$. Concentration gave 2-(2-methoxyethoxy)ethoxybenzene in 77% yield. 2-(2-Methoxyethoxy)ethoxybenzene (0.20 mol) were placed in a two neck flask and dissolved in DCM (350 ml). The solution was cooled down in an ice-water bath, and $ClSO_3H$ (0.20 mol) was added. The ice-water bath was removed and stirring was continued at room temperature for 45 minutes, after which PCl_5 (0.20 mol) was added. The mixture was stirred overnight at room temperature and then concentrated. The concentrate was dissolved in EtOAc, filtered through silica and concentrated. Compound **22** was collected in 90% yield.

6.3.2 Synthesis of alkyl *p*-methoxyethoxyethyl benzenesulfonates

General procedure

Alcohol (0.05 mol) was stirred with compound **23** (0.05 mol) in an ice-water bath. Pyridine (6.0 ml) was added and stirring was continued for one hour in the ice-water bath and one hour at room temperature. The mixture was dissolved in EtOAc and washed with 1 M HCl. The combined extracts were washed with water and dried over $MgSO_4$. If additional purification was needed, the product was purified by flash chromatography and elution with EtOAc/DCM 5:1.

Ethyl *p*-(2-(2-methoxyethoxy)ethoxy) benzenesulfonate (**23**)

Purification by flash chromatography gave 54% yield of liquid compound. **^{1}H NMR** ($CDCl_3$): δ 1.30 (3H, m), 3.40 (3H, s), 3.59 (2H, m), 3.72 (2H, m), 3.90 (2H, m) 4.10 (2H, m), 4.21 (2H, m), 7.02 (2H, d, *J* = 8.9 Hz), 7.83 (2H, d, *J* = 9.0 Hz). **^{13}C NMR** ($CDCl_3$): δ 14.90, 59.29, 66.81, 68.13, 69.64, 71.06, 72.14, 115.19, 128.10, 130.18, 163.15.

Butyl *p*-(2-(2-methoxyethoxy)ethoxy) benzenesulfonate (**24**)

Purification by flash chromatography gave 63% yield of liquid compound. **^{1}H NMR** ($CDCl_3$): δ 0.86 (3H, m), 1.38 (2H, m), 1.63 (2H, m), 3.39 (3H, s), 3.58 (2H, m), 3.71 (2H, m), 3.89 (2H, m) 4.01 (2H, m), 4.21 (2H, m), 7.02 (2H, d, *J* = 8.7 Hz), 7.83 (2H, d, *J* = 9.3 Hz). **^{13}C NMR** ($CDCl_3$): δ 13.58, 18.82, 30.98, 59.29, 68.13, 69.64, 70.42, 71.06, 72.15, 115.18, 128.03, 130.19, 163.12.

Hexyl *p*-(2-(2-methoxyethoxy)ethoxy) benzenesulfonate (**25**)

Isolation gave 63% yield of liquid compound. **^{1}H NMR** ($CDCl_3$): δ 0.85 (3H, m), 1.23 (6H, m), 1.60 (2H, m), 3.39 (3H, s), 3.58 (2H, m), 3.71 (2H, m), 3.89 (2H, m) 4.00 (2H, m), 4.21 (2H, m), 7.02 (2H, d, *J* = 9.0 Hz), 7.82 (2H, d, *J* = 9.0 Hz). **^{13}C NMR** ($CDCl_3$): δ 14.11, 22.61, 25.23, 28.98, 31.31, 59.30, 68.13, 69.65, 70.75, 71.06, 72.15, 115.16, 128.03, 130.19, 163.12.

Octyl *p*-(2-(2-methoxyethoxy)ethoxy) benzenesulfonate (**26**)

Isolation gave 77% yield of liquid compound. **^{1}H NMR** ($CDCl_3$): δ 0.86 (3H, m), 1.22 (10H, m), 1.61 (2H, m), 3.39 (3H, s), 3.57 (2H, m), 3.71 (2H, m), 3.90 (2H, m) 4.01 (2H, m), 4.21 (2H, m), 7.02 (2H, d, *J* = 8.9 Hz), 7.81 (2H, d, *J* = 9.0 Hz). **^{13}C NMR** ($CDCl_3$): δ 14.25, 22.79, 25.56, 29.02, 29.10, 29.24, 31.89, 59.30, 68.13, 69.66, 70.76, 71.07, 72.16, 115.16, 128.06, 130.20, 163.12.

6.3.3 Synthesis of alkylmethylimidazolium *p*-(2-(2-methoxyethoxy)ethoxy) benzenesulfonate

General procedure

Methylimidazole (3.1 mmol) and alkyl *p*-(2-(2-methoxyethoxy)ethoxy) benzenesulfonate (2.6 mmol) were stirred under argon at 45 °C for 24 hours. The mixture was washed with EtOAc and dried under reduced pressure.

1-Ethyl-3-methylimidazolium *p*-(2-(2-methoxyethoxy)ethoxy) benzene sulfonate **[emim][meebs]** (**27**)

Isolation gave 75% yield. **^{1}H NMR** ($CDCl_3$): δ 1.52 (3H, m), 3.43 (3H, s), 3.58 (2H, m), 3.71 (2H, m), 3.83 (2H, m) 3.99 (3H, s), 4.14 (2H, m), 4.28 (2H, m), 6.86 (2H, d, *J* = 9), 7.27 (1H, s), 7.31 (1H, s), 7.81 (2H, d, *J* = 8.7 Hz), 9.91 (1H, s). **^{13}C NMR** ($CDCl_3$): δ 15.61, 36.50, 59.22, 67.75, 69.86, 70.91, 72.11, 114.13, 121.88, 123.79, 127.68, 137.58, 139.52, 159.80. MS(ESI+) $C_6H_{11}N_2^+$:111

1-Butyl-3-methylimidazolium *p*-(2-(2-methoxyethoxy)ethoxy) benzene sulfonate, **[bmim][meebs]** (**28**)

Isolation gave 80% yield. **^{1}H NMR** ($CDCl_3$): δ 0.91 (3H, m), 1.30 (2H, m), 1.80 (2H, m) 3.38 (3H, s), 3.58 (2H, m), 3.71 (2H, m), 3.84 (2H, m) 3.98 (3H, s), 4.14 (2H, m), 4.22 (2H, m), 6.86 (2H, d, *J* = 9) 7.27 (1H, s), 7.37 (1H, s), 7.81 (2H, d, *J* = 8.7 Hz), 9.87 (1H, s). **^{13}C NMR** ($CDCl_3$): δ 13.56, 19.60, 32.24, 36.54, 49.85, 59.25, 67.75, 69.88, 70.94, 72.13, 114.11, 122.13, 123.80, 127.70, 138.12, 139.75, 159.76. MS(ESI+) $C_8H_{15}N_2^+$: 139. DSC: T_g -35 °C (238 K), liquid range -100 – +190 °C, TGA: 334 °C.

1-Octyl-3-methylimidazolium *p*-(2-(2-methoxyethoxy)ethoxy) benzene sulfonate, **[omim][meebs]** (**29**)

Isolation gave 83% yield. **^{1}H NMR** ($CDCl_3$): δ 0.87 (3H, m), 1.26 (10H, m), 1.81 (4H, m) 3.38 (3H, s), 3.58 (2H, m), 3.71 (2H, m), 3.84 (2H, m) 4.03 (3H, s), 4.14 (2H, m), 4.22 (2H, m), 6.86 (2H, d, J = 8.7) 7.20 (1H, s), 7.26 (1H, s), 7.83 (2H, d, J = 8.7 Hz), 9.98 (1H, s). **^{13}C NMR** ($CDCl_3$): δ 14.25, 22.78, 26.42, 29.13, 29.22, 30.39, 31.88, 36.61, 50.18, 59.25, 67.74, 69.89, 70.96, 72.14, 114.11, 121.95, 123.72, 127.72, 138.29, 139.72, 159.76. MS(ESI+) $C_{12}H_{23}N_2^+$: 195.

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