Novel Low Antimicrobial Toxicity Imidazolium Ionic Liquids: Design, Synthesis and Their Applications in Organic Synthesis

By Rohitkumar G. Gore (M. Sc.)

Under the supervision of
Dr. Nicholas Gathergood

School of Chemical Sciences
Dublin City University

For the award of Ph.D

September 2012

Declaration

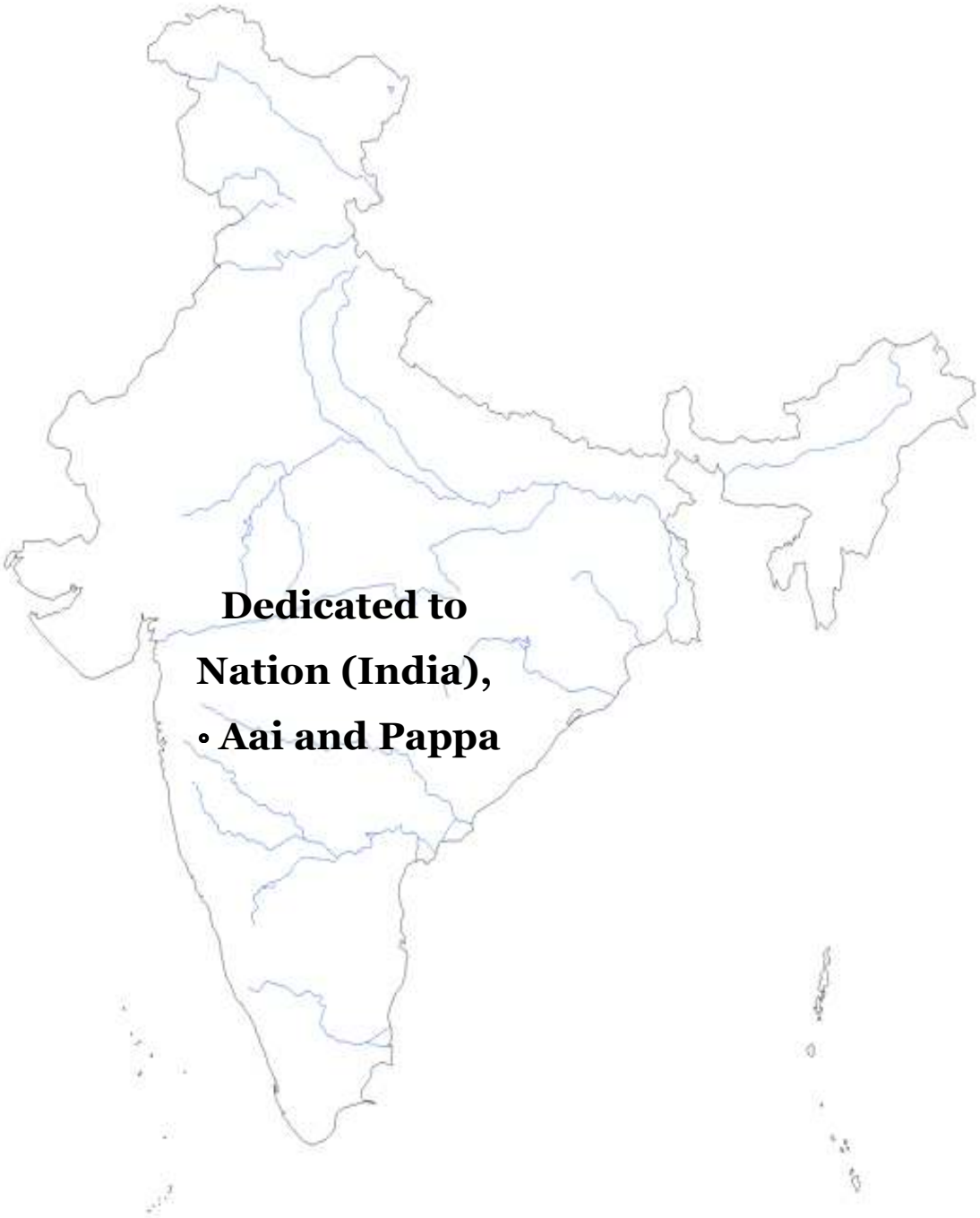
I hereby certify that this material, which I now submit for assessment on the programme of study leading to the award of PhD is entirely my own work, and that I have exercised reasonable care to ensure that the work is original, and does not to the best of my knowledge breach any law of copyright, and has not been taken from the work of others save and to the extent that such work has been cited and acknowledged within the text of my work.

Signed: _____

(Rohitkumar G. Gore)

ID No.: __58114793__

Date: _____



Dedicated to

Nation (India),

◦ Aai and Pappa

Abstract:

This thesis is focused on the synthesis and application of ionic liquids in organic synthesis. A library of novel imidazolium ionic liquids was designed and synthesised in efforts to find molecules which had reduced anti-microbial toxicity and increased aerobic biodegradation. Synthesis of novel ionic liquids has been carried with efficient and easy methods to achieve atom economy, reduced number of steps and high yields. Ionic liquids synthesized in the lab have been tested either as a catalyst in acetalization reactions, or as a solvent in Carbonyl-Ene reactions. These studies have given excellent results and clearly demonstrated the potential and applicability of ionic liquids in organic synthesis. Working with our collaborators, anti-microbial toxicity and biodegradation of these ionic liquids has been studied. Preliminary studies of the toxicity of all ionic liquids were performed against a panel of 12 fungi and 8 bacterial strains. Antifungal and antibacterial toxicity studies demonstrated that most of these ionic liquids did not inhibit the growth of any organism screened at concentrations of 2.0 mM. Biodegradation studies of the novel of novel ionic liquids have also been performed and have given valuable information on the next step in rational design towards novel readily biodegradable ionic liquids.

Acknowledgements

I would like to thank Dr. Nick Gathergood for giving me the opportunity to carry out this work in his research group and for his kind support and guidance during my Ph.D.

I also want to thank Prof. Stephen Connon for his support and guidance during my Ph.D.

I'd also like to thank the EPA for funding this research.

A special thanks to all in the Gathergood research group, especially Thu, Ian, Shelly, Monika, Mukund, Thomas, Debie, Dan, Dong, Ewa, Mads, Pavel and Wioleta. Big thanks also to Alan and Adam for all their help with the proof reading of my thesis (without this I would have never finished in time)!

A special thanks to all the friends that I have made during this tenure. Especially Andy and Will for keeping a joyful environment in the lab. I would like to thank all my friends in the school Tushar, Sanjay, Zeliha, Sharon, Kieran, Brian, Pavle and Sue.

A massive thanks to all the great technical staff for all their help, especially Damien, Ambrosent, John, Vinny, Catherine, Veronica, Mary and Brendan.

I would like to thank Dr. Florence Mc Carthy in UCC for mass spectrometry analysis. Also to our collaborators Lauren, Dr. Marcel Špulák for the work performed on the antimicrobial studies and Dr. Teresa M. Garcia for the work performed on the biodegradation studies. I would also like to thanks to Prof. Alexei Lapkin for providing me a template for the calculation of Green Chemistry metrics.

And last, and very importantly, I would like to thank all my family, especially to my Aai, Pappa, my little brother Pavan and my wife Ashwini for supporting and encouraging me!

Table of Contents

Abbreviations:

A

ACN: Acetonitrile

B

$BdMIM^+$: 1-Butyl-2,3-dimethylimidazolium

BINAP: (1,1′-Binaphthalene-2,2′-diyl)*bis*(diphenylphosphine)

BINAPHANE: 1,2-*Bis*[4,5-dihydro-3*H*-binaphtho(1,2-c:2′,1′-e)phosphepino]benzene

BINOL: 1,1′-Bi(2-naphthol)

Br^-: Bromide

BF_4^-: Tetrafluoroborate

$BMIM^+$: 1-Butyl-3-methylimidazolium

$bmpy^+$: 1-Butyl-1-methyl-pyrrolidinium

BOD: Biochemical Oxygen Demand

BATIL: Biodegradation And Toxicity of Ionic Liquids

C

Cl^-: Chloride

CILs: Chiral Ionic Liquids

COD: Chemical Oxygen Demand

CO_2: Carbon dioxide

COSY: Correlation Spectroscopy

CuI: Copper iodide

D

DHEABTBAB: 4-Di(hydroxyethyl)aminobutyl tributylammonium bromide

DCC: Dicyclohexylcarbodiimide

DCM: Dichloromethane

DCU: *N, N'*-Dicyclohexylurea

DEPT: Distortionless enhancement by polarization transfer

DMSO: Dimethyl sulfoxide

DOC: Dissolved Organic Carbon

E

EC_{50}: 50% effective concentration of a drug that gives half-maximal response

EDTA: Ethylenediaminetetraacetic acid

EIC: Extracted Ion Count

$EMIM^+$: 1-Ethyl-3-methylimidazolium

ESI-MS: Electrospray Ionisation Mass spectrometry

F

$FeCl_3$: Iron(III) chloride

FT-IR: Fourier transform infrared spectroscopy

G

GC: Gas chromatography

H

HBF_4: Tetrafluoroboric acid

HBr: Hydrobromic acid

HCl: Hydrochloric acid

H_2SO_4: Sulfuric acid

$HMIM^+$: 1-Hexyl-3-methylimidazolium

HMQC: Heteronuclear multiple quantum coherence

HPLC: High Performance Liquid Chromatography

HSO_4: Hydrogen sulfate

I

I^-: Iodide

IC_{50}: half maximal inhibitory concentration of the effectiveness of a compound in inhibiting biological function

IL: Ionic Liquid

IR: Infrared

L

Lac: L-lactate

LC_{50}: Lethal Concentration of the chemical that kills 50% of the test animals in a given time

M

m.p.: Melting point

m/z: Mass to charge ratio

Me: Methyl

MIC: Minimum inhibitory concentration

$MOEMIM^+$: 1-Methoxyethyl-3-methylimidazolium

MRSA: Methicillin Resistant *Staphylococcus aureus*

MS: Mass spectrometry

MITI: Ministry of International Trade and Industry, Japan

N

$N(CN)_2$: Dicyanamide

NMR: Nuclear Magnetic Resonance

NMP: *N*-methyl-2-pyrrolidone

NTf_2^-: *Bis*(trifluoromethanesulfonimide)

O

$OctOSO_3^-$: Octyl sulfate

OECD: Organisation for Economic Co-operation and Development

OAc^-: Acetate

OTf^-: Triflate

P

Pd: Palladium

PDVB: Polydivinylbenzene

PF_6^-: Hexafluorophosphate

p-TSA: *p*-Toluenesulfonic acid

PyBOX: Pyridine-2,6-*bis*(oxazolines)

R

RT: Room temperature

RTILs: Room temperature ionic liquids

S

$Sc(OTf)_3$: Scandium(III) triflate

SbF_6^-: Hexafluoroantimonate

T

TEA: Triethylamine

TEM: Transmission electron microscopy

TFA: Trifluoroacetic acid

THF: Tetrahydrofuran

TIC: Total Inorganic Carbon

TOC: Total Organic Carbon

TSILs: Task Specific Ionic Liquids

TMS-Cl: Chlorotrimethylsilane

$TMPSA^+$: *N,N,N*-trimethyl-*N*-propanesulfonic acid ammonium

V

$VAIM^+$: 1-Aminoethyl-3-vinylimidazolium

VOC: Volatile organic compound

Z

$ZnCl_2$: Zinc(II) chloride

Project Aims:

- To design and synthesise a library of novel ester and amide functionalised side chain achiral imidazolium ionic liquids.
- To investigate the anti-microbial toxicity and biodegradation potential of a series of achiral (ester and amide side chain) ionic liquids.
- To evaluate the application of these novel achiral ionic liquids in organocatalytic processes; such as a Brønsted acidic catalyst in the 'Acetalisation Reaction'.
- To test the potential of novel achiral ionic liquids as a recyclable and functional solvent in the 'Carbonyl-Ene Reaction' and establish methods for recovery and reuse of expensive reaction organometallic catalysts.
- To synthesise a variety of chiral ionic liquids derived from the chiral pool, such as mandelic and lactic acids, for the evaluation of their toxicological effects on a panel of fungi and bacteria. (Application of this class of ILs was already completed by a previous group member and as such not part of this project.)
- To investigate the anti-microbial toxicity of chiral ionic liquids.
- To design and synthesise a library of novel imidazolium core modified ionic liquids with ester and amide substitutions on to the C-2, C-4 and both C-4 and C-5 positions of the imidazole ring, in order to enhance catalytic activity in the 'Acetalisation Reaction' and to promote complete biodegradation.
- To investigate the anti-microbial toxicity and biodegradation of novel imidazolium core modified ionic liquids.

Chapter 1: Literature Review

Ionic Liquids

1.0 Literature Review

1.1 Introduction:

Molten salts which are ionic (i.e. a mixture of cation and anion) in nature and have a melting point below 100 °C are termed as Ionic liquids (ILs).[1] Preferably salts which are liquid at room temperature are called room temperature ionic liquids (RTILs). ILs have received great attention in the last couple of decades due to their unique properties such as low vapour pressure, high thermal stability, recyclability, non-flammability, and control over the product distribution.[2] Due to the control over fugative emission; ILs can be a replacement for volatile organic compounds (VOCs) which are commonly used as solvents in organic processes. Since the first ionic liquid was reported,[3] there has been a large number of articles been published with different types of cations and anions. One can easily design 10^{18} possible structures of ILs by varying cations and anions.[4] This makes them "*designer*" molecules.[4,5] These designed combinations have already been found useful in different fields of chemistry, such as organic chemistry,[6] electrochemistry,[7] analytical chemistry,[8] and biochemistry.[7a,9]

There are five major classes of cations in ILs e.g. ammonium, pyridinium, imidazolium, phosphonium and sulfonium (Fig. 1.1).

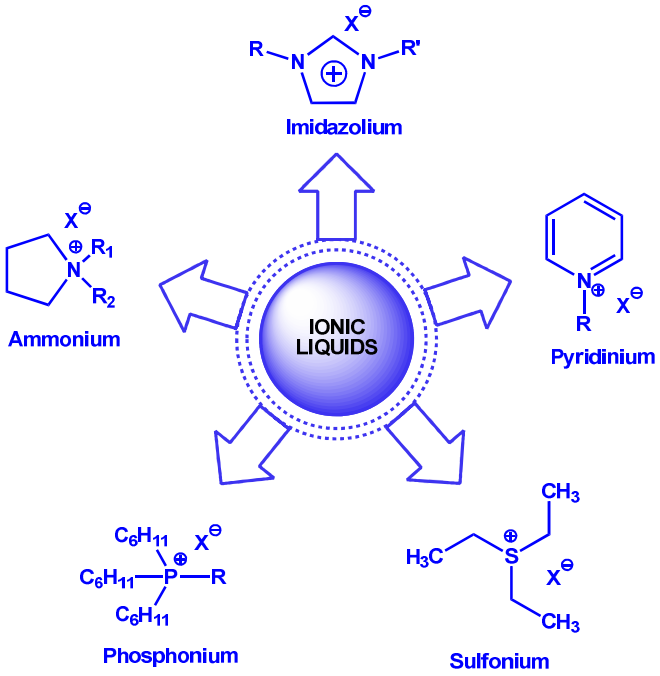


Fig 1.1: Major types of cations in ionic liquids

Along with these, there are a large number of commonly used anions such as halides (chloride, bromide, iodide), *bis*(trifluoromethanesulfonimide) (NTf_2^-), tetrafluoroborate

(BF_4^-), hexafluorophosphate (PF_6^-), octyl sulfate ($OctOSO_3^-$), acetate (OAc^-) and dicynamide ($N(CN)_2^-$) to name a few. Change in the anionic component can drastically affect physical properties of an ionic liquid such as hydrophilicity, viscosity and melting point.

1.2 Applications of Ionic Liquids in Organic Synthesis:

Ionic liquids have been widely exploited in numerous organic reactions due to the versatility in the physical properties such as ease of product separation,[10] enhancement in rate of reaction,[11] catalyst immobilization,[12] and recyclability.[13] Modifications in cations and/or anions have facilitated their use in organic reactions while playing a role of reagent, solvent or catalyst. This can be reflected in a huge number of publications. Hence we are discussing, in our opinion only interesting representative examples here in this chapter.

In this chapter the aim is to demonstrate the versatility of ionic liquids in organic synthesis. We are also going to discuss the environmental fate of ionic liquids by addressing the importance of toxicity, eco(toxicity), biodegradation and green chemistry metrics. By exploring these parameters one can design and synthesise safer and greener catalyst/solvent.

1.2.1 Heck Reaction:

The palladium catalysed C-C bond forming reaction between aryl halide or vinyl halide (or triflate) and activated alkene in presence of base is known as the Heck reaction.[14] This reaction is named after Prof. Richard F. Heck, for which he was awarded Nobel Prize in Chemistry 2010, "*for palladium-catalyzed cross couplings in organic synthesis*" jointly with Prof. Ei-ichi Negishi and Prof. Akira Suzuki. This reaction is also known as Mizoroki-Heck reaction, as Tsutomu Mizoroki was the first to report this reaction.[15] A large variety of organic and inorganic bases can be used in this reaction. Phosphine ligands have been used to stabilize the catalytic system in molecular solvents. Although the reaction conditions are mild, the major drawback is that it is difficult to recycle the palladium catalyst in traditional solvents. Kaufmann and co-workers (1996) were first to demonstrate the use of tetraalkylammonium salts as an effective solvent in Heck reaction.[16] Since then a large number of publications have shown that different class of

ILs can be used as solvent, catalyst or as a ligand in the Heck reaction.[17] L. Wang and co-workers have reported the Heck reaction of aryl halide and styrene (Scheme 1.1) in an ethanolamine-functionalized quaternary ammonium bromide which act as base, ligand and solvent.[18]

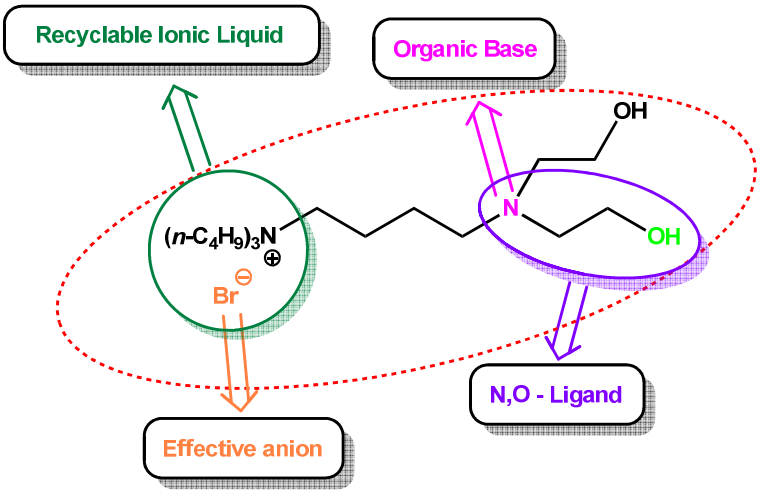
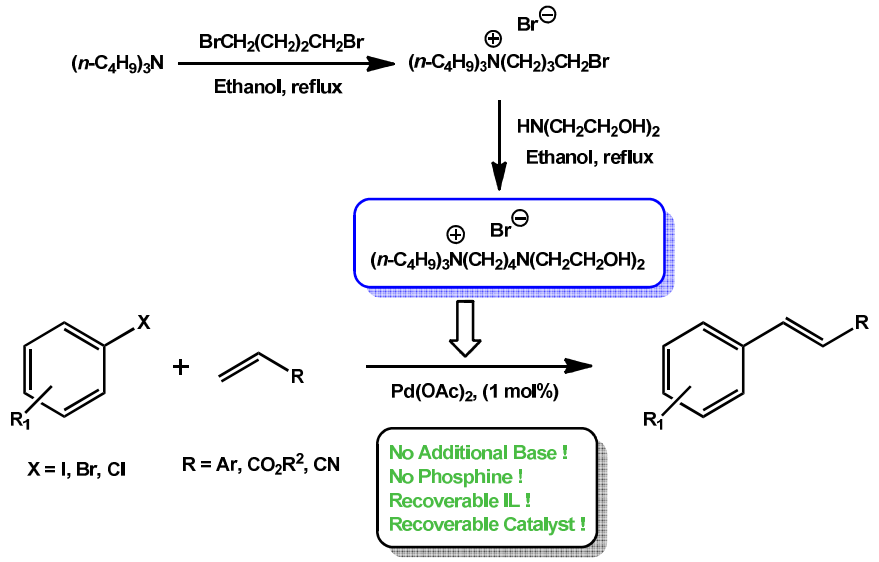


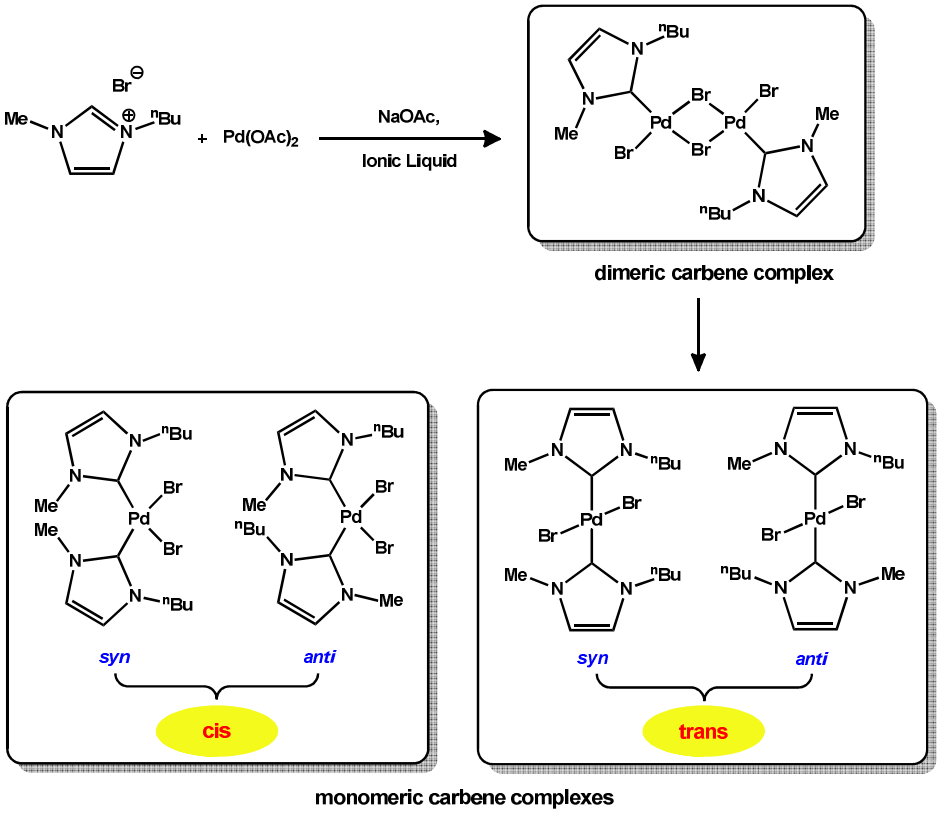
Fig. 1.2. The functions of DHEABTBAB ionic liquid in the Heck reaction

The task specific ionic liquid i.e. 4-Di(hydroxyethyl)aminobutyl tributylammonium bromide (DHEABTBAB) (Fig. 1.2) and palladium acetate served as an excellent catalytic system for the cross-coupling of a variety of olefins and aryl halides to give good to excellent results. The Heck reactions of styrene and iodobenzene/bromobenzene have shown excellent conversions and yield (>99%), whereas reaction of styrene and chlorobenzene have given only 66% yield. The reactions of activated and deactivated bromobenzenes and styrene/acrylates generated good to excellent yields (82% to 99%). This catalytic system was also successfully recycled and reused up to 6 times without significant loss of activity. Transmission electron microscopy (TEM) image of Pd-nanoparticles formed in (DHEABTBAB) showed even distribution due to ethanolamine moiety of the ionic liquid, which can either coordinate to the palladium or point away from the surface of the nanoparticle.



Scheme 1.1. Synthesis of ionic liquid and its application in the Heck reaction

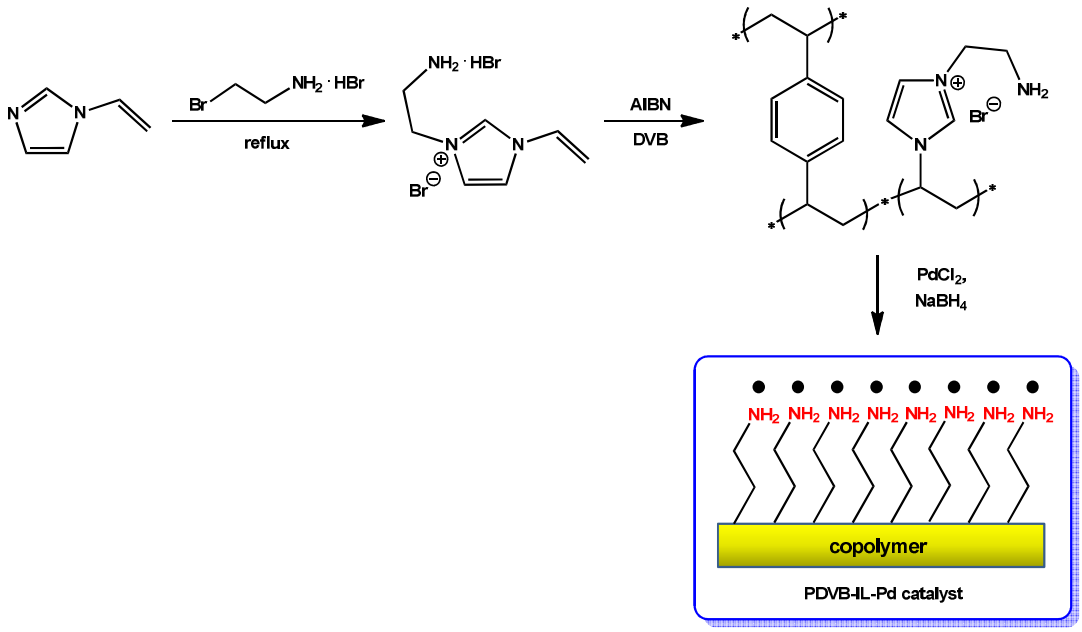
In an attempt to eliminate the use of phosphine ligands, Xaio and co-workers demonstrated the in situ formation of a *N*-heterocyclic carbene complex with palladium when 1,3-dialkylimidazolium ILs were used as a solvent under basic conditions to generate carbene ligand.[19] They had successfully isolated the palladium carbene complex, by deprotonation of imidazolium-based ionic liquids in presence of base to form the catalytic precursor. Such participation of *N*-heterocyclic carbene as a ligand was predicted by Seddon.[20]



Scheme 1.2. Stepwise formation of *N*-hetrocyclic carbene complex of palladium

[BMIM] based ionic liquid and palladium acetate in presence of base such as sodium acetate first formed dimeric carbene complex, which eventually gave monomeric carbene complexes (Scheme 1.2). Existence of all four isomers of monomeric carbene complex was confirmed by ^{1}H-NMR. The Heck reaction of aryl halides with acrylates/styrene in ionic liquid under the reaction conditions have performed better than the isolated *trans* isomer of *N*-hetrocyclic carbene complex in ionic liquid. This might be due to the presence of other active palladium species formed in situ. Shrinivasan and co-workers have further supported such formation of Pd-carbene complex in [BMIM] based IL and accelerated the reaction under ultrasonic irradiation even at room temperature.[21]

Attempts and further efforts into increasing the recyclability of palladium catalyst and to reduce the use of solvent resulted in exploration of solid supported ionic liquids for use in the Heck reaction.[22] B. Han and co-workers have reported copolymerized ionic liquid supported palladium nanoparticles as an effective catalyst for the Heck reaction under solvent-free conditions.[23] The 1-aminoethyl-3-vinylimidazolium bromide i.e. [VAIM][Br] ionic liquid was grafted on cross-linked polymer polydivinylbenzene (PDVB). The palladium nanoparticles were anchored onto the polymer via the amino group in the ionic liquid (Scheme 1.3). Formation of the catalyst was confirmed by a number of analytical techniques such as X-ray photoelectron spectroscopy, transmission electron microscopy, Fourier transform infrared spectroscopy (FT-IR), etc.



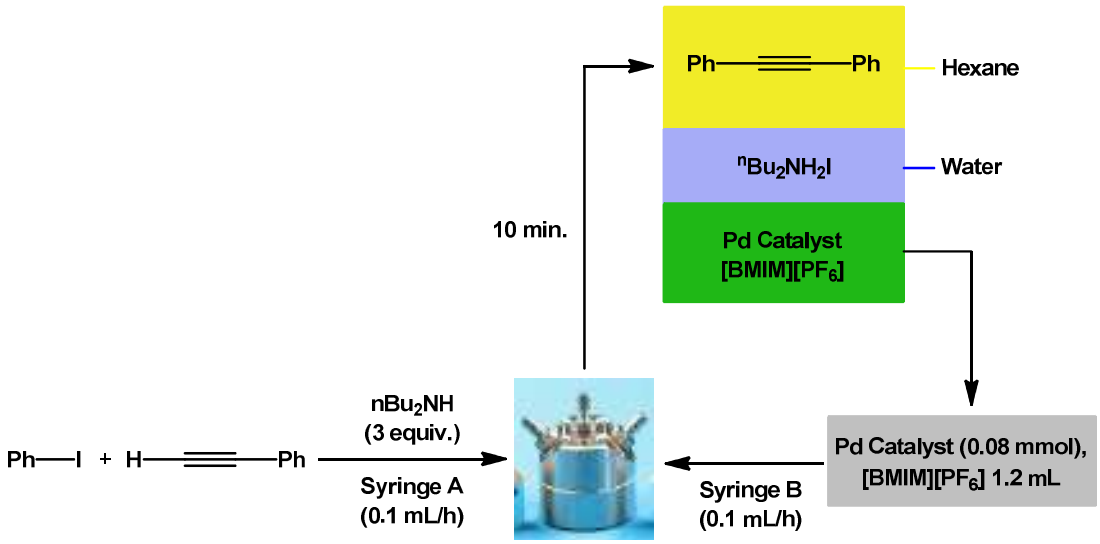
Scheme 1.3: Preparation of copolymerized ionic liquid supported palladium nanoparticles

The Heck reactions of a variety of iodobenzenes and acrylates have shown excellent conversions (above 93%) irrespective to the substitution on benzene ring. Triethylamine served as a good base under the reaction conditions. Due to the insoluble nature of cross-linked polymer and strong co-ordination between amino group and palladium nanoparticles, the catalyst was recovered very easily by filtration and washed with ethanol. The PDVB-IL-Pd catalyst was very active even after the 4^{th} recycle and was confirmed by TEM image. The excellent stability of the catalyst was due to its insoluble nature in both reactants and product, and high thermal stability i.e. up to above 220 °C.

1.2.2 Sonogashira Reaction:

The palladium catalysed C-C coupling reaction of aryl halide and terminal acetylene is known as the Sonogashira reaction. Copper iodides have also been used as a co-catalyst in this reaction.[24] A stoichiometric amount of base is always used as acid (HX) scavenger. This is a widely used and efficient way to prepare substituted or unsubstituted acetylenes. Although Sonogashira coupling reactions works well under mild conditions, the drawback of this reaction is that copper catalysts used can promote side reactions, such as Glaster-type homocoupling of acetylenes.[25]

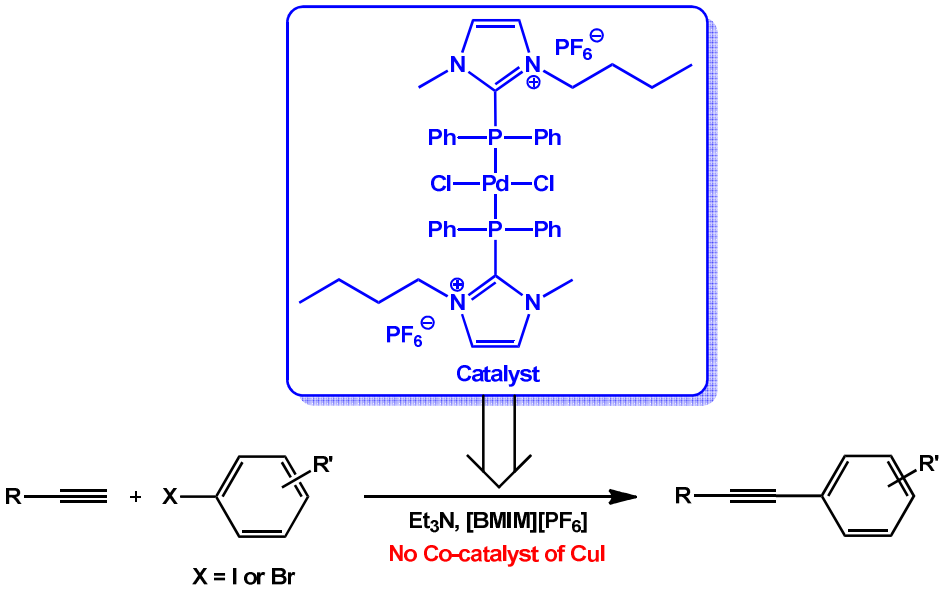
Ryu and co-workers have reported a palladium(II) catalysed efficient Sonogashira coupling in ionic liquid, without any copper co-catalyst.[26] The reactions with an aryl halides and alkyl/aryl acetylenes were carried out in [BMIM][PF_6] as a solvent and diisopropylamine or piperidine as a base. A number of palladium catalyst were screened in the Sonogashira reaction, where *bis*(triphenylphosphine)palladium(II) dichloride showed high catalytic activity in absence of copper co-catalyst. The Sonogashira reactions of aryl halides and alkyl/aryl acetylenes gave respective dialkyl/diaryl acetylenes in good yields (87-97%).



Scheme 1.4: Sonogashira reaction in a Microflow system

The group has successfully demonstrated the application of this reaction in a microflow reactor with IMM micromixer. Iodobenzene, phenylacetylene and base dibutylamine (syringe A) was added via one inlet to IMM's micromixer and Pd catalyst and [BMIM][PF_6] (syringe B) at the other inlet by using syringe pump (Scheme 1.4). After reacting in micromixer for 10 min., the product was easily isolated by Hexane/Water extraction, where Pd catalyst in ionic liquid was recycled and reused with slight loss of activity.

In an effort to develop an air stable copper free Sonogashira reaction, Wu, Liu and co-workers have reported palladium complex functionalized ionic liquid as a catalyst in Sonogashira reaction in [BMIM][PF_6] under aerobic and copper free conditions.[27]



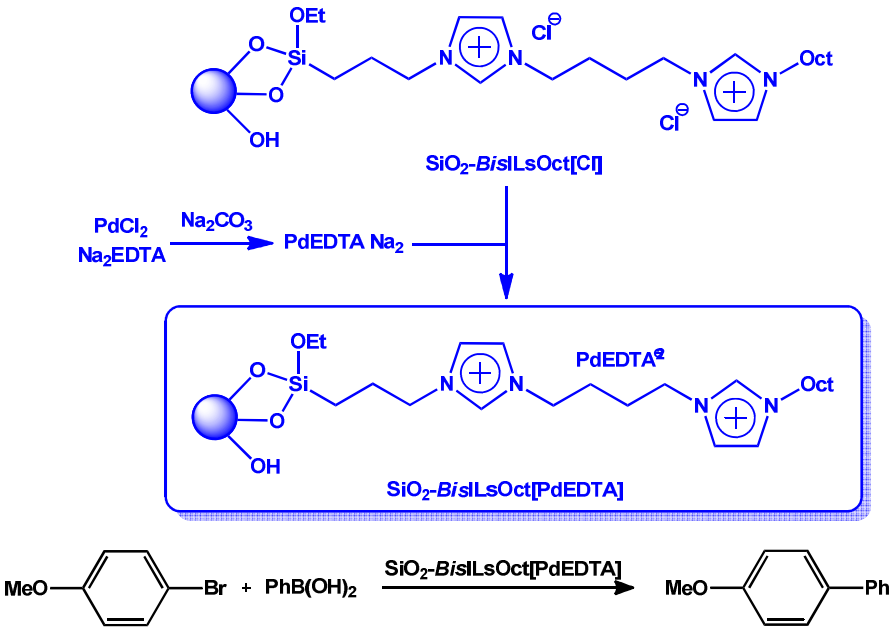
Scheme 1.5: The Sonogashira reactions in [BMIM][PF_6]

The functionalized ionic liquid i.e. di-(1-butyl-2-diphenylphosphino-3-methylimidazolium)-dichloridopalladium(II) hexafluorophosphate showed efficient catalytic activity and recyclability in coupling reactions (Scheme 1.5). A clear trend i.e. I>Br>Cl was observed in aryl halide and phenylacetylene couplings. Iodobenzene have shown excellent reactivity with variety of terminal acetylenes (90-99%) in Sonogashira coupling. The phosphine-ligated palladium complex functionalized ionic liquid was easily recycled and reused. Recyclability experiments displayed a gradual loss of activity of the catalyst in [BMIM][PF_6] after 6 recycles (100% to 68% yields), whereas rapid loss of activity in CH_3CN after 4 recycles (98% to 48% yields).

1.2.3 Suzuki Coupling:

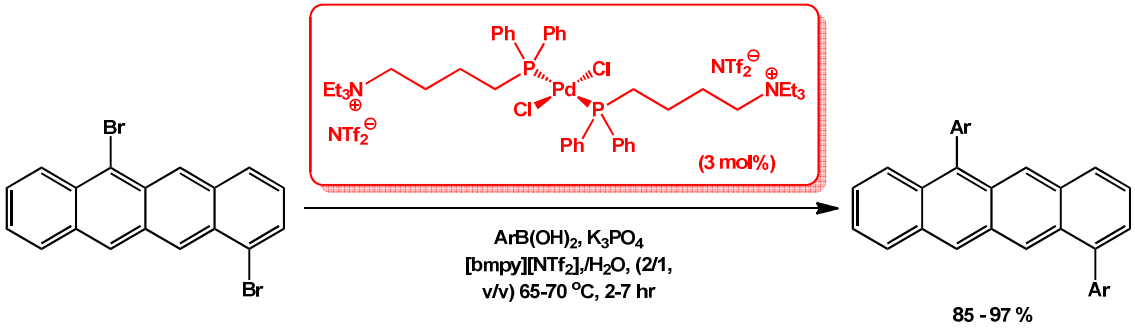
The Suzuki reaction is a palladium catalysed coupling between aryl/vinyl boronic acid and aryl/vinyl halide in presence of base. This reaction is named after Prof. Akira Suzuki (Nobel Prize in Chemistry, 2010) and also referred to as Suzuki-Miyaura coupling.[28] It is one of the important C-C bond forming reaction in the synthesis of styrene and substituted biaryl compounds.

Wei and co-workers have developed a highly efficient silica supported ionic liquid with palladium incorporated anion catalyst for the Suzuki-Miyaura cross-coupling in water under reflux conditions.[29] The catalyst was prepared by an anion exchange reaction between silica-immobilized diimidazolium ionic liquid brushes with the sodium salt of Pd-EDTA (Scheme 1.6). This catalyst has shown great stability in air and excellent reactivity without any phosphine ligands. The Suzuki coupling of a large variety of aryl bromide and aryl iodides with phenylboric acid in water and PdEDTA-Ionic liquid brush as a catalyst gave very high yields ranging from 89% to 100%. This catalyst did not show loss of activity even after 10 recycles. Another advantage of SiO_2-*Bis*ILsOct[PdEDTA] catalyst was that it also act as a phase transfer catalyst in the reaction of water insoluble aryl halides.



Scheme 1.6: Suzuki reaction with SiO_2-*Bis*ILsOct[PdEDTA] catalyst

Lombardo and co-workers have reported the triethylammonium ion-tagged diphenylphosphine palladium(II) complex for Suzuki-Miyaura reaction in pyrrolidinium ionic liquids under mild reaction conditions.[30] In an effort towards increasing the recyclability of palladium catalyst, triethylammonium ionic liquid supported diphenylphosphine ligand have been prepared. 1-Butyl-1-methyl-pyrrolidinium *bis*(trifluoromethanesulfonimide) ([bmpy][NTf_2]) prove to be the best solvent along with water in presence of potassium phosphate as a base in the coupling of o-bromotoluene and phenylboronic acid. A Suzuki reaction of a number of electron donating and electron withdrawing groups on aryl halides and aryl boronic acids showed good to excellent results. 2-methylphenylboronic acid has given 99% yields when coupled with 1-naphthylbromide and also with 4-bromobiphenyl. The coupling of *p*-anisylboronic acid and 4-bromobiphenyl gave 84% yield with triethylammonium ion-tagged diphenylphosphine palladium(II) complex.

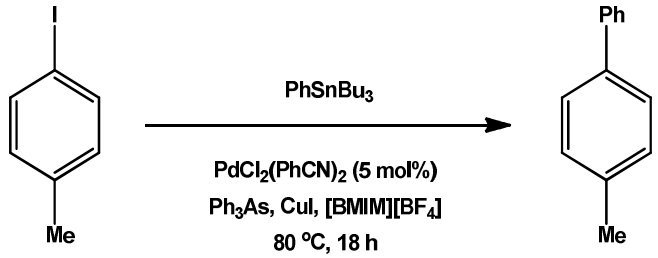


Scheme 1.7: Suzuki cross-coupling between 5,11-dibromotetracene with arylboronic acids

Miozzo and co-workers have demonstrated an excellent use of such ionic liquid ligated palladium complex in the challenging Suzuki cross-coupling between 5,11-dibromotetracene with arylboronic acids under mild conditions (Scheme 1.7).[31] These couplings have given very high yields with phenyl and substituted phenylboronic acid (93-97%) even with 2-naphthylboronic acid (95% yield).

1.2.4 Stille Coupling:

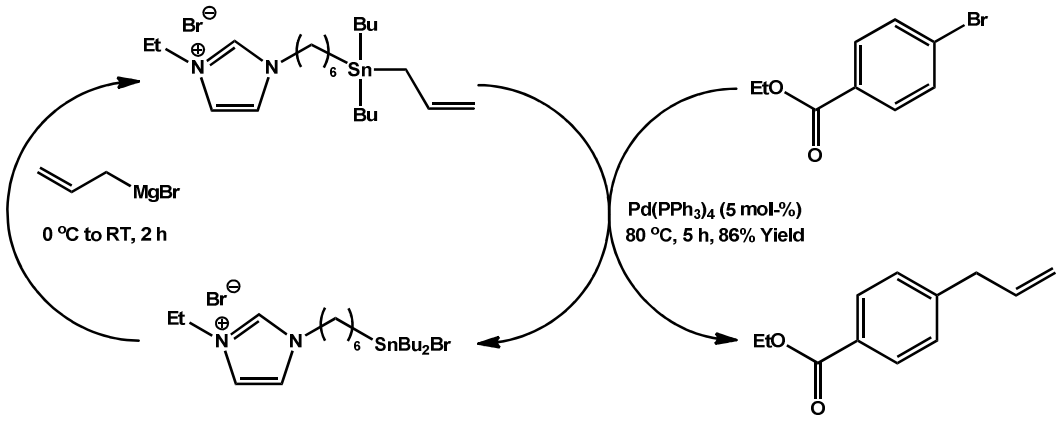
The palladium catalyzed C-C bond formation reaction between organotin reagents and sp^2-hybridised organohalides are typically classed as Stille coupling reactions.[32] It is an important method of alkylation/arylation of vinyl/aryl halide. Organotin reagents used in this reaction are stable and easily stored in air. But the major drawbacks of Stille reaction are the toxicity (e.g. cytotoxicity) of organotin reagents and recyclability of palladium catalyst. To increase the recyclability of palladium catalyst and solvent, Handy and Zhang have reported the use of ionic liquid as a effective media for Stille coupling.[33] Stille coupling reactions were compared between NMP and [BMIM][BF_4] as a solvent with *bis*(benzonitrile)palladium(II) chloride as a catalyst and in the presence of triphenylarsine and Copper(I) iodide. These reactions demonstrated the compatibility of ionic liquid in Stille reactions.



Scheme 1.8: Stille coupling of 4-iodotoluene and tributylphenyltin in [BMIM][BF_4]

Aryl coupling of a variety of aryl iodides and bromides and tributylphenyltin afforded the respective products with good yields (Scheme 1.8). The coupling of 4-iodotoluene and tributylphenyltin showed the highest conversion with 95% yield, whereas *p*-bromoanisole and tributylphenyltin gave only 15% yield towards the desired product. Ionic liquid and the catalyst *bis*(benzonitrile)palladium(II) chloride were recycled without loss of activity even after 5^{th} cycle.

Due to the toxicity of organotin reagents and contamination of product by tin, organotin reagents have been boycotted by the pharmaceutical industry. Legoupy and co-workers reported an ionic liquid supported organotin reagent which can recycled and minimise contamination of product by organotin compound, without the use of solvent and additives.[34] Ionic liquids supported dibutylphenyltin was successfully synthesized and used as a reagent in palladium catalyzed Stille cross-coupling reactions involving brominated substrates under solvent-free conditions.



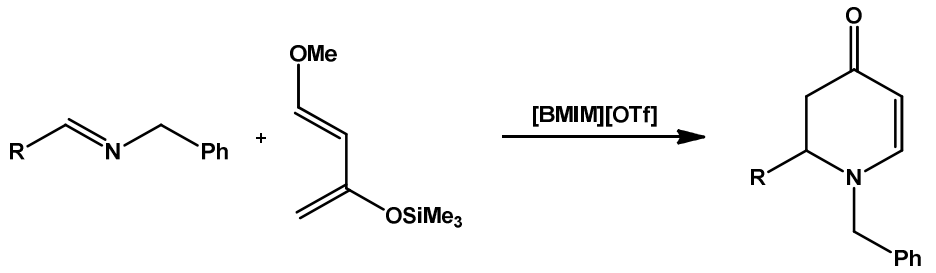
Scheme 1.9: Recyclable organotin reagent for Stille coupling

An effective use of different ionic liquid supported vinyl, allyl, aryl and heteroaryl organotin reagents with aryl bromides have seen use in Stille cross-coupling reaction. Such ionic liquid incorporated organotin reagent was recycled and reused 5 times with good yields and without loss of reactivity by using Grignard reaction (Scheme 1.9). It also helped to minimise tin contamination to less than 3 ppm.

1.2.5 Diels-Alder Reaction:

The cycloaddition reaction between the conjugated diene and dienophile/substituted alkene is known as Diels-Alder reaction.[35] Prof. Otto Paul Hermann Diels and Prof. Kurt Alder was awarded Nobel Prize in Chemistry in 1950 for "*for their discovery and development of the diene synthesis*". Diels-Alder reaction is an important tool in synthesis of huge and complex cyclic molecules such as cholesterol, reserpine, etc. Heterocyclic compounds can also be prepared with this reaction by using heteroatom (most of the times N and O) either as the diene or dienophile component. Diels-Alder reaction has immense importance due to the 100% atom economy in product formation.

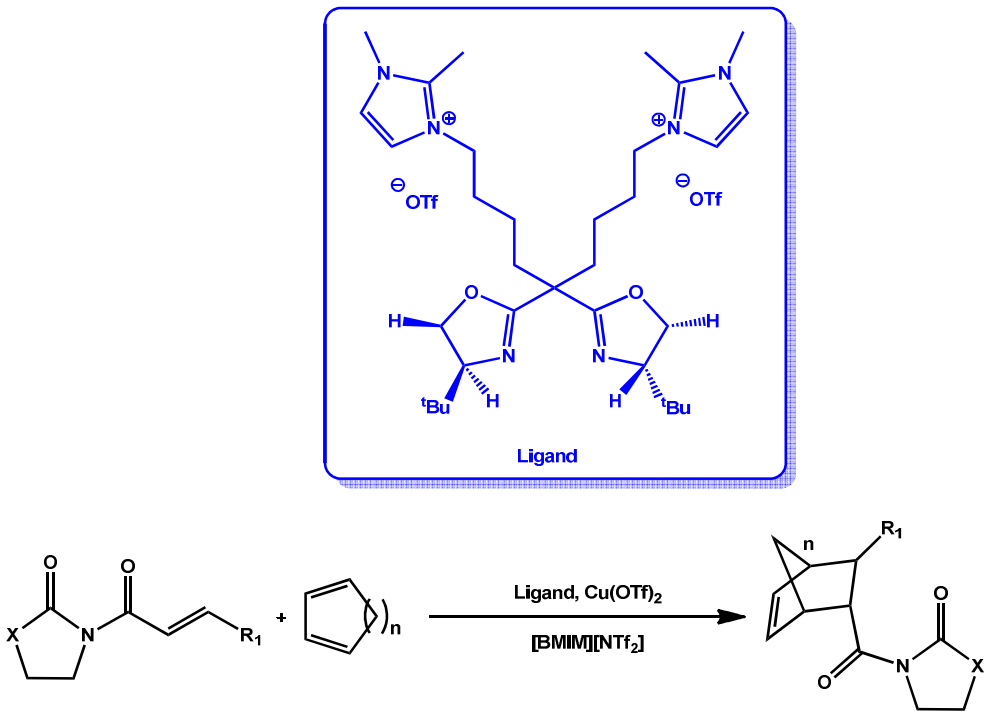
The reaction can be performed either by heating or by using Lewis/Brønsted acid catalysts such as $ZnCl_2$, HBF_4, $Sc(OTf)_3$ etc. in organic solvents.



Scheme 1.10: Aza-Diels-Alder reaction of Danishefsky's diene with imines

Pégot and Vo-Thanh have reported aza-Diels-Alder reaction of Danishefsky's diene with imines in ionic liquids, at room temperature without any acid catalyst and organic solvents.[36] The reaction of *N*-benzylidenebenzylamine and Danishefsky's diene in [BMIM][OTf] showed high i.e. 94% conversion (91% yield) in 1 hour at room temperature (Scheme 1.10). Only half an equivalent amount of ionic liquid is used with respect to *N*-benzylidenebenzylamine. In the study of an effect of counter anion of [BMIM] cation, triflate (OTf^-) and *bis*(trifluoromethanesulfonimide) (NTf_2^-) has shown high yields i.e. 91% and 94% respectively in comparison with tetrafluoroborate (BF_4^-) and hexafluorophosphate (PF_6^-) i.e. 62% and 53% respectively. Reactions using pyridinium and ammonium cations with triflate anion gave good yields (91% and 89% respectively). These studies have shown that ionic liquids can be used as both polar solvent and as a catalyst in Aza-Diels-Alder reaction.

Zhou and co-workers reported C_2-symmetric ionic liquid-tagged *bis*(oxazoline) copper catalyst for Diels-Alder reaction in ionic liquid.[37] *Bis*(oxazoline)-copper(II) complexes have already been used as a Lewis acid catalyst in enantioselective Diels-Alder reactions.[38] In order to increase recyclability of the catalyst, the imidazolium-tagged *bis*(oxazoline) ligand copper catalyst was synthesized. (Scheme 1.11) The ionic liquid part of the ligand increased the insolubility of the copper catalyst in typical reaction solvents like diethyl ether, which makes workup procedure very simple. The product was separated from catalyst just by washing with diethyl ether.



Scheme 1.11: Screening of the ligands in an asymmetric Diels–Alder reaction

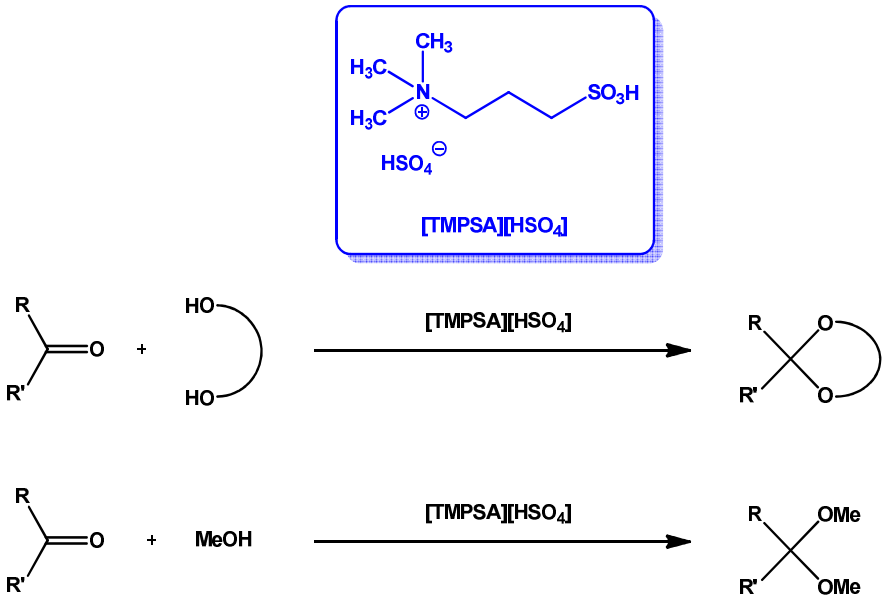
The ionic liquid-tagged *bis*(oxazoline) copper catalyst did not show any conversion in the Diels-Alder reaction of *N*-acryloyloxazolidinone and cyclohexa-1,3-diene in DCM as a solvent. When the same reaction was carried out in [BMIM][NTf_2] has given required product with 98% conversion and 97% ee. *N*-Acryloyloxazolidinone was found to be more active than *N*-acryloylpyrrolidinone with cyclopentadine/cyclohexadiene in presence of C_2-symmetric ionic liquid-tagged (*S*,*S*)-*t*-Bu-box copper catalyst in [BMIM][NTf_2]. This efficient catalytic system (catalyst + IL) was recycled 20 times without loss of activity or enantioselectivity. This excellent recyclability was due to the ionic character of the ligand. The toxicity testing of the ligands synthesized were carried out on luminescent bacteria. The traditional *t*-Bu-box ligand has shown higher LC_{50} values (45 µg/mL) than most active ligand (11 µg/mL).

1.2.6 Acetalisation reactions:

The acid catalysed nucleophilic addition of an alcohol to aldehyde or ketone to form respective acetal or ketal is termed as an acetalisation reaction. It is one of the important reactions in organic synthesis. As the carbonyl functionality is very reactive, it's important to protect against the attack of nucleophiles, acidic, basic or reducing agents.[39] There are several methods to protect aldehydes/ketones. Acetalisation i.e. formation of acetal has its own advantages, as it is stable to all nucleophilic and basic

reagents. This reaction can be catalysed by traditional liquid acids such as HCl, H_2SO_4, etc. and also by solid acids i.e. Lewis/Brønsted acid catalysts such as $ZnCl_2$, $FeCl_3$, Zeolites, *p*-TSA, etc.[39,40] A water molecule is formed as a by-product in this reaction, which is important from a Green Chemistry perspective. The major drawback of this reaction is involvement of harmful liquid acids, which also involves handling hazards.

Forbes, Davis and co-workers reported Brønsted acidic ionic liquids with covalently bonded sulfonic acid functionality containing imidazolium and phosphonium cations.[41] These ILs has shown dual use as both catalyst and solvent in Fisher esterification and pinacol/benzopinacol rearrangement. Fang and co-workers further exploited such covalently bonded sulfonic acid functionality in ionic liquid and its dual use in acetalisation reaction.[42]

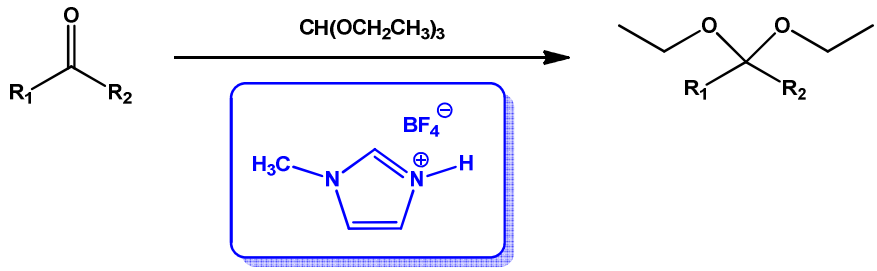


Scheme 1.12: Protection of aldehydes/ketones with alcohols in presence of [TMPSA][HSO_4]

The Brønsted acidic ionic liquid *N,N,N*-trimethyl-*N*-propanesulfonic acid ammonium hydrogen sulfate ([TMPSA][HSO_4]) has been prepared economically and used as a catalyst and as a solvent in acetalisation reactions. A number of aldehydes and ketones were reacted with 1,2-diols and methanol to form acetal/ketal in [TMPSA][HSO_4] (Scheme 1.12). All reactions showed 100% selectivity with excellent conversions within 5-60 minutes. Most of the reactions gave quantitative yields, except the protection of acetophenone with methanol with 65% conversion. This Brønsted acidic ionic liquid was recycled 9 times without loss of catalytic activity and selectivity.

Du and Tian have also demonstrated the use of simple protonated 1-methylimidazolium ionic liquids as a Brønsted acid catalyst in the protection of aldehydes and ketones.[43]

The IL catalyst was inexpensively prepared by protonation of 1-methylimidazole. The protection of various aldehydes and ketones with triethyl orthoformate in presence of 1-methylimidazolium tetrafluoroborate displayed very high conversions (84% - 93% yields) at room temperature (Scheme 1.13). The catalyst was easily recycled just by filtration and reused without any loss of activity.



Scheme 1.13: Protection of aldehydes/ketones with triethyl orthoformate and IL catalyst

1.3 Environmental fate of ionic liquids:

Due to the wide range of applications and versatility, ionic liquids are continually being used extensively in industry,[2a] which has triggered an issue of waste management. Also, many of these are totally synthetic novel compounds. Hence it is important to study the environmental impact of such ionic liquids before releasing into the natural environment. Due to their low vapour pressure, ILs can reduce the possibility of air pollution. But bearing an ionic nature; ILs have a notably high solubility in water[4c,44] (except NTf_2^- & PF_6^-) which is a viable and common means by which these ILs get released in nature. In order to check the biocompatibility of ILs, toxicity, eco-toxicity and biodegradation studies have to be carried out. ILs are usually referred to as "Green" alternatives to Volatile Organic Compounds (VOCs). Instead of the "Green" label, ILs can be categorized in the pattern of '*Traffic Signal Lights*' as discussed at the BATIL (Biodegradation And Toxicity of Ionic Liquids) meeting in DECHEMA, Frankfurt, 2009 (Fig. 1.3).[45a] As we start classifying ILs in three colours (Red, Yellow and Green), we can find that most ILs are in the Red and Yellow regions, although this information was solely based on toxicity data. For an IL to be classified more accurately by a 'Traffic Signal Lights' pattern, detailed information about the toxicity, biodegradation and ease of synthesis etc. are required. For example, [OMIM][Cl] (Log IC_{50}: 1.6 μM in *Bacillaria paxillifer*) can be catagorised as red, [BMIM][$N(CN)_2$] (EC_{50}: 1400 μM in WST-1 cell viability assay using the IPC-81 cell line) as yellow and [EMIM][Cl] (EC_{50}: 13,573 μM in *Oocystis submarina*) as green. Similar classification can be applied to

commonly used organic solvents (Fig. 1.3).[45a] Water is not toxic at all, hence it is a green solvent, where as Toluene (IC_{50}: 9 mM in mRNA for specific N-methyl-D-aspartate receptors) can be considered yellow and Benzene can be red, as it is well known to cause cancer.

Fig 1.3: Recommendation for data representation of toxicity of ionic liquids and commonly used organic solvents[45]

1.3.1 Toxicity and eco(toxicity) of ionic liquids:

As mentioned before, many ionic liquids are non-natural (synthetic) molecules. While a single toxicological test yields useful, albeit limited data, over the last decade, a large number of publications have demonstrated a wide variety of 'biological test systems' for toxicity testing of ionic liquids (Fig. 1.4).[46] This includes fungi, bacteria, algae, enzymes, rat cell line, fish, etc. Only by assessing the toxicity of IL across a broad range of organisms can a 'true' understanding of how environmentally friendly the compound is?

Stock and co-workers reported the effect of ionic liquids on acetylcholinesterase.[47] Enzymes are a crucial part of the human nervous system. Acetylcholinesterase is known to catalyse the hydrolysis of the neurotransmitter acetylcholine, to acetate and choline. Inhibition of acetylcholinesterase results in muscular paralysis and other medically significant nervous problems. Organophosphates are a major class of acetylcholinesterase inhibitors. A range of commonly used imidazolium, pyridinium and phosphonium ionic liquids were tested in this assay. Imidazolium and pyridinium ionic liquids showed high toxicity to acetylcholinesterase at very low concentrations,

whereas phosphonium ionic liquids were non-toxic within the test limits. This testing showed that toxicity of these ionic liquids lies in the cationic part and alkyl side chain and not in the anionic part.

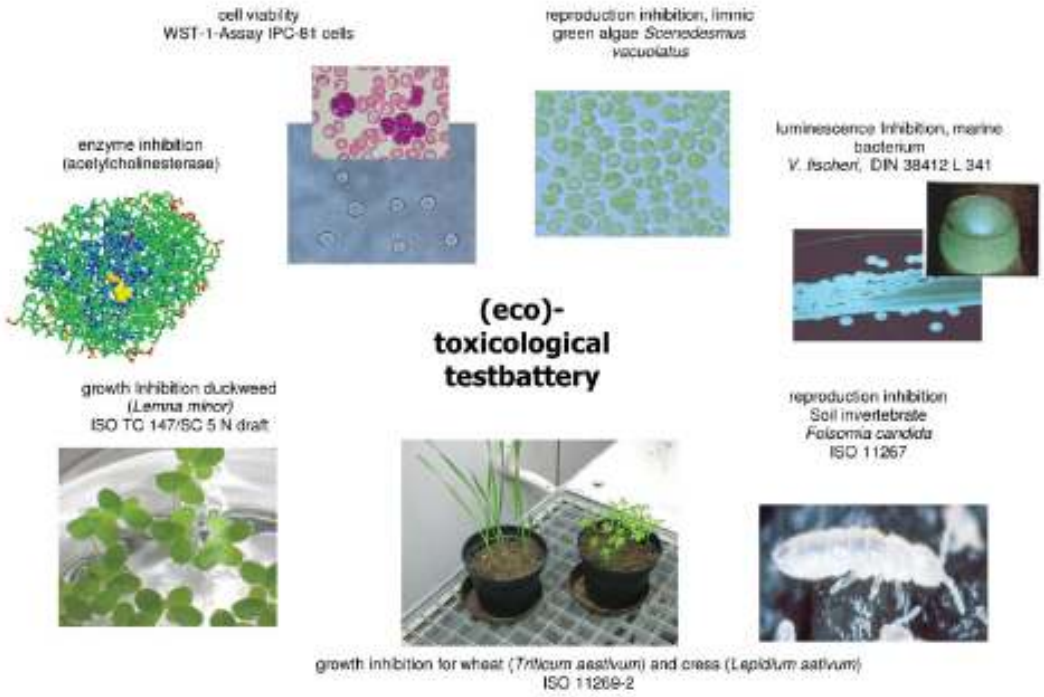


Fig 1.4: Toxicological test battery[46b]

Another important finding of this assay was that increasing the length of alkyl side chains increase the toxicity. This can be explained as long alkyl chain increases lipophilic nature of the ionic liquids, which can then easily incorporate within the biological membrane of nerve cell synapses.[48] Similar trends between the toxicity and length of alkyl chain on luminescence inhibition of *Vibrio fischeri* and *promyelocytic leukemia rat cell line* IPC-81 were reported by Ranke and co-workers.[49] Leukemia rat cell line IPC-81 was also used to observe the cytotoxic effect of commercially available anions.[50] No significant anion effect was found under the test system.

Bernot and co-workers demonstrated that acute toxicity of certain 1-butyl-3-methyl imidazolium ionic liquids on *Daphnia Magna* were mainly due to the cationic part.[51] *Daphnia Magna* has been extensively used for ecotoxicological evaluation of chemicals in invertebrates. Ionic liquids were found to influence the reproduction of *Daphnia Magna*. 1-Butyl-3-methylimidazolium bromide was found to be most toxic in the test system (LC_{50}: 8.03 mg/L). This study demonstrated that the toxicity of ionic liquids was influenced by the cation component, which was confirmed by high LC_{50} values for sodium salts of similar anions. Yu and co-workers reported the toxicity study of 1-alkyl-3-methylimidazolium bromide ionic liquids towards the antioxidant defence system of

Daphnia Magna.[52] Increasing the length of alkyl side chain was found again to increase toxicity. Toxicity of ionic liquids in this case was due to oxidative stress in *Daphnia Magna*, which was evaluated by measuring the activity of antioxidant defence enzymes, levels of the antioxidant glutathione and malondialdehyde i.e. peroxidation by-product of lipid. [C_{12}MIM][Br] showed very high toxicity with an LC_{50} of 0.05 mg/L under 48h incubation time. Samorì and co-workers reported the toxicity effect of oxygenated alkyl side chain imidazolium ionic liquids in *Daphnia Magna* and *Vibrio Fischeri*.[53] A direct comparison between the toxicity of 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM][BF_4]) and 1-methoxyethyl-3-methylimidazolium tetrafluoroborate and dicyanamide ([MOEMIM][BF_4] and [MOEMIM][$N(CN)_2$]) proved that incorporation of oxygen functionality helps to lower the toxicity of the ionic liquids (Fig. 1.5). The 50% effective concentration (EC_{50}) for [BMIM][BF_4] towards the inhibition of *Daphnia Magna* and *V. Fischeri* was lower (5.18 and 300 mg/L, respectively) than for [MOEMIM][BF_4] (209-222 and 3196 mg/L, respectively) and [MOEMIM][$N(CN)_2$] (209 and 2406 mg/L, respectively).

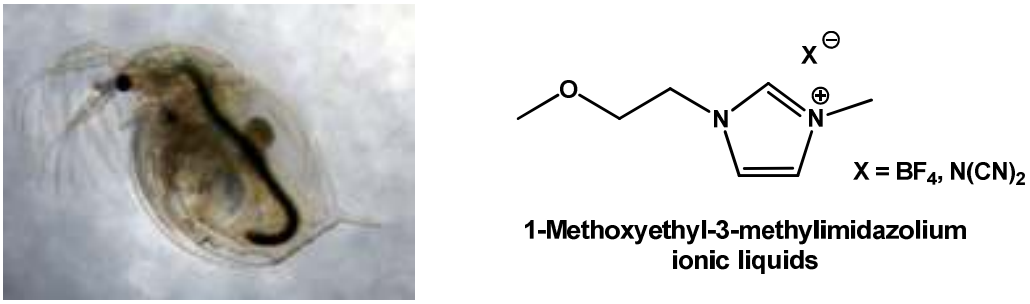


Fig. 1.5: Schematic of 1-methoxyethyl-3-methylimidazolium ILs towards Daphnia Magna

Gathergood and co-workers further demonstrated that imidazolium based ionic liquids with an oxygen functionality i.e. ester and ether side chains, have reduced antimicrobial activity to a great extent.[54] Four Gram negative bacteria (*Pseudomonas aeruginosa, Escherichia coli, Klebsiella sp., Salmonella sp.*) and three Gram positive bacteria (*Staphylococcus aureus, Enterococcus sp., Bacillus subtilis*) were screened in the assay. A range of long ether and poly ether ester side chain imidazolium ionic liquids showed a huge reduction in the toxicity in this test system, compared with similar number of atoms in long alkyl side chains.

In order to check the toxicity effect of ionic liquids in humans, a cytotoxicity assay with human cell lines was designed. HeLa is one of the most extensively used cell lines in medicinal research. HeLa is a human tumor cell line, which is a prototype of epithelium.

Due to the first contact of an organism with toxic materials, HeLa cell line has great importance. Stepnowski and co-workers reported the cytotoxic effect of imidazolium ionic liquids in Hela cell line.[55] The EC_{50} values of a range of 1-alkyl-3-methylimidazolium ionic liquids were evaluated on human epithelium HeLa cells. Ionic liquids with a decyl side chain with tetrafluoroborate as the anion component demonstrated high toxicity (EC_{50} = 0.07 mM). This was supportive of the results with other test systems. The cytotoxicity of ionic liquids were compared with the known 50% effective concentrations (EC_{50} values) of traditional organic solvents such as dichloromethane (71.43 mM), phenol (42.68 mM), xylene (52.43 mM) and ethanol (1501.43 mM). These studies revealed that the tested ionic liquids had significant toxicity against human cell line HeLa, compared with organic solvents. Lu and co-workers utilised this assay for testing the cytotoxicity of a large range of ionic liquids containing imidazolium, pyridinium, choline, triethylammonium and phosphonium cations with halide, NTf_2^-, and BF_4^- anions.[56] In general, choline and alkyl-triethylammonium ionic liquids were found to be less toxic than their imidazolium and pyridinium salt counterparts.

In an effort to evaluate the eco(toxicity) of ionic liquids, Yun and co-workers reported an assay of freshwater microalgae *Selenastrum capricornutum*.[57] The bromide salts of commonly used 1-butyl-3-methylimidazolium, 1-butyl-3-methylpyridinium, 1-butyl-1-methylpyrrolidinium, tetrabutylammonium, and tetrabutylphosphonium ILs were tested against the *S. capricornutum* and compared with traditional water miscible organic solvents such as dimethylformamide, 2-propanol and methanol. Increase in the toxicity of imidazolium and pyridinium cations were observed with an increase in incubation time, whereas the opposite trend was found in the case of tetrabutylammonium, and tetrabutylphosphonium ILs. The growth inhibition of *S. capricornutum* was higher in ionic liquids than organic solvents. A similar test system was applied to investigate the toxicological effect of anions.[58] Toxicity of various anions incorporated with 1-butyl-3-methylimidazolium cation were compared with their respective sodium and potassium salts. The anions were found to inhibit the growth of freshwater algae *S. capricornutum*. The clear trend in algae toxicity was observed as hexafluoroantimonate (SbF_6^-) > hexafluorophosphate (PF_6^-) > tetrafluoroborate (BF_4^-) > triflate ($CF_3SO_3^-$) > octyl sulphate ($OctOSO_3^-$) > halide (Br^-, Cl^-). Toxicity studies (in fish, aquatic plants/invertebrates) on anionic surfactants have shown that toxicity is dependent on a number of factors such as alkyl chain length, solubility and stability in water.[59] As the length of alkyl chain increases, toxicity increases until certain limits. Further increase in

chain length can decrease the hydrophilic nature of these materials, reducing bioavaibility of compound which results in a general decrease in the toxicity.[60]

1.3.2 Biodegradation of ionic liquids:

Ionic liquids are well known for being stable to heating and in a variety of reaction conditions. Although this is an important property in their applications, it can raise issues regarding degradation and bioaccumulation when released in nature. Accumulated data on the anti-microbial toxicity of novel ionic liquids can be used as a preliminary guideline before performing the biodegradation tests. The biological test system has its limitations, such as when reported toxicity data is only available for certain individual organisms, whereas biodegradation assays usually have a large sample group of organisms. Also, breakdown products/intermediates of ionic liquids can be toxic, which can be resistant to further degradation, which leads to the issue of bioaccummulation. Hence it is important to perform biodegradation studies of ionic liquids. [61] Boethling and co-workers in their review article "*Designing Small Molecules for Biodegradability*", gave useful and general guidelines for the design and synthesis of environmental friendly chemicals.[62] According to their observations, compounds containing unsubstituted alkyl chains, benzene rings, oxygen functionalities such as esters, aldehydes, and carboxylic acids (potential sites for enzymatic hydrolysis) greatly increase biodegradation. Whereas compounds containing halogens, branched chains, heterocycles, functional groups such as nitro, nitroso and arylamines motifs, adversely affect the biodegradation. There are several biodegradation study methods approved by the Organisation for Economic Cooperation and Development (OECD) (See Table 1.1).

Data collected from all of the tests mentioned in Table 1.1 can be catagorised according to OECD guidelines as - (a) Ultimate biodegradation: Denotes complete degradation/utilisation of a test compound to produce carbon dioxide (CO_2), water, biomass and inorganic substances. Such biodegradation can achieved due to the mineralisation by microorganisms. This is one of the significant characteristics, before classed as a 'biocompatible' compound. (b) Readily biodegradable: These are positive results showing rapid ultimate degradation of the test compound under aerobic conditions in stringent screening tests. Both mineralisation and elimination/alteration (abiotic process such as hydrolysis, oxidation and photolysis) of the test substance can

be observed. (c) Primary biodegradation: An elimination or alteration of the test sample by microorganisms, in order to lose its specific properties.[63]

Table 1.1: Biodegradation methods in use

Test No.	Name	Analytical method
OECD 301 A	DOC Die-Away	Dissolved organic carbon
OECD 301 B	CO_2 evolution	CO_2 evolution
OECD 301 C	MITI (Ministry of International Trade and Industry, Japan)	Oxygen consumption
OECD 301 D	Closed bottle	Dissolved oxygen
OECD 301 E	Modified OECD screening	Dissolved organic carbon
OECD 301 F	Manometric respirometry	Oxygen consumption
ISO 14593	CO_2 headspace test	CO_2 evolution
OECD 309	OECD 309	^{14}C labelling
ASTM 5988	ASTM 5988	CO_2 production / Biochemical oxygen demand

Gathergood and Scammells reported the synthesis of ester and amide functionalised side chain imidazolium ionic liquids[64] according to the guidelines outlined by Dr. Boethling.[65] All of the novel alkyl ester and amide side chain methylimidazolium ionic liquids were subjected to biodegradation studies. A biodegradation study of bromide salts of these ionic liquids along with commonly used [BMIM][BF_4] and [BMIM][PF_6] ILs was carried out under the 'Closed Bottle Test' (OECD 301D)[66] although none of the tested ionic liquids passed the minimum 60% biodegradation threshold in order to be classified as 'readily biodegradable'. However, [BMIM][BF_4] and [BMIM][PF_6] did not show biodegradation in the test system. Ester functionalised side chain ionic liquids demonstrated improved biodegradation. Increasing the length of the ester side chain increased the biodegradation, for example a methyl ester derivative showed 17% biodegradation, whereas biodegradation of an octyl ester derivative was 32% after 28 days. Another important observation was that amide side chain ionic liquids showed very negligible biodegradation. The effect of different anion on the rate of biodegradation was tested under the same test system. A range of 1-butyl-3-methylimidazolium and ester functionalised 3-methyl-1-(propoxycarbonylmethyl)-imidazolium ionic liquids were prepared with different anions such as Br^-, BF_4^-, PF_6^-, NTf_2^-, $N(CN)_2^-$ and $OctOSO_3^-$. $BMIM^+$ based ionic liquids showed poor biodegradation, except with an octyl sulphate as anion. The biodegradation of 3-methyl-

1-(propoxycarbonylmethyl)-imidazolium ionic liquid was increased from 19% with bromide anion to 49% with octyl sulphate anion after 28 days. Gathergood and co-workers further demonstrated that incorporation of ether and polyether linkages along with ester functionality in the side chain can increase biodegradation to a great extent.[54] The biodegradation of a large range of ether and polyether ester side chain methylimidazolium ionic liquids were studied using the CO_2 Headspace test. Octyl sulphate salts of 1-methylimidazolium ionic liquids with propoxyethoxy and butoxyethoxy esters were found to be readily biodegradable (> 60% biodegradation in 28 days).

Docherty and co-workers reported biodegradation studies of imidazolium and pyridinium based ionic liquids by OECD dissolved organic carbon Die-Away test. The test was carried out with the activated sludge microorganisms from wastewater treatment plant.[67] Denaturing gradient gel electrophoresis (DGGE) was also used to investigate the microbial community profile. The results showed that the tested pyridinium based ionic liquids has better biodegradability than the corresponding imidazolium salts. Octyl-3-methyl-pyridinium bromide was found to be readily biodegradable with complete degradation within 15-25 days of incubation, whereas hexyl-3-methyl-pyridinium bromide was degraded within 40-50 days. Such complete biodegradation was further supported by the work of Stolte and co-workers in their investigation of the primary biodegradation of a variety of ionic liquids by the modified OECD 301 D test.[68] A range of 1-alkyl-3-methylimidazolium, 1-alkylpyridinium and 4-(dimethylamino)pyridinium halide salts were screened under the test system. The biodegradation products were identified by HPLC-MS analysis. 1-Octyl-3-methylimidazolium chloride gave a result of 100% primary biodegradation within 31 days. The stepwise degradation by two possible metabolic pathways was predicted based on HPLC-MS analysis. This predicted breakdown pathway was due to enzymatic oxidation of the terminal carbon.

Scammells and co-workers also reported biodegradation of ester functionalised pyridinium ionic liquids using the CO_2 Headspace test (ISO 14593).[69] Pyridinium ionic liquids with alkyl and ester side chains, along with ester derivatives of nicotinic acid with alkyl side chain were tested under aerobic conditions. The halide salts of pyridinium ionic liquids with alkyl side chain (C_4, C_{10} and C_{16}) showed poor biodegradation, whereas it was improved up to a max. of 45% after 28 days by the use of octyl sulfate anion. Switching from alkyl chain to ester side chain in pyridinium ILs

increased the biodegradation dramatically. Such substitution made them readily biodegradable, independent of the chosen anionic component. Bromide, hexafluorophosphate and octyl sulfate showed a high level of biodegradability (85% to 90%), whereas NTf_2^- gave 64% biodegradation after 28 days. Ionic liquids derived from the nicotinic acid ester derivative i.e. ester group at 3-position of the pyridine ring were found to be readily biodegradable even with methyl or butyl side chain. Amide side chain derivatives showed low biodegradability, even with using octyl sulfate as the anion (30% biodegradation after 28 days). Scammells and co-workers further studied the effect of the incorporation of ester, ether and hydroxyl side chain in phosphonium based ionic liquids.[70] All phosphonium ionic liquids showed poor biodegradation independent of ester, ether and hydroxyl side chains and anions in CO_2 Headspace test. Only heptyl ester side chain ionic liquid with octyl sulfate anion showed highest 30% biodegradation after 28 days.

Most of the ionic liquids prepared are not 'readily biodegradable'; however, several structural modifications have shown a positive improvement in the biodegradability of ionic liquids.[61,71] Striving towards compounds with 'Ultimate biodegradation' is preferred over 'readily biodegradable' examples and is a major research area. Hence it is important to study the biodegradation pathways of ionic liquids along with kinetics and metabolite studies to assist the 'benign by design' approach.

1.3.3 Guidelines for designing 'Green' ionic liquid catalysts/solvents:

From the literature, the following observations were made and are summarised in Fig. 1.6:

- Linear alkyl chains in general can increase biodegradation compared to branched hydrocarbon chains.
- Oxygen containing functionalities, such as ester and hydroxyl groups in the side chain of imidazolium cation, not only reduces microbial toxicity but also increases rate of biodegradation. This is, however, not effective in phosphonium based ionic liquids.
- Ether substitution reduces bactericidal toxicity.

- Ester substitutions at 1 and 3 position of pyridinium cation can improve biodegradation.

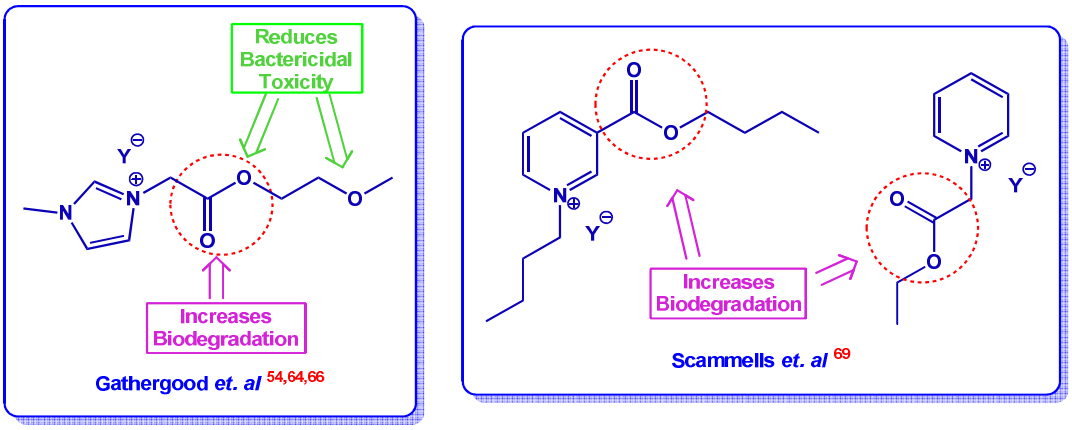


Fig. 1.6: Guidelines for designing 'Green' ionic liquids

1.4. Green chemistry metrics:

To achieve 'Green' synthesis of any chemical, the '*12 Principles of Green Chemistry*' given by Anastas and Warner serves as the most useful set of guidelines and gives us the important message that 'Prevention is better than cure'.[72] These principles suggest not only to consider toxicity and biodegradation, but also to measure the 'greenness' of the chemical process. To evaluate the 'greenness' of any process, a number of factors associated with the chemical process has to studied. Green Chemistry metrics can help to measure the efficiency and 'greenness' of the chemical process. There are several well established methods to determine the sustainability of a chemical process under areas such as the economical, technical and social effects of such processes. Economical methods mainly consist of profit related analysis, whereas technical methods analyses quality, productivity and related issues. Social methods concern the society and environmental aspect of the chemical process.[73] Porteous has shown that it is easy to correlate Green Chemistry metrics with the "*12 Principles of Green chemistry*".[74] There are several metrics available to measure efficiency, use of energy and resources, toxicity, biodegradation, safety and life cycle impact of the chemical process, which are closely related to the 12 Principles.

The Environmental (E) factor is one of the most widely used and efficient methods to measure the amount of waste generated in the process.[75] This is also known as Sheldon's E-factor.

$$\text{E factor} = \frac{\text{Total mass of waste (kg)}}{\text{Mass of product (kg)}}$$

E-factor calculations is one of the important methods to calculate the waste associated with the process, which includes all unwanted side products, reagents, solvents and energy. Water used in the process is usually excluded from the calculations. The higher the E-factor value, the higher the waste generated which has an adverse effect on environment. Economically this adds on to the profit and the cost of disposal. Many modifications on the measurement of E-factor were adopted in industry. GlaxoSmithKline (GSK) has introduced a concept of 'Mass Intensity' based on Sheldon's E-factor.[76]

$$\text{Mass Intensity} = \frac{\text{Mass all materials used (excluding water)}}{\text{Mass of product}}$$

Mass Intensity measures the amount of reagents, solvents and workup reagents used in the process. Hence it takes an account of product yields and stoichiometry of the reagents. In order to measure the synthetic efficiency of the process, the "Atom Economy" concept was found to be useful. Atom economy in chemical reactions is one of the 12 Principles of Green Chemistry, which gives indications as to the overall efficiency of a chemical reaction.[77]

$$\text{Atom Economy} = \frac{\text{Molecular weight of desired product}}{\text{Molecular weight of all products/reactants}} \text{ X } 100\%$$

Although this is an important concept, which suggests to minimise the waste. It does not consider the actual mass, yield, solvents and other reagents used in the process. Reaction mass efficiency (RME) has overcome these drawbacks.[76] Reaction mass efficiency considers actual mass of reactants and product. This is one of the commonly used metrics to evaluate the efficiency of the chemical process.

$$\text{Reaction Mass Efficiency} = \frac{\text{Mass of product}}{\text{Mass of all reactants}} \text{ X } 100\%$$

Apart from these, real time analysis is also important to analyse the chemical process. Real time analysis is again one of the "12 Principles of Green Chemistry", which enables the chemist to identify the formation of waste along the process. A number of analytical techniques such as HPLC, GC, NMR, FT-IR, and sensors etc. were already found to be useful in real time analysis. It's also important to determine the robustness of the process, which will allow preparing chemicals on a large scale. The measurement

of toxicity and biodegradation are also important metrics to evaluate 'greenness' of the chemical products.

1.5 Conclusion:

In this chapter we have demonstrated that ionic liquids have great potential and versatility in organic synthesis, with the dualistic ability to act as a solvent and as a catalyst. Ionic liquids were found to be possible replacements over traditional volatile organic solvents. Such ionic liquid solvents were found to be useful in transition metal catalysed reactions. They not only enabled catalyst immobilisation, but also increased recyclability of expensive transition metal catalysts. Ease of product separation and their stability against a variety of reagents has proved their important characteristics. We have seen that modification in the cationic part of the ionic liquids, according to the requirements of the aforementioned reactions, enabled them to act as organocatalysts or ligands for transition metal catalysts. These ionic liquid catalysts have shown comparative catalytic activity against known organocatalysts but such materials had a distinct advantage in that the ionic liquids could be recycled, with no discernable loss of activity. In order to increase recyclability, ionic liquid catalysts/ligands were grafted onto a solid/ polymer support. These modifications helped to separate ionic liquid catalysts from the reaction mixture.

We have also illustrated the efforts attempted by the scientific community to evaluate the 'greenness' of ionic liquids, by using toxicity and biodegradation methods. The majority of ionic liquids are non-natural molecules, hence it's important to check their biocompatibility. Toxicity studies can serve as a "first post" primary evaluation of biodegradation. A variety of test systems including fungi, bacteria, algae, enzymes, rat cell line, human cell line and fish etc. were implemented to check the toxicity of ionic liquids. Most of these test systems have shown that toxicity of the ionic liquids comes from the cationic component. Important observations from such test systems also included that (a) toxicity depends on the alkyl chain length and (b) incorporation of oxygen functionalities (ether, ester, and hydroxyl etc.) reduces the toxicity.

A number of Organisation for Economic Cooperation and Development (OECD) tests were found to be useful in the estimation of biodegradation. These tests mainly involve calculation of CO_2 evolution and oxygen consumed. These tests showed that most of the 1,3-dialkyl imidazolium ionic liquids are non-biodegradable, in most of the test

systems. Although the alkyl side chain can undergo degradation, the imidazole core can still persist during biodegradation studies. Introduction of oxygen functionality such as ether / ester, either in the side chain of the imidazolium cation or at the C_1 or C_3 position of the pyridinium cation, were found to increase the rate of biodegradation.

Target ionic liquids were designed and selected based on the literature discussed in this chapter. According to guidelines, ionic liquids with ester and amide functionality in the side chains or heterocyclic core were designed. Ionic liquids which pass 'ultimate biodegradation' tests have low microbial toxicity and can be synthesised by short routes, was a major goal of this project.

1.6 References:

1. ACS Symp. Ser. 818, ed. R. D. Rogers and K. R. Seddon, American Chemical Society, USA, 2002
2. (a) N. V. Plechkova and K. R. Seddon, *Chem. Soc. Rev.*, 2008, **37**, 123-150, (b) P. Wasserscheid and A. Stark (Eds.), *Handbook of Green Chemistry*, Volume 6: Ionic Liquids, Wiley-VCH, 2010
3. J. S. Wilkes, *Green Chem.,* 2002, **4**, 73-80
4. (a) K. R. Seddon, *J. Chem. Technol. Biotechnol.*, 1997, **68**, 351-356, (b) K. N. Marsh, J. A. Boxall, R. Lichtenthaler, *Fluid Phase Equilibr.*, 2004, **219**, 93-98, (c) J. McFarlane, W. B. Ridenour, H. Luo, R. D. Hunt, D. W. Depaoli, R. X. Ren, *Sep. Sci. Technol.*, 2005, **40**, 1245-1265, (d) R. A. Sheldon, *Green Chem.*, 2005, **7**, 267-278
5. M. Freemantle. *Chem. Eng. News* 76, (30th March), **1998,** 32-37
6. (a) J. P. Hallett, T. Welton, *Chem. Rev.*, 2011, **111**, 3508-3576, (b) C. D. Hubbard, P. I. and R. Eldik, *Chem. Soc. Rev.*, 2011, **40**, 272-290, (c) P. Wasserscheid, J. Joni, Handbook of *Green Chem.,* 2010, **6**, 41-63, (e) S. M. Chowdhury, S. Ram, J. L. Scott, *Tetrahedron,* 2007, **63**(11), 2363-2389, (f) A. Stark and K. R. Seddon, in *Kirk-Othmer Encyclopaedia of Chemical Technology*, A. Seidel, JohnWiley & Sons, Inc., Hoboken, New Jersey, USA, 5, 2007, **26**, 836-920
7. (a) M. Opallo, A. Lesniewski, *J. Electroanal. Chem.,* 2011, **656**, 2-16, (b) M. J. A. Shiddiky, A. A. J. Torriero, *Biosensors & Bioelectronics*, 2011, **26** (5), 1775-1787, (c) H. Liu, Y. Liu, J. Li, *Phys. Chem. Chem. Phys.,* 2010, **12**(8), 1685-1697, (d) W. R. Pitner, P. Kirsch, K. Kawata, H. Shinohara, *Handbook of Green Chemistry,*

2010, **6**, 191-201, (e) M. C. Buzzeo, R. G. Evans, R. G. Compton, *ChemPhysChem.,* 2004, **5**, 1106-1120

8. (a) C. F. Poole, S. K. Poole, *Journal of Separation Science,* 2011, **34**(8), 888-900, (b) T. D. Ho, A. J. Canestraro, J. L. Anderson, *Anal. Chim. Acta*, 2011, **695**, 18-43, (c) P. Sun, D. W. Armstrong, *Anal. Chim. Acta*, 2010, **661** (1), 1-16, (d) S. Pandey, *Anal. Chim. Acta*, **2006**, *556*, 38-45, (e) M. Koel, *Crit. Rev. Anal. Chem.*, 2005, **35**, 177-192
9. P. Dominguez de Maria, Z. Maugeri, *Cur. Opin. Chem. Biol.*, 2011, **15** (2), 220-225
10. (a) M. A. Klingshirn, R. D. Rogers, K. H. Shaughnessy, *J. Organomet. Chem.,* 2005, **690**, 3620-3626, (b) E. Mizushima, T. Hayashi, M. Tanaka, *Green Chem.,* 2001, **3**, 76-79
11. (a) M. J. Earle, P. B. McCormac, K. R. Seddon, *Green Chem.,* 1999, **1**, 23-25, (b) R. Vijayaraghavan, D. R. MacFarlane, *Aust. J. Chem.,* 2004, **57**, 129-133, (c) J. N. Rosa, C. A. M. Afonso, A. G. Santos, *Tetrahedron,* 2001, **57**, 4189-4193
12. (a) J. S. Yadav, B. V. S. Reddy, G. Baishya, K. V. Reddy, A. V. Narsaiah, *Tetrahedron,* 2005, **61**, 9541-9544, (b) M. Johansson, A. A. Linden, J.-E. Baeckvall, *J. Organomet. Chem.*, 2005, **690**, 3614-3619, (c) A. Serbanovic, L. C. Branco, M. Nunes da Ponte, C. A. M. Afonso, *J. Organomet. Chem.*, 2005, **690**, 3600-3608
13. (a) M. Picquet, S. Stutzmann, I. Tkatchenko, I. Tommasi, J. Zimmermann, P. Wasserscheid, *Green Chem*., 2003, **5**, 153-162, (b) S. A. Forsyth, H. Q. N. Gunaratne, C. Hardacre, A. McKeown, D. W. Rooney, K. R. Seddon, *J. Mol. Catal. A: Chem*., 2005, **231**, 61-66, (c) M. T. Reetz, W. Wiesenhoefer, G. Francio, W. Leitner, *Chem. Commun*., 2002, 992-993
14. R. F. Heck, *Acc. Chem. Res.*, 1979, **12**, 146-151
15. T. Mizoroki, K. Mori, A. Ozaki, *Bull. Chem. Soc. Jpn.*, 1971, **44**, 581
16. D. E. Kaufmann, M. Nouroozian, H. Henze, *Synlett,* 1996, **11**, 1091-1092
17. F. Bellina and C. Chiappe, *Molecules,* 2010, **15**, 2211-2245
18. L. Wang, H. Li, P. Li, *Tetrahedron*, 2009, **65**, 364-368
19. L. Xu, W. Chen, J. Xiao, *Organometallics*, 2000, **19**, 1123-1127
20. A. J. Carmichael, M. J. Earle, J. D. Holbrey, P. B. McCormac, K. R. Seddon, *Org. Lett.,* 1999, **1**(7), 997-1000
21. R. R. Deshmukh, R. Rajagopal, K. V. Srinivasan, *Chem. Commun.*, 2001, **17**, 1544-1545

22. (a) C. M. Crudden, M. Sateesh, R. Lewis, *J. Am. Chem. Soc.*, 2005, **127**, 10045-10050, (b) X. Ma, Y. Zhou, J. Zhang, A. Zhu, T. Jiang, B. Han, *Green Chem.*, 2008, **10**, 59-66
23. G. Liu, M. Hou, J. Song, T. Jiang, H. Fan, Z. Zhang, B. Han, *Green Chem.*, 2010, **12**, 65-69
24. K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, **16**, 4467-4470
25. (a) C. Glaser, *Ber. Dtsch. Chem. Ges.* **1869**, 2, 422-424. (b) A. S. Hay, *J. Org. Chem.* 1962, **27**, 3320-3323. (c) R. Rossi, A. Carpita, C. Begelli, *Tetrahedron Lett.* 1985, **26**, 523-526. (d) Q. Liu, D. J. Burton, *Tetrahedron Lett.* 1997, **38**, 4371-4374. (e) For a review of alkyne coupling, see: P. Siemsen, R. C. Livingston, F. Diederich, *Angew. Chem., Int. Ed.* 2000, **39,** 2632-2657
26. T. Fukuyama, M. Shinmen, S. Nishitani, M. Sato, I. Ryu, *Org. Lett.,* 2002, **4**(10), 1691-1694
27. J. Zhang, M. Dakovic, Z. Popovic, H. Wu and Y. Liu, *Catal. Commun.,* 2012, **17**, 160-163
28. (a) N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett.*, 1979, **20**(36), 3437-3440, (b) N. Miyaura and A. Suzuki, *J. Chem. Soc., Chem. Commun.*, 1979, 866-867, (c) N. Miyura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457-2493
29. J. Wei, J. Jiao, J. Feng, J. Lv, X. Zhang, X. Shi, Z. Chen, *J. Org. Chem.,* 2009, **74**, 6283-6286
30. M. Lombardo, M. Chiarucci, C. Trombini, *Green Chem.,* 2009, **11**, 574-579
31. A. Papagni, C. Trombini, M. Lombardo, S. Bergantin, A. Chams, M. Chiarucci, L. Miozzo and M. Parravicini, *Organometallics,* 2011, **30**, 4325-4329
32. (a) J. K. Stille, *Angew. Chem.*, 1986, **98**, 504-519, (b) J. K. Stille, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 508-524
33. S. T. Handy and X Zhang, *Org. Lett.*, 2001, **3**(2), 233-236
34. N. Louaisil, P. D. Pham, F. Boeda, D. Faye, A.-S. Castanet, S. Legoupy, *Eur. J. Org. Chem.,* 2011, **1**, 143-149
35. O. Diels, K. Alder, *Justus Liebigs Ann. Chem.*, 1928, **460**, 98-122
36. B. Pégot, G. Vo-Thanh, *Synlett*, 2005, **9**, 1409-1412
37. Z. Zhou, Z. Li, X. Hao, X. Dong, X. Li, L. Dai, Y. Liu, J. Zhang, H. Huang, X. Li, J. Wang, *Green Chem.,* 2011, **13**, 2963-2971
38. D. A. Evans, S. J. Miller, T. Lectka, P. von Matt, *J. Am. Chem. Soc., 1999, 121, 7559-7573*

39. T. W. Greene, Protective groups in Organic Synthesis, Wiley-Interscience, New York, 1981, p. 178
40. (a) J. Bornstein, S. F. Bedell, P. E. Drummond, C. F. Kosoloki, *J. Am. Chem. Soc.*, 1956, **78**, 83-86, (b) C. A. McKinzie, J. H. Stocker, *J. Org. Chem.*, 1955, 20, 1695-1701
41. A. C. Cole, J. L. Jensen, I. Ntai, T. Tran, K. J. Weaver, D. C. Forbes, J. H. Davis Jr., *J. Am. Chem. Soc.*, 2002, **124**, 5962-5963
42. D. Fang, K. Gong, Q. Shi and Z. Liu, *Catal. Commun.,* 2007, **8**, 1463-1466
43. Y. Du and F. Tian, *Synth. Commun.,* 2005, **35**, 2703-2708
44. (a) J. L. Anthony, E. J. Maginn, J. F. Brennecke, *J. Phys. Chem. B*, 2001, **105**, 10942-10949, (b) D. S. H. Wong, J. P. Chen, J. M. Chang, C. H. Chou, *Fluid Phase Equilibr*, 2002, **194-197**, 1089-1095
45. (a) N. Wood and G. Stephens; *Phys. Chem. Chem. Ph*ys., 2010, **12**, 1670-1674, (b) K. Alfonsi, J. Colberg, P. J. Dunn, T. Fevig, S. Jennings, T. A. Johnson, H. P. Kleine, C. Knight, M. A. Nagy, D. A. Perry, M. Stefaniak, *Green Chem*., 2008, **10**, 31–36
46. (a) T. P. T. Pham, C.-W. Cho, Y.-S. Yun, *Water Res.*, 2010, **44**, 352-372, (b) M. Matzke, S. Stolte, K. Thiele, T. Juffernholz, J. Arning, J. Ranke, U. Welz-Biermann, B. Jastorff, *Green Chem.*, 2007, **9**, 1198-1207
47. F. Stock. J. Hoffmann, J. Ranke, R. Störmann, B. Ondruschka, B. Jastorff, *Green Chem.*, 2004, **6**, 286-290
48. D. J. Couling, R. J. Bernot, K. M. Docherty, J. K. Dixon, E. J. Maginn, *Green Chem.*, 2006, **8**, 82-90
49. J. Ranke, K. Mölter, F. Stock, U. Bottin-Weber, J. Poczobutt, J. Hoffmann, B. Ondruschka, J. Filser, B. Jastorff, *Ecotoxicol. Environ. Saf.*, 2004, **58**, 396-404
50. S. Stolte, J. Arning, U. Bottin-Weber, M. Matzke, F. Stock, K. Thiele, M. Uerdingen, U. Welz-Biermann, B. Jastorff, J. Ranke, *Green Chem.*, 2006, **8**, 621-629
51. R. J. Bernot, M. A. Brueseke, M. A. Evans-White, G. A. Lamberti, *Environ. Toxicol. Chem.,* 2005, **21**, 87-92
52. M. Yu, S.-H. Wang, Y.-R. Luo, Y.-W. Han, X.-Y. Li, B.-J. Zhang, J.-J. Wang, *Ecotoxicol. Environ. Saf.*, 2009, **72**, 1798-1804
53. C. Samorì, A. Pasteris, P. Galletti, E. Tagliavini, *Environ. Toxicol. Chem.*, 2007, **26**, 2379-2382

54. S. Morrissey, B. Pegot, D. Coleman, M. T. Garcia, D. Ferguson, B. Quilty, N. Gathergood, *Green Chem.*, 2009, **11**, 475-483
55. P. Stepnowski, AC. Składanowski, A. Ludwiczak, E. Łaczyńska, *Hum. Exp. Toxicol.*, 2004, **23**, 513-517
56. X. Wang, C. A. Ohlin, Q. Lu, Z. Fei, J. Hu, P. J. Dyson, *Green Chem.*, 2007, **9**, 1191-1197
57. C.-W. Cho, Y.-C. Jeon, T. P. T. Pham, K. Vijayaraghavanc, Y.-S. Yun, *Ecotoxicol. Environ. Saf.*, 2008, **71**, 166-171
58. C.-W. Cho, Y.-C. Jeon, T. P. T. Pham, Y.-S. Yun, *Green Chem.*, 2008, **10**, 67-72
59. G. Könnecker, J. Regelmann, S. Belanger, K. Gamon, R. Sedlak, *Ecotox. and Environ. Safety*, 2011, **74**, 1445-1460
60. S. D. Dyer, J. R. Lauth, S. W. Morrall, R. R. Herzog, D. S. Cherry, *Environ. Toxicol. Water Qual.*, 1997, **12**, 295-303
61. D. Coleman and N. Gathergood, *Chem. Soc. Rev.,* 2010, **39**, 600-637
62. R. S. Boethling, E. Sommer, D. DiFiore, *Chem. Rev.*, 2007, **107**, 2207-2227
63. Introduction to the OECD guidelines for testing of chemicals, Section 3, 2003
64. N. Gathergood and P. J. Scammells, *Aust. J. Chem.*, 2002, **55**, 557-560
65. R. S. Boethling, *ACS Symp. Ser.*, 1996, **640**, 156-171
66. M. T. Garcia, N. Gathergood, P. J. Scammells, *Green Chem.*, 2004, **6**, 166-175
67. K. M. Docherty, J. K. Dixon, C. F. Kulpa Jr., *Biodegradation*, 2007, **18**, 481-493
68. S. Stolte, S. Abdulkarim, J. Arning, A. Blomeyer-Nienstedt, U. Bottin-Weber, M. Matzke, J. Ranke, B. Jastorff, J. Thoeming, *Green Chem.*, 2008, **10**, 214-224
69. J. R. Harjani, R. D. Singer, M. T. Garcia, P. J. Scammells, *Green Chem.*, 2009, **11**, 83-90
70. F. Atefi, M. T. Garcia, R. D. Singer, P. J. Scammells, *Green Chem.*, 2009, **11**, 1595-1604
71. S. Stolte, S. Steudte, A. Igartua, P. Stepnowski, *Current Organic Chemistry*, 2011, **15**, 1946-1973
72. P. T. Anastas, J. C. Warner, 1998, *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, UK
73. C. A. Heaton, An Introduction to Industrial Chemistry, 3rd edn, *Blackie Academic and Professional* (Springer), London, UK, 1995
74. A. Porteous, Dictionary of Environmental Science and Technology, *John Wiley & Sons Ltd*, Chichester, UK, 1992
75. R. A. Sheldon, *Chem. Ind.* (London), 1992, 903-906

76. D. J. C. Constable, A. D. Curzons, V. L. Cunningham, *Green Chem.*, 2002, **4**, 521-527
77. B. M. Trost, *Science*, 1991, **254**, 1471-1477

Chapter 2: Results and Discussion

Synthesis of Ionic Liquids

2.0 Synthesis of Ionic Liquids:

2.1 Rationale:

In order to design "Green" ionic liquids (ILs), factors such as toxicity, eco-toxicity and biodegradation have to be considered.[1] There are some commonly used cations, such as imidazolium, pyridinium, phosphonium, and sulphonium, used in the design of ionic liquids. Among these classes of ionic liquids, the imidazolium class was studied in most detail due to their unique properties, such as easy preparation, low viscosity and low melting points.[2] The Gathergood group have previously described how incorporation of oxygen functionalities into the side-chain of imidazolium based ionic liquids, such as esters[3] and ether[4] helps to improve biodegradability and reduce antimicrobial toxicity. Ionic liquids with long hydrocarbon side chains have been reported to be toxic to bacteria and fungi, due to their lipophilicity.[5] According to these guidelines above, achiral and chiral ionic liquids, with ester and amide functionality in the side chains, were selected as a target for this project.

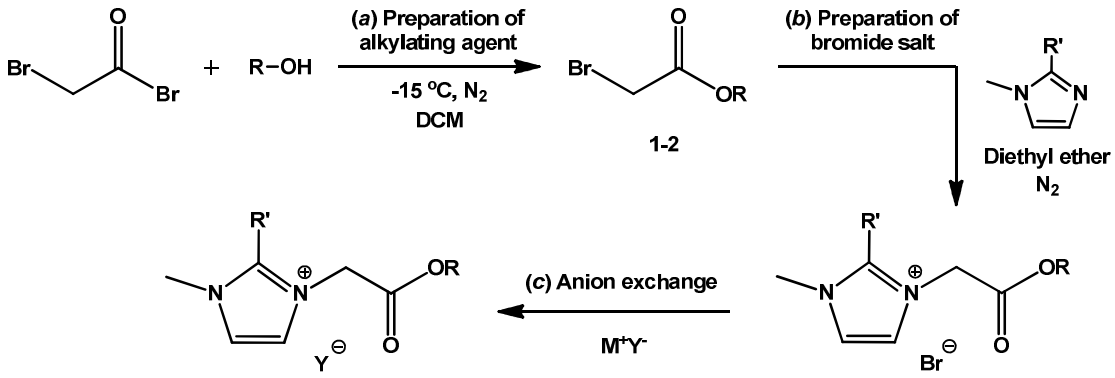
The main objective of this work was to design and synthesise a range of antimicrobially non-toxic and biodegradable ionic liquids and to explore their use in several classes of reactions in organic synthesis, as both catalyst and/or solvent.

2.2 Synthesis of Achiral Ionic Liquids:

2.2.1 Synthesis of Alkyl Imidazolium Ionic Liquids:

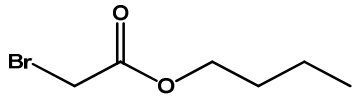
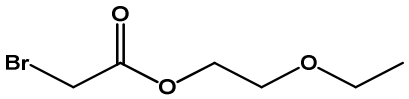
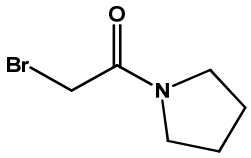
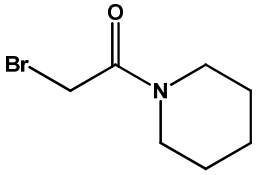
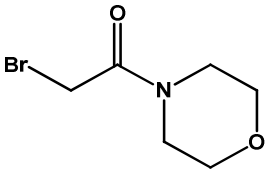
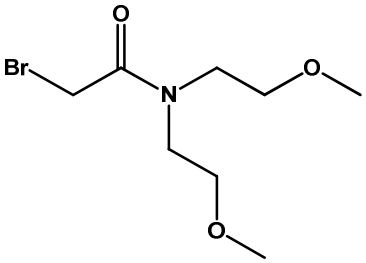
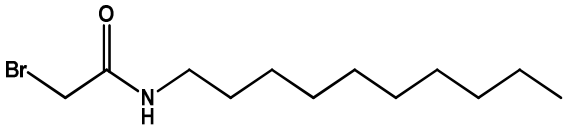
The achiral ionic liquids have been designed to be used as catalysts in acetalisation reactions and as a solvent in Carbonyl-Ene reactions. Several amide side chain ionic liquids have been synthesized along with ester side chains, due to the unknown stability of the latter in the above reactions. The preparation of ionic liquids has been carried out in three simple steps (see Scheme 2.1).

The first step involved: (a) preparation of alkylating reagents by esterification of bromoacetyl bromide with respective alcohols in presence of base. The methyl/ethyl bromoacetate was commercially available. Low temperature (-15 °C) was used during the addition of bromoacetyl bromide.



Scheme 2.1: Synthesis of ester side chain ionic liquids

Table 2.1: α-Bromoesters/amides intermediates

Alkylating reagent	Compound No.	Yield (%)
	**1**	89
	**2**	84
	**3**	55
	**4**	49
	**5**	52
	**6**	47
	**7**	52

The α-bromoesters prepared (**1** & **2**) were pure by ^{1}H-NMR, so no further purification was needed (Scheme 2.1). The α-bromoamides i.e. **3-6** have been made by using secondary amines i.e. pyrrolidine, piperidine, morpholine, *bis*(2-methoxyethyl)amine and **7** by using decylamine (Table 2.1). In general, high yields were achieved in the preparation of α-bromoesters (84-89%) than α-bromoamides (47-55%). This might be due to the basicity of the amines, which could have been partially consumed after formation of HBr under the reaction conditions.

(b) Subsequent alkylation of 1-methylimidazole or 1,2-dimethylimidazole with α-bromoesters lead to the bromide salts (**8-18**) respectively (Table 2.2). In these reactions, diethyl ether was used as a solvent due to the ease of product separation as the product precipitates from solution. The 1-alkyl or 1,2-dialkyl imidazole was added to a solution of α-bromoester/α-bromoamide dissolved in diethyl ether at room temperature under inert atmosphere. The product precipitated from the reaction mixture and was easily purified by diethyl ether washes (5 x 20 mL). Product was then further dried via rotary evaporator and *in vacuo*. The bromide salts formed were solid at room temperature in most cases (with the exception of ionic liquid **11**).

In last step in synthesis (c) anion metathesis was performed on the synthesised bromide salts (**8-18**). A series of anion exchange reactions were performed on the bromide salts to obtain *bis*(trifluoromethanesulfonimide) (NTf_2^-), tetrafluoroborate (BF_4^-), hexafluorophosphate (PF_6^-), dicyanamide ($N(CN)_2^-$) and octyl sulfate ($OctOSO_3^-$) anion analogues. (Table 2.3) *Bis*(trifluoromethanesulfonimide) and octyl sulfate anion exchange was carried out in water by stirring imidazolium bromide salts with lithium *bis*(trifluoromethanesulfonimide) and sodium octyl sulfate respectively. Hexafluorophosphate anion metathesis was achieved by vigorous stirring of imidazolium bromide salts with potassium hexafluorophosphate in acetone for 4 days, under reflux and inert atmosphere. Similarly tetrafluoroborate and dicyanamide anions of imidazolium salts were prepared by using sodium tetrafluoroborate and sodium dicyanamide.

Table 2.2: Bromide salts of 1-alkyl or 1,2-dialkyl imidazoles

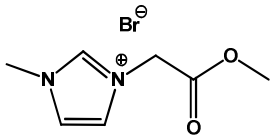
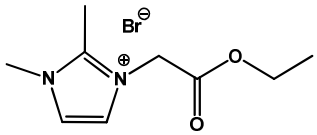
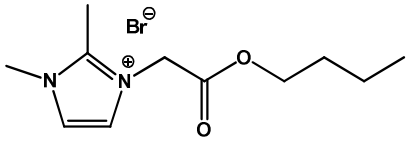
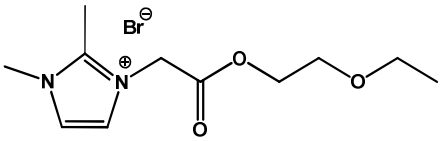
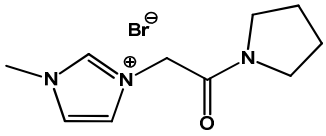
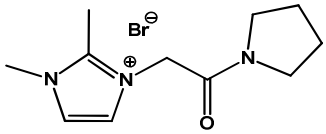
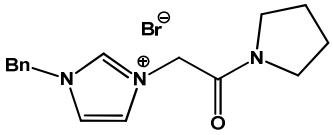
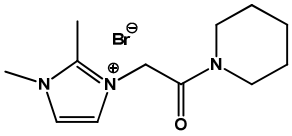
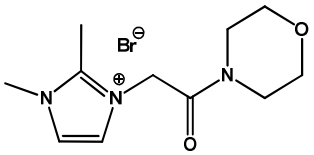
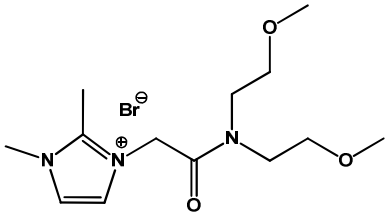
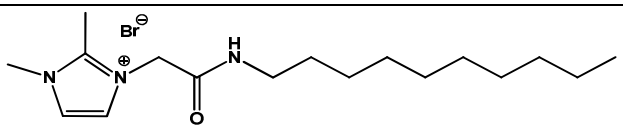
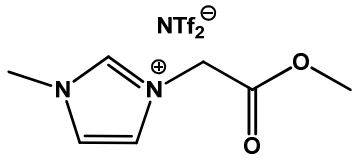
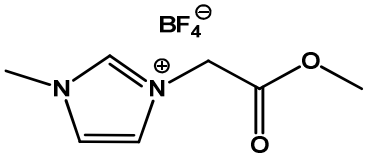
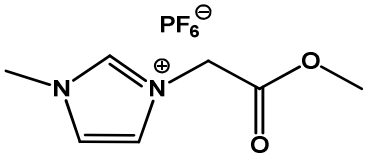
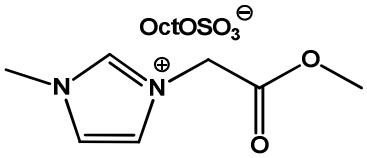
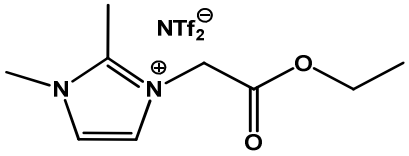
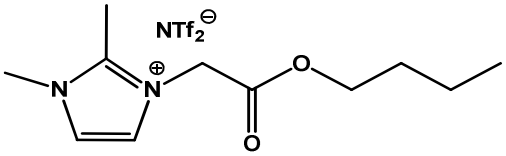
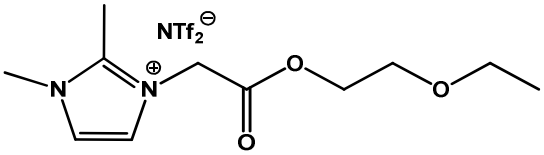
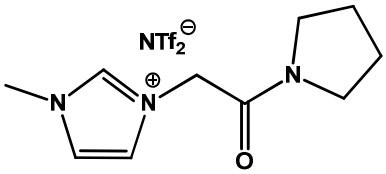
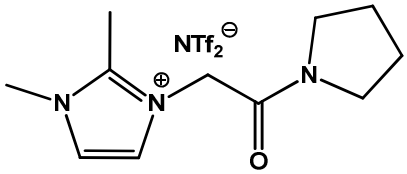
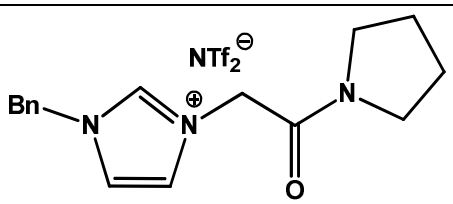
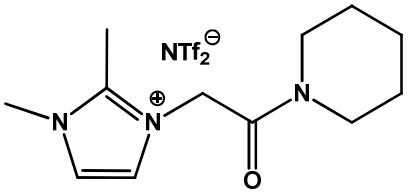
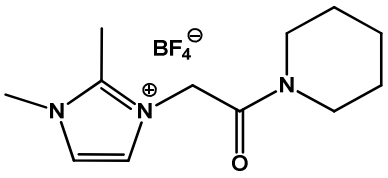
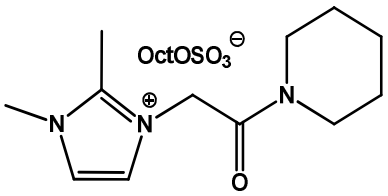
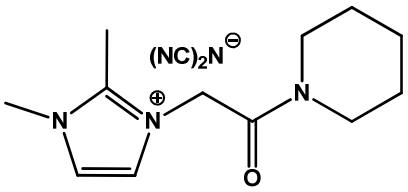
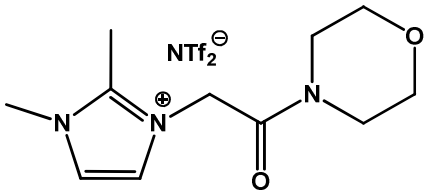
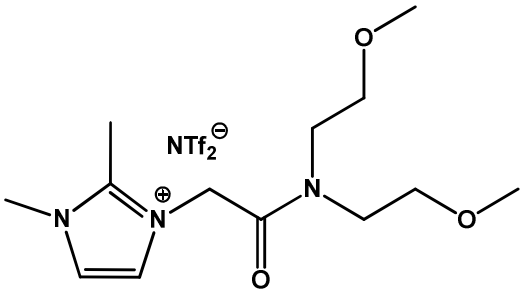
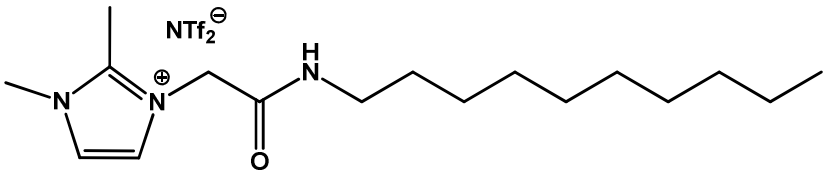
Ionic liquids	Compound No.	Yield
	**8**	96
	**9**	95
	**10**	61
	**11**	71
	**12**	94
	**13**	71
	**14**	76
	**15**	56
	**16**	77
	**17**	85
	**18**	67

Table 2.3: Results obtained for counter ion exchange reactions

Ionic liquids	Compound No.	Yield
	**19**	70
	**20**	95
	**21**	95
	**22**	64
	**23**	85
	**24**	91
	**25**	49
	**26**	69
	**27**	75
	**28**	86

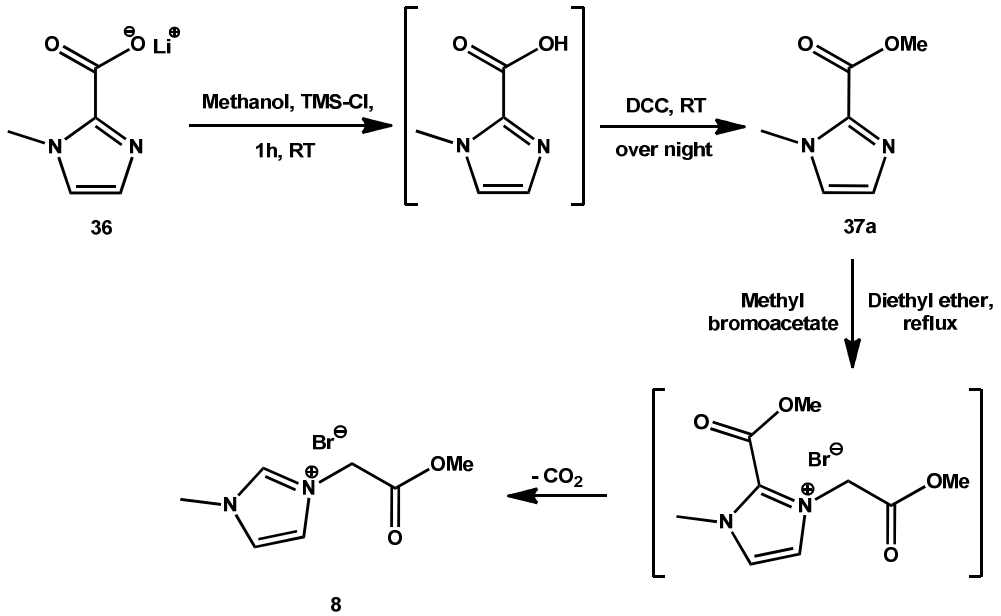
	**29**	95
	**30**	100
	**31**	79
	**32**	99
	**33**	85
	**34**	68
	**35**	95

2.2.2 Synthesis of Modified Imidazolium Ionic Liquids:

Biodegradation studies of pyridinium-based ionic liquids have shown that esters at either the 1 or 3-position have a beneficial effect on degradation of the heterocyclic core, independent of the anion.[6] Such incorporation of ester substitution onto the

imidazole ring could help to increase biodegradability of imidazolium cation as a result. The 2-position was selected while the 4 and 5-position derivatives were examined by other group members. Also, substitution at the 2-position of 1-methylimidazole, with electron-withdrawing groups, had the potential to increase catalytic activity in acetalisation reactions.[7]

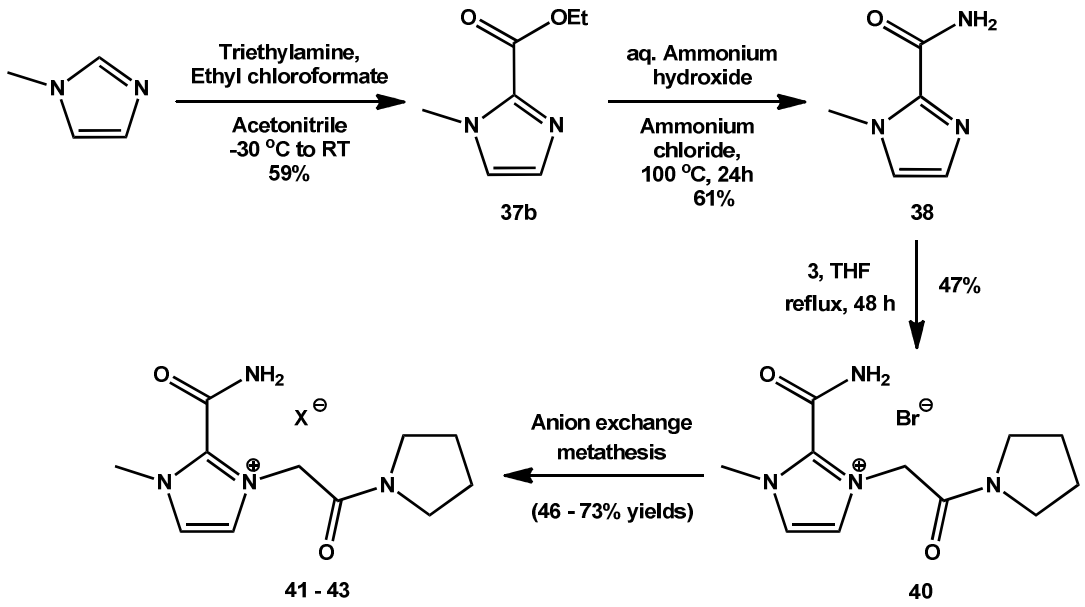
The commercially available lithium salt of 1-methylimidazole-2-carboxylic acid (**36**) was subjected to esterification under reflux conditions with methanol. However, decarboxylation was observed because of the favorability of carbene formation. To prevent decarboxylation milder coupling conditions were investigated. One equivalent of trimethylsilyl chloride (TMS-Cl) in methanol was used to convert **36** into the carboxylic acid followed by esterification using *N,N′*-dicyclohexylcarbodiimide.[8] Under these conditions, the methyl ester at the 2-position was isolated, albeit in very low yield (10%), as difficulties were encountered in separating the product from dicyclohexyl urea. The product was unstable and was found to undergo decarboxylation within 2-3 days while standing on the bench in air. Synthetic routes were continued by alkylation at the 3-position with methyl bromoacetate at room temperature and then under reflux. The white powder precipitate from the solution was found to be decarboxylated ionic liquid **8** (Scheme 2.2).



Scheme 2.2: Attempt to synthesis of IL with 2-position ester substituted imidazole

As the 1*H*-Imidazole-2-carboxylic acid, 1-methyl-, methyl ester (**37a**) was unstable, the 1*H*-Imidazole-2-carboxylic acid, 1-methyl-, ethyl ester (**37b**) reported by Krowicki[9a] was synthesized by treating 1-methylimidazole with ethyl chloroformate in the presence of triethylamine. The product (**37b**) thus obtained was subjected to alkylation with

methyl bromoacetate. But again decarboxylation was observed as before to the extent of 50%. Next the more stable primary amide (**38**) was prepared by heating the 2-ethyl ester (**37b**) to 100 °C with an aqueous ammonium hydroxide and ammonium chloride (5 mol-%) as a catalyst under atmospheric pressure. The product (**38**) precipitated from the reaction mixture as needle shaped crystals when cooled to the room temperature.[9]

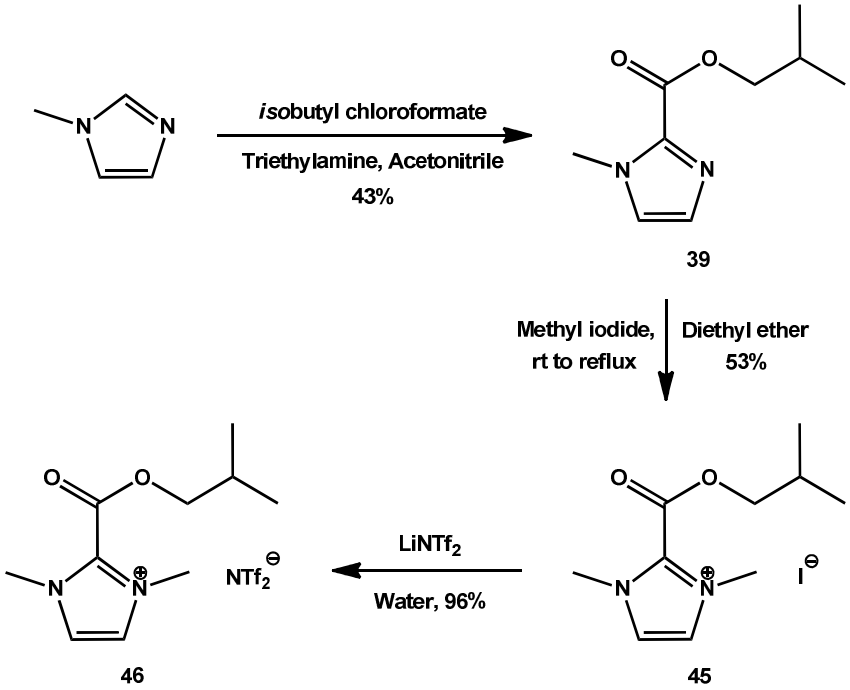


Scheme 2.3: Synthesis of 2-position amide substituted ionic liquid

N-alkylation of the imidazole **38** by methyl bromoacetate gave the required product (**44**) as a pink powder in 17% yield (not shown in Scheme 3, see Table 4). However, alkylation with α-bromoamides **3** was more efficient, giving the pyrrolidine amide side chain product (**40**) as a white powder in 47% yield. Anion exchange of **40** with sodium tetrafluoroborate, lithium *bis*(trifluoromethanesulfonimide) and sodium octylsulfate gave tetrafluoroborate (BF_4^-) **42**, *bis*(trifluoromethanesulfonimide) (NTf_2^-) **41**, and octyl sulfate ($OctOSO_3^-$) **43** salts, respectively. Both NTf_2^- and $OctOSO_3^-$ anion exchange were carried out in water, where as tetrafluoroborate anion exchange was carried out in ethanol. (Scheme 2.3)

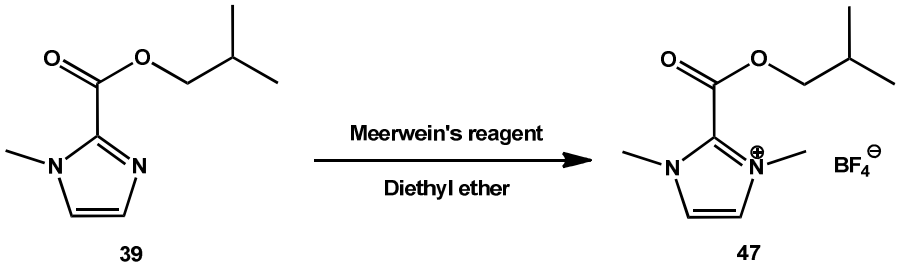
The reaction scope and stabilities of these amide ionic liquids would later be compared with similar ester ionic liquids. With this objective in mind, the hindered *iso*butyl ester was synthesized. However, due to its steric bulk, the *iso*butyl ester rendered the imidazole difficult to alkylate using methyl bromoacetate, and no alkylation was observed even after reflux in toluene. To overcome this difficulty, the less hindered alkylating agent methyl iodide was selected. At room temperature no product formed, then at reflux in diethyl ether which gave the product **45** as a white solid in 53% yield. (Scheme 2.4) Anion exchange was carried out using aqueous lithium

bis(trifluoromethanesulfonimide) to give the NTf_2^- salt as a pale yellow solid (**46**) in 96% yield.



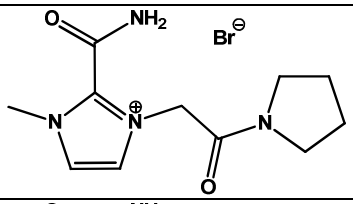
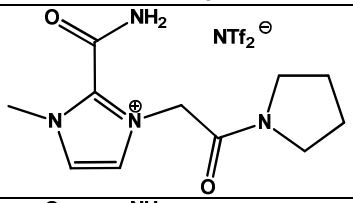
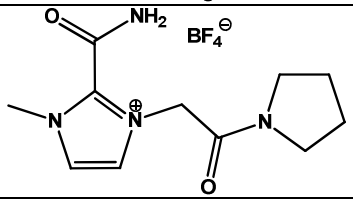
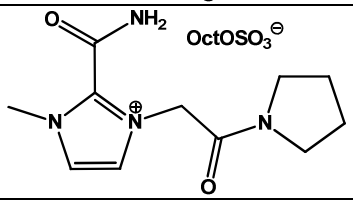
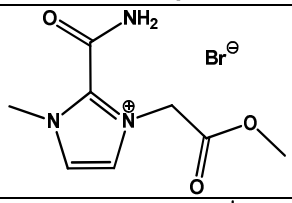
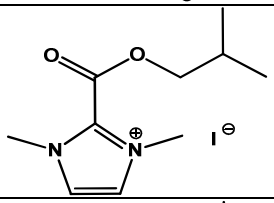
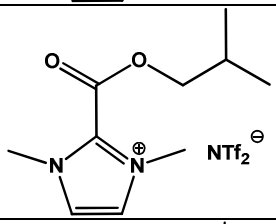
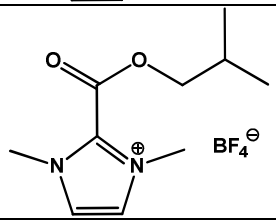
Scheme 2.4: Synthesis of 2-position ester substituted Iodide and NTf_2^- salts

Instead of exchanging the iodide to the tetrafluoroborate salt, imidazole **39** was directly reacted with Meerwein's salt i.e. trimethyloxonium tetrafluoroborate to give tetrafluoroborate salt **47** in excellent yield (97%).[10] This reaction was performed in diethyl ether at room temperature. (Scheme 2.5) Product separation and purification was easily completed with (2 x 10 mL) diethyl ether washes.



Scheme 2.5: Synthesis of BF_4 ionic liquid **47** by excluding an extra step

Table 2.4: 2-position substituted imidazolium based ionic liquids

Ionic liquids	Compound No.	Yield (%)
	**40**	47
	**41**	73
	**42**	62
	**43**	46
	**44**	17
	**45**	62
	**46**	96
	**47**	97

2.2.3 Synthesis of Chiral Ionic Liquids (CILs):

As a part of the project and as part of the studies for toxicity of Ionic Liquids (ILs), some chiral ionic liquids (CILs) previously synthesized within the group were reproduced.[11] The original aim was to study the toxicity of these ionic liquids as a chiral solvents in asymmetric catalysis reactions. All those ionic liquids synthesised are as follows:

Table 2.5: Mandelate/Lactate derivatives with bromide salts

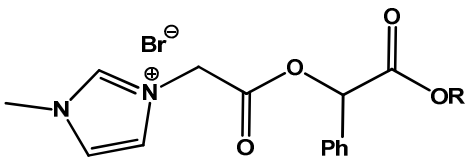
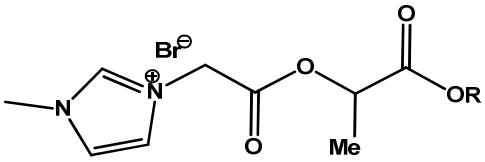
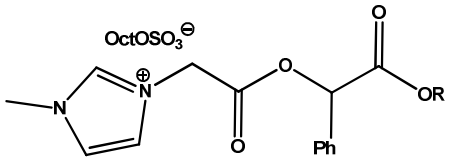
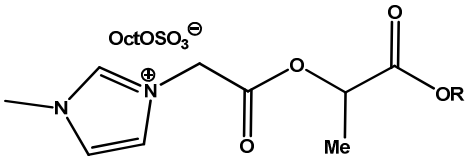
Mandelate derivatives	**IL No.**	**R**	**Configuration**
	**48**	CH_3	*RS*
	49	CH_3	*R*
	50	CH_3	*S*
	51	C_5H_{11}	*RS*
	52	C_5H_{11}	*R*
	53	C_5H_{11}	*S*
	54	$C_2H_4OC_2H_5$	*RS*
	55	$C_2H_4OC_2H_5$	*R*
	56	$C_2H_4OC_2H_5$	*S*
Lactate derivatives	**IL No.**	**R**	**Configuration**
	**57**	$C_2H_4OC_2H_5$	*RS*
	58	C_5H_{11}	*S*
	59	$C_2H_4OC_2H_5$	*S*

Table 2.6: Mandelate/Lactate derivatives with octyl sulfate salts

Mandelate derivatives	IL no.	R	Configuration
	**60**	CH_3	*RS*
	61	CH_3	*R*
	62	CH_3	*S*
	63	C_5H_{11}	*RS*
	64	C_5H_{11}	*R*
	65	C_5H_{11}	*S*
	66	$C_2H_4OC_2H_5$	*RS*
	67	$C_2H_4OC_2H_5$	*R*
	68	$C_2H_4OC_2H_5$	*S*
Lactate derivatives	**IL no.**	**R**	**Configuration**
	**69**	$C_2H_4OC_2H_5$	*RS*
	70	C_5H_{11}	*S*
	71	$C_2H_4OC_2H_5$	*S*

2.3 Conclusion:

A range of imidazolium ionic liquids, with ester and amide side chains and their intermediates, were designed and prepared in order to use them in acetalisation and Carbonyl-Ene reactions. Concern about the stability of ester side chain ionic liquids, some amide side chain ionic liquids were also designed and synthesized. A variety of *α*-bromoesters and *α*-bromoamides (**1-7**) were prepared followed by preparation of respective bromide salts by using 1-methyl/benzyl and 1,2-dimethyl imidazoles (**8-18**). In order to use these ionic liquids in organic synthesis, the physico-chemical properties were altered by anion exchange metathesis (**19-35**). In order to increase the biodegradation, ester and amide substituted derivatives at C-2 position of imidazole ring was designed and synthesized successfully (**40-47**). All the novel compounds prepared were characterized by using a range of spectroscopic techniques such as ^{1}H-NMR, ^{13}C-NMR, LC-MS, HR-MS and IR.

2.4 References:

1. (*a*) J. Ranke, S. Stolte, R. Stormann, J. Arning, B. Jastorff, *Chem. Rev.*, 2007, **107,** 2183-2206; (*b*) J. Ranke and B. Jastorff, *Environ. Sci. Pollut. Res.*, 2000, **7**, 105-114; (c) D. Coleman and N. Gathergood, *Chem. Soc. Rev.*, 2010, **39**, 600-637
2. P. Wasserscheid and T. Welton (Eds.), *Ionic liquids in synthesis*, Wiley-VCH, 2003
3. (*a*) N.Gathergood and P. J. Scammells, *Aust. J. Chem.*, 2002, **55**, 557-560; (*b*) M. T. Garcia, N. Gathergood, P. J. Scammells, *Green Chem.*, 2004, **6**, 166-175; (*c*) M. T. Garcia, N. Gathergood, P. J. Scammells, *Green Chem.*, 2005, **7**, 9-14; (*d*) N. Gathergood, P. J. Scammells, M. T Garcia, *Green Chem.*, 2006, **8**, 156-160
4. S. Morrissey, B. Pegot, D. Coleman, M. T. Garcia, D. Ferguson, B. Quilty, N. Gathergood, *Green Chem.*, 2009, **11**, 475-483
5. (a) L. Carson, P. Chau, M. Earle, M. Gilea, B. Gilmore, S. Gorman, M. McCann, K. Seddon, *Green Chem.*, 2009, **11**, 492-497 (b) K. M. Docherty and C. F. Kulpa, Jr., *Green Chem.*, 2005, **7**, 185-189. (c) R. J. Bernot, M. A. Brueseke, M. A. Evans-White, G. A. Lamberti, *Environ. Toxicol. Chem.*, 2005, **24**, 87-92. (d) R. J. Bernot, E. E. Kennedy, G. A. Lamberti, *Environ. Toxicol. Chem.*, 2005, **24**, 1759-1765. (e) R. P. Swatloski, J. D. Holbrey, S. B. Memon, G. A. Caldwell, K. A. Caldwell, R. D. Rogers, *Chem. Commun.*, 2004, 668-669. (f) C. Pretti, C. Chiappe, D. Pieraccini, M. Gregori, F. Abramo, G. Monni, L. Intorre, *Green Chem.*, 2006, **8**, 238-240. (g) T. P. T. Pham, C. W. Cho, J. Min, Y. S. Yun, *J. Biosci. Bioeng.*, 2008, **105**, 425-428
6. J. Harjani, R. Singer, M. T. Garcia, P. Scammells, *Green Chem.*, 2009, **11**, 83-90
7. L. Myles, R. Gore, M. Spulak, N. Gathergood, S. Connon, *Green Chem*., 2010, **12**, 1157-1162
8. B. Neises and W. Steglich, *Angew. Chem., Int. Ed.,* 1978, **17**, 522-24
9. (a) Krzysztof Krowicki and J. William Lown, *J. Org. Chem.,* 1987, **52**(16), 3493-3501, (b) David D. Davey, *J. Org. Chem.*, 1987, **52**(19), 4379-4381
10. M. Egashira, Y. Yamamoto, T. Fukutake, N. Yoshimoto, M. Morita, *J. Fluorine Chem.*, 2006, **127**, 1261-1264
11. S. Morrissey, Thesis - '*Environmentally-Benign Imidazolium Based Ionic Liquids: Synthesis, Characterisation and Applications in Hydrogenation Reactions*', Dublin City University, 2008

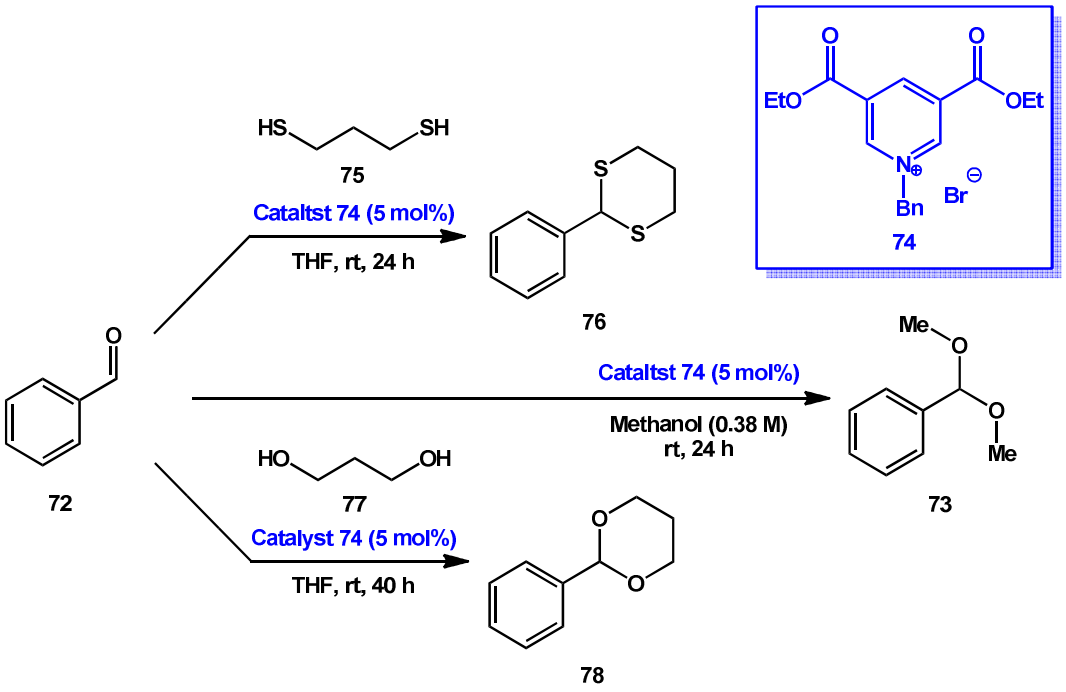
Chapter 3: Results and Discussion

Applications of Ionic Liquids in Acetalisation Reaction

3.0 Applications of Ionic Liquids in Acetalisation Reactions:

3.1 Rationale:

Connon and co-workers reported an application of pyridinium salts as effective catalysts of acetalisation reactions.[1] An ester group at either the 3 or both the 3 and 5 positions of the pyridinium ring has shown excellent catalytic activity with very low catalyst loading in the acetalisation of benzaldehyde with methanol. Interestingly, the catalyst is not acidic in nature, but can act as a Brønsted acid in the presence of protic media. The most active catalyst Pyridinium, 3,5-*bis*(ethoxycarbonyl)-1-(phenylmethyl) bromide showed excellent catalytic activity in the protection of a variety of aldehydes with methanol and was also found to be useful in diol and dithiol protections as shown in Scheme 3.1. Its catalytic activity was predicted to occur through nucleophilic attack of the alcohol to the pyridinium to generate Brønsted acidic species.



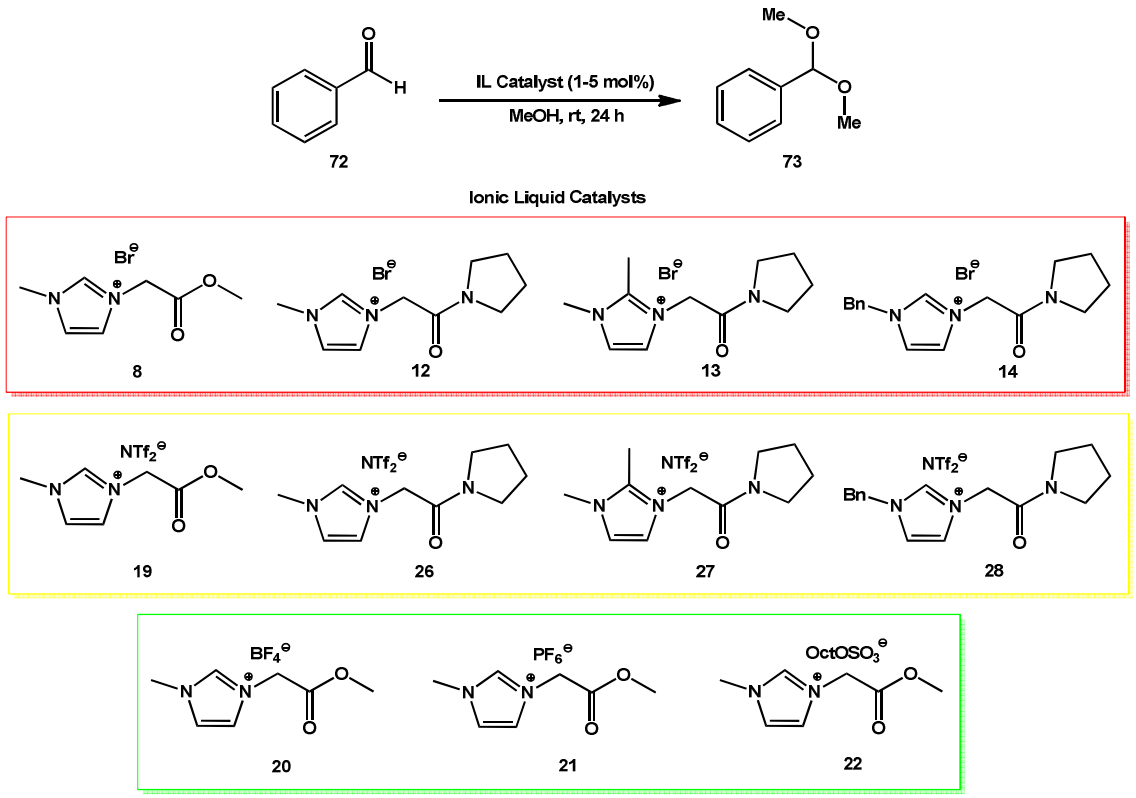
Scheme 3.1: Acetalisation of Benzaldehyde (**72**) with Methanol Catalysed by Pyridinium ionic liquid (**74**)

On the basis of these studies, imidazolium ionic liquid catalysts for acetalisation reactions have been designed.

3.2 Results and discussion:

3.2.1 1st Generation Imidazolium Catalyst for Acetalisation Reactions

A range of ester and amide side chain imidazolium ionic liquids were prepared. The catalytic activity of all these imidazolium salts was evaluated by their performance in the acetalisation of benzaldehyde in methanol (Scheme 3.2). In the absence of catalyst acetalisation was not found to occur after 24 hours. Each of the bromide salts showed poor catalytic activity, independent of ester or amide side chain (9% to 13% conversions) and 1,2-dimethylimidazolium and 1-benzylimidazolium cations did not demonstarte any significant effect. When the anion, *bis*(trifluoromethanesulfonimide) was used, conversions using amide side chain ionic liquids were increased marginally (up to max. 29%), whereas ester side chain ionic liquids (**19**) with the NTf_2 anion gave 51% conversion.



Scheme 3.2: Acetalisation of Benzaldehyde using ionic liquid as a Catalyst [Red (**9-13**), Amber (**23-51**) and Green (**12-85**)]

The BF_4^- salt of the methyl ester side chain imidazolium cation (**20**) gave the highest conversion, 85%, to the required product. Hexafluorophosphate (PF_6^-) and octyl sulfate ($OctOSO_3^-$) anions performed poorly in this reaction with 33% (**21**) and 12% (**22**) yields obtained respectively (Table 3.1). Hence anion exchange from Br^- to BF_4^- greatly influenced the acetalisation of benzaldehyde with methanol.

Table 3.1: Results of the Acetalisation of Benzaldehyde using ionic liquid as a Catalyst

Entry	IL Catalyst	Loading (mol %)	Conversion (%)
1	**8**	5	11
2	**12**	5	13
3	**13**	5	11
4	**14**	5	9
5	**19**	5	51
6	**26**	5	23
7	**27**	5	27
8	**28**	5	29
9	**20**	5	85
10	**21**	5	33
11	**22**	5	12

One of the important characteristics of this ionic liquid catalyst was its lack of acidity which eliminates handling hazards. It was proposed that, the catalyst was able to generate an active Brønsted acidic species, but only in the presence of a protic medium (Fig. 3.1). In the presence of methanol, methanol probably attacks the 2-position of the imidazole, as it is the most electron deficient, to generate the Brønsted acid HBF_4.

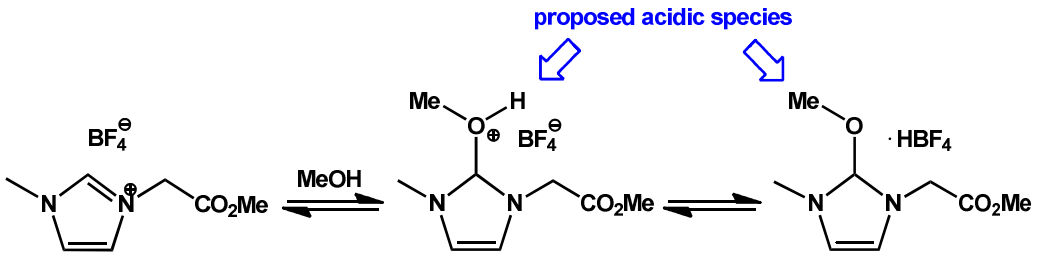
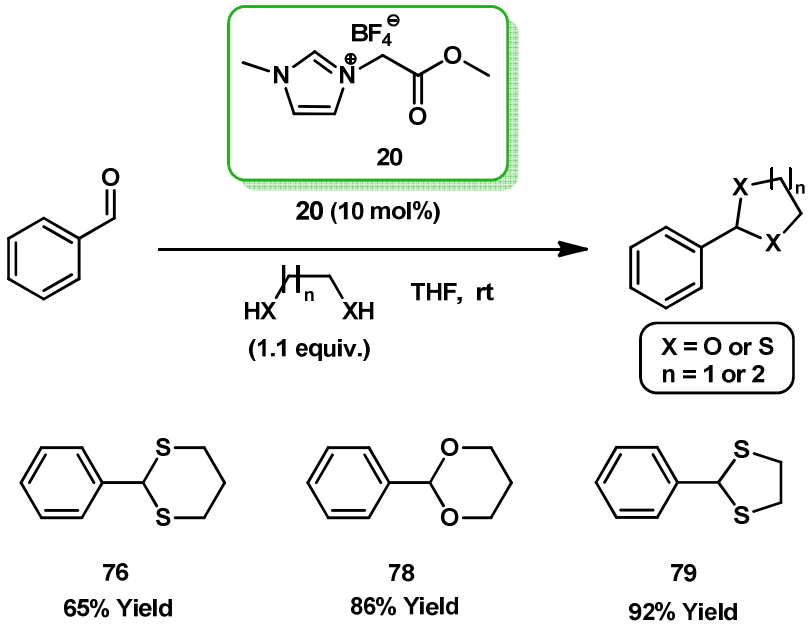


Fig. 3.1: Proposed Mode of Action of Catalytic Aprotic Imidazolium Ions

The most active catalyst **20**, was further studied in the acetalisation of a variety of aldehydes with methanol at room temperature. These reactions showed good to excellent conversions with 5-10% catalyst loading. The saturated aldehyde 3-phenylpropanal reacted with deuterated methanol in the presence of 1 mol% catalyst and gave quantitative conversion in only 1 minute and the diol and dithiol protection of benzaldehyde also showed very good results.



Scheme 3.3: Diol/dithiol Protection of Benzaldehyde

The BF_4^- catalyst **20** promoted protection of benzaldehyde with 1,2-ethanedithiol and gave 92% conversion (**79**), whereas 1,3-propanedithiol and 1,3-propanediol gave **76** (65% conversion) and **78** (86% conversion) respectively (Scheme 3.3). Recyclability evaluation of the most active BF_4 anion catalyst **20** was performed using the 1,3-dithiolane protection of benzaldehyde. After 24h of reaction, hexane was added in order to precipitate the catalyst from the reaction mixture and the dissolved product could then be decanted in order to isolate the catalyst. The catalyst was further dried using rotary evaporation and in vacuo to remove water and could then be further used in another reaction. Catalyst **20** was recycled and reused 15 times without any significant decrease in activity (Fig. 3.2).

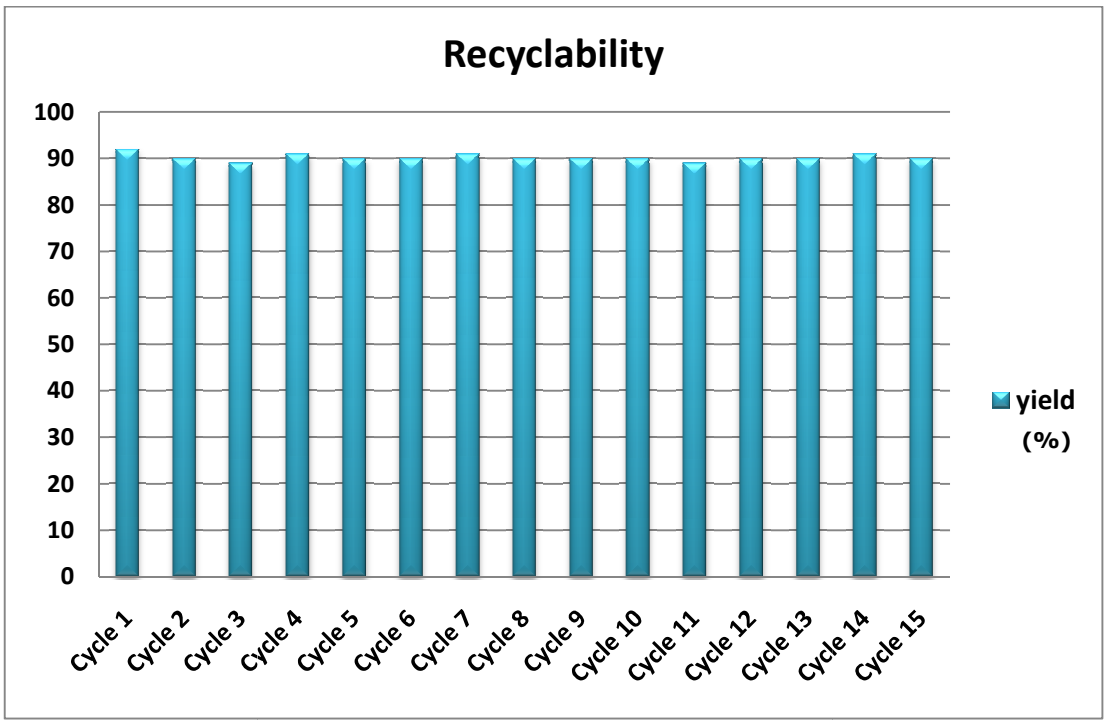
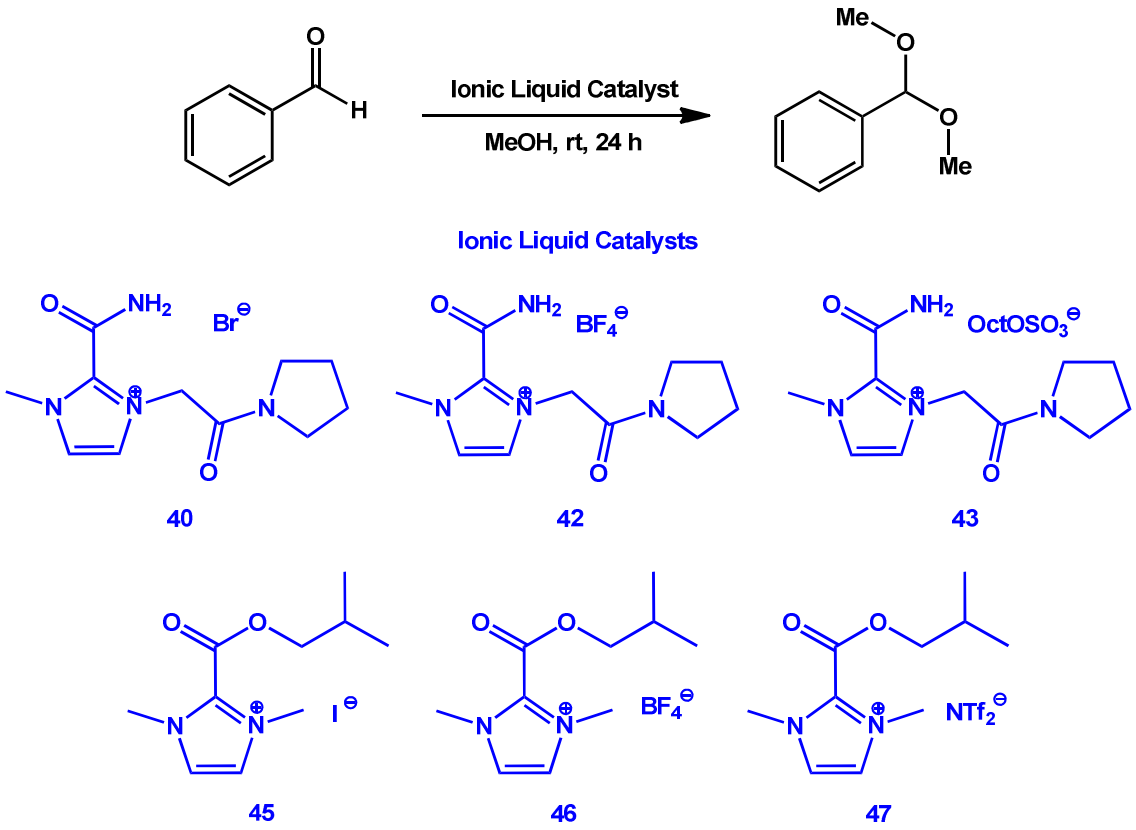


Fig. 3.2: Recyclability of Ionic Liquid Catalyst **20**

3.2.2 2nd Generation Imidazolium Core Modified Catalysts for the Acetelisation Reactions

Biodegradation studies of pyridinium-based ILs have shown that ester substitution at either the 1 or 3 position has a beneficial effect on the degradation of the heterocyclic core, regardless of the anion.[2] Also, biodegradation studies published have shown that only the side chain of the imidazolium ionic liquids undergo degradation, whereas the imidazole core was found to persist in most of the OECD tests.[3] Hence, in an effort to increase the biodegradation, ester substitution of the imidazole ring was designed. Also incorporation of electron withdrawing groups via ester substitution of the imidazole ring was expected to increase catalytic activity of the ionic liquids in the acetalisation reaction. A series of ester and amide substituted derivatives at the C-2, C-4 and both the C-4 and C-5 positions of the imidazolium ionic liquids were designed, prepared and tested using the acetalisation of benzaldehyde with methanol.[4,5] We have completed the study on C-2 substituted imidazolium ionic liquids. Synthesis and catalytic study of C-4 and C-4 and C-5 di-subtituted imidazolium ionic liquids was performed by another co-worker.



Scheme 3.4: Acetalisation of Benzaldehyde using modified imidazolium ionic liquid

Table 3.2: Acetalisation of Benzaldehyde using modified imidazolium ionic liquid as a Catalyst

Entry	Ionic Liquid Catalyst	Loading (mol %)	Conversion (%)
1	**42**	10	94
2	**46**	10	99
3	**40**	1	83
4	**42**	1	86
5	**43**	1	80
6	**45**	1	86
7	**46**	1	91
8	**47**	1	85
9	**46**	0.1	72

Ester and amide substitution at the C-2 position of imidazolium ionic liquids (Scheme 3.4) has been found to greatly increase the catalytic activity. At the starting point of the catalyst screening process, BF_4^- salts of both ester and amide substituted ionic liquids

were selected as catalysts in the acetalisastion of benzaldehyde. Catalyst **42** with amide substitution at the C-2 position showed 94% conversion, whereas ester substituted ionic liquid **46** gave quantitative conversion (Table 3.2). Furthermore, all C-2 substituted ionic liquid catalysts were tested at 1 mol% loading for the acetalisation of benzaldehyde and when the amount of the catalyst **46** was decreased to 0.1 mol%, conversion decreased to 72% (Entry 9, Table 3.2). This can be supported by the proposed mode of action (Fig. 3.1). C-2 substituted ionic liquids are more sterically hindered which may account for this drop in yield. Almost all C-4 and C-5 di-subtituted imidazolium ionic liquid catalysts have shown quantitative conversions with 1 mol% catalyst loading.

3.3 Conclusion:

In conclusion, we have designed a small library of aprotic ionic liquid catalysts which can behave as Brønsted acids in a controlled fashion without requiring the same precautions usually associated with the storage and use of strongly acidic substances. The anion exchange study has demonstrated that counterion exchange of the ionic liquid from Br^- to BF_4^- dramatically increases catalytic activity. The most active catalyst developed **20** promotes acetalisation and thioacetalisation reactions of a range of aldehydes at room temperature and low catalyst loading (5 mol%), and after the reaction the catalyst can be recovered by the simple addition of hexane and decanting the product. The recycled catalyst can then be used in 15 iterative recycles without any discernible loss of catalytic activity. Hence our hypothesis of the introduction of electron withdrawing functional groups to the imidazolium ring to increase the catalytic activity of imidazolium ionic liquids has been proved.

In order to increase the catalytic activity and reduce catalyst loading, 2nd generation ionic liquid catalysts with electron withdrawing functional groups were designed and prepared. Each of these 2nd generation imidazolium core modified ionic liquid catalysts has resulted in comparative conversions to the 1st generation catalyst **20** even at 1 mol% catalyst loading. Although no significant effect of anions was observed in these studies, catalyst **46** with BF_4^- anion showed the highest conversion (91%) amongst all 2nd generation ionic liquid catalysts. Further reduction of the loading of catalyst **46** to 0.1 mol% was found to decrease the conversion to 72%.

3.4 References:

1. B. Procuranti, S. J. Connon, *Chem. Commun.* 2007, 1421-1423, B. Procuranti and S. J. Connon, *Org. Lett.*, 2008, **10**, 4935-4938, B. Procuranti, L. Myles, N. Gathergood, S. J. Connon, *Synthesis*, 2009, **23**, 4082-4086
2. J. Harjani, R. Singer, M. T. Garcia and P. Scammells, *Green Chem.*, 2009, **11**, 83-90
3. S. Stolte, S. Abdulkarim, J. Arning, A. Blomeyer-Nienstedt, U. Bottin-Weber, M. Matzke, J. Ranke, B. Jastorff, J. Thoeming, *Green Chem.*, 2008, **10**, 214-224
4. L. Myles, R. G. Gore, N. Gathergood, S. J. Connon, 2012, submitted
5. R. G. Gore, L. Myles, M. Spulak, T. M. Garcia, S. J. Connon, N. Gathergood, 2012, submitted

Chapter 4: Results and Discussion

Applications of Ionic Liquids in Carbonyl-Ene Reaction of Phenylglyoxal

4.0 Applications of Ionic Liquids in Asymmetric Carbonyl-Ene Reaction of Phenylglyoxal

4.1 Rationale:

As an atom-economic reaction and one of the most reliable, convenient processes for generating homoallylic alcohols, which are important building blocks for the synthesis of many natural products and pharmaceutical compounds,[1,2] the enantioselective carbonyl-ene reaction has gained much attention in the past two decades.[3] A wide variety of metal complexes have been investigated as chiral Lewis acid catalysts for the asymmetric carbonyl-ene reaction. The achievement of high enantioselectivity has been reported, for instance, in 1988 Yamamato presented the first asymmetric carbonyl-ene reaction using modified Al-BINAP complexes,[4] subsequently Mikami and other groups developed the Ti-BINOL catalysts,[5] whilst Evan and co-workers reported that both Cu-Box[6] and Sc-PyBox[7] are efficient catalysts for this reaction. Other metal complexes derived from Pd and Pt,[8] Co,[9] Ni,[10] Cr,[11] In,[2] and several lanthanides[12] were also used to catalyze the asymmetric carbonyl-ene reaction. These studies mainly focused on glyoxylate with only a few examples of highly enantioselective carbonyl-ene reactions using arylglyoxal derivatives reported. For example, Yamada and co-workers obtained high enantioselectivities of up to 95 % for the reaction between phenylglyoxal and α-methylstyrene catalyzed by optically active 3-oxobutylideneaminatocobalt(III) complexes.[9b] Luo and co-workers described the palladium(II)-BINAP-catalyzed enantioselective carbonyl-ene reactions between ten arylglyoxals and five alkenes. These catalysts were demonstrated to give high enantioselectivities of up to 93.8%.[8l] Recently, they obtained excellent enantioselectivities with *ee* values as high as 99.0% albeit in low yields for the carbonyl-ene reaction between phenylglyoxal and alkenes with Pd(II)-BINAPHANE catalyst.[8m] In 2008, Feng and co-workers presented excellent enantioselectivities of up to 99% *ee* for a broad range of substrates including aromatic and aliphatic glyoxal derivatives with various alkenes using a novel and efficient chiral catalyst system based on *N*,*N*′-dioxide-nickel(II) complexes.[10]

Although the chiral transition metal complexes in asymmetric catalysis have the evident advantages of giving high enantioselectivity, they are very expensive. Therefore, recycling these catalysts has attracted great interest in industrial applications. Immobilization of chiral catalysts on solid supports or polymers is an example of how

to recover and reuse these catalysts.[13] However, sometimes solid support catalysts result in decreased enantioselectivity and/or activity. Recently, ionic liquids (ILs) have been shown to extend catalyst lifetime in a variety of asymmetric catalytic reactions such as dihydroxylation, Diels-Alder, allylic amination, hydrogenation, Michael, fluorination, epoxidation and Aldol,[14] facilitating product isolation by simple extraction using non-polar solvents or facile distillation. In enantioselective carbonyl-ene reactions between various alkenes and ethyl- or phenylglyoxal catalyzed by chiral platinum complexes, the *ee* obtained in 1-ethyl-2-methylimidazolium *bis*(trifluoromethanesulfonimide) i.e [EMIM][NTf_2] is higher (up to 95%) or at least, comparable to those obtained in dichloromethane.[8j] Recycling of the ionic liquid phase after three runs resulted in the same enantioselectivity but with decreased yields. Recently, Luo and coworkers reported that the chiral Lewis acid palladium(II) catalyst incorporating (R)-BINAP, which is a conformationally restricted chiral ligand, is very stable in ionic liquids 1-butyl-2,3-dimethylimidazolium *bis*(trifluoromethylsulfonimide) i.e. [BdMIM][NTf_2] and could be recycled 21 times with the retention of high enantioselectivity.

Our research effort is directed by the development of environmentally friendly ILs which can also offer performance advantages over established methods. In previous studies, these ILs have shown their performance in reactions such as Diels-Alder,[15] Hydrogenation,[15,16] and Acetalisation.[17] Herein, we present the 'Enantioselective Carbonyl-Ene Reactions of phenylglyoxals catalyzed by chiral Palladium(II)-BINAP catalyst in low toxicity Ionic Liquids'. The performance of these ionic liquids is investigated with comparison to conventional ILs and common organic solvents, as well as the recyclability of the catalyst/IL media.

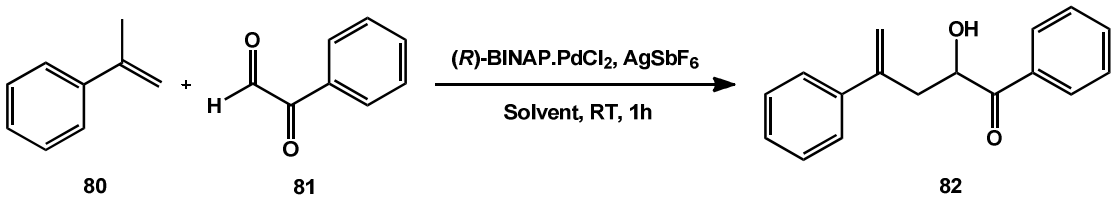
4.2 Results and Discussion:

4.2.1 Solvent effect:

The study of the effect of the solvent in carbonyl-ene reactions was carried out by the selection of a range of traditional molecular solvents along with ester and amide side chain ionic liquids. The enantiomeric excess of the product was measured using *high performance liquid chromatography* (HPLC) with the chiral column Lux Cellulose 2. Dichloromethane (DCM) is the commonly used solvent for carbonyl-ene reactions with the literature for this reaction in DCM reporting a yield of 40% and an ee of 80% (Table 4.1).[8l] For reference, the same reaction was carried out under the exact same conditions

and a yield of 53% and an ee of 77% was achieved. A similar absolute conformation (*S*) was also observed. [8m] Along with DCM some commonly used molecular solvents were also screened in these studies such as diethyl ether, tetrahydrofuran (THF) and toluene. Diethyl ether showed an increase in the enantiomeric excess with a slight decrease in the isolated yield, whereas toluene as a solvent showed a decrease in ee with comparison to DCM. The reaction in THF showed no product formation.

Table 4.1: Study of the effect of molecular solvents in the carbonyl-ene reaction

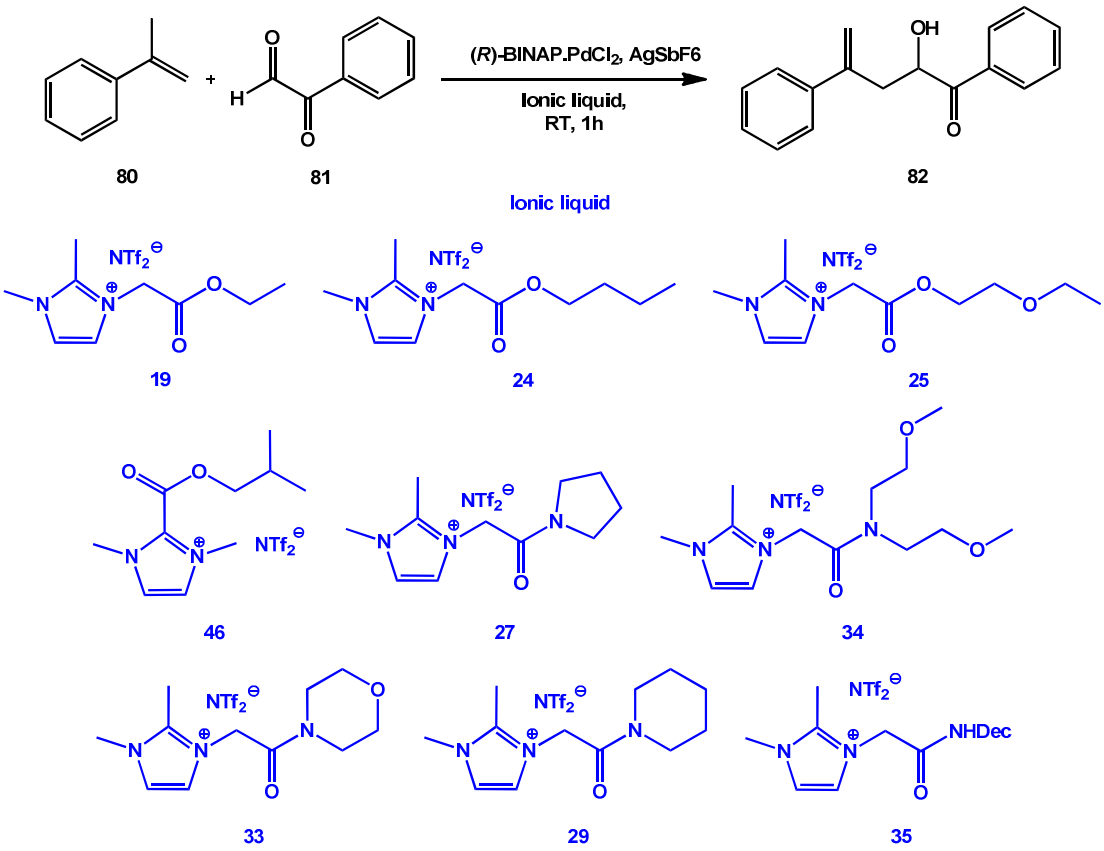


80 81 82

Entry	Solvent	Isolated Yield (%)	ee (%)[a]
1	Dichloromethane	53	77
2	Diethyl ether	49	83
3	Tetrahydrofuran	--	--
4	Toluene	52	70

Conditions: {[(*R*)-BINAP]Pd}$(SbF_6)_2$ (0.0125 mmol) phenylglyoxal monohydrate (0.25 mmol), α-methylstyrene (0.25 mmol), [a] The enantiomeric excess was determined by HPLC [column: Lux Cellulose 2, elution with a mixture of hexane/isopropanol 80/20, flow rate 1 mL/min, (*R*)-enantiomer rt_1:7.72 min. (minor), (*S*)-enantiomer rt_2: 11.14 min. (major), λ = 258 nm] (See Experimental Section)

A wide range of ester and amide side chain ionic liquids were used in this solvent study. Before using ionic liquids as a solvent in the carbonyl-ene reactions, the chiral palladium catalyst was pre-formed in dichloromethane by reacting (*R*)-BINAP.$PdCl_2$ with silver hexafluoroantimonate ($AgSbF_6$) for 30 minutes at room temperature. The orange coloured reaction mixture turned yellow after 30 minutes with a white precipitate of silver chloride (AgCl) on the wall of the round bottom flask. The catalyst, dissolved in dichloromethane, was then filtered through cotton wool into a round bottomed flask containing the ionic liquid in order to remove any AgCl. The DCM was then removed by rotary evaporation and the catalyst further dried under high vacuum. The ionic liquid and catalyst mixture could then be used in the carbonyl-ene reaction.



Scheme 4.1: Ionic liquids as a solvent in carbonyl-ene reaction

Table 4.2: Study of the effect of ionic liquids (Scheme 4.1) as a solvent in carbonyl-ene reaction

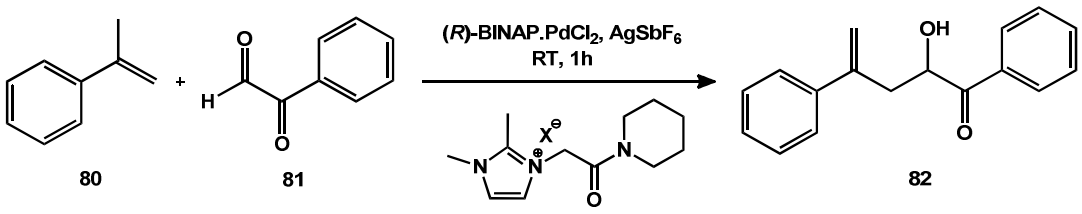
Entry	Ionic liquid as a solvent	Isolated Yield (%)	ee (%)[a]
1	**19**	69	79
2	**24**	70	81
3	**25**	70	80
4	**46**	68	77
5	**27**	67	78
6	**34**	65	68
7	**33**	67	78
8	**29**	65	79
9	**35**	61	78

Conditions: IL (0.25 mmol), {[(*R*)-BINAP]Pd}$(SbF_6)_2$ (0.0125 mmol) phenylglyoxal monohydrate (0.25 mmol), α-methylstyrene (0.25 mmol), [a] The enantiomeric excess was determined by HPLC [column: Lux Cellulose 2, elution with a mixture of hexane/isopropanol 80/20, flow rate 1 mL/min, (*R*)-enantiomer rt_1:7.72 min. (minor), (*S*)-enantiomer rt_2: 11.14 min. (major), λ = 258 nm] (See Experimental Section)

These reactions in ionic liquids have shown exciting results with enhanced product formation. [BdMIM][NTf_2] was used in this reaction and found to give high ee with moderate isolated yields, whereas ester/amide side chain ionic liquids have given comparable ee with an increase in yields.[8l] Among all ionic liquids screened in this reaction, butyl ester side chain ionic liquid **24** (Entry 2, Table 4.1) served as the best solvent. In general, ester side chain ionic liquids (Scheme 4.1) performed better than amide side chain ionic liquids in the solvent study. Also absolute conformation '*S*' was obtained, which was reported for the catalyst (in DCM) in the literature.[8l] Enantiomeric excess was similar within the limits of error (exception Entry 6, Table 4.2) irrespective of ester/amide side chain. Amongst the ethyl, butyl and ethoxyethyl ester side chain ionic liquids, the butyl ester side chain ionic liquid facilitated the most smooth reaction and subsequent product separation which can be explained by its difference in viscosity with respect to the other two.

4.2.2 Influence of counterion:

Table 4.3: Study of anion effect in carbonyl-ene reaction



Entry	X	IL No.	Isolated Yield (%)	ee (%)[a]
1	NTf_2^-	**29**	65	79
2	Br^-	**15**	--	--
3	$N(CN)_2^-$	**32**	--	--
4	$OctOSO_3^-$	**31**	--	--
5	BF_4^-	**30**	--	--

Conditions: IL (0.25 mmol), {[(*R*)-BINAP]Pd}$(SbF_6)_2$ (0.0125 mmol) phenylglyoxal monohydrate (0.25 mmol), α-methylstyrene (0.25 mmol), [a] The enantiomeric excess was determined by HPLC [column: Lux Cellulose 2, elution with a mixture of hexane/isopropanol 80/20, flow rate 1 mL/min, (*R*)-enantiomer rt_1:7.72 min. (minor), (*S*)-enantiomer rt_2: 11.14 min. (major), λ = 258 nm] (See Experimental Section)

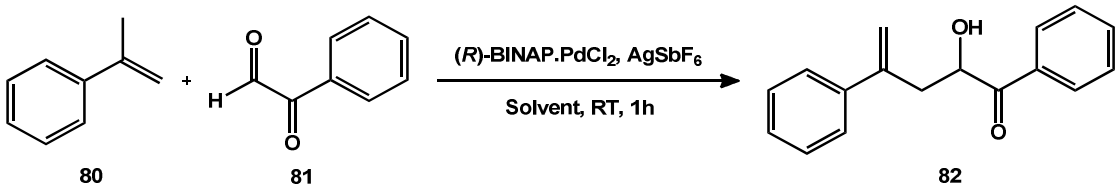
After investigating the effect of cation (Table 4.2) on the carbonyl-ene reaction, the effect of the anion on these reactions was studied. Ionic liquids with a piperidine amide side chain cation and some commonly used anions such as bromide (**15**), dicyanamide (**32**), octyl sulfate (**31**), and tetraflouroborate (**30**) were all used. All these ILs have been shown to have a detrimental effect on the reaction with no product formed (Entry 2-5, Table 4.3). This was possibly due to the Pd-catalyst being deactivated by the anion.

4.2.3 Optimization of reaction conditions

Optimization of the reaction conditions was carried out with both ester and amide side chain ILs in order to follow the trend and the effect of side chain. For this purpose, ionic liquids **24** and **29** (from Entry 2 & 8, Table 4.2) were selected in order to optimise the reaction conditions. Selection was based on observations such as smooth handling and viscosity which allows ease of product separation. A similar trend was observed by using ester and amide side chain ionic liquids in the optimization of reaction conditions (Table 4.4 and 4.5). A number of parameters such as the amount of ionic liquid, stoichiometric ratio of the substrates, temperature, amount of catalyst and time required for the reaction have been considered.

For the optimization of the reaction conditions using the ester side chain ionic liquid **24**, (Table 4.4) first of all the quantity of ionic liquid was reduced to half. This was due to the number of steps involved in the synthesis of the ionic liquid to restrict the unnecessary use of an excess amount of the ionic liquid. It was observed that the reaction mixture was difficult to stir, the effect of which being a significant decrease in the isolated yield, i.e. 56% along with a slightly decreased ee of 77% (Entry 1, Table 4.4). Changes in the stoichiometric ratio of the phenylglyoxal and α-methylstyrene did not show any enhancement in the formation of product. A slight increase in the isolated yield (73%) was observed after warming the reaction to 40 °C (Entry 5, Table 4.4), but ee was decreased to 77%. Further heating the reaction to 60 °C adversely affected the reaction with both the yield and ee showing a decrease to 49% and 70% respectively (Entry 6, Table 4.4). Extending the duration of the reaction time to 2h and 24h did not affect the ee but the yield dropped to 57% and 56% respectively (Entry 9 and 10, Table 4.4) with a large number of side products formed as observed by TLC.

Table 4.4: Optimization the reaction conditions with ester side chain ionic liquid (**24**)



80 81 82

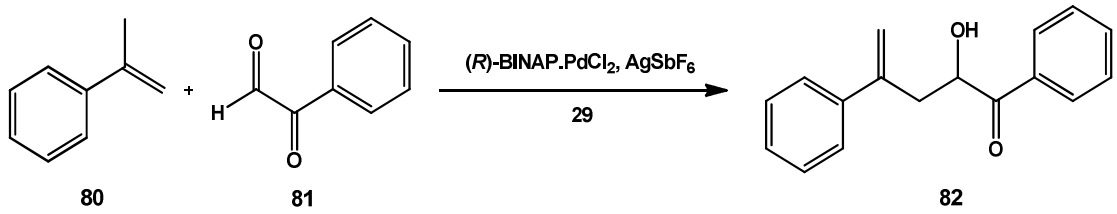
No	80	81	Catalyst	IL	Temperature	Time	Yield (%)	ee (%)[a]
1	1 eq	1 eq	0.05 eq	0.5 eq	25 °C	1 h	56	77
2	1 eq	1 eq	0.05 eq	1 eq	25 °C	1 h	70	81
3	2 eq	1 eq	0.05 eq	1 eq	25 °C	1 h	71	80
4	1 eq	2 eq	0.05 eq	1 eq	25 °C	1 h	68	80
5	1 eq	1 eq	0.05 eq	1 eq	40 °C	1 h	73	77
6	1 eq	1 eq	0.05 eq	1 eq	60 °C	1 h	49	70
7	1 eq	1 eq	0.02 eq	1 eq	25 °C	1 h	51	76
8	1 eq	1 eq	0.1 eq	1 eq	25 °C	1 h	54	78
9	1 eq	1 eq	0.05 eq	1 eq	25 °C	2 h	57	78
10	1 eq	1 eq	0.05 eq	1 eq	25 °C	24 h	56	78

[a] The enantiomeric excess was determined by HPLC [column: Lux Cellulose 2, elution with a mixture of hexane/isopropanol 80/20, flow rate 1 mL/min, (*R*)-enantiomer rt_1:7.72 min. (minor), (*S*)-enantiomer rt_2: 11.14 min. (major), $\lambda = 258$ nm]

In the optimization of reaction conditions using ionic liquid **29** (Table 4.5), the isolated yield of the product decreased to 57% when the amount of the IL used was reduced (Entry 1, Table 4.5). Again a difficulty in the stirring of reaction mass was observed. A slight increase in the yield (68%) was found when the amount of *α*-methylstyrene was doubled (Entry 3, Table 4.5) retaining the same ee. In contrast, the yield was decreased to 54% when the quantity of phenylglyoxal used was doubled (Entry 4, Table 4.5). No significant results were obtained by heating the reaction mixture at 40 and 60 °C. However, when the amount of catalyst was varied from 0.05 equivalents to 0.02 and 0.1 equivalents, the yield was decreased to 30% and 41% respectively (Entry 7 and 8 respectively, Table 4.5) without any substantial loss/gain in ee. In the case of 0.1 equivalents of catalyst, the reaction mass was found to be difficult to stir. Lengthening

the reaction time did not benefit the formation of product with the yield decreased to 52% after stirring the reaction for 1 day (Entry 10, Table 4.5).

Table 4.5: Optimization of reaction conditions with amide side chain ionic liquids (**29**)



80 81 82

Entry	80	81	Catalyst	IL	Temperature	Time	Yield (%)	ee (%)
1	1 eq	1 eq	0.05 eq	0.5 eq	25 °C	1 h	57	78
2	1 eq	1 eq	0.05 eq	1 eq	25 °C	1 h	65	79
3	2 eq	1 eq	0.05 eq	1 eq	25 °C	1 h	68	79
4	1 eq	2 eq	0.05 eq	1 eq	25 °C	1 h	54	78
5	1 eq	1 eq	0.05 eq	1 eq	40 °C	1 h	66	77
6	1 eq	1 eq	0.05 eq	1 eq	60 °C	1 h	62	75
7	1 eq	1 eq	0.02 eq	1 eq	25 °C	1 h	30	77
8	1 eq	1 eq	0.1 eq	1 eq	25 °C	1 h	41	79
9	1 eq	1 eq	0.05 eq	1 eq	25 °C	2 h	64	77
10	1 eq	1 eq	0.05 eq	1 eq	25 °C	24 h	52	77

[a] The enantiomeric excess was determined by HPLC [column: Lux Cellulose 2, elution with a mixture of hexane/isopropanol 80/20, flow rate 1 mL/min, (*R*)-enantiomer rt_1:7.72 min. (minor), (*S*)-enantiomer rt_2: 11.14 min. (major), $\lambda = 258$ nm]

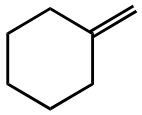
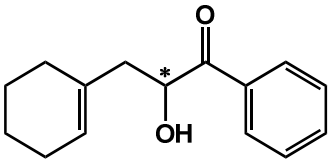
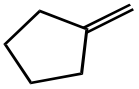
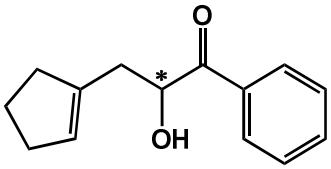
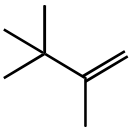
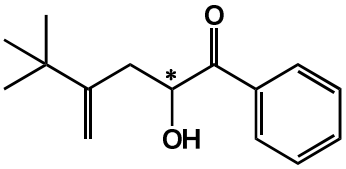
4.2.4 Studying of other substrates:

In order to evaluate the scope of the reactions which could be carried out, ionic liquid, **24** was chosen for use in the study with other substrates as it was found to be best of all the ionic liquids tested.

To this end, different types of alkenes, both cyclic and acyclic, were used. By replacing the bulky α-methylstyrene with methylenecyclohexane in the carbonyl-ene reaction of

phenylglyoxal, **86** was obtained with a moderate yield (62%), but the enantiomeric excess was increased to 85%, whereas methylenecyclopentane has given **87** with 76% yield and 86% ee (Entry 2, Table 4.6). An acyclic alkene such as 2,3,3-trimethyl-1-butene gave **88** with very high ee (93%), but with only 45% isolated yield (Entry 3, Table 4.6). The absolute configuration (*S*) was in good argument with the literature.[8m]

Table 4.6: Study of substrate scope in carbonyl-ene reaction

Entry	Alkene	Product	Yield (%)	ee (%)
1	 **83**	 **86**	62	85[a]
2	 **84**	 **87**	76	86[b]
3	 **85**	 **88**	45	93[c]

Conditions: IL **24** (0.25 mmol), {[(*R*)-BINAP]Pd}$(SbF_6)_2$ (0.0125 mmol) phenylglyoxal monohydrate (0.25 mmol), alkene (0.25 mmol), rt, 1h. [a] The ^1H NMR and ^{13}C NMR of the product were consistent with the reported data.[2] The enantiomeric excess was determined by HPLC: column Lux Cellulose 1, elution with a mixture of hexane/isopropanol 80/20, flow rate 1 mL/min, (*R*)-enantiomer rt_1:7.05 min. (minor), (*S*)-enantiomer rt_2: 11.67 min. (major), λ = 254 nm, [b] The enantiomeric excess was determined by HPLC: column Lux Cellulose 1, elution with a mixture of hexane/isopropanol 80/20, flow rate 1 mL/min, (*R*)-enantiomer rt_1:6.98 min. (minor), (*S*)-enantiomer rt_2: 11.79 min. (major), λ = 258 nm. [c] The enantiomeric excess was determined by HPLC: column Lux Cellulose 2, elution with a mixture of hexane/isopropanol 80/20, flow rate 1 mL/min, (*R*)-enantiomer rt_1:5.87 min. (minor), (*S*)-enantiomer rt_2: 8.35 min. (major), λ = 254 nm. (See Experimental Section)

4.2.5 Recyclability:

To evaluate the recyclability of the palladium catalyst immobilised in the ionic liquid, the reaction of phenylglyoxal monohydrate and α-methylstyrene was carried out in ionic liquid **24** with [(*R*)-BINAP]Pd.$(SbF_6)_2$ as the catalyst. After the reaction, the product was separated by washing the catalyst-ionic liquid mixture with diethyl ether (10 mL). Excess solvent was then removed by rotary evaporation and the catalyst-IL mixture further dried on high vacuum. After drying the catalyst and ionic liquid mixture, it was reused in same reaction. The product obtained was purified by column chromatography and analysed by ^{1}H-NMR with the enantiopurity of the product evaluated by chiral HPLC analysis. Results of the recyclability experiments have shown that the product yield dropped significantly from 76% to 35%, whereas ee was stable within the limits of error. (Fig. 4.1) This could be explained by the loss of a small amount of palladium catalyst during the washing of the product.

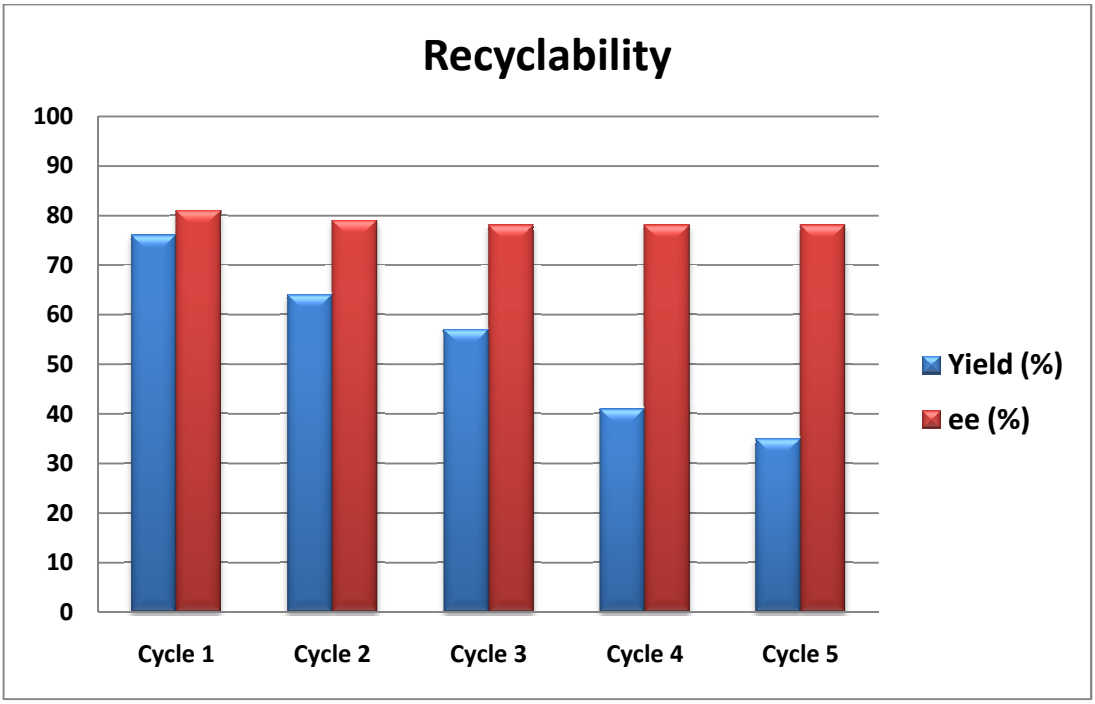


Fig 4.1: Recyclability of ionic liquid **24** in the Carbonyl-Ene reaction of phenylglyoxal and α-methylstyrene

4.3 Conclusion:

In conclusion, volatile organic solvents were successfully replaced with less hazardous ionic liquids for the carbonyl-ene reaction. (for toxicity study see chapter 6) A variety of ester and amide chain ionic liquids were used as a solvent in the reaction and the results were compared with more traditional molecular solvents. In general, ionic liquids performed extremely well in the carbonyl-ene reaction of phenylglyoxal with yields of this reaction improved to 76%, which is significantly better than the yields obtained within literature (DCM, 40% yield) whilst managing to retain a similar enantioselectivity and absolute configuration (*S*). The reaction conditions were optimised also by varying different parameters such as catalyst loading, amount of reagents, temperature and time.

4.4 References:

1. (a) K. C. Nicolaou, D. W. Kim, R. Baati, *Angew. Chem., Int. Ed.*, 2002, **41**, 3701-3704, (b) K. R. Hornberger, C. L. Hamblet, J. L. Leighton, *J. Am. Chem. Soc.*, 2000, **122**, 12894-12895, (c) F. X. Felpin, J. Lebreton, *J. Org. Chem.*, 2002, **67**, 9192-9199
2. J.-F. Zhao, H.-Y. Tsui, P.-J. Wu, J. Lu, T.-P. Loh, *J. Am. Chem. Soc.*, 2008, **130**, 16492-16493
3. For a general review of the ene reaction, see: (a) K. Mikami, M. Shimizu, *Chem. Rev.*, 1992, **92**, 1021-1050, (b) K. Mikami, M. Terada, S. Narisawa, T. Nakai, *Synlett*, 1992, **4**, 255-265, (c) D. J. Berrisford, C. Bolm, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1717-1719, (d) K. Mikami, *Pure Appl. Chem.*, 1996, **68**, 639-644, (e) M. L. Clarke, M. B. France, *Tetrahedron*, 2008, **64**, 9003-9031
4. K. Maruoka, Y. Hoshino, Y. H. Shirasaka, H. Yamamoto, *Tetrahedron Lett.*, 1988, **29**, 3967-3970
5. (a) K. Mikami, M. Terada, T. Nakai, *J. Am. Chem. Soc.*, 1989, **111**, 1940-1941, (b) K. Mikami, M. Terada, T. Nakai, *J. Am. Chem. Soc.*, 1990, **112**, 3949-3954, (c) K. Mikami, S. Matsukawa, *J. Am. Chem. Soc.*, 1993, **115**, 7039-7040, (d) K. Mikami, T. Yajima, M. Terada, E. Kato, M. Maruta, *Tetrahedron: Asymm.*, 1994, 1087-1090, (e) K. Mikami, Y. Tomoko, T. Takasaki, S. Matsukawa, M. Terada, T. Uchimaru, M. Maruta, *Tetrahedron*, 1996, **52**, 85-98, (f) S. Pandiaraju, G. Chen, A. Lough, A. K. Yudin, *J. Am. Chem. Soc.*, 2001, **123**, 3850-3851, (g) E. M. Carreira,

W. Lee, R. A. Singer, *J. Am. Chem. Soc.*, 1995, **117**, 3649-3650, (h) G. Manickam, G. Sundararajan, *Tetrahedron: Asymm.*, 1999, 2913-2925

6. (a) D. A. Evans, C. S. Burgey, N. A. Paras, T. Vojkovsky, S.W. Tregay, *J. Am. Chem. Soc.*, 1998, **120**, 5824-5825, (b) D. A. Evans, S. W. Tregay, C. S. Burgey, N. A. Paras, T. Vojkovsky, *J. Am. Chem. Soc.*, 2000, **122**, 7936-7943
7. D. A. Evans, J. Wu, *J. Am. Chem. Soc.*, 2005, **127**, 8006-8007
8. For catalysts based on Pd and Pt, see: (a) J. Hao, M. Hatano, K. Mikami, *Org. Lett.*, 2000, **2**, 4059-4062, (b) K. Aikawa, S. Kainuma, M. Hatano, K. Mikami, *Tetrahedron Lett.*, 2004, **45**, 183-185, (c) M. Hatano, K. Mikami, *J. Am. Chem. Soc.*, 2003, **125**, 4704-4705, (d) K. Mikami, Y. Kawakami, K. Akiyama, K. Aikawa, *J. Am. Chem. Soc.*, 2007, **129**, 12950-12951, (e) J. H. Koh, A. O. Larsen, M. R. Gagné, *Org. Lett.*, 2001, **3**, 1233-1236, (f) K. Mikami, K. Aikawa, *Org. Lett.*, 2002, **4**, 99-101, (g) J. J. Becker, P. S. White, M. R. Gagné, *J. Am. Chem. Soc.*, 2001, **123**, 9478-9479, (h) H.- K. Luo, H. Schumann, *J. Mol. Cat. A: Chem.*, 2006, **248**, 42-47, (i) H.-K. Luo, H.-Y. Yang, T. X. Jie, O. S. Chiew, H. Schumann, L. B. Khim, C. Lim, *J. Mol. Cat. A: Chem.*, 2007, **261**, 112-119, (j) S. Doherty, P. Goodrich, C. Hardacre, H.-K. Luo, M. Nieuwenhuyzen, R. K. Rath, *Organometallics*, 2005, **24**, 5945-5955, (k) S. Doherty, J. G. Knight, C. H. Smyth, R. W. Harrington, W. Clegg, *J. Org. Chem.*, 2006, **71**, 9751-9764, (*l*) H.-K. Luo, L. B. Khim, H. Schumann, C. Lim, T. X. Jie, H.-Y. Yang*, Adv. Synth. Catal.,* 2007, **349**, 1781-1795, (*m*) H.-K. Luo, Y-L. Woo, H. Schumann, C. Jacob, M. V. Meurs, H.-Y. Yang*,* Y-T. Tan, *Adv. Synth. Catal.*, 2010, **352**, 1356-1364
9. (a) S. Kezuka, T. Ikeno, T.Yamada, *Org. Lett.*, 2001, **3**, 1937-1939, (b) S. Kezuka, Y. Kogami, T., Ikeno, T. Yamada, *Bull. Chem. Soc. Jpn.*, 2003, **76**, 49-58, (c) G. E. Hutson, A. H. Dave, V. H. Rawal, *Org. Lett.*, 2007, **9**, 3869-3872
10. K. Zheng, J. Shi, X. Liu, X. Feng, *J. Am. Chem. Soc.*, 2008, **130**, 15770-15771
11. (a) R. T. Ruck, E. N. Jacobsen, *J. Am. Chem. Soc.*, 2002, **124**, 2882-2883, (b) R. T. Ruck, E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2003, **42**, 4771-4774, (c) M. L. Grachan, M. T. Tudge, E. N. Jacobsen, *Angew. Chem.,Int. Ed.*, 2008, **47**, 1469-1472
12. C. Qian, L. Wang, *Tetrahedron: Asymmetry*, 2000, **11**, 2347-2357
13. (a) D. E. DeVos, I. F. J. Vankelecom, P. A. Jacobs, *Wiley-VCH: Weinheim*, 2000, (b) Q. H. Fan, Y. M. Li, A. S. C. Chan, *Chem. Rev.*, 2002, **102**, 3385-3465, (c) M. Lemaire, *Pure Appl. Chem.*, 2004, **76**, 679-688
14. (a) L. C. Branco, C. A. M. Afonso, *Chem. Commun.*, 2002, 3036-3037, (b) L. C. Branco, C. A. M. Afonso, *J. Org. Chem.*, 2004, **69**, 4381-4389, (c) C. E. Song, D.-

U. Jung, E. J. Roh, S.-G. Lee, D. Y. Chi, *Chem. Commun.*, 2002, 3038-3040, (d) J. Durand, E. Teuma, M. C. Gomez, *R. Chim.*, 2007, **10**, 152-177, (e) Z. M. Zhou, F. Jiang, F. Y. Mo, *Prog. Chem.*, 2007, **19**, 42-50, (f) K. Takahashi, H. Nakano, R. Fujita, *Chem. Commun.*, 2007, 263-265, (g) S. E. Lyubimov, V. A. Davankov, K. N. Gavrilov, *Tetrahedron Lett.*, 2006, **47**, 2721-2723, (h) Y. Hamashima, H. Takano, D. Hotta, M. Sodeoka, *Org. Lett.*, 2003, **5**, 3225-3228, (i) C. E. Song, E. J. Roh, *Chem. Commun.*, 2000, 615-616, (j) R. A. Brown, P. Pollet, E. McKoon, C. A. Eckert, C. L. Liotta, P. G. Jessop, *J. Am. Chem. Soc.*, 2001, **123**, 1254-1255, (k) Z. Tang, F. Jiang, L. T. Yu, X. Cui, L. Z. Gong, A. Q. Mi, Y. Z. Jiang, Y. D. Wu, *J. Am Chem. Soc.*, 2003, **125**, 5262-5263

15. S. Bouquillon, T. Courant, D. Dean, N. Gathergood, S. Morrissey, B. Pegot, P. J. Scammells, R. D. Singer, *Aust. J. Chem.*, 2007, *60*, 843-847
16. S. Morrissey, I. Beadham, N. Gathergood, *Green Chem.*, 2009, **11**, 466
17. L. Myles, R. Gore, M. Špulák, N. Gathergood, S. J. Connon, *Green Chem.*, 2010, **12**, 1157-1162

Chapter 5: Results and Discussion

Applications of Ionic Liquids in Carbonyl-Ene Reaction of Ethyl Trifluoropyruvate

5.0 Applications of Ionic Liquids in Asymmetric Carbonyl-Ene Reaction of Ethyl Trifluoropyruvate

5.1 Rationale:

The enantioselective carbonyl-ene reaction[1] has gained much attention in the past two decades. It is widely known as an atom-economic reaction and one of the most reliable and convenient processes for the generation of homoallylic alcohols, which are important building blocks for the synthesis of many natural products and pharmaceutical compounds.[2,3] Different groups have investigated several metal complexes as chiral Lewis acid catalysts for this reaction. Yamamato and co-workers reported the first asymmetric carbonyl-ene reaction using modified Al-BINAP complexes.[4] Subsequently Mikami and other groups developed Ti-BINOL[5] catalysts for use in this reaction. Evan and co-workers reported that both Cu-Box[6] and Sc-PyBox[7] were efficient catalysts. Other metal complexes derived from Pd and Pt,[8] Co,[9] Ni,[10] Cr,[11] In,[3] and several lanthanides[12] have also been used to catalyze the asymmetric carbonyl-ene reaction. Among these studies, the enantioselective carbonyl-ene reactions of trifluoropyruvate have been reported. Mikami and co-workers obtained high enantioselectivities with *ee* values between 84% and 98% in the reactions of ethyl trifluoropyruvate and alkenes, catalyzed by a "naked" palladium (II) complex with the chiral *atropos*-SEGPHOS (Fig. 5.1).[8b,n,o]

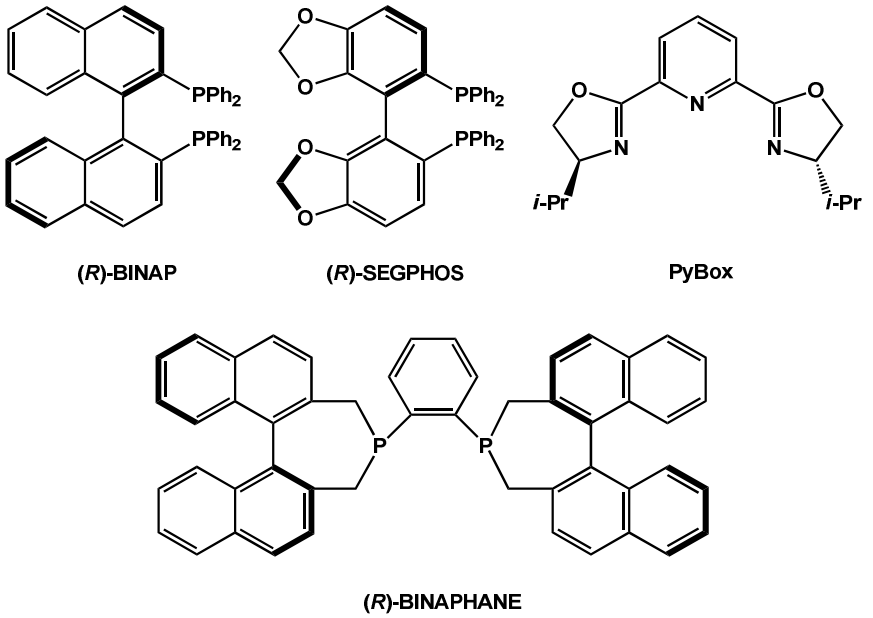


Fig 5.1: Some commonly used chiral ligands in carbonyl-ene reaction

Doherty and co-workers reported a comparative study of the carbonyl-ene reaction between a range of 1,1'-disubstituted or trisubstituted alkenes and ethyl trifluoropyruvate catalyzed by Lewis acid-platinum group metal complexes of the type $[M\{(R)\text{-BINAP}\}]^{2+}$ (M = Pt, Pd, Ni).[8k] This study revealed subtle but significant differences in the reactivity of these catalysts. For instance, the palladium-based Lewis acid $[Pd\text{-}\{(R)\text{-BINAP}\}]^{2+}$ catalyzes the *ene* reaction between methylene cycloalkane and trifluoropyruvate to afford the expected α-hydroxy ester in good yield, with excellent diastereo- and enantioselectivity. In contrast, under the same conditions, the corresponding $[M\{(R)\text{-BINAP}\}]^{2+}$ (M = Pt, Ni) catalyzes isomerization of the methylene cycloalkane and the *ene* reaction of the resulting mixture of methylene cycloalkane and 1-methylcycloalkene react at similar rates to afford a range of α-hydroxy esters in high regioselectivity, good diastereoselectivity, and good to excellent enantioselectivity. In addition, $[Pt\{(R)\text{-BINAP}\}]^{2+}$also catalyzes a post reaction isomerization of the *ene* product, as well as consecutive *ene* reactions, to afford a double carbonyl-ene product. In another study of this research group with the same reaction model, it revealed that platinum complexes of enantiopure conformationally flexible *tropos* NUPHOS diphosphines rival or outperform their atropisomeric enantiopure BINAP counterparts.[8p] Recently, Luo and co-worker reported that the Pd(II)-BINAPHANE catalyst (Fig. 5.1) afforded both good yields and extremely high enantioselectivities with *ee* values as high as 99.6% for the carbonyl-ene reaction between ethyl trifluoropyruvate and alkenes.[8m]

Chiral transition metal complexes in asymmetric catalysis have clear and distinct advantages in giving high enantioselectivity for many reactions. However, they are very expensive. Therefore recycling these catalysts has attracted great interest in industrial applications. Immobilization of chiral catalysts with solid supports or polymers is a representative method to recover and reuse catalysts.[13] However, sometimes solid catalysts result in decreased enantioselectivity and/or activity. Recently, ionic liquids (ILs) have been shown to extend catalyst lifetime in a variety of asymmetric catalytic reactions such as dihydroxylation, Diels-Alder, allylic amination, hydrogenation, Michael addition, fluorination, epoxidation and Aldol reactions[14] and also facilitate product isolation, by simple extraction with non-polar solvents or facile distillation. In enantioselective carbonyl-ene reactions between various alkenes and ethyl or phenylglyoxal catalyzed by chiral platinum complexes, the *ee* obtained in 1-ethyl-2-methylimidazolium *bis*(trifluoromethanesulfonimide) i.e. $[EMIM][NTf_2]$ is higher (up

to 95%) or at least, comparable to those obtained in dichloromethane.[8j] Recycling of the ionic liquid phase afforded after three runs the same enantioselectivity, but yields decreased . Recently, Luo and coworkers reported that the chiral Lewis acid palladium(II) catalyst incorporating (*R*)-BINAP, which is a conformationally restricted chiral ligand, is very stable in ionic liquids such as 1-butyl-2,3-dimethylimidazolium *bis*(trifluoromethanesulfonimide) i.e. [BdMIM][NTf_2] and could be recycled 21 times with retention of high enantioselectivity.

Our research effort is directed by the development of environmentally friendly ionic liquids, which can also offer performance advantages over established methods. As a part of our interest in performing asymmetric carbonyl-ene and other organic reactions (Diels-Alder,[15] Hydrogenation,[16] Acetalisation[17]) in such ionic liquids, we present herein enantioselective carbonyl-ene reactions of ethyl trifluoropyruvate and alkenes catalyzed by a chiral Pd(II)-BINAP catalyst in biodegradable/ or low toxicity ionic liquids. This catalyst was chosen because it gives the expected α-hydroxy ester in good yield and excellent diastereo- and enantioselectivity.[8k] Furthermore, to our knowledge, the use of chiral Pd(II)-BINAP catalyzed carbonyl-ene reactions of ethyl trifluoropyruvate and alkenes in ionic liquids and recovery/ reuse of the chiral catalyst has not been reported so far. The performance of these Ionic Liquids in comparison with common organic solvents, and recycling of the catalyst/ionic liquid media are thus investigated.

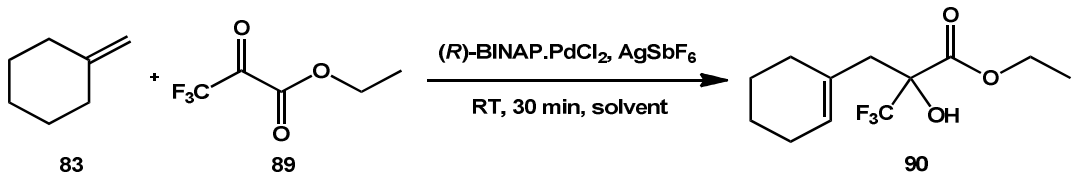
5.2 Results and discussions:

5.2.1 Solvent effect:

In an effort to check the compatibility of ionic liquids in the Carbonyl-Ene reaction, a variety of ester and amide side chain ILs were screened along with some common organic solvents such as dichloromethane, diethyl ether, toluene and tetrahydrofuran in solvent effect studies. Dichloromethane (DCM) has reported to be the most useful solvent in the preparation of [(*R*)-BINAP.Pd]SbF_6 catalyst for the Carbonyl-Ene reaction. However, due to the low boiling point of DCM, high toxicity and issues related to work place safety, DCM is not an environmentally friendly solvent.[18] It is also an important consideration according to the '12 principles of Green Chemistry' proposed by Anastas and Warner.[19] Interestingly, diethyl ether and toluene gave an

increase in enantiomeric excess but a decrease in product yield, whereas THF did not facilitate any conversion (Table 5.1). The results of Carbonyl-Ene reaction in ionic liquids were comparable with DCM. The absolute configuration (*S*) of **90** was determined by comparing with the product reported in the literature.

Table 5.1: Study the effect of molecular solvents in carbonyl-ene reaction.



83 89 90

Entry	Solvent	Isolated Yield[a] (%)	ee[b] (%)
1	Dichloromethane	93	90
2	Diethyl ether	68	98
3	Tetrahydrofuran	-	-
4	Toluene	84	96

[a] Isolated yield with flash chromatography. [b] Determined by chiral GC (column: CP-Cyclodextrin-beta-2,3,6-M-19, i.d. 0.25mm· 25 m, VARIANT; carrier gas, Helium 1mL/min.; column, 120°C; injection temp, 150°C, Detector: 230°C), (*R*)-enantiomer rt_1: 9.90 min. (minor), (*S*)-enantiomer rt_2: 10.18 min. (major). The absolute configuration (*S*) of **90** was determined by comparing with the product reported in the literature. (See Experimental Section)

A wide range of ester and amide side chain ionic liquids (Fig. 5.2) were used in this solvent study. Before using ionic liquids as a solvent in the carbonyl-ene reactions, the chiral palladium catalyst was pre-formed in dichloromethane (DCM) by reacting (*R*)-BINAP.$PdCl_2$ with silver hexafluoroantimonate ($AgSbF_6$) for 30 minutes at room temperature. The orange coloured reaction mixture turned yellow after 30 minutes with a white precipitate of silver chloride (AgCl) on the wall of the round bottom flask. The catalyst, dissolved in dichloromethane, was then filtered through cotton wool into a round bottomed flask containing the ionic liquid in order to remove any AgCl. The DCM was then removed by rotary evaporation and the catalyst further dried under high vacuum. The ionic liquid and catalyst mixture could then be used in the carbonyl-ene reaction.

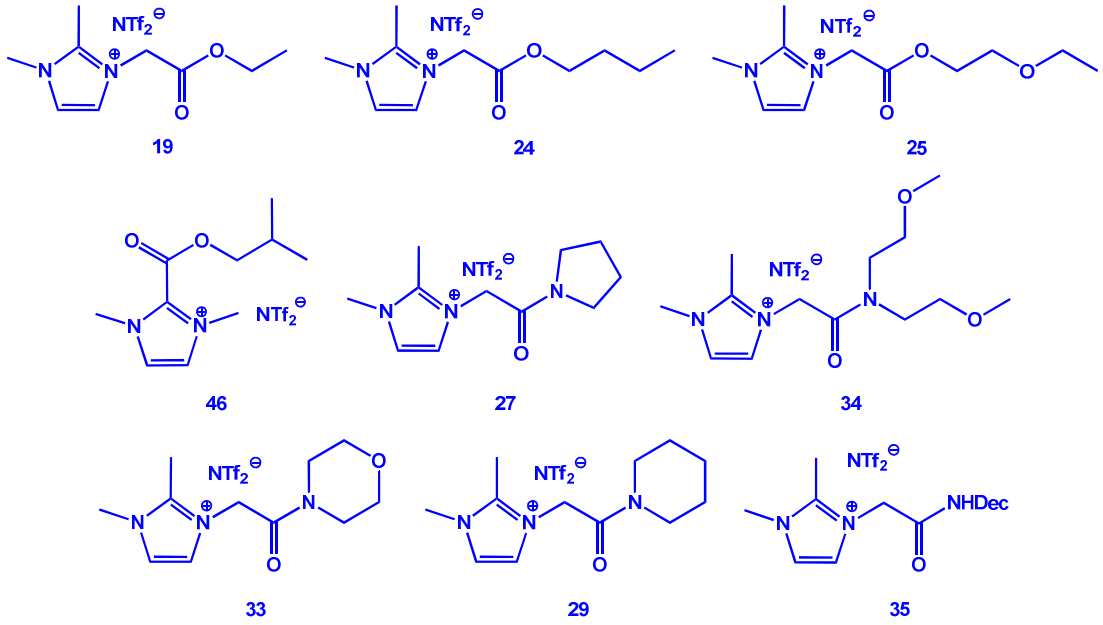
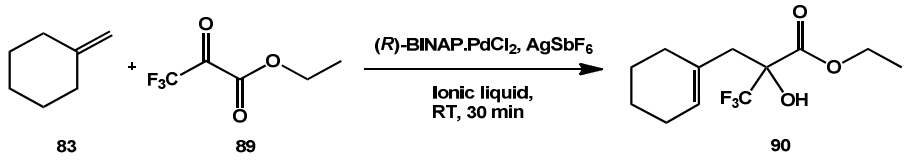


Fig. 5.2: Ionic liquids used in the carbonyl-ene reaction

Table 5.2: Study the effect of ionic liquids as a solvent in carbonyl-ene reaction.



Entry	Ionic liquids	Isolated Yield (%)[a]	ee (%)[b]
1	**19**	76	85
2	**24**	78	90
3	**25**	77	89
4	**46**	89	91
5	**27**	89	92
6	**34**	85	89
7	**33**	87	90
8	**29**	89	91
9	**35**	90	80

[a] Isolated yield with flash chromatography. [b] Determined by chiral GC (column: CP-Cyclodextrin-beta-2,3,6-M-19, i.d. 0.25mm· 25 m, VARIANT; carrier gas, Helium 1mL/min.; column, 120°C; injection temp, 150°C, Detector: 230°C), (*R*)-enantiomer rt_1: 9.90 min. (minor), (*S*)-enantiomer rt_2: 10.18 min. (major). The absolute configuration of **90** was determined by comparing with the product reported in the literature. (See Experimental Section)

Good to excellent results were obtained with these ionic liquids. Ethyl ester side chain ionic liquid gave the lowest yield (76%) with 85% enantioselectivity. Ionic liquids **47,**

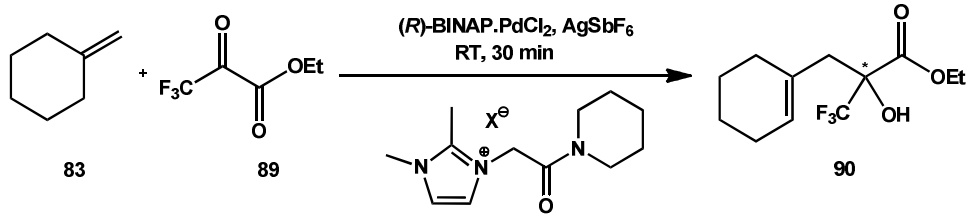
27 & **29** (entry no. 4, 5 & 8, Table 5.2) were found to be highly effective with 89% isolated yields (each) and high enantiomeric excess. In general, amide side chain ionic liquids performed better than ester side chain ionic liquids. The '*S*' enatiomer was found to be in excess.[8k]

The product obtained was easily separated from ionic liquid + catalyst mix by just washing the reaction mass with diethyl ether. Working with ionic liquid **47** has advantages relating to product separation. Ionic liquid **47,** was solid and the ionic liquid + catalyst mixture was also solid in nature. Hence it was very easy to separate the product from this mixture, as the ionic liquid + catalyst mixture precipitated and settled at the bottom of the round bottom flask.

5.2.2 Anion Effect of Ionic Liquids:

To investigate the anion effect of ionic liquid, a number of ionic liquids were synthesized with piperidine amide side chains as the cation. Commonly use anions such as Br^- (**15**), NTf_2^- (**29**), BF_4^- (**30**), $OctOSO_3^-$ (**31**) and $N(CN)_2^-$ (**32**) were used. Ionic liquid **29** gave good conversion (89%) with 91% enantiomeric excess.

Table 5.3: Effect of anion of ionic liquids in carbonyl-ene reaction.



Entry	X	IL	Yield (%)[a]	ee (%)[b]
1	NTf_2^-	**29**	89	91
2	Br^-	**15**	-	-
3	$N(CN)_2^-$	**32**	-	-
4	$OctOSO_3^-$	**31**	-	-
5	BF_4^-	**30**	10	-

[a] Isolated yield with flash chromatography.[b] Determined by chiral GC (column: CP-Cyclodextrin-beta-2,3,6-M-19, i.d. 0.25mm· 25 m, VARIANT; carrier gas, Helium 1mL/min.; column, 120°C; injection temp, 150°C, Detector: 230°C), (*R*)-enantiomer rt_1: 9.90 min. (minor), (*S*)-enantiomer rt_2: 10.18 min. (major). The absolute configuration (*S*) of **90** was determined by comparing with the product reported in the literature. (See Experimental Section)

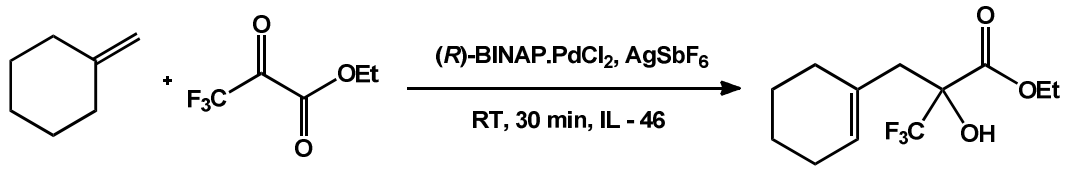
In the case of ionic liquid with bromide (**15**) and dicynamide anions (**32**), no conversion was observed with a change in colour of the catalyst (yellow to orange) observed. This can be explained as the parent catalyst has an orange colour, which after reaction with $AgSbF_6$, changes to a yellow colour. In this reaction, the SbF_6 anion replaced the chlorides to form AgCl, which precipitates from the reaction mixture. So we postulate that in the case of Br^- (**15**) and $N(CN)_2^-$ (**32**) ionic liquids, both these anions replaced the SbF_6^- and deactivated the catalyst. The ionic liquid with octyl sulfate anion (**31**) also failed to form the required product. In case of BF_4^- ionic liquid (**30**) only 10% racemic product was prepared (Table 5.3).

5.2.3 Optimization of reaction conditions:

Ionic liquid **46** was studied in the optimization of reaction conditions (Table 5.4), as this gave high yields and enantiomeric excess, along with ease of product separation.

A number of steps were involved in the synthesis of the ionic liquid. Hence in efforts to make the process cost effective, the amount of ionic liquid used was reduced to half. The isolated yield was increased dramatically from 89% to 96% although retaining the same enantiomeric excess (Entry 2, Table 5.4). In order to achieve quantitative yields, the stoichiometric ratio of the methylenecyclohexane and trifluoroethylpyruvate was varied, but it caused an adverse effect on the isolated yields. Average yield dropped to 78%, when 1 equivalent of each reactant was used (Entry 3, Table 5.4). A further drop in the yield was observed (68%), when 1.5 equivalents alkene was reacted with 1 equivalent of trifluoroethylpyruvate (Entry 4, Table 5.4). Altering the amount of catalyst did not result in any major change to enantioselectivity. Reducing the amount of catalyst loading to 2 mol% (Entry 5, Table 5.4), altered both yield (90%) and enantioselectivity (87%). When 10 mol% catalyst was used (Entry 6, Table 5.4), the reaction mass became difficult to stir, which was reflected in 51% isolated yield and 88% ee. Varying temperature and reaction time did not lead to significant improvements.

Table 5.4: Optimization of reaction conditions with ionic liquid **46**



83 89 90

Entry	83	89	Catalyst	IL	Temperature	Time	Yield (%)[a]	ee (%)[b]
1	1 eq	1.5 eq	0.05 eq	1 eq	25 °C	30 min	89	91
2	1 eq	1.5 eq	0.05 eq	0.5 eq	25 °C	30 min	96	91
3	1 eq	1 eq	0.05 eq	0.5 eq	25 °C	30 min	78	89
4	1.5 eq	1 eq	0.05 eq	0.5 eq	25 °C	30 min	68	91
5	1 eq	1.5 eq	0.02 eq	0.5 eq	25 °C	30 min	90	87
6	1 eq	1.5 eq	0.1 eq	0.5 eq	25 °C	30 min	51	88
7	1 eq	1.5 eq	0.05 eq	0.5 eq	40 °C	30 min	92	87
8	1 eq	1.5 eq	0.05 eq	0.5 eq	0 °C	30 min	93	90
9	1 eq	1.5 eq	0.05 eq	0.5 eq	25 °C	1 h	88	87
10	1 eq	1.5 eq	0.05 eq	0.5 eq	25 °C	2 h	93	87
11	1 eq	1.5 eq	0.05 eq	0.5 eq	25 °C	15 min	90	88

[a] Isolated yield with flash chromatography. [b] Determined by chiral GC (column: CP-Cyclodextrin-beta-2,3,6-M-19, i.d. 0.25mm· 25 m, VARIANT; carrier gas, Helium 1mL/min.; column, 120°C; injection temp, 150°C, Detector: 230°C), (*R*)-enantiomer rt_1: 9.90 min. (minor), (*S*)-enantiomer rt_2: 10.18 min. (major). The absolute configuration (*S*) of **90** was determined by comparing with the product reported in the literature. (See Experimental Section)

A similar trend was observed in case of amide side chain ionic liquid **27**, when a couple of optimization reaction conditions were performed (Table 5.5).

Table 5.5: Optimization of reaction conditions with ionic liquid **27**

Entry	Catalyst	IL (equiv.)	Temperature	Time (min)	Isolated yield (%)[a]	ee (%)[b]
1	5%	1	25°C	30	90	92
2	2%	1	25°C	30	82	89
3	5%	0.5	25°C	30	90	93
4	5%	0.5	0°C	30	81	92
5	5%	0.5	25°C	15	86	92

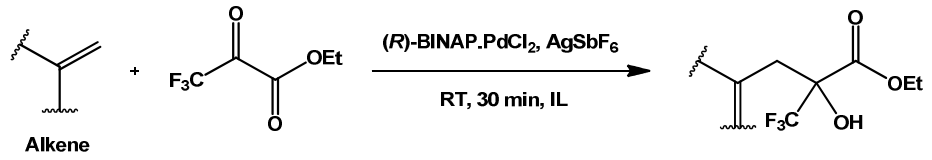
[a] Isolated yield with flash chromatography. [b] Determined by chiral GC (column: CP-Cyclodextrin-beta-2,3,6-M-19, i.d. 0.25mm· 25 m, VARIANT; carrier gas, Helium 1mL/min.; column, 120°C; injection temp, 150°C, Detector: 230°C), (*R*)-enantiomer rt_1: 9.90 min. (minor), (*S*)-enantiomer rt_2: 10.18 min. (major). The absolute configuration (*S*) of **90** was determined by comparing with the product reported in the literature. (See Experimental Section)

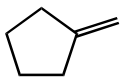
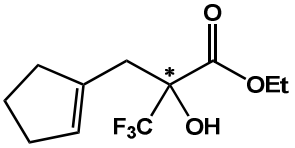
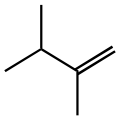
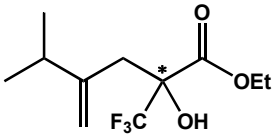
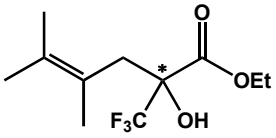
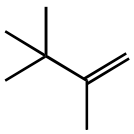
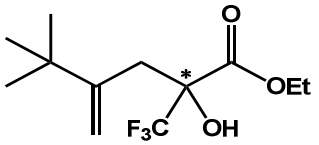
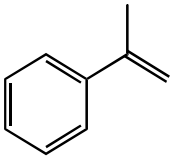
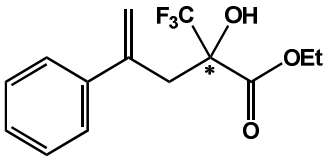
5.2.4 Study of other substrates:

In the evaluation of the scope of this reaction in ionic liquids, a variety of alkenes [methylenecyclohexane (**83**) methylenecyclopentane (**84**), 2,3-dimethyl-1-butene (**91**), 2,3,3-trimethyl-1-butene (**85**) and α-methylstyrene (**80**)] were also used (Table 5.6) in the reaction with ethyl trifluoropyruvate.

In the reaction of ethyl trifluoropyruvate with methylenecyclopentane (**84**), **92** was obtained with 82% yield and 96% ee (Entry 1, Table 5.6). Although enantiomeric excess was higher with **84**, when methylenecyclohexane (**83**) was used as the substrate (91 % ee, Table 5.4, Entry 2), yield was decreased from 96% to 82%. For 2,3-dimethyl-1-butene, two products (**93a** and **93b**) were observed with an 80% combined yield and both compounds giving 94% ee (Entry 2, Table 5.6). This can be explained by the proposed possible catalytic mechanism (Fig. 5.3). As both 2,3-dimethyl-1-butene (**91**) and ethyl trifluoropyruvate are small substrates, this can allow the Pd-catalyst to facilitate the alkene approach to the coordinated ethyl trifluoropyruvate in two different ways (Path A & B).[8m] The '*S*' enatiomer was found to be in excess for all products.

Table 5.6: Substrate scope for the enantioselective carbonyl-ene reaction of Ethyl Trifluoropyruvate.



Entry	Alkene	Product	Yield (%)[a]	ee (%)
1	 **84**	 **92**	82	96[b]
2	 **91**	 **93a**  **93a'**	80 (**93a/93a'** = 1.8)[c]	94[d] 94[d]
3	 **85**	 **94**	81	96[e]
4	 **80**	 **95**	71	75[f]

[a] Isolated yield with flash chromatography, [b] Determined by chiral GC, [c] Ratio of 2 product was determined by ^{1}H-NMR and ^{19}F-NMR, [d] Determined by chiral GC, [e] Determined by chiral GC, [f] Determined by chiral GC. The absolute configuration (*S*) of **90** was determined by comparing with the product reported in the literature. (See Experimental Section)

The reaction ethyl trifluoropyruvate with 2,3,3-trimethyl-1-butene (**85**) gave **94** with 96% enantiomeric excess and 81% yield (Entry 3, Table 5.6). Reaction between ethyl trifluoropyruvate and α-methylstyrene generated **95** with the lowest (71%) yield and enantiomeric excess (75%) (Entry 4, Table 5.6). The enantiomeric excess of the product **95** was analysed by chiral HPLC.

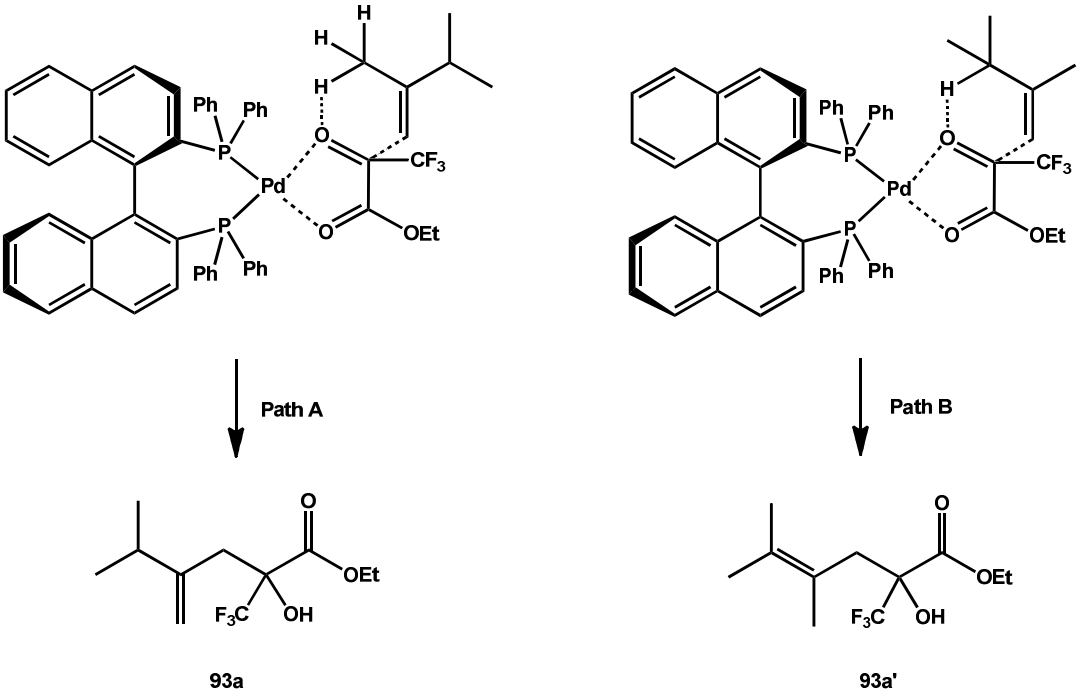


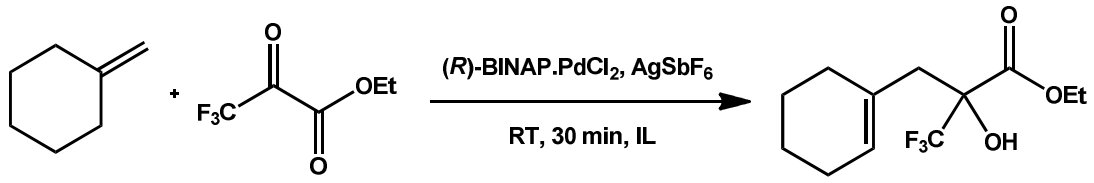
Fig. 5.3: Proposed mode of action of [BINAP].Pd-catalyst (based on the mechanism of forming two products with Pd(II)-BINAPHANE catalyst[8m])

5.2.5 Recyclability:

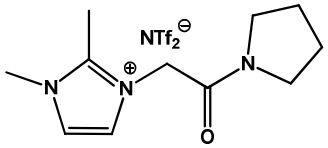
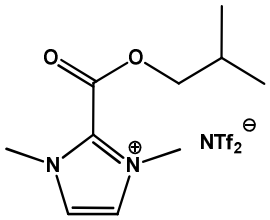
The optimized conditions (from Table 5.4 and 5.5) were used to perform recyclability experiments. The recycling experiments were carried out on methylenecyclohexane and ethyl trifluoropyruvate in the corresponding ionic liquids. On the completion of the reaction, the product was washed off from the ionic liquid and catalyst mixture, by using diethyl ether and *n*-hexane (6 mL) solvent mix (1:1). After the removal of product, the catalyst mixture was dried in *vacuo* and was then used in the next reaction. A direct comparison was made between ester and amide functionalised ionic liquids.

When amide side chain ionic liquid **27** was used in recyclability experiments, an significant decrease in both yield and ee was observed. The yield dropped from 90% to 69% after the 4th recycling of the catalyst and ionic liquid mixture. Whereas ionic liquid **46** had performed extremely well while keeping steady yields and ee up to the 6th recycle. On the 7th recycle, the yield and ee dropped to 77% & 84% respectively (Table 5.7). The exponential drop in yields and enantiomeric excess in the case of ionic liquid **27** was probably due to the small losses of ionic liquid and catalyst mixture in the workup procedure.

Table 5.7: Recyclability of ionic liquids and catalyst mixture



83 89 90

Cycle	amide IL	Yield (%)[a]	ee (%)[b]	ester IL	Yield (%)[a]	ee (%)[b]
1	 **27**	90	93	 **46**	96	91
2		88	92		92	91
3		84	89		90	92
4		75	86		92	93
5		69	73		92	93
6		-	-		90	92
7		-	-		92	91
8		-	-		77	84

Conditions: methylenecyclohexane 0.25 mmol, ethyl trifluoropyruvate 0.375 mmol (1.5 equiv), Catalyst {[(*R*)-BINAP]Pd}$(SbF6)_2$ 0.0125 mmol (5mol %) for the first cycle, IL 0.125 mmol (0.5 equiv) for the first cycle, RT, 30 min. [a] Isolated yield with flash chromatography. [b] Determined by chiral GC [column: CP-Cyclodextrin-beta-2,3,6-M-19, i.d. 0.25mm· 25 m, VARIANT; carrier gas, Helium 1mL/min.; column, 120°C; injection temp, 150°C, Detector: 230°C), (*R*)-enantiomer rt_1: 9.90 min. (minor), (*S*)-enantiomer rt_2: 10.18 min. (major). The absolute configuration (*S*) of **90** was determined by comparing with the product reported in the literature. (See Experimental Section)

5.3 Conclusion:

In conclusion, a series of novel ester and amide side chain 1,2-dimethylimidazolium or C_2-ester (**46**) substituted ionic liquids were successfully applied and used in the Carbonyl-Ene reactions of ethyl trifluoropyruvate. A chiral catalyst i.e. $[Pd\{(R)\text{-}BINAP\}]^{2+}(SbF_6)_2$ was used to act as catalyst and influence the enantioselectivity for the reaction. Excellent yields and enantioselectivities (both up to 96%) were obtained. All of the results were comparable with conventional volatile solvents, such as DCM. Furthermore, the ionic liquid immobilized expensive catalyst $[Pd\{(R)\text{-}BINAP\}]^{2+}(SbF_6)_2$ was recycled and reused up to 7 times without significant loss of

activity. The absolute configuration was found to be '*S*', which found to be common in all the products isolated from the reaction with either DCM or ionic liquids as a solvent. Overall, the novel ionic liquids were found to be good solvents with the potential to act as replacements for harmful VOCs and to be an efficient trap for expensive catalysts in the Carbonyl-Ene reactions of ethyl trifluoropyruvate.

5.4 References:

1. For a general review of the ene reaction, see: (a) K. Mikami, M. Shimizu, *Chem. Rev.*, 1992, **92**, 1021-1050, (b) K. Mikami, M. Terada, S. Narisawa, T. Nakai, *Synlett*, 1992, **4**, 255-265, (c) D. J. Berrisford, Bolm, C. *Angew. Chem., Int. Ed.*, Engl. 1995, **34**, 1717-1719, (d) K. Mikami, *Pure Appl. Chem.*, 1996, **68**, 639-644, (e) M. L. Clarke, M. B. France, *Tetrahedron*, 2008, **64**, 9003-9031
2. (a) K. C. Nicolaou, D. W. Kim, R. Baati, *Angew. Chem., Int. Ed.*, 2002, **41**, 3701-3704, (b) K. R. Hornberger, C. L. Hamblet, J. L. Leighton, *J. Am. Chem.*, Soc. 2000, **122**, 12894-12895, (c) F. X. Felpin, J. Lebreton, *J. Org. Chem.*, 2002, **67**, 9192-9199
3. J.-F. Zhao, H.-Y. Tsui, P.-J. Wu, J. Lu, T.-P. Loh, *J. Am. Chem. Soc.*, 2008, **130**, 16492-16493
4. K. Maruoka, Y. Hoshino, Y. H. Shirasaka, H. Yamamoto, *Tetrahedron Lett.*, 1988, 29, 3967-3970
5. (a) K. Mikami, M. Terada, T. Nakai, *J. Am. Chem. Soc.*, 1989, 111, 1940-1941, (b) K. Mikami, M. Terada, T. Nakai, T. *J. Am. Chem. Soc.*, 1990, 112, 3949-3954, (c) K. Mikami, S. Matsukawa, *J. Am. Chem. Soc.*, 1993, 115, 7039-7040, (d) K. Mikami, T. Yajima, M. Terada, E. Kato, M. Maruta, *Tetrahedron: Asymm.*, 1994, 1087-1090, (e) K. Mikami, Y. Tomoko, T. Takasaki, S. Matsukawa, M. Terada, T. Uchimaru, M. Maruta, *Tetrahedron*, 1996, **52**, 85-98, (f) S. Pandiaraju, G. Chen, A. Lough, A. K. Yudin, *J. Am. Chem. Soc.*, 2001, **123**, 3850-3851, (g) E. M. Carreira, W. Lee, R. A. Singer, *J. Am. Chem. Soc.*, 1995, **117**, 3649-3650, (h) G. Manickam, G. Sundararajan, *Tetrahedron: Asymm.*, 1999, 2913-2925
6. D. A. Evans, C. S. Burgey, N. A. Paras, T. Vojkovsky, S. W. Tregay, *J. Am. Chem. Soc.*, 1998, **120**, 5824-5825, (b) D. A. Evans, S. W. Tregay, C. S. Burgey, N. A. Paras, T. Vojkovsky, *J. Am. Chem. Soc.*, 2000, **122**, 7936-7943
7. D. A. Evans, J. Wu, *J. Am. Chem. Soc.*, 2005, **127**, 8006-8007

8. For catalysts based on Pd and Pt, see: (a) J. Hao, M. Hatano, K. Mikami, *Org. Lett.*, 2000, **2**, 4059-4062, (b) K. Aikawa, S. Kainuma, M. Hatano, K. Mikami, *Tetrahedron Lett.*, 2004, **45**, 183-185, (c) M. Hatano, K. Mikami, *J. Am. Chem. Soc.*, 2003, **125**, 4704-4705, (d) K. Mikami, Y. Kawakami, K. Akiyama, K. Aikawa, *J. Am. Chem. Soc.*, 2007, **129**, 12950-12951, (e) J. H. Koh, A. O. Larsen, M. R. Gagné, *Org. Lett.*, 2001, **3**, 1233-1236, (f) K. Mikami, K. Akiyama, *Org. Lett.*, 2002, **4**, 99-101, (g) J. J. Becker, P. S. White, M. R.Gagné, *J. Am. Chem. Soc.*, 2001, **123**, 9478-9479. (h) H.-K. Luo, H. Schumann, *J. Mol. Cat. A: Chem.*, 2006, **248**, 42-47, (i) H.-K. Luo, H.-Y. Yang, T. X. Jie, O. S. Chiew, H. Schumann, L. B. Khim,, C. Lim, *J. Mol. Cat. A: Chem.*, 2007, **261**, 112-119, (j) S. Doherty, P. Goodrich, C. Hardacre, H.-K. Luo, M. Nieuwenhuyzen, R. K.Rath, *Organometallics*, 2005, **24**, 5945-5955, (k) S. Doherty, J. G. Knight, C. H. Smyth, R. W. Harrington, W. Clegg, *J. Org. Chem.*, 2006, **71**, 9751-9764. (l) H.-K. Luo, L. B. Khim, H. Schumann, C. Lim, T. X. Jie, H.-Y. Yang, *Adv. Synth. Catal.*, 2007, **349**, 1781-1795, (m) H.-K. Luo, Y.-L. Woo, H. Schumann, C. Jacob, M. V. Meurs, H.-Y. Yang, Y.-T. Tan, *Adv. Synth. Catal.*, 2010, **352**, 1356-1364, (n) K. Mikami, K. Aikawa, S. Kainuma, Y. Kawakami, T. Saito, N. Sayo, H. Kumobayashi, *Tetrahedron: Asymm.*, 2004, **15**, 3885-3889, (o) K. Mikami, H. Kakuno, K. Aikawa, *Angew. Chem.*, 2005, **117**, 7423-7426, *Angew. Chem. Int. Ed.*, 2005, **44**, 7257-7260, (p) S. Doherty, J. G. Knight, C. H. Smyth, R. W. Harrington, W. Clegg, *Organometallics*, 2007, **26**, 6453-6461
9. S. Kezuka, T. Ikeno, T.Yamada, *Org. Lett.*, 2001, **3**, 1937-1939, (b) S. Kezuka, Y. Kogami, T., Ikeno, T. Yamada, *Bull. Chem. Soc. Jpn.*, 2003, **76**, 49-58, (c) G. E. Hutson, A. H. Dave, V. H. Rawal, *Org. Lett.*, 2007, **9**, 3869-3872
10. K. Zheng, J. Shi, X. Liu, X. Feng, *J. Am. Chem. Soc.*, 2008, 130, 15770-15771
11. R. T. Ruck, E. N. Jacobsen, *J. Am. Chem. Soc.*, 2002, **124**, 2882-2883, (b) R. T. Ruck, E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2003, **42**, 4771-4774, (c) M. L. Grachan, M. T. Tudge, E. N. Jacobsen, *Angew. Chem.,Int. Ed.*, 2008, **47**, 1469-1472
12. C. Qian, L. Wang, *Tetrahedron: Asymm*, 2000, **11**, 2347-2357
13. D. E. DeVos, I. F. J. Vankelecom, P. A. Jacobs, *Wiley-VCH: Weinheim*, 2000, (b) Q. H. Fan, Y. M. Li, A. S. C. Chan, *Chem. Rev.*, 2002, **102**, 3385-3465, (c) M. Lemaire, *Pure Appl. Chem.*, 2004, **76**, 679-688
14. L. C. Branco, C. A. M. Afonso, *Chem. Commun.*, 2002, 3036-3037, (b) L. C. Branco, C. A. M. Afonso, *J. Org. Chem.*, 2004, **69**, 4381, (c) C. E. Song, D.-U.

Jung, E. J. Roh, S.-G. Lee, D. Y. Chi, *Chem. Commun.*, 2002, 3038-3040, (d) J. Durand, E. Teuma, M. C. Gomez, *R. Chim.*, 2007, **10**, 152-177, (e) Z. M. Zhou, F. Jiang, F. Y. Mo, *Prog. Chem.*, 2007, **19**, 42-50, (f) K. Takahashi, H. Nakano, R. Fujita, *Chem. Commun.*, 2007, 263-265, (g) S. E. Lyubimov, V. A. Davankov, K. N. Gavrilov, *Tetrahedron Lett.*, 2006, **47**, 2721-2723, (h) Y. Hamashima, H. Takano, D. Hotta, M. Sodeoka, *Org. Lett.*, 2003, **5**, 3225-3228, (i) C.E. Song, E.J. Roh, *Chem. Commun.*, 2000, 615-616, (j) R.A. Brown, P. Pollet, E. McKoon, C. A. Eckert, C. L. Liotta, P. G. Jessop, *J. Am. Chem. Soc.*, 2001, **123**, 1254-1255, (k) Z. Tang, F. Jiang, L. T. Yu, X. Cui, L. Z. Gong, A. Q. Mi, Y. Z. Jiang, Y. D. Wu, *J. Am Chem. Soc.*, 2003, **125**, 5262-5263

15. S. Bouquillon, T. Courant, D., Dean, N. Gathergood, S. Morrissey, B. Pegot, P. J. Scammells, R. D. Singer, *Aust. J. Chem.,* 2007, **60**, 843-847
16. S. Morrissey, I. Beadham, N. Gathergood, *Green Chem.*, 2009, **11**, 466
17. L. Myles, R. Gore, M. Špulák, N. Gathergood, S. J. Connon, *Green Chem.*, 2010, **12**, 1157-1162
18. K. Alfonsi, J. Colberg, P. J. Dunn, T. Fevig, S. Jennings, T. A. Johnson, H. P. Kleine, C. Knight, M. A. Nagy, D. A. Perry, M. Stefaniak, *Green Chem*., 2008, **10**, 31-36
19. P. T. Anastas, J. C. Warner, 1998, *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, UK

Chapter 6: Results and Discussion

Anti-microbial and Biodegradation Study and Green Chemistry Metrics Calculation of Ionic Liquids

6.0 Anti-microbial and Biodegradation Study and Green Chemistry Metrics Calculation of Ionic Liquids

6.1 Rationale:

Ionic liquids have been extensively studied in Organic chemistry due to their unique properties such as low vapour pressure, high thermal stability, recyclability, non-flammability, and control over the product distribution.[1] They have shown tremendous potential as reagents, non-volatile solvents and catalysts.[2] As a result, ionic liquids have already and are continually generating great interest from the chemical industry. Also, many of these ionic liquids are totally synthetic novel compounds. Hence it is important to check their toxicity and eco-toxicological properties, biodegradation and bioaccumulation of these materials has to be studied. Although toxicity testing can be useful as the primary step towards the study of biodegradation, computer modelling can also be useful to predict the biodegradation.[3]

6.2 Toxicity of Ionic Liquids:

The strategy of the Gathergood group is to combine clinically relevant bacteria and fungi in the preliminary assessment of the antimicrobial toxicity of novel ionic liquids. This approach has two benifits **1)** a wide range (20 strains) of bacteria and fungi can be rapidly screened as part of a high throughput screening methodology and **2)** ionic liquids with high toxicity to the strains in study, (in particular if high selectivity is demonstrated), yields 'hit' compounds as part of a drug discovery program. As these 'hits' also have been included in biodegradation studies, considerable data to ascertain their potential persistence in the environment is collected at the drug discovery programs inception. We propose this could lead to less environmentally damaging pharmaceuticals in the future. Working with our collaborator in Czech Republic, a panel of 12 fungi and 8 bacteria was selected. Ionic liquids which have low antimicrobial toxicity in CZ screen (test only validated to maximum concentration of 2 mM) are then prioritised for addition antimicrobial toxicity screening at high concentrations at DCU. The strains screened in DCU are more commonly found in the environment.

6.2.1 Procedure:

6.2.1.1 Antifungal activity:

In vitro antifungal activities of the compounds were evaluated on a panel of four ATCC strains (*Candida albicans* ATCC 44859, *Candida albicans* ATCC 90028, *Candida parapsilosis* ATCC 22019, *Candida krusei* ATCC 6258) and eight clinical isolates of yeasts (*Candida krusei* E28, *Candida tropicalis* 156, *Candida glabrata* 20/I, *Candida lusitaniae* 2446/I, *Trichosporon asahii* 1188) and filamentous fungi (*Aspergillus fumigatus* 231, *Absidia corymbifera* 272, *Trichophyton mentagrophytes* 445) from the collection of fungal strains deposited at the Department of Biological and Medical Sciences, Faculty of Pharmacy, Charles University, Hradec Králové, Czech Republic. Three ATCC strains were used as the quality control strains. All the isolates were maintained on Sabouraud dextrose agar prior to being tested.

Minimum inhibitory concentrations (MICs) were determined by modified CLSI standard of microdilution format of the M27-A3 and M38-A2 documents.[4,5] Dimethyl sulfoxide (100 %) served as a diluent for all compounds, the final concentration of which did not exceed 2 %. RPMI 1640 (Sevapharma, Prague) medium supplemented with *L*-glutamine and buffered with 0.165 M morpholinepropanesulfonic acid (Serva) to pH 7.0 by 10 M NaOH was used as the test medium. The wells of the microdilution tray contained 200 µl of the RPMI 1640 medium with 2-fold serial dilutions of the compounds (2000 to 0.488 µmol/l for the new compounds) and 10 µl of inoculum suspension. Fungal inoculum in RPMI 1640 was prepared to give a final concentration of $5 \times 10^3 \pm 0.2$ cfu.ml^{-1}. The trays were incubated at 35°C and MICs were read visually after 24 h and 48 h. The MIC values for the dermatophytic strain (*T. mentagrophytes*) were determined after 72 h and 120 h. The MICs were defined as 80 % inhibition (IC_{80}) of the growth of control for yeasts and as 50 % inhibition (IC_{50}) of the growth of control for filamentous fungi. MICs were determined twice and in duplicate. The deviations from the usually obtained values were no higher than the nearest concentration value up and down the dilution scale.

6.2.1.2 Antibacterial activity:

In vitro antibacterial activity[6] of the compounds were evaluated on a panel of three ATCC strains (*Staphylococcus aureus* ATCC 6538, *Escherichia coli* ATCC 8739, *Pseudomonas aeruginosa* ATCC 9027) and five clinical isolates (*Staphylococcus*

aureus MRSA HK5996/08, *Staphylococcus epidermidis* HK6966/08, *Enterococcus* sp. HK14365/08, *Klebsiella pneumoniae* HK11750/08, *Klebsiella pneumoniae* ESBL HK14368/08) from the collection of bacterial strains deposited at the Department of Biological and Medical Sciences, Faculty of Pharmacy, Charles University, Hradec Králové, Czech Republic. The above-mentioned ATCC strains also served as the quality control strains. All the isolates were maintained on Mueller-Hinton agar prior to being tested.

Dimethyl sulfoxide (100 %) served as a diluent for all compounds, the final concentration did not exceed 2 %. Mueller-Hinton agar (MH, HiMedia, Čadersky-Envitek, Czech Republic) buffered to *p*H 7.4 (±0.2) was used as the test medium. The wells of the microdilution tray contained 200 µl of the Mueller-Hinton medium with 2-fold serial dilutions of the compounds (2000 to 0.488 µmol/l) and 10 µl of inoculum suspension. Inoculum in MH medium was prepared to give a final concentration of 0.5 McFarland scale (1.5×10^8 cfu.ml^{-1}). The trays were incubated at 37°C and MICs were read visually after 24 h and 48 h. The MICs were defined as 95 % inhibition of the growth of control. MICs were determined twice and in duplicate. The deviations from the usually obtained values were no higher than the nearest concentration value up and down the dilution scale.

6.2.2 Results and discussions:

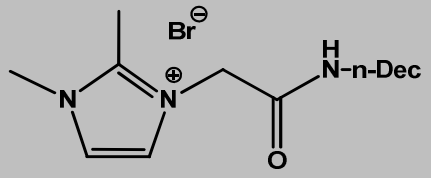
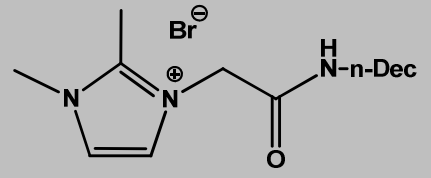
In order to evaluate the environmental impact of the ionic liquids synthesized (Chapter 2, page 34 to 45), a test system inclusive of 12 fungi and 8 bacteria was applied. The antimicrobial toxicity effects of ester/amide side chains in the synthesized ionic liquids and their respective anions were studied.

6.2.2.1 Study of toxicological effect of imidazolium cations with ester and amide side chain:

The bromide salts of ionic liquids containing ester and amide side chains were non-toxic up to 2000 µM with the exception of compound **18**. Ionic liquids with ester side chain **8**, **10** and **11** (methyl, butyl and ethoxyethyl respectively) were found to not inhibit the growth of all fungi and bacteria up to 2000 µM concentration after 48 hours (see Table A1.1 and A1.2, Appendix 1). A similar response was observed in ionic liquids with

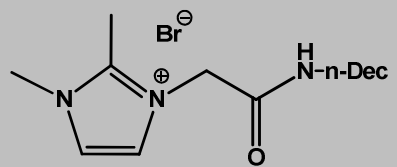
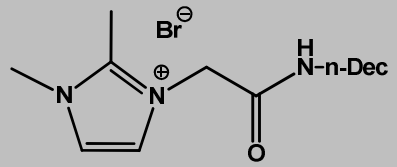
amide side chains of cyclic amines **12-14, 15, 16** (pyrrolidine, piperidine and morpholine respectively). Ionic liquid **18** demonstrated inhibition of growth in the tested fungi and bacterial strains at different concentrations (Table 6.1 and 6.2). This is due to the long alkyl side chain of the cationic component. This observation is in agreement with literature observations.[7] In most of the strains, antifungal and antibacterial toxicity of **18** observed after 24h was retained after 48h, whereas in some cases toxicity was decreased after 48h. This is probably due to the parent IL being broken down into metabolites that have a lower toxicity profile toward the test microrganism.

Table 6.1: MIC_{80} values of ionic liquids **18** and **35** in antifungal screening

	Time / Strain	*Candida albicans* ATCC 44859	*Candida albicans* ATCC 90028	*Candida parapsilosis* ATCC 22019	*Candida krusei* ATCC 6258	*Candida krusei* E28	*Candida tropicalis* 156	*Candida glabrata* 20/I	*Candida lusitaniae* 2446/I	*Trichosporon beigelii* 1188	*Aspergillus fumigates* 231*	*Absidia corymbifera* 272*	*Trichophyton mentagrophytes* 445*
 18	24h	125	125	62.5	7.81	3.9	3.9	31.25	250	250	250	250	250 [a]
	48h	250	125	62.5	7.81	3.9	3.9	62.5	250	250	250	250	250 [b]
 35	24h	250	250	62.5	31.25	15.62	15.62	62.5	250	250	250	>1000	250 [a]
	48h	250	250	125	31.25	31.25	31.25	125	250	500	500	>1000	250 [b]

* MIC_{50} values were determined, [a] MIC_{50} after 72h, [b] MIC_{50} after 120h

Table 6.2: MIC_{95} values of ionic liquids **18** and **35** in antibacterial screening

	Strain	*Staphylococcus aureus* ATCC 6538	*Staphylococcus aureus* HK 5996/08	*Staphylococcus epidermidis* HK 6966/08	*Enterococcus sp.* HK 14365/08	*Escherichia coli* ATCC 8739	*Klebsiella pneumonia* HK 11750/08	*Klebsiella pneumonia ESBL* HK 14368/08	*Pseudomonas aeruginosa* ATCC 9027
 18	24h	62.5	125	31.25	125	250	500	1000	1000
	48h	125	125	62.5	125	500	1000	1000	1000
 35	24h	62.5	125	250	62.5	250	250	250	1000
	48h	62.5	125	250	125	250	250	250	>1000

6.2.2.2 Study of toxicological effect of anions:

In order to check the effect of anions in the test system, a variety of commonly used anions incorporated with cations discussed above, were selected. All the anions of methyl ester side chain ionic liquids i.e. NTf_2^- (**19**), BF_4^- (**20**), PF_6^- (**21**) and $OctOSO_3^-$ (**22**) were found to be non-toxic up to 2000 μM concentration in the test system (see Table A1.1 and A1.2, Appendix 1).

The NTf_2 salt of 1,2-dimethylimidazolium cation with ethyl ester side chain (**23**), showed inhibition at the 1000 μM concentration against two *Candida albicans* strains (ATCC 44859 and ATCC 90028) after 24 hours of incubation. Due to lower solubility of **23** (c.f. **19-22**), the highest concentration prepared was 1000 μM (see Table A1.3 and A1.4, Appendix 1). Other ester side chain 1,2-dimethylimidazolium ionic liquids **24** and **25** (butyl and ethoxyethyl, respectively) with NTf_2 anions, were non-toxic up to 2000 μM concentration against all fungi and bacteria used (see Table A1.3 and A1.4, Appendix 1).

Similar results were obtained with amide side chain ionic liquids **26**, **27, 28** (pyrrolidine amides) and **33** (morpholine amides). Piperidine amide side chain salts of NTf_2^- (**29**), BF_4^- (**30**), $OctOSO_3^-$ (**31**) and $N(CN)_2^-$ (**32**) anions were non-toxic up to 2000 μM concentration. Again, only the decyl amide side chain ionic liquid (**35**) resulted in toxicity (<2000 μM) against all fungi (except *Absidia corymbifera* (272)) and bacteria (except *Pseudomonas aeruginosa,* (ATCC 9027)). It was significant that the toxicity of the decyl amide side chain ionic liquid decreased, when incorporated with NTf_2 anion, if compared with its bromide salt. Overall, significant toxicity effects of different anions incorporated with imidazolium ionic liquids was not found in the current test system.

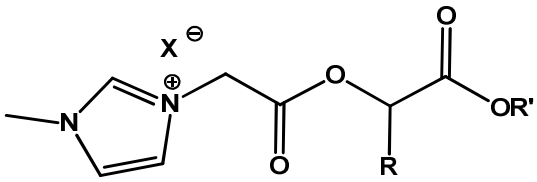
6.2.2.3 Study of toxicological effect of modifications at C2-position of imidazolium core:

Ester and amide substitution at the C2-position of the imidazole core was designed to facilitate biodegradation of the derivatised ionic liquids. Hence toxicity assessment, especially antimicrobial toxicity studies were an important step towards designing safer modified imidazolium ionic liquids.

All the ionic liquids (**40**-**47**), with different anions, were subjected to the test system. No significant toxicity was observed up to 2000 μM concentration. Ionic liquids with isobutyl ester (**45**, **46** and **47**) and primary amide functionalities (**40**-**44**) at 2-position did not show any anti-fungal (see Table A1.5, Appendix 1) and anti-bacterial (see Table A1.6, Appendix 1) toxicity. Although a variety of anions were incorporated with the imidazolium core modified ionic liquids, no significant anion effect was observed.

6.2.2.4 Study of toxicological effect of chiral ionic liquids:

Chiral ionic liquids derived from the chiral pool, such as mandelic and lactic acids, have been prepared in the group in order to use as a chiral solvent in asymmetric synthesis. Biodegradation studies of these ester functionalized chiral ionic liquids have already shown that they can be categorized as 'readily biodegradable'.[8] To evaluate the anti-fungal and anti-bacterial toxicity of these compounds; methyl, pentyl and ethoxyethyl esters of chiral ionic liquids (**48**-**71**)has been selected for the study (Fig. 6.1).



R = Me, Ph **R' = CH_3, C_5H_{11}, $C_2H_4OC_2H_5$**

X = Br, $OctOSO_3$

Fig. 6.1: Chiral ionic liquids used in the toxicological study(**48**-**71**)

Due to the poor solubility of the chiral ionic liquids in the test system, 1000 μM was the highest concentration used for the screening. All of the methyl mandelate chiral ionic liquids (**48**-**50**) with bromide anion were found to be non-toxic to all fungal strains up to 1000 μM concentration. A direct comparison between pentyl (**51**-**53**) and ethoxyethyl mandelate (**54**-**56**) ionic liquids was also possible. Pentyl derivatives (**51**-**53**) resulted in inhibition in most of the fungal strains (Table 6.3 and 6.4), which was an example of the toxicity effects of a moderately long chain in an ionic liquid. Incorporation of similar oxygen functionality (such as ether) with similar chain length as compared to the pentyl chain, was found to be non-toxic up to 1000 μM concentration. The ethoxyethyl lactate salts (**57**, **59**), the pentyl lactate ionic liquid **58** did not exhibit anti-fungal toxicity. Hence it is possible that the phenyl group can also contribute to the toxicity. Also, the

methyl mandelate ionic liquid, with octyl sulfate anion, caused inhibition of *Candida krusei* (ATCC 6258), *Candida krusei* (E28) at 1000 μM concentration after 24 hours, which was restrained after 48 hours.

Table 6.3: MIC_{80} values of bromide salts of mandelic acid chiral ionic liquid derivatives (**48-56**) in anti-fungal screening

Strain	Time (h)	**MIC_{80} Values of Chiral Ionic Liquids** (Concentration in μM)				
		Methyl	**Pentyl**			**Ethoxyethyl**
		48 (*RS*), 49 (*R*), 50 (*S*)	**51 (*RS*)**	**52 (*R*)**	**53 (*S*)**	**54 (*RS*), 55 (*R*), 56 (*S*)**
Candida albicans ATCC 44859	24h	>1000	**500**	**500**	**500**	>1000
	48h	>1000	**1000**	>1000	>1000	>1000
Candida albicans ATCC 90028	24h	>1000	**1000**	**1000**	**1000**	>1000
	48h	>1000	>1000	>1000	>1000	>1000
Candida parapsilosis ATCC 22019	24h	>1000	>1000	>1000	>1000	>1000
	48h	>1000	>1000	>1000	>1000	>1000
Candida krusei ATCC 6258	24h	>1000	**1000**	**1000**	**1000**	>1000
	48h	>1000	**1000**	>1000	>1000	>1000
Candida krusei E28	24h	>1000	**1000**	**1000**	**1000**	>1000
	48h	>1000	>1000	>1000	>1000	>1000
Candida tropicalis 156	24h	>1000	**1000**	**1000**	>1000	>1000
	48h	>1000	>1000	>1000	>1000	>1000
Candida glabrata 20/I	24h	>1000	**1000**	**1000**	**1000**	>1000
	48h	>1000	**1000**	>1000	>1000	>1000
Candida lusitaniae 2446/I	24h	>1000	>1000	>1000	>1000	>1000
	48h	>1000	>1000	>1000	>1000	>1000
Trichosporon beigelii 1188	24h	>1000	**1000**	**1000**	**1000**	>1000
	48h	>1000	>1000	>1000	>1000	>1000
Aspergillus fumigatus 231*	24h	>1000	**1000**	**1000**	**1000**	>1000
	48h	>1000	**1000**	**1000**	**1000**	>1000
Absidia corymbifera 272*	24h	>1000	**1000**	**1000**	**1000**	>1000
	48h	>1000	**1000**	**1000**	**1000**	>1000
Trichophyton mentagrophytes 445*	72h	>1000	**500**	**500**	**500**	>1000
	120h	>1000	**500**	**500**	**500**	>1000

* MIC_{50} values

Table 6.4: MIC_{80} values of octyl sulfate salts of mandalic acid derivatives of chiral ionic liquids (**48-56**) in antifungal screening

Strain	Time (h)	**MIC_{80} Values of Chiral Ionic Liquids** (Concentration in μM)					
		Methyl		**Pentyl**			**Ethoxyethyl**
		61 (*R*)	**60 (*RS*), 62 (*S*)**	**63 (*RS*)**	**64 (*R*)**	**65 (*S*)**	**66 (*RS*), 67 (*R*), 68 (*S*)**
Candida albicans ATCC 44859	24h	>1000	>1000	**1000**	**500**	**1000**	>1000
	48h	>1000	>1000	**1000**	>1000	**1000**	>1000
Candida albicans ATCC 90028	24h	>1000	>1000	>1000	**1000**	>1000	>1000
	48h	>1000	>1000	>1000	>1000	>1000	>1000
Candida parapsilosis ATCC 22019	24h	>1000	>1000	>1000	>1000	>1000	>1000
	48h	>1000	>1000	>1000	>1000	>1000	>1000
Candida krusei ATCC 6258	24h	**1000**	>1000	**1000**	**1000**	>1000	>1000
	48h	>1000	>1000	>1000	>1000	>1000	>1000
Candida krusei E28	24h	**1000**	>1000	>1000	**1000**	>1000	>1000
	48h	>1000	>1000	>1000	>1000	>1000	>1000
Candida tropicalis 156	24h	>1000	>1000	>1000	>1000	>1000	>1000
	48h	>1000	>1000	>1000	>1000	>1000	>1000
Candida glabrata 20/I	24h	>1000	>1000	>1000	>1000	>1000	>1000
	48h	>1000	>1000	>1000	>1000	>1000	>1000
Candida lusitaniae 2446/I	24h	>1000	>1000	>1000	>1000	>1000	>1000
	48h	>1000	>1000	>1000	>1000	>1000	>1000
Trichosporon beigelii 1188	24h	>1000	>1000	**500**	**1000**	**1000**	>1000
	48h	>1000	>1000	>1000	**1000**	>1000	>1000
Aspergillus fumigatus 231*	24h	>1000	>1000	**500**	**1000**	**1000**	>1000
	48h	>1000	>1000	>1000	**1000**	>1000	>1000
Absidia corymbifera 272*	24h	>1000	>1000	**1000**	**1000**	**1000**	>1000
	48h	>1000	>1000	**1000**	**1000**	>1000	>1000
Trichophyton mentagrophytes 445*	72h	**1000**	>1000	**500**	**250**	**250**	>1000
	120h	**1000**	>1000	**500**	**500**	**500**	>1000

* MIC_{50} values

Similar trends were observed in the anti-bacterial toxicity screening of the chiral ionic liquids. All methyl, ethoxyethyl mandelate and pentyl and ethoxyethyl lactate ionic liquids were found to be non-toxic up to 1000 μM concentration. Bromide salts of the '*R*' isomer (**52**) and racemic (**51**) pentyl mandelate ionic liquids exhibited anti-fungal toxicity to only *Staphylococcus aureus* (ATCC - 6538) at 1000 μM concentration after 24 hours (Table 6.5). Racemic pentyl mandelate ionic liquid **51** retained its toxicity even after 48 hours. This is probably either due to the toxicity of metabolite formed or or perhaps the IL is bactericidal. Toxicity of pentyl mandelate ionic liquids was increased with octyl sulfate anions (see Table 6.6), whereas the other ionic liquids with octyl sulfate anion did not give enhanced antibacterial toxicity. Growth inhibition of *Staphylococcus epidermidis,* HK 6966/08 was observed in case of ionic liquids containing a pentyl ester side chain (**63** and **65**) after 24h. This was decreased after 48h, which can be explained as elimination products (metabolites) formed were probably of low toxicity to the strain. Similar observations was noted in case of **63**, **64** and **65** in *Staphylococcus aureus,* HK 5996/08 and **63** in *Staphylococcus aureus,* ATCC 6538. Antibacterial toxicity of ionic liquid **64** was retained after 48h in *Staphylococcus aureus,* ATCC 6538.

Table 6.5: MIC_{95} values of bromide salts of mandalic acid derivatives of chiral ionic liquids (**48-56**) in antibacterial screening

Strain	Time (h)	**MIC_{95} Values of Chiral Ionic Liquids** (Concentration in μM)				
		Methyl	**Pentyl**			**Ethoxyethyl**
		48 (*RS*), 49 (*R*), 50 (*S*)	**51 (*RS*)**	**52 (*R*)**	**53 (*S*)**	**54 (*RS*), 55 (*R*), 56 (*S*)**
Staphylococcus aureus, ATCC 6538	24h	>1000	**1000**	**1000**	>1000	>1000
	48h	>1000	**1000**	>1000	>1000	>1000
Staphylococcus aureus, HK 5996/08	24h	>1000	>1000	>1000	>1000	>1000
	48h	>1000	>1000	>1000	>1000	>1000
Staphylococcus epidermidis, HK 6966/08	24h	>1000	>1000	>1000	>1000	>1000
	48h	>1000	>1000	>1000	>1000	>1000
Enterococcus sp. HK 14365/08	24h	>1000	>1000	>1000	>1000	>1000
	48h	>1000	>1000	>1000	>1000	>1000
Escherichia coli, ATCC 8739	24h	>1000	>1000	>1000	>1000	>1000
	48h	>1000	>1000	>1000	>1000	>1000
Klebsiella pneumonia, HK 11750/08	24h	>1000	>1000	>1000	>1000	>1000
	48h	>1000	>1000	>1000	>1000	>1000
Klebsiella pneumonia, ESBL HK 14368/08	24h	>1000	>1000	>1000	>1000	>1000
	48h	>1000	>1000	>1000	>1000	>1000
Pseudomonas aeruginosa, ATCC 9027	24h	>1000	>1000	>1000	>1000	>1000
	48h	>1000	>1000	>1000	>1000	>1000

Table 6.6: MIC_{95} values of octyl sulfate salts of mandalic acid derivatives of chiral ionic liquids (**60-68**) in antibacterial screening

Strain	Time (h)	**MIC_{95} Values of Chiral Ionic Liquids** (Concentration in μM)				
		Methyl	**Pentyl**			**Ethoxyethyl**
		60 (*RS*), 61 (*R*), 62 (*S*)	**63 (*RS*)**	**64 (*R*)**	**65 (*S*)**	**66 (*RS*), 67 (*R*), 68 (*S*)**
Staphylococcus aureus, ATCC 6538	24h	>1000	**1000**	**1000**	>1000	>1000
	48h	>1000	>1000	**1000**	>1000	>1000
Staphylococcus aureus, HK 5996/08	24h	>1000	**1000**	**1000**	>1000	>1000
	48h	>1000	>1000	>1000	>1000	>1000
Staphylococcus epidermidis, HK 6966/08	24h	>1000	**1000**	**500**	**1000**	>1000
	48h	>1000	>1000	**1000**	>1000	>1000
Enterococcus sp. HK 14365/08	24h	>1000	>1000	>1000	>1000	>1000
	48h	>1000	>1000	>1000	>1000	>1000
Escherichia coli, ATCC 8739	24h	>1000	>1000	>1000	>1000	>1000
	48h	>1000	>1000	>1000	>1000	>1000
Klebsiella pneumonia, HK 11750/08	24h	>1000	>1000	>1000	>1000	>1000
	48h	>1000	>1000	>1000	>1000	>1000
Klebsiella pneumonia, ESBL HK 14368/08	24h	>1000	>1000	>1000	>1000	>1000
	48h	>1000	>1000	>1000	>1000	>1000
Pseudomonas aeruginosa, ATCC 9027	24h	>1000	>1000	>1000	>1000	>1000
	48h	>1000	>1000	>1000	>1000	>1000

6.2.2.5 Anti-bacterial studies in DCU:

Further studies of some representative ionic liquids were carried out in DCU on a panel of bacteria including *Escherichia coli, Bacillus subtilis*, *Pseudomonas fluorescens*, *Pseudomonas Putida* (CP1) & *Pseudomonas Putida* (KT2440). Minimum inhibitory concentrations (MICs) for compounds were determined by serial two-fold dilutions in Mueller-hinton or nutrient broth using the microtiter broth dilution technique described by Amsterdam. All assays were done in triplicate.

6.2.2.5.1 Method:

Test strains were grown in nutrient broth at 30 °C overnight. Next day, cultures were centrifuged at 5000 rpm for 10 minutes. The pellet formed was washed twice with 10 ml of 0.01 M sodium phosphate buffer (pH 7.0). Optical density of cultures was adjusted to give an optical density of 0.07 at 660 nm. The compound solution and 96 well plates were ready before the cultures were adjusted to the desired optical density. For the stock solution of chemical, the ionic liquid was dissolved in 1 ml of sterile water or organic solvents such as methanol and DMSO, dependant on compound solubility.
For microplate preparation, 190 µl of Müeller-hinton broth was dispensed into wells in column 1. 100 µl of Müeller-hinton broth was dispensed into all wells from column 2 to column 12. 10 µl of the compound solution was pipetted into wells in column 1 (far left of plate). The compound was mixed into the wells in column 1 by pipetting up and down 6-8 times. 100 µl was withdrawn from column 1 and added to column 2. This made column 2 a two-fold dilution of column 1. This was mixed up and down 6-8 times. 100 µl was transferred to column 3. This procedure was repeated down to column 10 only. 100 µl was discarded from column 10 rather than putting it in column 11. 5 µl of the strain to be tested was dispensed into wells in columns 11 to 1 in that order. Column 11 was used as a growth control and column 12 was the sterility control. The plates were incubated at 30 °C overnight. Growth on the plates was noted and optical density measured after 24 hours.

6.2.2.5.2 Results:

The selection of compounds for this test system was based on the issue of solubility of some of the ionic liquids. Only water soluble ionic liquids were used in this test. Due to their poor solubility, the NTf_2^- salts were excluded from the test. Bromide salts of 1-

methylimidazolium ionic liquid with methyl ester side chain (**8**) and 1,2-dimethylimidazolium ionic liquid with pyrrolidine amide side chain (**13**) were non-toxic up to 200 mM concentration. Octyl sulfate anion of methyl ester side chain ionic liquid (**22**) was found to be toxic to *Escherichia coli, Pseudomonas fluorescens* and *Pseudomonas Putida* (CP1) at 200 mM concentration. Ionic liquid **12** containing a 1-methylimidazolium core with pyrrolidine amide side chain only showed inhibition to *Escherichia coli* above 100 mM concentration. Another pyrrolidine amide side chain 1-benzylimidazolium bromide salt was found to be toxic to *Escherichia coli, Bacillus subtilis*, *Pseudomonas fluorescens* and *Pseudomonas Putida* (CP1) above 50 mM concentration. C-2 amide substituted ionic liquids with bromide (**40**) and tetrafluoroborate anion (**42**) were non-toxic up to 200 mM concentration (Table 6.7), whereas the corresponding octyl sulfate anion (**43**) resulted in inhibition within the test system. The inhibition found in **22** and **43** was probably due to the presence of a long alkyl hydrocarbon chain in octyl sulphate anion. The iodide salt of a C-2 isobutyl ester substituted 1,3-dimethylimidazolium cation (**45**) demonstrated inhibition to *Escherichia coli, Bacillus subtilis*, *Pseudomonas fluorescens* and *Pseudomonas Putida* (CP1) above 100 mM concentration.

Table 6.7: MIC_{50} values of ILs performed in DCU in antibacterial screening

	Compounds (Concentration in mM)								
Strains	**8**	**12**	**13**	**14**	**22**	**40**	**42**	**43**	**45**
Escherichia coli	> 200	> 100	> 200	> 50	**200**	> 200	> 200	**100**	> 100
Bacillus subtilis	> 200	> 200	> 200	> 50	> 200	> 200	> 200	> 50	> 100
Pseudomonas fluorescens	> 200	> 200	> 200	> 50	**200**	> 200	> 200	> 50	> 100
Pseudomonas Putida (CP1)	> 200	> 200	> 200	> 50	**200**	> 200	> 200	**100**	**200**
Pseudomonas Putida (KT2440)	> 200	> 200	> 200	> 200	> 200	> 200	> 200	**100**	> 200

6.3 Biodegradation of ionic liquids

6.3.1 Biodegradation Method.

6.3.1.1 CO_2 Headspace test:

To evaluate the biodegradability of the test ionic liquids, the "CO_2 Headspace" test (ISO 14593) was applied.[9] There are several biodegradation study methods (Table 1.1, Chapter 1) but the CO_2 Headspace test was chosen as it is particularly suited for charged, volatile and water soluble compounds.[10,11] Also, this method allows for the evaluation of the ultimate aerobic biodegradability of an organic compound in an aqueous medium at a given concentration of microorganism, by analysis of the inorganic carbon produced. The test ionic liquid, as the only source of carbon and energy, was added to a buffer/mineral salts medium which had been inoculated with a mixed population of microorganisms derived from activated sludge collected from a sewage treatment plant located in Manresa (Barcelona), to give a final organic carbon concentration of 20 mg/L. These solutions were incubated in sealed vessels with a "headspace" of air, which provided a reservoir of oxygen for aerobic biodegradation. The volume of activated sludge used for inoculation was that which gave a concentration of 4 mg/L suspended solids in the final mixture. Based on experience, the use of this inoculum concentration in this test is suitable to give a population (102-105 colony-forming units in the final mixture) which offers adequate biodegradative activity and degrades the reference substance by the stipulated percentage.

Biodegradation (mineralization to carbon dioxide) was determined by measuring the net increase in total inorganic carbon (TIC) levels over time compared to unamended blanks. Sodium *n*-dodecyl sulfate (SDS) was used as a reference substance. The test ran for 28 days. The extent of biodegradation was expressed as a percentage of the theoretical amount of inorganic carbon (ThID) based on the amount of IL added initially. Assuming 100% mineralization of the test ionic liquid, the theoretical amount of inorganic carbon (ThID), in excess of that produced in the blank controls, equals the amount of total organic carbon (TOC) added as the test compound to each vessel at the start of the test, that is: (ThIC=TOC)

Percentage biodegradation D_t in each case is given by:

$$D_t = \frac{(\mathrm{TIC_t} - \mathrm{TIC_b})}{\mathrm{TOC_i}} \mathrm{x100}$$

where:

TIC_t is the TIC, in milligrams, in test vessel at time t,

TIC_b is the mean TIC, in milligrams, in blank control vessels at time t

TOC_i is the TOC, in milligrams, initially added to the test vessel

The measured data of the last day of the test (28 days) were used to calculate the mean biodegradation value and the precision with which the percentage of biodegradation was determined. To know the precision with which percentage of biodegradation was determined, four replicate test vessels and the same number of blanks control vessels on the 28th day were analysed:

- the mean total inorganic carbon in the blank vessels and the percentage of biodegradation for each individual vessel was calculated
- the mean of the separate degradation values and their standard deviation was calculated
- and finally the confidence limits for the mean value of biodegradation was evaluated as

  $\pm \frac{t.s}{\sqrt{n}}$

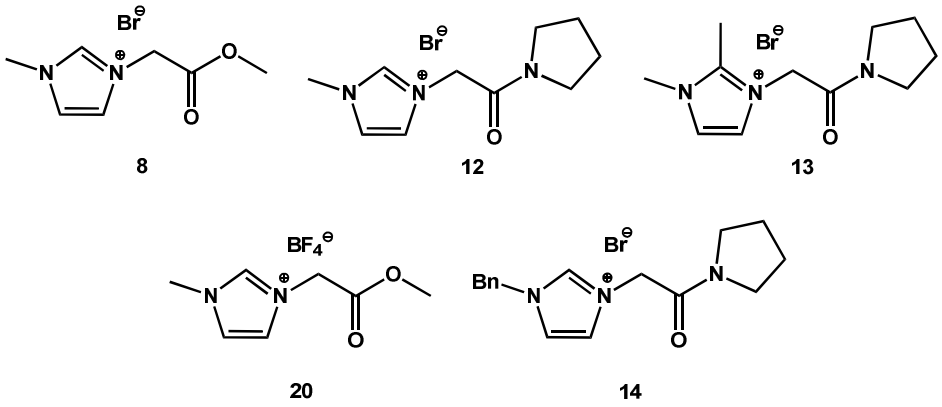
  where t is the Student's t value for (n-1) degrees of freedom at the 95% probability level, s is the standard deviation and n is the number of individual values used to determine the biodegradation percentage.

6.3.2 Results and discussions:

6.3.2.1 Biodegradation study of imidazolium ionic liquids with ester and amide side chains:

In order to evaluate the biocompatibility of the novel ester and amide side chain ionic liquids, a biodegradation study of their bromide salts was investigated by the 'CO_2 Headspace' test. Along with the bromide salts (Table 6.8), biodegradation of the most active 1st generation catalyst (for acetalisation reaction) with BF_4 anion was also studied (See Chapter 3).

Table 6.8: Biodegradation of ester and amide side chain imidazolium ionic liquids (**8**, **12**, **13**, **14**, **20**)



8 12 13 20 14

Entry	Ionic Liquid	Time (% biodegradation)				Confidence limits (95% CL)
		6 Days	14 Days	21 Days	28 Days	
1	**8**	14	14	11	10	(9 -10)[1]
2	**20**	12	12	13	14	(13-15)[1]
3	**12**	1	3	4	3	(2-4)[1]
4	**13**	0	1	0	3	(0-5)[1]
5	**14**	0	0	0	0	(0±1.2)[2]

[1] SDS reference 28 days 85% (95% CL = 80-91%), Confidence limits (CL) were calculated from 5 replicates. [2] SDS reference 28 days 94% (95% CL = 90-98%). Confidence limits (CL) were calculated from 4 replicates.

Ionic liquids (**8**, **12**, **13**, **14** and **20**) did not pass the CO_2 Headspace test (>60% required to pass). Low to negligible biodegradation was observed, with amide ionic liquids **12**, **13** and **14** resistant to breakdown. The presence of the amide and benzyl group in **14**, did not facilitate breakdown under the conditions of the test. This agrees with our previous results and studies from other groups, where amides[12] and benzyl[13,14] substituents did not lead to enhanced biodegradation. Reference experiments performed concurrently with the biodegradation tests confirm that ionic liquids (**8**, **12**, **13**, **14** and **20**) were non-toxic to the inoculum, albeit with poor biodegradation. Imidazolium ionic liquids containing a methyl ester (**8** and **20**) gave low biodegradation values of 10 and 14% respectively after 28 days (Table 6.8). No significant effect is observed between the bromide and BF_4 counterion. As both these anions do not contribute to the carbon dioxide evolved on breakdown, the propensity for the cation to biodegrade is

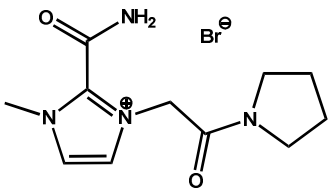
determined. Hydrolysis of the methyl ester, and the conversion of a single carbon in **9** and **10** to CO_2, can account for the degree of biodegradation observed. As is apparent due the increased stability of the amide vs methyl ester, ionic liquids **12**, **13** and **14** are postulated to remain intact during the biodegradation test. All of the biodegradation data in Table 1 for the amide and ester ionic liquids (**8**, **12**, **13**, **14** and **20**) suggest that the imidazolium core is not cleaved during the 'CO_2 Headspace' Test.

6.3.2.2 Biodegradation study of modified imidazolium ionic liquids:

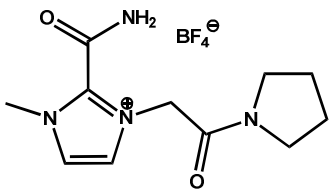
Biodegradation studies of pyridinium-based ILs have shown that ester substitution at either the 1 or 3-position have a beneficial effect on degradation of the heterocyclic core, independent of the anion.[14] Also biodegradation studies in the literature have shown that only the side chain of the imidazolium ionic liquids undergo degradation, whereas the imidazole core was found to persist in most of the OECD tests such as DOC Die-Away test and Closed bottle test.[15] Hence in an effort to increase the biodegradation such ester substitution onto the imidazole ring was designed. Based on the results from the antimicrobial toxicity studies, the C-2 substitued ionic liquids were thought to be suitable substrates for biodegradation studies. Bromide and tetrafluoroborate anions of ester (**45** and **46**) and amide (**40**, **42** and **44**) substituted C-2 imidazolium cations were selected.

Biodegradation data for **40**, **42**, **44**, **45** and **46** are shown in Table 6.9. Unfortunately, none of the ionic liquids passed the CO_2 Headspace test. Introduction of an isobutyl ester (**45** and **46**) or a primary amide (**40**, **42** and **44**) at C-2 did not lead to significant breakdown of the ionic liquid. Amides (**40**, **42** and **44**) gave the lowest values (12, 14 and 17% respectively, after 28 days). C-2 esters (**45** and **46**) gave moderate levels of biodegradation (30 and 35%, respectively, after 28 days). These values are similar to other CO_2 Headspace data for *n*-alkyl ester substituted imidazolium bromide ionic liquids, (propyl ester 24%, pentyl ester 41%).[16] While the C-2 amide example **44** also contains a methyl ester subunit, the increase in biodegradation 17%, (cf. 12% for **40**) is slight. The CO_2 Headspace biodegradation data in Table Y shows that introduction of an ester or amide at the C-2 position of the imidazolium ring does not necessarily promote cleavage of the ring, leading to further breakdown products and CO_2 formation.

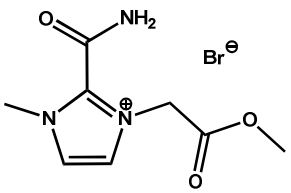
Table 6.9: Biodegradation of modified imidazolium ionic liquids



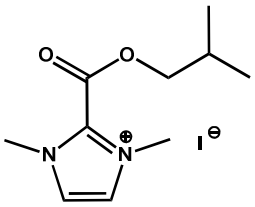
40



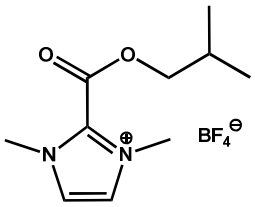
42



44



45



46

Entry	Ionic Liquid	Time (% biodegradation)				Confidence limits (95% CL)
		6 Days	14 Days	21 Days	28 Days	
1	**40**	2	7	8	12	(11-13)[1]
2	**42**	7	12	11	14	(11-17)[2]
3	**44**	9	13	10	17	(9-24)[1]
4	**45**	24	31	32	30	(26-34)[3]
5	**46**	26	31	30	35	(34-36)[1]

[1] SDS reference 28days 80% (95% CL = 76-84%), [2] SDS reference 28days 90% (95% CL = 85-95%), [3] SDS reference 28 days 85% (95% CL = 80-91%), Confidence limits (CL) were calculated from 5 replicates.

6.4 Green Chemistry Metrics

6.4.1 Method

In an effort to evaluate the 'greenness' of the synthetic method or route, a number of important green metrics were calculated. Calculation of these green metrics can give important information relating to the efficiency of the reaction, issues related to the waste, excess reactants and solvent use etc. All these metrics were calculated by using the following formulas and a useful 'Excel' template provided by Prof. Alexei Lapkin, School of Engineering, University of Warwick.

- **Mass intensity** (both excluding and including water):

$$Mass\ intensity = \frac{total\ mass\ of\ raw\ materials\ (incl. workup)}{mass\ of\ product\ recovered}$$

- **Solvent intensity** (both excluding and including water):

$$Solvent\ intensity = \frac{total\ mass\ of\ solvents\ (incl. workup)}{mass\ of\ product\ recovered}$$

- **Sheldon Environmental impact factor, E-Factor** (both excluding and including water):

$$E - Factor = \frac{total\ mass\ of\ wastes}{mass\ of\ product\ recovered}$$

$$E - Factor = \frac{total\ mass\ of\ raw\ materials - mass\ of\ product\ recovered}{mass\ of\ product\ recovered}$$

- **GSK Reaction Mass Efficiency**:

$$GSK\ RME = \frac{mass\ of\ product\ recovered}{total\ mass\ of\ reagents/reactants/catalysts}$$

- **Andraos Reaction Mass Efficiency**:

$$Andraos\ RME = \frac{mass\ of\ product\ recovered}{total\ mass\ of\ raw\ materials} = \frac{1}{mass\ intensity}$$

$$Andraos\ RME = \frac{1}{1 + E - factor}$$

$$Andraos\ RME = \frac{yield\ \times Atom\ Economy\ \times material\ recovery\ parameter}{Stoichiometric\ Factor}$$

- **Atom Economy**:

$$AE = \frac{eq_{product} \times\ MW_{product}}{\sum(eq._i^0 \times MW_i)}$$

where $eq._i^0$ is the ideal stoichiometry of reagent i for the reaction, and MW_i is the molecular weight of reagent i.

- **Stoichiometric Factor**:

$$SF = \frac{\sum mass_{total\ reagents}}{\sum mass_{stoichiometric\ reagents}} = 1 + \frac{\sum mass_{excess\ reagents}}{\sum mass_{stoichiometric\ reagents}}$$

and calculated as:

$$SF = \frac{\sum(eq._i \times MW_i)}{\sum(eq._i^0 \times MW_i)}$$

where $eq._i$ is the stoichiometry of reagent i in the current reaction.

- **Material recovery parameter**:

$$material\ recovery\ parameter\ = \frac{Andraos\ RME\ \times Stoichiometric\ Factor}{yield\ \times Atom\ Economy}$$

- **Yield**

After putting the amounts of the reagents and solvents in the template, a spreadsheet of detailed information about the synthetic step and all the metrics was generated as shown in Appendix 2.

6.5 Conclusion:

Antimicrobial screening of the novel ionic liquids has given useful information about their respective toxicological properties. The amide (pyrrolidine, piperidine and morpholine) and ester (methyl, butyl and ethoxyethyl) side chain ionic liquids were non-toxic to a panel of 12 fungal and 8 bacterial strains up to 2000 μM concentration. Only ionic liquids with decyl amide side chains showed high toxicity in the above test system. No significant anion effect was observed up to the 2000 μM concentration range. Toxicological effects of some ionic liquids were further tested at high concentration against a panel of 5 environmentally significant microbial strains. This study has shown that most of the ionic liquids were non-toxic up to very high i.e. 200 mM concentrations. Although this is only a preliminary test screening, further toxicological analysis will be needed to truly evaluate the toxicity of the novel ILs.

Biodegradation studies of some ester and amide side chain ionic liquids, along with substituted imidazolium salts, were carried out by using the "CO_2 Headspace" test (ISO 14593). All imidazolium ionic liquids prepared failed to pass the minimum 60% biodegradation threshold value, in order to be classified as 'readily biodegradable'. Ester functionalised ionic liquids displayed higher biodegradation levels than amide functionalised ionic liquids after 28 days. The 1st generation imidazolium ionic liquid catalysts showed 10% to 14% biodegradation for methyl ester side chain ionic liquids, where no significant biodegradation was observed in amide side chain ionic liquids after 28 days (Table 6.8). The 2nd generation ionic liquids with the modifications on the imidazole core did not help to breakdown the imidazolium ring to give complete biodegradation. C-2 substituted imidazolium ionic liquids from Table 6.9 with isobutyl ester gave moderate (30% to 35%) biodegradation in comparison with C-2 amide substituted ionic liquids. No significant improvement was observed after the ester/amide substitution at C-2 position of imidazolium ring.

The Green Chemistry metrics assisted improvements in the synthetic process, by reducing the amount of solvents in the work-up and purification procedure and reducing the number of steps to make required compounds. For example, the synthesis of tetrafluoroborate ionic liquids typically involves preparation of the corresponding halide salts, followed by anion exchange metathesis. A modified approach was used, in an effort to reduce the number of steps and amount of reagents and solvents in the synthesis, in which alkyl imidazoles were directly reacted to Meerwein's salt i.e. trimethyloxonium tetrafluoroborate to give tetrafluoroborate ionic liquids in excellent

yield. Hence Green Chemistry metrics assessment was important to assist in the design and implementation of "greener" synthetic methods.

6.6 References:

1. (a) N. V. Plechkova and K. R. Seddon, *Chem. Soc. Rev.*, 2008, **37**, 123-150, (b) P. Wasserscheid and A. Stark (Eds.), *Handbook of Green Chemistry*, Volume 6: Ionic Liquids, Wiley-VCH, **2010**
2. (a) J. P. Hallett, T. Welton, *Chem. Rev.*, 2011, **111**, 3508-3576. (b) C. D. Hubbard, P. I. and R. Eldik, *Chem. Soc. Rev.*, 2011, **40**, 272-290, (c) P. Wasserscheid, J. Joni, *Handbook of Green Chemistry*, 2010, **6**, 41-63 (d) A. C. Gujar, M. G. White, *Catalysis*, 2009, **21**, 154-190, (e) S. M. Chowdhury, S. Ram, J. L. Scott, *Tetrahedron*, 2007, **63**(11), 2363-2389, (f) L. Myles, R. Gore, M. Spulak, N. Gathergood and S. J. Connon, *Green Chem.*, 2010, **12**, 1157-1162, (g) A. Stark and K. R. Seddon, in *Kirk-Othmer Encyclopaedia of Chemical Technology*, A. Seidel, JohnWiley & Sons, Inc., Hoboken, New Jersey, USA, 5, 2007, **26**, 836-920
3. C. Rücker and K. Kummerer, *Green Chem.*, 2012, **14**, 875-887
4. Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts. Approved standard. Document M27-A3. Clinical Laboratory Standard Institute, Wayne, PA, **2008**
5. Reference Method for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi. Approved standard. Document M38-A2. Clinical Laboratory Standard Institute, Wayne, PA, **2008**
6. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically. Approved Standard - Seventh Edition. Document M07-A7. Clinical Laboratory Standard Institute, Wayne, PA, **2006**
7. D. Coleman, M. Špulák, M. T. Garcia, N. Gathergood, *Green Chem.*, 2012, **14**, 1350-1356
8. N. Gathergood, B. Pegot, I. Beadham, M. Gurbisz, M. Ghavre, S. Morrissey, *PCT Int. Appl*., 2010, WO 2010097412 A1 20100902
9. ISO 14593: Water quality, Evaluation of ultimate aerobic biodegradability of organic compounds in aqueous medium. Method by analysis of inorganic carbon in sealed vessels 'CO_2 headspace' test

10. U. Merretting-Bruns, Przeglad znormalizowanych testow do badania biodegracji, Gaz, woda i technika sanitarna, 2000, 9, 6-11 (from Korrespondenz Abwasser-Wasserwirtschaft, Abwasser, Abfall 2000, 47, 520-526)
11. B. Alexander, Biodegradation testing in the regulatory environment, 1995, 199-213 - in M. RICHARDSON, Environmental toxicology assessment, England, 1995.
    M. Evans and K. Moore, Some observations on biodegradability testing of chemicals, 1995, 215-226 - in M. RICHARDSON, Environmental toxicology assessment, England, 1995
12. M. T. Garcia, N. Gathergood, P. J. Scammells, *Green Chem*., 2005, **7**, 9-14
13. S. Stolte, S. Abdulkarim, J. Arning, A. Blomeyer-Nienstedt, U. Bottin-Weber, M. Matzke, J. Ranke, B. Jastorff and J. Thoeming, *Green Chem.*, 2008, **10**, 214-224
14. J. R. Harjani, J. Farrell,M. T. Garcia, R. D. Singer, P. J. Scammells, *Green Chem.,* 2009, **11**(6), 821-829
15. S. Stolte, S. Abdulkarim, J. Arning, A. Blomeyer-Nienstedt, U. Bottin-Weber, M. Matzke, J. Ranke, B. Jastorff, J. Thoeming, *Green Chem.*, 2008, **10**, 214-224
16. N. Gathergood, M. T. Garcia and P. J. Scammells, *Green Chem*., 2006, **8**, 156-160

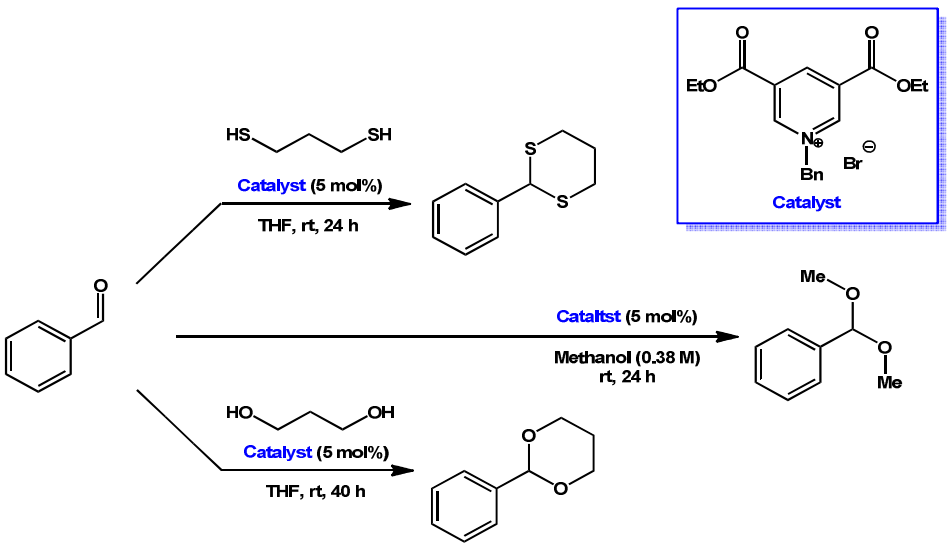
Chapter 7: Case Study

7.0 Case Study:

7.1 Discussion

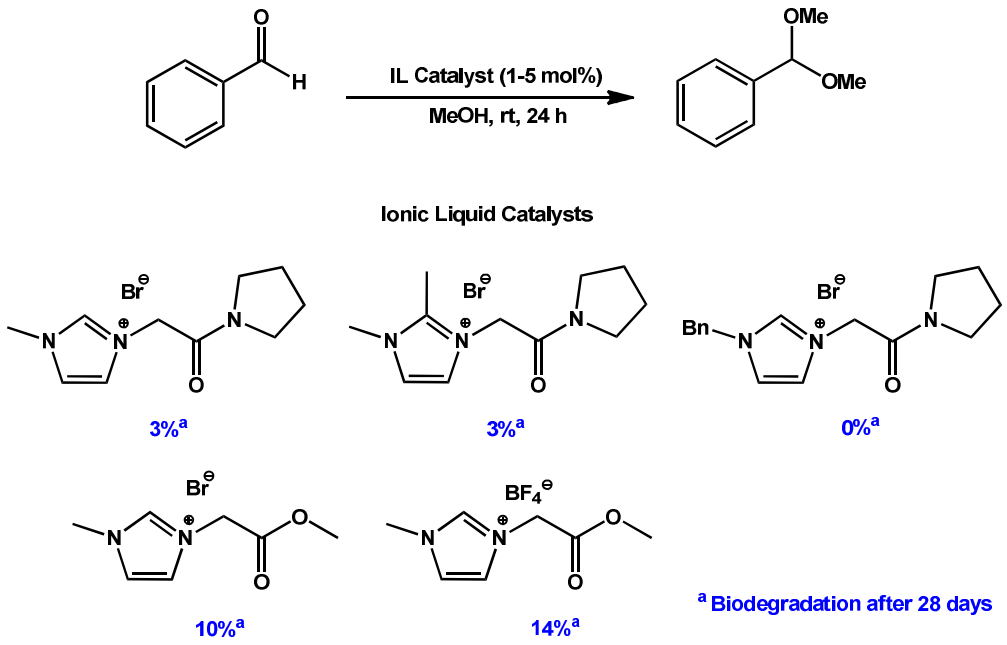
In order to design and synthesise 'Green' ionic liquid catalysts, guidelines prepared from toxicity and biodegradation studies can be helpful. Novel ionic liquids have been extensively prepared and used in organic synthetic applications, but only few research groups have published complimentary toxicity and biodegradation data to support its environmental impact.[1,2,3] Herein we discuss the tandem investigation with Connon and Myles (as part of the EPA Project to support this collaboration) to develop 'safer and greener' imidazolium compounds, whether their role is solvent, catalysts or both.

Connon and co-workers reported an application of pyridinium salts as an effective catalyst in acetalisation reactions.[4] Ester group substitution at either the 3 or both 3 and 5 positions of the pyridinium ring displayed excellent catalytic activity with very low catalyst loading in the acetalisation of benzaldehyde with methanol. The most fascinating characteristic of the catalyst was that it's not acidic in nature, but can act as a Brønsted acid in the presence of protic media. The most actively catalytic pyridinium salts, 3,5-*bis*(ethoxycarbonyl)-1-(phenylmethyl) bromide showed, excellent catalytic activity in the protection of a variety of aldehydes with methanol. The catalyst was also found to be useful in diol and dithiol protections (Scheme 7.1). Catalytic activity of the catalyst was predicted based on anticipated nucleophilic attack of the alcohol to the pyridinium to generate the Brønsted acidic active species.



Scheme 7.1: Acetalisation of benzaldehyde with methanol catalysed by pyridinium IL

On the basis of previous findings, Gathergood, Connon and co-workers reported the design, synthesis and application of imidazolium ionic liquid catalysts in acetalisation reactions.[3] A range of ester and amide side chain imidazolium ionic liquids was prepared. The catalytic activity of all of these imidazolium salts was evaluated in the acetalisation of benzaldehyde in methanol (Scheme 7.2). The absence of catalyst resulted in no formation of the corresponding acetal after 24 hours. All of the imidazolium bromide salts showed poor catalytic activity independent of ester or amide side chain (9 to 13% conversions). When switched to the NTf_2 anion, reaction conversions in amide side chain ionic liquids were increased marginally. Whereas ester side chain ionic liquids with NTf_2 anion gave 51% conversion. A tetrafluoroborate salt of a methyl ester side chain imidazolium ionic liquid gave high (85%) conversion towards required product. Hexafluorophosphate and octyl sulfate anions performed poorly in this reaction. The anion exchange from bromide to tetrafluoroborate had greatly influenced the acetalisation reaction of benzaldehyde with methanol, which gave 85% conversion.



Scheme 7.2: Acetalisation of benzaldehyde using imidazolium IL as a catalyst

The ionic liquid did not appear to have an acidic nature, but in the presence of a protic medium was proposed to generate a Brønsted acid species to catalyse the acetalisation reaction.(Fig. 7.1) The most active catalyst with tetrafluoroborate anion was further exploited in the acetalisation reactions of a variety of aldehydes with methanol at room temperature. These reactions showed good to excellent conversions with 5-10% catalyst

loading. When saturated aldehyde such as 3-phenylpropanal reacted with deuterated methanol in presence of 1 mol% catalyst, the reaction gave quantitative conversion in only 1 minute. Diol and dithiol protection of benzaldehyde showed very good results. The BF_4 catalyst promoted protection of benzaldehyde with 1,2-ethanedithiol gave 92% conversion, whereas 1,3-propanedithiol and 1,3-propanediol gave 65% and 86% conversion respectively. Recyclability of the most active BF_4 anion catalyst was performed on the 1,3-dithiolane protection of benzaldehyde. The catalyst was recycled and reused 15 times without significant loss of activity.

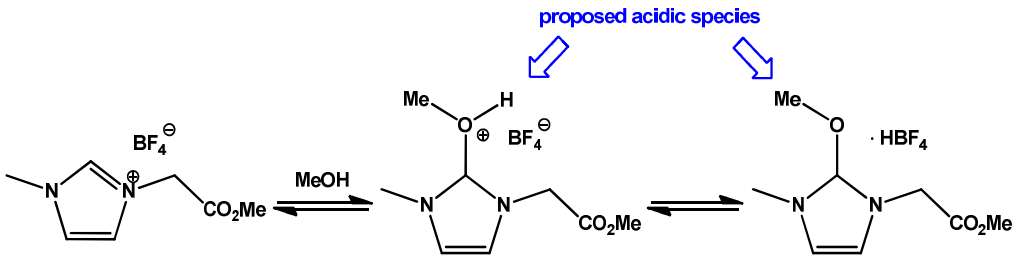


Fig. 7.1: Proposed mode of action of catalytic aprotic imidazolium ions

Biodegradation studies of pyridinium-based ILs have shown that esters substitution at either the 1 or 3-position have a beneficial effect on degradation of the heterocyclic core, independent of the anion.[2] Also biodegradation studies in the literature have shown that only the side chain of the imidazolium ionic liquids undergo degradation, whereas imidazole core was found to persist in most of the OECD tests.[5] Hence in an effort to increase the biodegradation such ester substitution onto the imidazole ring was designed. Also incorporation of electron withdrawing groups via ester substitution on the imidazole ring was expected to increase catalytic activity of the ionic liquids in the acetalisation reaction. A series of ester and amide substituted derivatives at C-2 (Fig. 7.2), C-4 (Fig. 7.3) and both C-4 and C-5 (Fig. 7.4) positions of the imidazolium ionic liquids with ester and amide side chains was tested in acetalisation of benzaldehyde with methanol with 1 mol% of catalyst loading.[6]

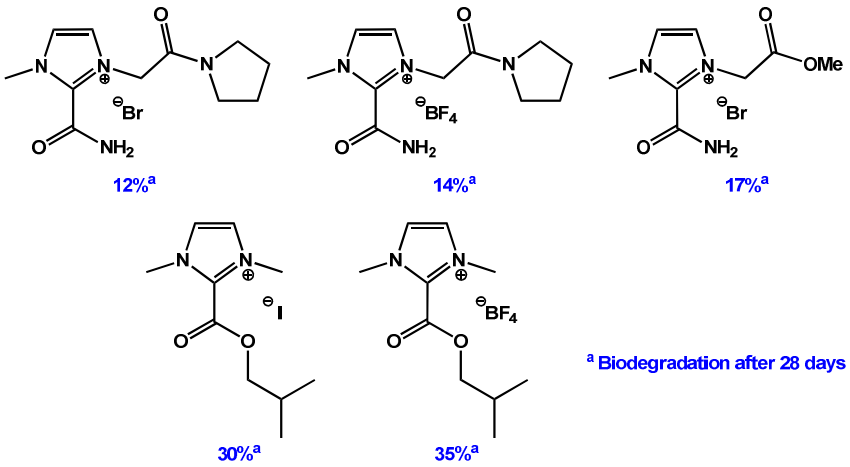


Fig. 7.2: C-2 substituted imidazolium ionic liquids

All C-2 substituted ionic liquid catalysts have given similar conversions between the range 82% to 86%, except the 1,3-dimethylimidazolium catalyst with isobutyl ester at 2-position and BF_4 anion (which gave 91% conversion). When the amount of this BF_4 catalyst was decreased to 0.1 mol%, conversion was decreased to 72% (Fig. 7.2). This can be supported by our proposed mode of action (Fig. 7.1). C-2 substituted ionic liquids are more sterically hindered (ionic liquids from Scheme 7.2), which may account for the drop in yields. Hence Gathergood and Connon moved to the C-4 substituted ionic liquid catalysts. Quantitative yields were obtained by using 1 mol% of C-4 substituted ionic liquid catalysts (Fig. 7.3), but when catalyst loading was reduced to 0.1 mol%, conversions dropped between 78 to 88%, dependent on the IL catalyst structure

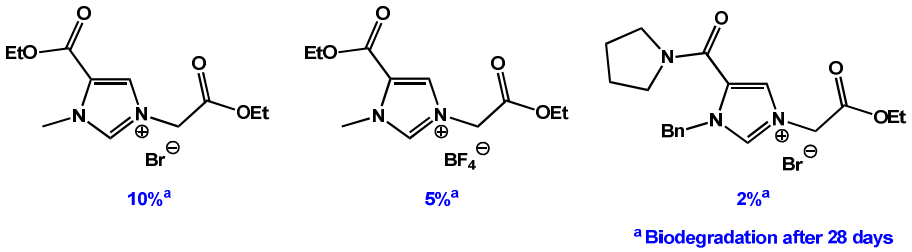


Fig. 7.3: C-4 substituted imidazolium ionic liquids

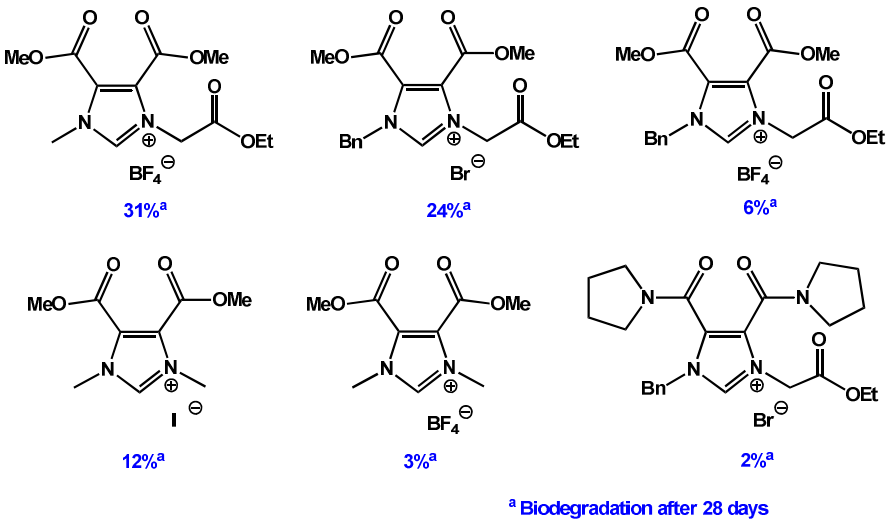


Fig. 7.4: C-4 and C-5 di-substituted imidazolium ionic liquids

As an electron withdrawing group at C-2 and C-4 positions showed increase in the conversions at 1 mol% catalyst loading, C-4 and C-5 di-substituted ionic liquid catalysts were designed with the expectation of increased catalytic activity. With 2 electron withdrawing groups at C-4 and C-5 position of imidazolium cation, ionic liquid catalysts (Fig. 7.4) gave quantitative conversions for the acetylization of benzyaldehyde at 1 mol% catalyst loading. Of note, high yields were obtained even after reducing the amount of catalyst to 0.1 mol% (86% to 94%). Hence a clear trend in the conversions was observed as C-2 < C-4 < C-4 and C-5 substituted ionic liquid catalysts, when catalyst loading was decreased to 0.1 mol%.

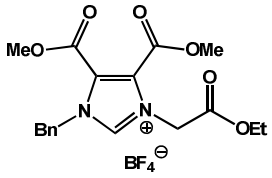
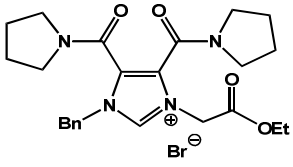
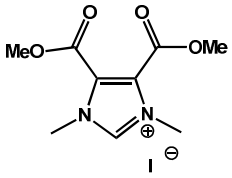
Biodegradation studies of ester and amide side chain ionic liquids along with substituted imidazolium salts was also carried out by using the "CO_2 Headspace" test (ISO 14593) (Scheme 7.2, Figs. 7.1-7.4).[7] All imidazolium ionic liquids prepared failed to pass the minimum 60% biodegradation threshold value in order to be classified as 'readily biodegradable'. Ester functionalised ionic liquids displayed higher biodegradation levels than amide functionalised ionic liquids in 28 days. The first generation imidazolium ionic liquid catalysts showed 10% to 14% biodegradation for methyl ester side chain ionic liquids, where as maximum 3% biodegradation was observed in amide side chain ionic liquids after 28 days. The modifications on imidazole core did not help to breakdown to give complete biodegradaton. C-2 substituted imidazolium ionic liquids (Fig. 7.2) with isobutyl ester gave moderate (30% to 35%) biodegradation in comparison with C-2 amide substituted ionic liquids. Further substitution at C-4 position of imidazole ring did not improve the biodegradation. Poor biodegradation (2% to 10%) was observed in C-4 substituted imidazolium ionic liquids (Fig 7.3). The C-4

and C-5 di-substituted imidazolium ionic liquids also failed to pass the 60% biodegradation threshold in order to be classified as 'readily biodegradable' (Fig. 7.4).

The toxicity of all ionic liquids was tested in an environmental and medicinally significant microbial assay including 12 fungal and 8 bacterial strains.[7,3] *In vitro* antifungal activities of the compounds were evaluated on a panel of four ATCC strains (*Candida albicans* ATCC 44859, *Candida albicans* ATCC 90028, *Candida parapsilosis* ATCC 22019, *Candida krusei* ATCC 6258) and eight clinical isolates of yeasts (*Candida krusei* E28, *Candida tropicalis* 156, *Candida glabrata* 20/I, *Candida lusitaniae* 2446/I, *Trichosporon asahii* 1188) and filamentous fungi (*Aspergillus fumigatus* 231, *Absidia corymbifera* 272, *Trichophyton mentagrophytes* 445). Whereas *In vitro* antibacterial activities of the compounds were evaluated on a panel of three ATCC strains (*Staphylococcus aureus* ATCC 6538, *Escherichia coli* ATCC 8739, *Pseudomonas aeruginosa* ATCC 9027) and five clinical isolates (*Staphylococcus aureus* MRSA HK5996/08, *Staphylococcus epidermidis* HK6966/08, *Enterococcus* sp. HK14365/08, *Klebsiella pneumoniae* HK11750/08, *Klebsiella pneumoniae* ESBL HK14368/08).

All ester and amide side chain ionic liquids shown in Scheme 15 were non-toxic up to the 2000 μM concentration. Ionic liquids with ester and amide functionality either at C-2 (Fig 7.2) or at C-4 position (Fig 7.3) were found to be non-toxic within 2000 μM concentration. C-4 and C-5 di-substituted imidazolium ionic liquids were found to inhibit the growth of both fungi and bacteria (Table 7.1). In general, C-2 or at C-4 substituted ionic liquids were less toxic than the C-4 and C-5 di-substituted imidazolium ionic liquids, independent of ester or amide functionality. However, of significance is the level of toxicity for the iodide salt in Table 2. IC_{95} values of 500 μM are reported, while this is more toxic than traditional BMIM ionic liquids, this is less toxic than values reported for antimicrobial QAC (IC_{95} >10 μM).[8]

Table 7.1. Antimicrobial toxicity data for catalysts which showed activity in screen.

Organisms	Time (h)	MIC Values (μM) for C-4 and C-5 di-substituted imidazolium ionic liquid catalysts		
				
Candida albicans ATCC 44859	24	> 2000	> 1000	**500**
	48	> 2000	> 1000	**500**
Staphylococcus aureus ATCC6538	24	**2000**	> 1000	**500**
	48	**2000**	> 1000	**500**
Staphylococcus epidermidis HK 6966/08	24	**1000**	> 1000	**500**
	48	**1000**	> 1000	**500**
Escherichia coli ATCC 8739	24	> 2000	> 1000	**1000**
	48	> 2000	> 1000	**2000**

In order to evaluate the 'greenness' of the synthesis of ionic liquid catalysts some important Green Chemistry metrics were used, such as -

- Sheldon E-factor
- GSK Reaction Mass Efficiency,
- Andraos Reaction Mass Efficiency
- Atom economy
- 1 / stoichiom. factor (excess reagents)

These metrics assisted improvements in the synthetic process, by reducing amount of solvents in the work-up and purification procedure, reduce number of steps to make required compounds. For example, as the synthesis of tetrafluoroborate ionic liquids involves preparation of halide salts followed by anion exchange metathesis. In an effort to reduce the number of steps and amount of reagents and solvents in the synthesis, alkyl imidazoles were directly reacted to Meerwein's salt i.e. trimethyloxonium

tetrafluoroborate to give tetrafluoroborate ionic liquids in excellent yield. Hence Green Chemistry metrics assessment is important to achieve green synthesis.

7.2 Conclusion:

In the case study, we have demonstrated the schematic approach towards the design and synthesis of ionic liquid catalysts for acetalisation reactions and evaluation of the biocompatibility of such catalysts, by using toxicity and biodegradation methods. According to the guidelines laid by the toxicity and biodegradation testing, ionic liquid catalysts were designed and prepared. Such ester and amide side chain imidazolium catalysts were found to be useful in acetalisation and thioacetalisation reactions. These catalysts have shown low toxicity against a variety of fungal and bacterial strains, but poor biodegradability in the "CO_2 Headspace Test". Further modifications in the cationic part were designed to increase biodegradation and catalytic activity. Although biodegradation was not improved by such modifications, the catalytic activity was modified and increased to a great extent. Green Chemistry metrics had given useful information about the 'greenness' of the synthetic route. Which allowed us to modify the process by reducing the number of steps, amount of solvents, etc. This case study was a clear example of the importance, in the design of organocatalysts, of what the potential environmental impact of such compounds might be, and why it is important to understand that a truly "green" catalyst needs to possess a balance of both activity and eco-friendliness.

7.3 References:

1. D. A. Evans, S. J. Miller, T. Lectka, P. von Matt, *J. Am. Chem. Soc.*, 1999, **121**, 7559-7573
2. J. R. Harjani, R. D. Singer, M. T. Garcia, P. J. Scammells, *Green Chem.*, 2009, **11**, 83-90
3. L. Myles, R. Gore, N. Gathergood, S. J. Connon, *Green Chem.*, 2010, **12**, 1157-1162

4. (a) B. Procuranti, S. J. Connon, *Chem. Commun.* 2007, 1421-1423, (b) B. Procuranti and S. J. Connon, *Org. Lett.*, 2008, **10**, 4935-4938, (c) B. Procuranti, L. Myles, N. Gathergood, S. J. Connon, *Synthesis*, 2009, **23**, 4082-4086
5. S. Stolte, S. Abdulkarim, J. Arning, A. Blomeyer-Nienstedt, U. Bottin-Weber, M. Matzke, J. Ranke, B. Jastorff, J. Thoeming, *Green Chem.*, 2008, **10**, 214-224
6. L. Myles, R. G. Gore, N. Gathergood, S. J. Connon, 2012, submitted
7. R. G. Gore, L. Myles, M. Spulak, T. M. Garcia, S. J. Connon, N. Gathergood, 2012, submitted
8. T. P. T. Pham, C.-W. Cho, Y.-S. Yun, *Water Res.*, 2010, **44**, 352-372

Chapter 8: Thesis Conclusion and Future Work

8.0 Thesis Conclusions and Future Work:

Short and effective synthesis of a series of ester side chain achiral ionic liquids has been achieved. Considering the issue of stability of ester side chain ionic liquids, some amide side chain salts also have been prepared. Bromide salts prepared were solid at room temperature with high melting point. Whereas anion exchange metathesis helped to reduce the melting point. Successful synthesis of a number of C2-position ester substituted ionic liquids (**45**-**47**) has been achieved. Along with this, C2-position amide substituted ionic liquids (**40**-**44**) have been synthesized. Anion exchange metathesis on all halide ionic liquids was done with successful conversion in near quantitative yields. Highly efficient synthesis of IL **47** was carried out with using Meerwein's reagent, eliminating the need for anion exchange metathesis, with quantitative yield.

1st generation methyl ester and pyrrolidine amide side chain ionic liquid catalysts were screened in acetalisation reactions. The results showed that aprotic ionic liquids can catalyze reactions in the presence of protic media such as methanol, dithiol etc. Bromide salts of ester and amide side chain ionic liquid catalysts gave 10-14% conversion, whereas *bis*(trifluoromethanesulfonimide) anion of respective cations gave an increase in the conversion (i.e. 23% to 56%). Tetrafluoroborate (BF_4^-) anion of methyl ester side chain ionic liquid (**20**) gave the maximum yield value i.e. 85% yield. This most active catalyst was recycled 15 times without loss of catalytic activity. The introduction of electron withdrawing ester groups at the C-2 position of the imidazole core dramatically improved the catalytic activity of ionic liquid catalysts. All 2nd generation imidazolium core modified ionic liquids (**40**-**47**) gave similar conversions (80% to 91%) when compared with the best 1st generation catalyst **20** even at 1 mol% catalyst loading. The catalyst **46**, with BF_4^- anion, resulted in the highest 91% conversion (1 mol%), which dropped to 72% after reducing the amount of catalyst to 0.1 mol%.

Ionic liquids with either methyl or ester group at the C2-position were screened as a solvent in a Carbonyl-Ene reaction and performed well compared to molecular solvents, such as dichloromethane, diethyl ether, & toluene. All ester and amide side chain ionic liquids have proved to be possible replacements for volatile organic solvents in such reactions. Novel 2-position modified ionic liquid (**46)** gave excellent yield (96%) with 91% enantioselectivity in the reaction of methylenecyclohexane and ethyl trifluoropyruvate. The expensive (*R*)-BINAP palladium catalyst was immobilized in the ionic liquid, and recycled at least 6 times without loss of yield and catalytic activity.

The environmental impact of the novel ionic liquids was tested via anti-microbial and biodegradation studies. Green chemistry metrics were also used to evaluate the 'greenness' of the synthetic processes used in the production of the ionic liquids. Antimicrobial testing has been performed on all synthesized ionic liquids against 12 strains of fungi and 8 strains of bacteria. Most of the ester and amide side chain ionic liquids were found to be non-toxic up to 2 mM concentration in the test system (with the only exception being decyl amide side chain derivatives). Novel imidazolium core modified ionic liquids haven't shown any anti-microbial activity in the test system. Some representative examples from these ionic liquids were tested against some common bacterial strains with higher concentrations (up to 200mM). This study has shown that certain ionic liquids can be tolerated by bacteria, even at high concentrations.

Biodegradation studies of some selected ester and amide side chain ionic liquids, along with substituted imidazolium salts, was also carried out by using the "CO_2 Headspace" test (ISO 14593). All imidazolium ionic liquids prepared failed to pass the minimum 60% biodegradation threshold value in order to be classified as 'readily biodegradable'. Ester functionalised ionic liquids displayed higher biodegradation levels than amide functionalised ionic liquids after 28 days. The first generation imidazolium ionic liquids showed 10% to 14% biodegradation for methyl ester side chain ionic liquids, where as maximum of 3% biodegradation was observed in amide side chain ionic liquids after 28 days. The modifications on the imidazole core did not help to breakdown to give complete biodegradation. C-2 substituted imidazolium ionic liquids (Table 2.4, Chapter 2) with *iso*butyl ester gave moderate (30% to 35%) biodegradation in comparison with C-2 amide substituted ionic liquids.

In order to evaluate the 'greenness' of the synthesis of ionic liquid catalysts, Gathergood and Connon have also applied some important Green Chemistry metrics (Section 4), such as the (a) Sheldon E-factor, (b) GSK Reaction Mass Efficiency, (c) Andraos Reaction Mass Efficiency, (d) Atom Economy, (e) 1/Stoichiometric Factor (excess reagents). These metrics assisted improvements in the synthetic process, by reducing the amount of solvents used in the work-up and purification procedure and reduced number of steps to make the required compounds.

In order to design and synthesise more environmentally friendly 'Green' solvents and catalysts, further efforts to increase the aerobic biodegradation of imidazolium ionic liquids need to be emphasised in future studies. As our aim is to to follow green chemistry principles to achieve "greener" organic synthesis, high atom economical

reactions, such as the Baylis-Hillman and Diels-Alder reactions, should be studied in low-toxicity and preferably biodegradable ionic liquids in the future. Further exploitation of Brønsted acidic imidazolium ionic liquid catalysts should be studied in other appropriate reactions such as in *trans*-acetalisation reactions and esterification reactions.

Chapter 9: Experimental

9.0 Experimental:

9.1 Introduction

9.1.1 Chemicals:

All chemicals were purchased from Sigma Aldrich, with the exception of lithium *bis*(trifluromethanesulfonyl) imide ($LiNTf_2$) which was purchased from Solvionic. Methanol, ethanol, hexane and triethylamine were dried over molecular sieves and distilled before use. 1-butanol, 1-pentanol, 1-decanol were dried over molecular sieves and used without further purification. THF and diethyl ether were dried over sodium/benzophenone ketyl and was distilled before use. DCM was dried over calcium hydride, and distilled before use. Riedel de Haën silica gel was used for flash and thin layer chromatography. Formic acid, water with 0.1% formic acid (HPLC-MS grade), acetonitrile with 0.1% formic acid (HPLC-MS grade). Ammonium chloride (NH_4Cl), calcium chloride anhydrous ($CaCl_2.2H_2O$) and Magnesium sulphate heptahydrate ($MgSO_4.7H_2O$) were obtained from Riedel de Haën. and Fluka respectively.

9.1.2 NMR:

All NMR analysis was performed on either a Bruker AC 400 MHz or Bruker AC 600 MHz spectrometer in deuterated chloroform ($CDCl_3$), acetonitrile (CD_3CN) or dimethyl sulfoxide (DMSO-d_6), operating at 400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR. A 600 MHz spectrometer, operating at 600 MHz for ^1H NMR and 150 MHz for ^{13}C NMR, was also used for analysis of some examples. Chemical shifts are reported in parts per million (ppm) and are relative to the internal standard (TMS) and coupling constants (*J*) are reported in Hertz (Hz). When stating multiplicity of peaks in NMR the following abbreviations are used; s-singlet, d-doublet, t-triplet, q-quartet, qt-quintet, dd-doublet of doublets, tt-triplet of triplets, sept-septate of triplet, m-multiplet, br-broad.

9.1.3 Optical Rotation

Optical rotations were measured using a Perkin Elmer 343 Polarimeter in chloroform at 20 °C.

9.1.4 Melting point

Melting points, were appropriate and determined using a Griffin melting point apparatus and the values are expressed in degrees Celsius (°C).

9.1.5 MS

High resolution mass spectrometry was obtained for all ionic liquids in the 'High Resolution Mass Spectrometer Centre', UCC, Cork.

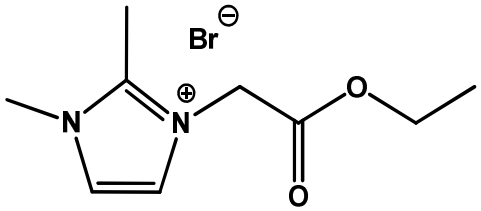
9.1.6 LC-MS

High Performance Liquid Chromatography (HPLC) analysis of ionic liquids was carried out on an Agilent Technologies 1200 Series Liquid Chromatography system, with a degasser and quaternary pump (G1311A), and Dual Loop Autosampler (DLA-G2258A). Agilent Chemstation software was also utilised in processing obtained spectral data (Agilent ChemStation Rev.B.03.01-SR1 [317]). MS analysis was performed on an Agilent Technologies 6110 Mass Spectrometer (Quadrupole G6110A) and a Bruker Esquire 3000 Mass spectrometer. Direct Infusion Electrospray Ionization (DI-ESI MS) was carried out using a Cole Palmer 749000 Series 100 μL syringe pump.

9.2 Procedures for synthesis of ionic liquids:

Compounds **1-7,** 3-methyl-1-(methoxycarbonylmethyl)imidazolium bromide (**8**), 3-methyl-1-(methoxycarbonylmethyl)imidazolium *bis*(trifluoromethanesulfonimide) (**19**), 3-methyl-1-(pyrrolidinecarbonylmethyl)imidazolium bromide (**12**), 2,3-dimethyl-1-(pyrrolidinecarbonyl-methyl)imidazolium bromide (**13**) and all chiral ionic liquids **48-71** were prepared according to literature methods.[1]

1*H*-Imidazolium, 1,2-dimethyl-3-(2-ethoxy-2-oxoethyl)-1-methyl- bromide (9):



Procedure:

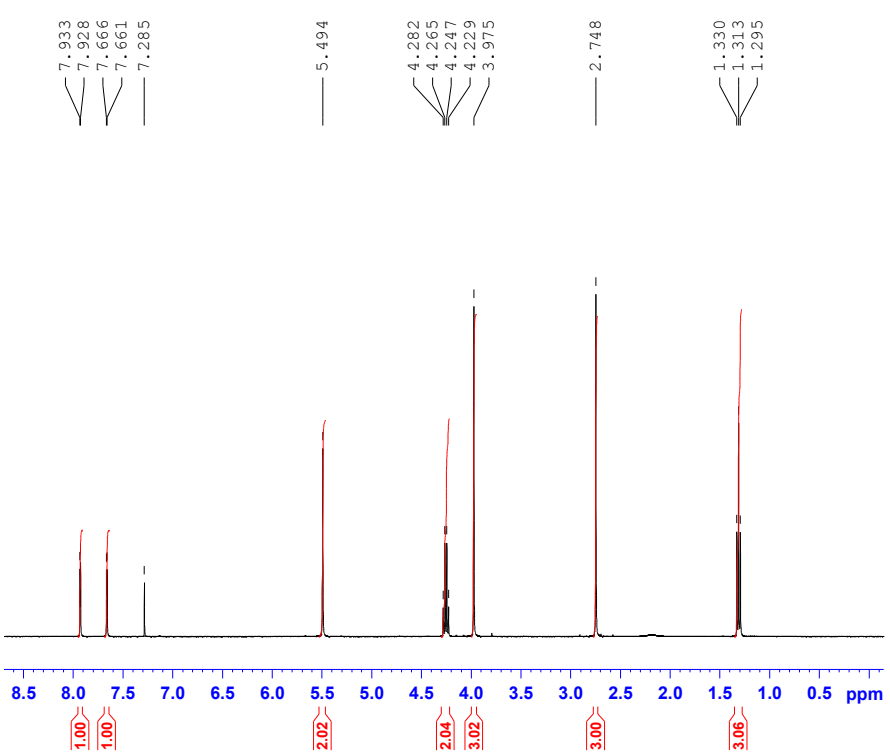
A RB flask was charged with ethyl bromoacetate (1.00 g, 5.90 mmol) and diethyl ether (20 mL) under nitrogen. To this solution was added 1,2-dimethylimidazole (0.575 g, 5.90 mmol). The reaction mixture was stirred vigorously for 24 h. The product precipitated out as a white solid. The product was then washed with diethyl ether (10 x 10 mL). The solvent was removed on the rotary evaporator. The product was dried *in vacuo* for 72 h to give **9** as a white solid at RT in 95% yield (1.50 g, 5.60 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.93 (d, J = 2.0 Hz, 1H), 7.66 (d, J = 2.0 Hz, 1H), 5.49 (s, 2H), 4.25 (q, J = 7.2 Hz, 2H), 3.97 (s, 3H), 2.75 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): 166.28, 145.62, 123.00, 122.41, 62.89, 50.01, 36.10, 14.10, 11.26

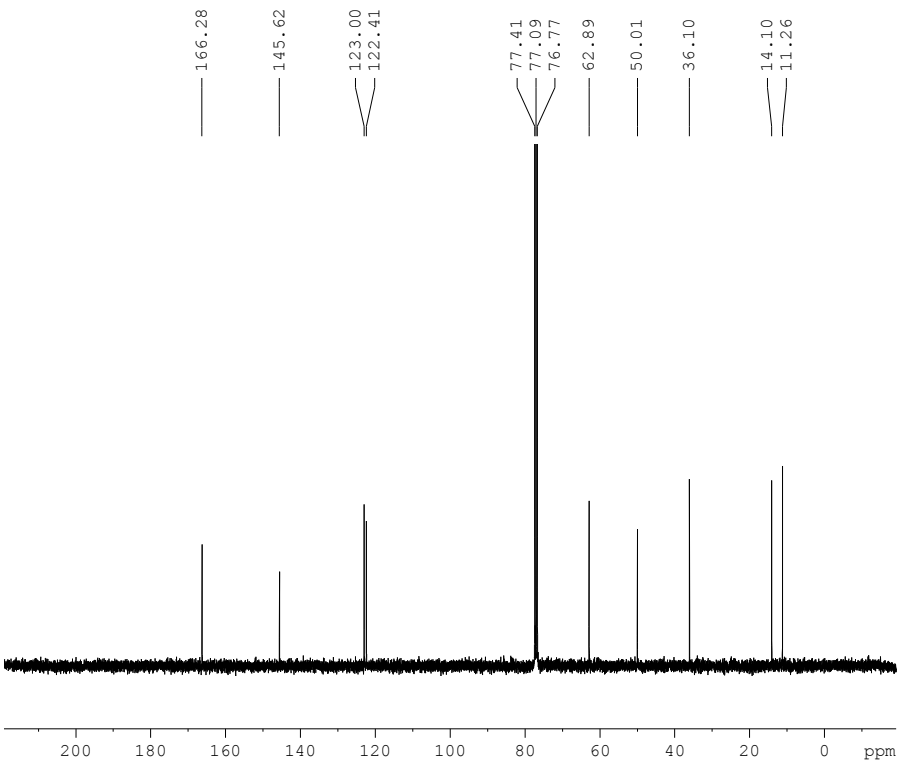
Melting point: 130-131 ºC

ES-MS (+ve) m/z: Found $[M–Br^–]^+$ 183.1127, $C_9H_{13}N_2O_2^+$ requires 183.1128



BRUKER

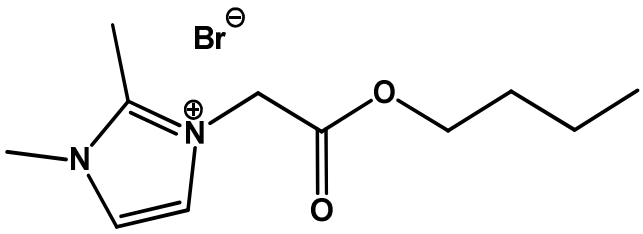
```
Current Data Parameters
NAME                  Jul14-2010
EXPNO                         10
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20100714
Time_                      16.46
INSTRUM                    spect
PROBHD  5 mm QNP 1H/13
PULPROG                    zg30
TD                        65536
SOLVENT                   CDCl3
NS                           16
DS                            2
SWH                    8278.146 Hz
FIDRES                 0.126314 Hz
AQ                     3.9584243 sec
RG                          181
DW                        60.400 usec
DE                         6.00 usec
TE                        294.2 K
D1                     1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         1H
P1                        12.25 usec
PL1                        0.00 dB
SFO1                  400.1324710 MHz

F2 - Processing parameters
SI                         32768
SF                    400.1300000 MHz
WDW                           EM
SSB                            0
LB                          0.30 Hz
GB                             0
PC                          1.00
```



BRUKER

```
Current Data Parameters
NAME                  Jul14-2010
EXPNO                         11
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20100714
Time_                      17.46
INSTRUM                    spect
PROBHD  5 mm QNP 1H/13
PULPROG                  zgpg30
TD                        65536
SOLVENT                   CDCl3
NS                         1024
DS                            4
SWH                   23980.814 Hz
FIDRES                 0.365918 Hz
AQ                     1.3664756 sec
RG                         2580.3
DW                        20.850 usec
DE                         6.00 usec
TE                        294.2 K
D1                     2.00000000 sec
d11                    0.03000000 sec
DELTA                  1.89999998 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         13C
P1                        10.00 usec
PL1                        0.00 dB
SFO1                  100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                  waltz16
NUC2                         1H
PCPD2                     80.00 usec
PL2                       -3.00 dB
PL12                      12.00 dB
PL13                      12.00 dB
SFO2                  400.1316005 MHz

F2 - Processing parameters
SI                         32768
SF                    100.6127690 MHz
WDW                           EM
SSB                            0
LB                          1.00 Hz
GB                             0
PC                          1.40
```

1*H*-Imidazolium, -1,2-dimethyl-3-(2-butoxy-2-oxoethyl)-1-methyl- bromide (10):



Procedure:

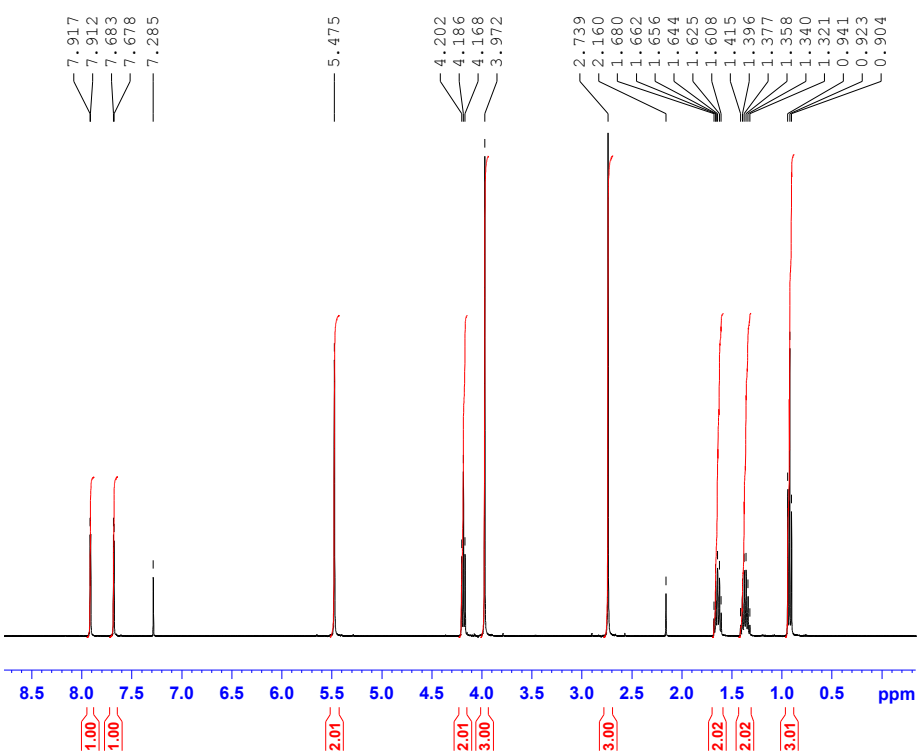
A RB flask was charged with butyl bromoacetate (**1**) (8.17 g, 41.9 mmol) and diethyl ether (150 mL) under nitrogen. To this solution was added 1,2-dimethylimidazole (4.02 g, 41.9 mmol). The reaction mixture was stirred vigorously for 24 h. The product precipitated out as a white solid. The product was then washed with diethyl ether (10 x 100 mL). The solvent was removed on the rotary evaporator. The product was dried *in vacuo* for 72 h to give **10** as a white solid at RT in 71% yield (8.66 g, 29.75 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.91 (d, J = 2.0 Hz, 1H), 7.68 (d, J = 2.0 Hz, 1H), 5.47 (s, 2H), 4.18 (t, J = 6.8 Hz, 2H), 3.97 (s, 3H), 2.74 (s, 3H), 1.65 (m, 2H), 1.36 (m, 2H), 0.92 (t, J = 7.6 Hz, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): 166.33, 145.60, 122.97, 122.44, 66.68, 49.98, 36.09, 30.35, 18.96, 13.65, 11.26

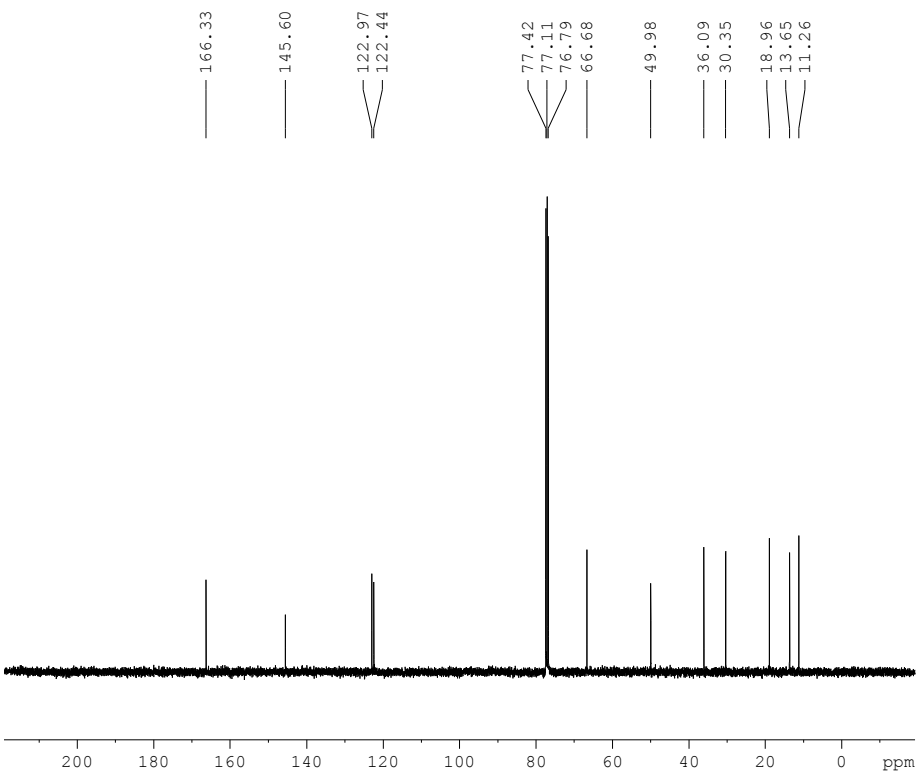
Melting point: 75-76 ºC

ES-MS (+ve) m/z: Found $[M–Br^–]^+$ 211.1453, $C_{11}H_{19}N_2O_2^+$ requires 211.1441



BRUKER

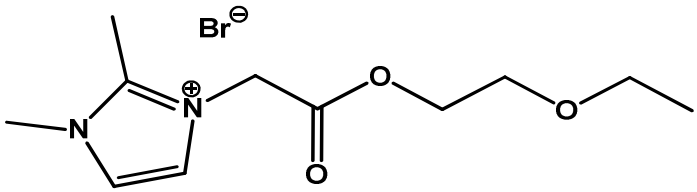
```
Current Data Parameters
NAME                  Oct28-2010
EXPNO                         80
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20101028
Time                       11.10
INSTRUM                    spect
PROBHD  5 mm QNP 1H/13
PULPROG                     zg30
TD                         65536
SOLVENT                    CDCl3
NS                            16
DS                             2
SWH                     8278.146 Hz
FIDRES                  0.126314 Hz
AQ                      3.9584243 sec
RG                           128
DW                        60.400 usec
DE                         6.00 usec
TE                        293.2 K
D1                      1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                          1H
P1                         12.25 usec
PL1                         0.00 dB
SFO1                  400.1324710 MHz

F2 - Processing parameters
SI                         32768
SF                    400.1300000 MHz
WDW                           EM
SSB                            0
LB                          0.30 Hz
GB                             0
PC                          1.00
```



BRUKER

```
Current Data Parameters
NAME                  Oct28-2010
EXPNO                         11
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20101028
Time                       18.21
INSTRUM                    spect
PROBHD  5 mm QNP 1H/13
PULPROG                  zgpg30
TD                         65536
SOLVENT                    CDCl3
NS                          1024
DS                             4
SWH                    23980.814 Hz
FIDRES                  0.365918 Hz
AQ                      1.3664756 sec
RG                          6502
DW                        20.850 usec
DE                         6.00 usec
TE                        294.2 K
D1                      2.00000000 sec
d11                     0.03000000 sec
DELTA                   1.89999998 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         13C
P1                         10.00 usec
PL1                         0.00 dB
SFO1                  100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                  waltz16
NUC2                          1H
PCPD2                      80.00 usec
PL2                        -3.00 dB
PL12                       12.00 dB
PL13                       12.00 dB
SFO2                  400.1316005 MHz

F2 - Processing parameters
SI                         32768
SF                    100.6127690 MHz
WDW                           EM
SSB                            0
LB                          1.00 Hz
GB                             0
PC                          1.40
```

1*H*-Imidazolium, 1,2-dimethyl-3-[2-(2-ethoxyethoxy)-2-oxoethyl]-1-methyl-bromide (11):



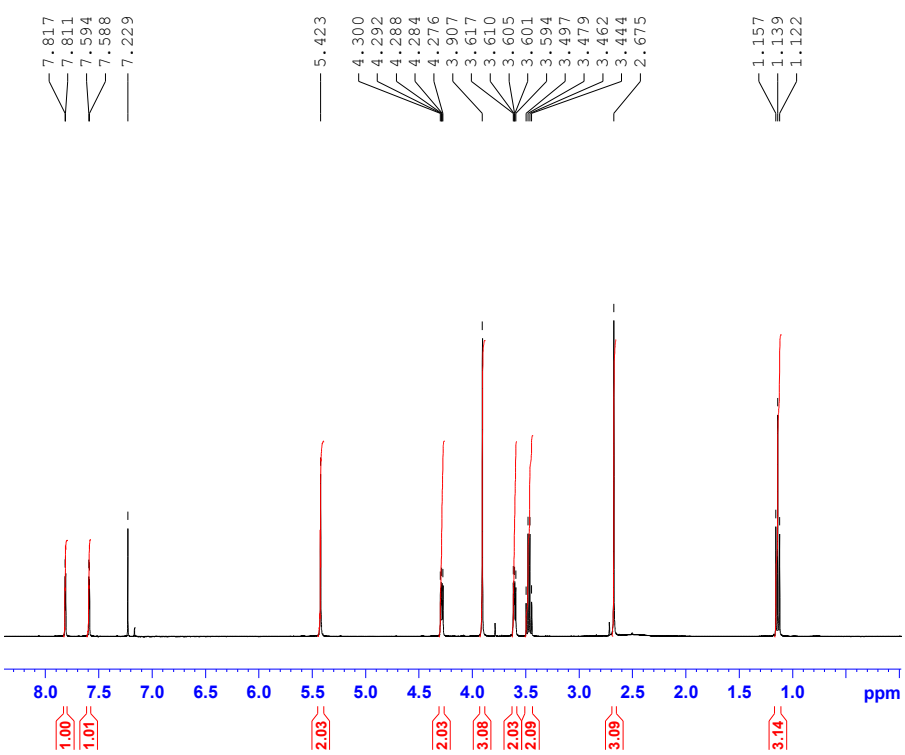
Procedure:

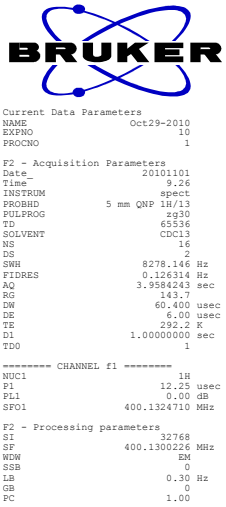
A RB flask was charged with 2-ethoxyethyl bromoacetate (**2**) (3.51 g, 16.58 mmol) and diethyl ether (75 mL) under nitrogen. To this solution was added 1,2-dimethylimidazole (1.75 g, 18.24 mmol). The reaction mixture was stirred vigorously for 24 h and the product precipitated out as a brown liquid. The product was then washed with diethyl ether (10 x 100 mL) solvent removed on the rotary evaporator and dried *in vacuo* for 72 h to give **11** as a brown liquid at RT in 61% yield (3.11 g, 10.13 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.81 (d, J = 2.4 Hz, 1H), 7.59 (d, J = 2.4 Hz, 1H), 5.42 (s, 2H), 4.28 (m, 2H), 3.90 (s, 3H), 3.62-3.59 (m, 2H), 3.47 (q, J = 7.1 Hz, 1H), 2.67 (s, 3H), 1.14 (t, J = 7.1 Hz, 3H)

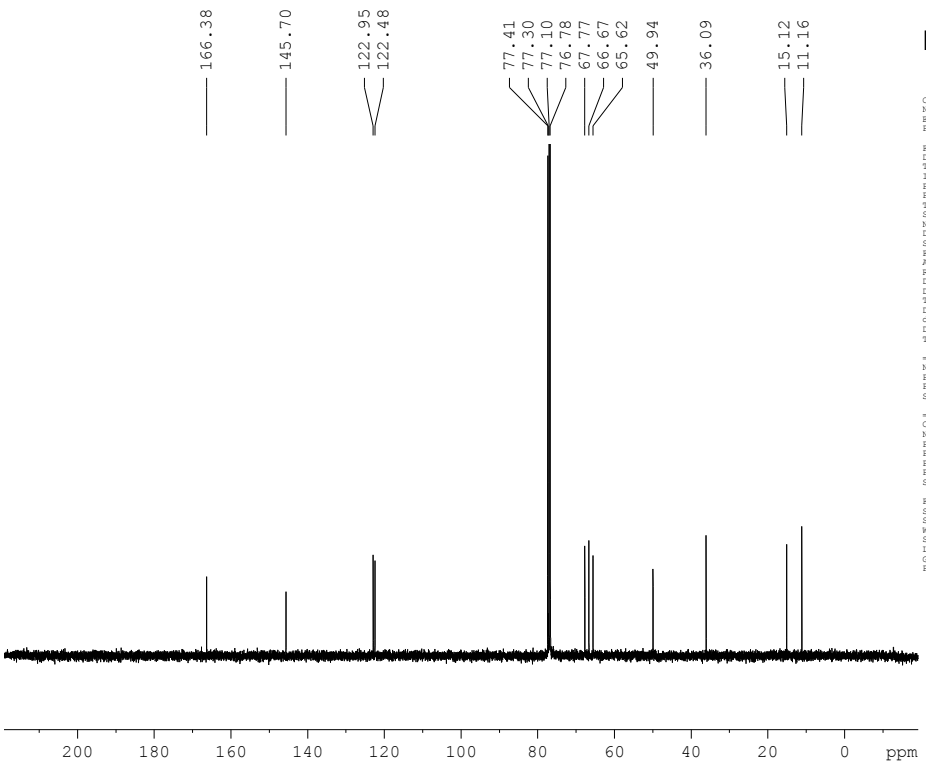
^{13}C-NMR (100 MHz, $CDCl_3$): 166.38, 145.70, 122.95, 122.48, 67.77, 66.67, 65.62, 49.94, 36.09, 15.12, 11.16

ES-MS (+ve) m/z: Found $[M–Br^–]^+$ 227.1397, $C_{11}H_{19}N_2O_3^+$ requires 227.1390



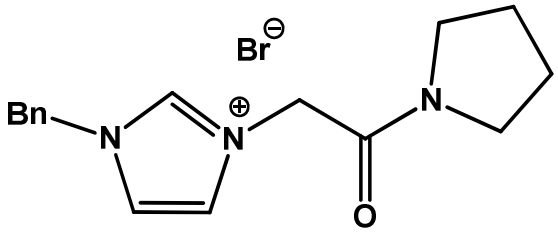



```
Current Data Parameters
NAME                  Oct29-2010
EXPNO                         10
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20101101
Time                        9.26
INSTRUM                    spect
PROBHD  5 mm QNP 1H/13
PULPROG                    zg30
TD                        65536
SOLVENT                   CDCl3
NS                           16
DS                            2
SWH                    8278.146 Hz
FIDRES                0.126314 Hz
AQ                    3.9584243 sec
RG                        143.7
DW                       60.400 usec
DE                        6.00 usec
TE                       292.2 K
D1                    1.00000000 sec
TD0                           1

======== CHANNEL f1 ========
NUC1                         1H
P1                       12.25 usec
PL1                       0.00 dB
SFO1                400.1324710 MHz

F2 - Processing parameters
SI                        32768
SF                  400.1300226 MHz
WDW                          EM
SSB                           0
LB                         0.30 Hz
GB                            0
PC                         1.00
```




```
Current Data Parameters
NAME                  Oct29-2010
EXPNO                         11
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20101101
Time                       20.14
INSTRUM                    spect
PROBHD  5 mm QNP 1H/13
PULPROG                  zgpg30
TD                        65536
SOLVENT                   CDCl3
NS                         1024
DS                            4
SWH                   23980.814 Hz
FIDRES                0.365918 Hz
AQ                    1.3664756 sec
RG                         6502
DW                       20.850 usec
DE                        6.00 usec
TE                       294.2 K
D1                    2.00000000 sec
d11                   0.03000000 sec
DELTA                 1.89999998 sec
TD0                           1

======== CHANNEL f1 ========
NUC1                        13C
P1                       10.00 usec
PL1                       0.00 dB
SFO1                100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                         1H
PCPD2                    80.00 usec
PL2                      -3.00 dB
PL12                     12.00 dB
PL13                     12.00 dB
SFO2                400.1316005 MHz

F2 - Processing parameters
SI                        32768
SF                  100.6127690 MHz
WDW                          EM
SSB                           0
LB                         1.00 Hz
GB                            0
PC                         1.40
```

1*H*-Imidazolium, 3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-1-(phenylmethyl)- bromide (14):



Procedure:

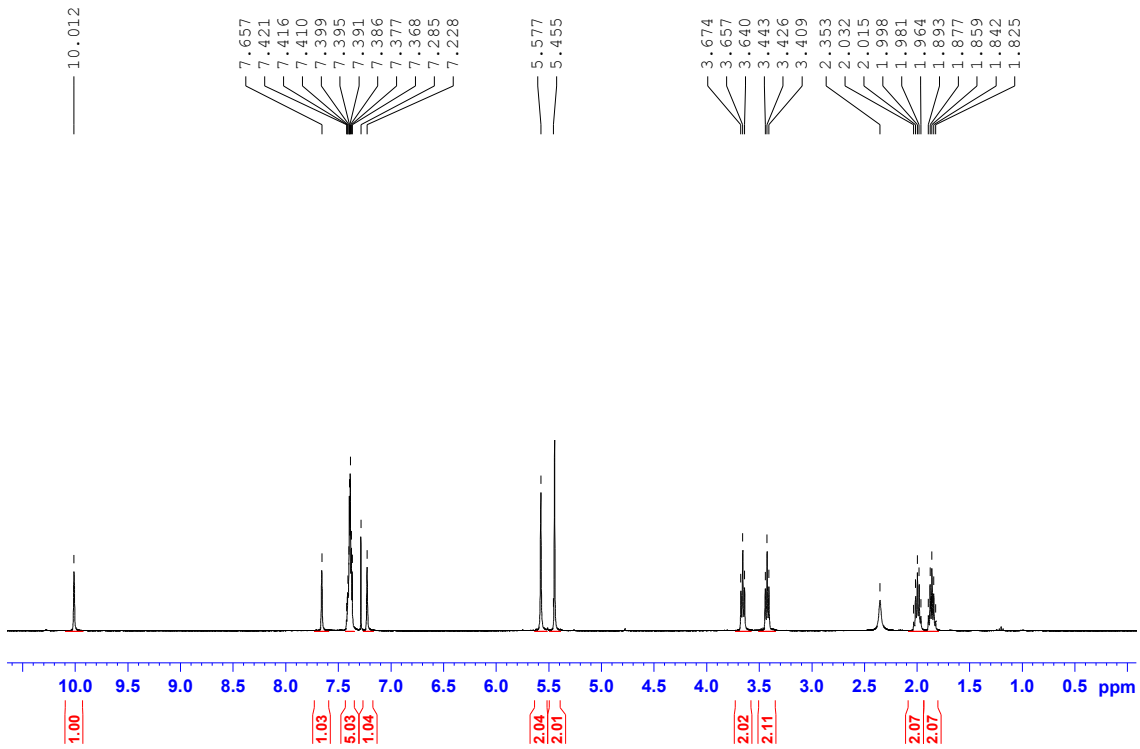
To a stirred solution of pyrrolidine bromoacetate (**3**) (2.00 g, 10.41 mmol) in diethyl ether (100 mL) at 0 ºC, under nitrogen atmosphere, was added dropwise 1-benzylimidazole (1.65 g, 10.41 mmol). The reaction mixture was stirred vigorously at 0 ºC for 1 h, then at RT overnight. The upper diethyl ether phase was decanted and the IL washed with diethyl ether (5 x 50 mL), then residual solvent was removed on the rotary evaporator. The product was dried *in vacuo* for 1 day to give **14** as a white solid at RT in 76 % yield (2.78 g, 7.94 mmol).

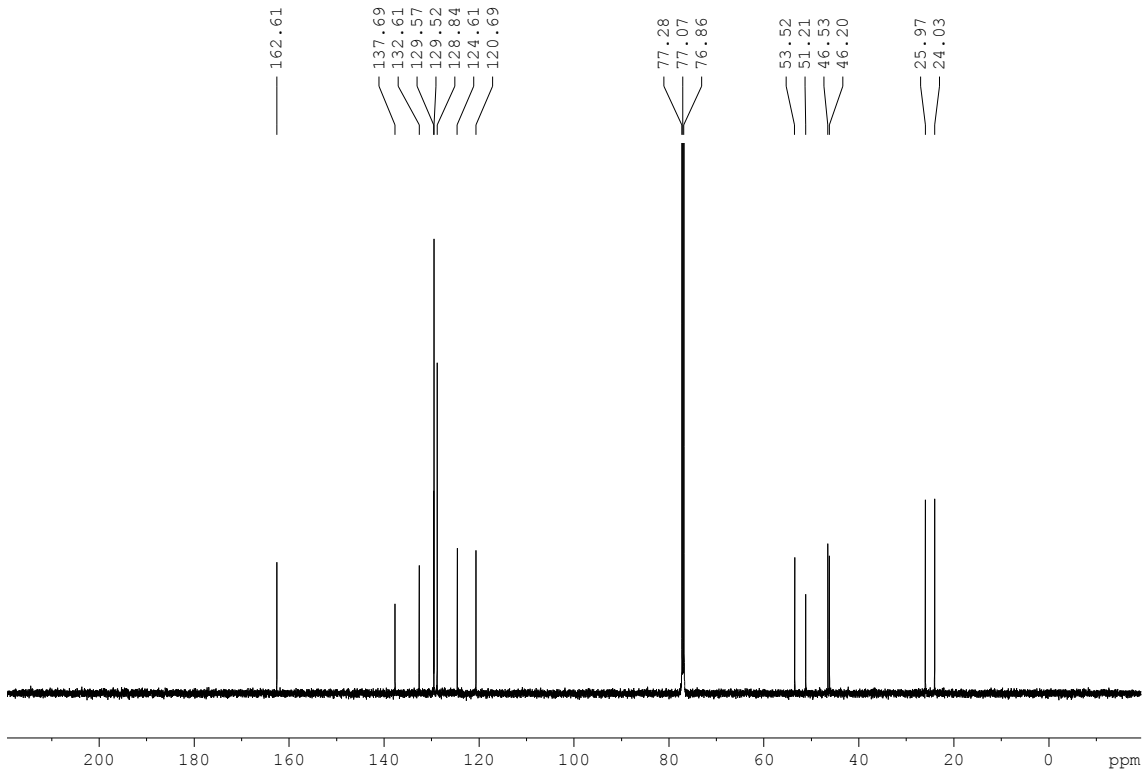
^{1}H NMR (400 MHz, $CDCl_3$): 10.01 (s, 1H), 7.65 (s, 1H), 7.42-7.36 (m, 5H), 7.22 (s, 1H) 5.57 (s, 2H), 5.45 (s, 2H) 3.65 (t, J = 6.8 Hz, 2H), 3.42 (t, J = 6.8 Hz, 2H), 2.03-1.96 (m, 2H), 1.89-1.82 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): 162.61, 137.69, 132.61, 129.57, 129.52, 128.84, 124.61, 120.69, 53.52, 51.21, 46.53, 46.20, 25.97, 24.03.

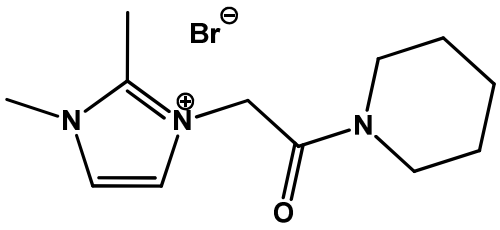
Melting point: 150-152 ºC.

ES-MS (+ve) m/z: Found $[M–Br^–]^+$ 270.1602, $C_{16}H_{20}N_3O^+$ requires 270.1601


10.012
7.657
7.421
7.416
7.410
7.399
7.395
7.391
7.386
7.377
7.368
7.285
7.228
5.577
5.455
3.674
3.657
3.640
3.443
3.426
3.409
2.353
2.032
2.015
1.998
1.981
1.964
1.893
1.877
1.859
1.842
1.825
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
1.03
5.03
1.04
2.04
2.01
2.02
2.11
2.07
2.07


162.61
137.69
132.61
129.57
129.52
128.84
124.61
120.69
77.28
77.07
76.86
53.52
51.21
46.53
46.20
25.97
24.03
200 180 160 140 120 100 80 60 40 20 0 ppm

1*H*-Imidazolium, 1,2-dimethyl-3-[2-oxo-2-(1-piperidinyl)ethyl]bromide (15):



Procedure:

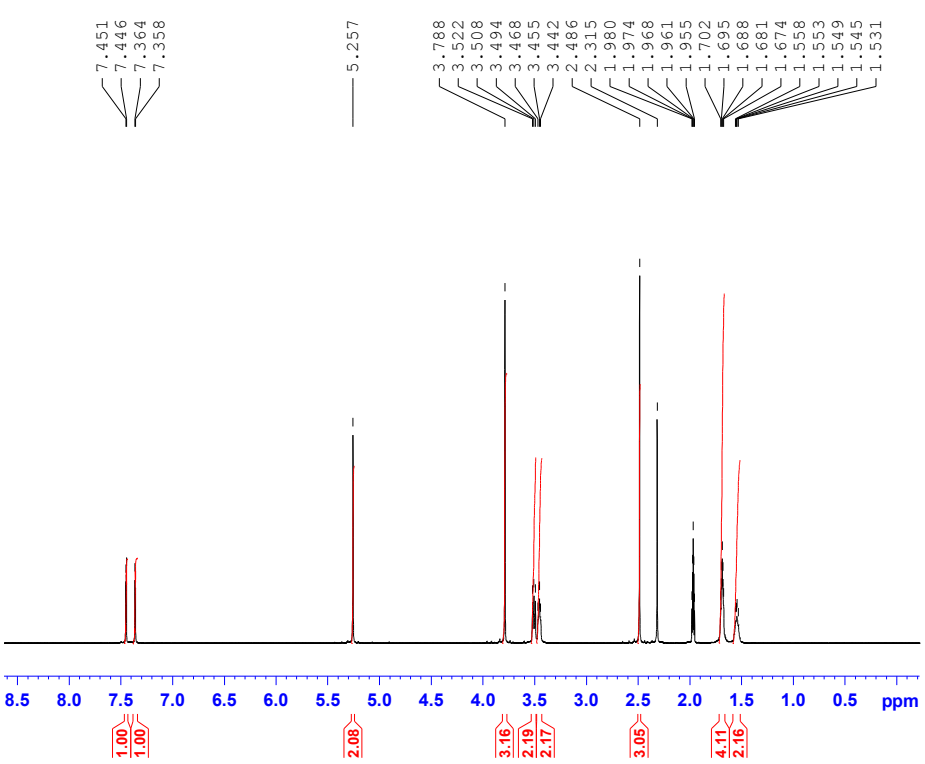
A RB flask was charged with 2-bromo-1-(piperidin-1-yl)ethanone (**4**) (4.61 g, 48 mmol) and diethyl ether (400 mL) under nitrogen. To this solution was added 1,2-dimethylimidazole (9.00 g, 43.6 mmol). The reaction mixture was stirred vigorously for 24 h. The product precipitated out as a white solid. The product was then washed with diethyl ether (10 x 100 mL). The solvent was removed on the rotary evaporator. The product was dried *in vacuo* for 72 h to give **15** as a white solid at RT in 56% yield (7.36 g, 24.45 mmol).

^{1}H-NMR (400 MHz, CD_3CN): 7.45 (d, J = 2.0 Hz, 1H), 7.36 (d, J = 2.4 Hz, 1H), 5.26 (s, 2H), 3.79 (s, 3H), 3.51 (t, J = 5.6 Hz, 2H), 3.45 (t, J = 5.2 Hz, 2H), 2.49 (s, 3H), 1.70-1.67 (m, 4H), 1.56-1.55 (br m, 2H).

^{13}C-NMR (100 MHz, CD_3CN): 163.76, 147.67, 123.75, 123.24, 118.78, 51.14, 47.01, 44.42, 36.46, 27.23, 26.63, 25.32, 10.90.

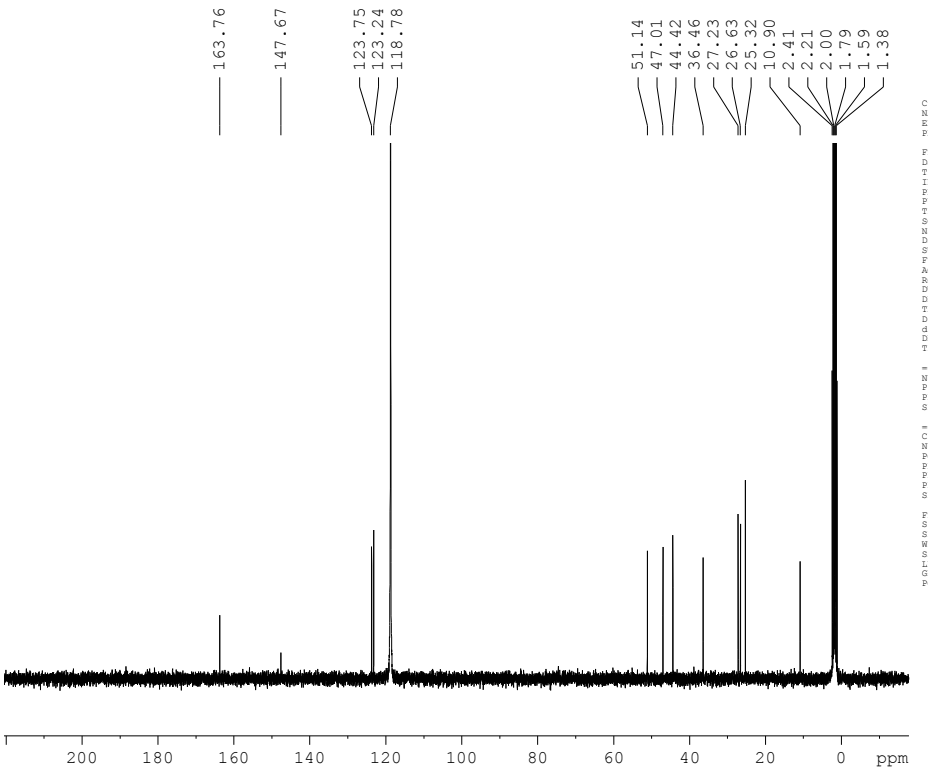
Melting point: 123-124 ºC

ES-MS (+ve) m/z: Found $[M–Br^–]^+$ 222.1610, $C_{12}H_{20}N_3O^+$ requires 222.1601



BRUKER

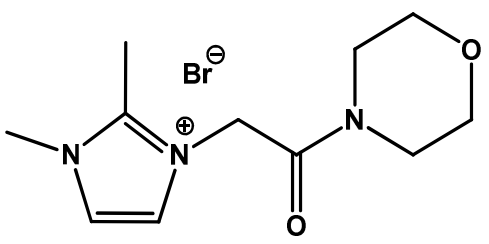
```
Current Data Parameters
NAME                  Aug03-2010
EXPNO                         40
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20100803
Time                       13.55
INSTRUM                    spect
PROBHD  5 mm QNP 1H/13
PULPROG                    zg30
TD                        65536
SOLVENT                   CD3CN
NS                            16
DS                             2
SWH                  8278.146 Hz
FIDRES               0.126314 Hz
AQ                   3.9584243 sec
RG                         143.7
DW                      60.400 usec
DE                       6.00 usec
TE                       294.2 K
D1                  1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         1H
P1                       12.25 usec
PL1                       0.00 dB
SFO1                400.1324710 MHz

F2 - Processing parameters
SI                         32768
SF                  400.1300000 MHz
WDW                           EM
SSB                            0
LB                        0.30 Hz
GB                             0
PC                          1.00
```



BRUKER

```
Current Data Parameters
NAME                  Aug03-2010
EXPNO                         81
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20100804
Time                       4.19
INSTRUM                    spect
PROBHD  5 mm QNP 1H/13
PULPROG                  zgpg30
TD                        65536
SOLVENT                   CD3CN
NS                          1024
DS                             4
SWH                  23980.814 Hz
FIDRES                0.365918 Hz
AQ                   1.3664756 sec
RG                        2896.3
DW                      20.850 usec
DE                       6.00 usec
TE                       294.2 K
D1                  2.00000000 sec
d11                 0.03000000 sec
DELTA               1.89999998 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         13C
P1                       10.00 usec
PL1                       0.00 dB
SFO1                100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                         1H
PCPD2                    80.00 usec
PL2                      -3.00 dB
PL12                     12.00 dB
PL13                     12.00 dB
SFO2                400.1316005 MHz

F2 - Processing parameters
SI                         32768
SF                  100.6126280 MHz
WDW                           EM
SSB                            0
LB                        1.00 Hz
GB                             0
PC                          1.40
```

1*H*-Imidazolium,1,2-dimethyl-3-[2-oxo-2-(1-morpholinyl)ethyl]bromide (16):



Procedure:

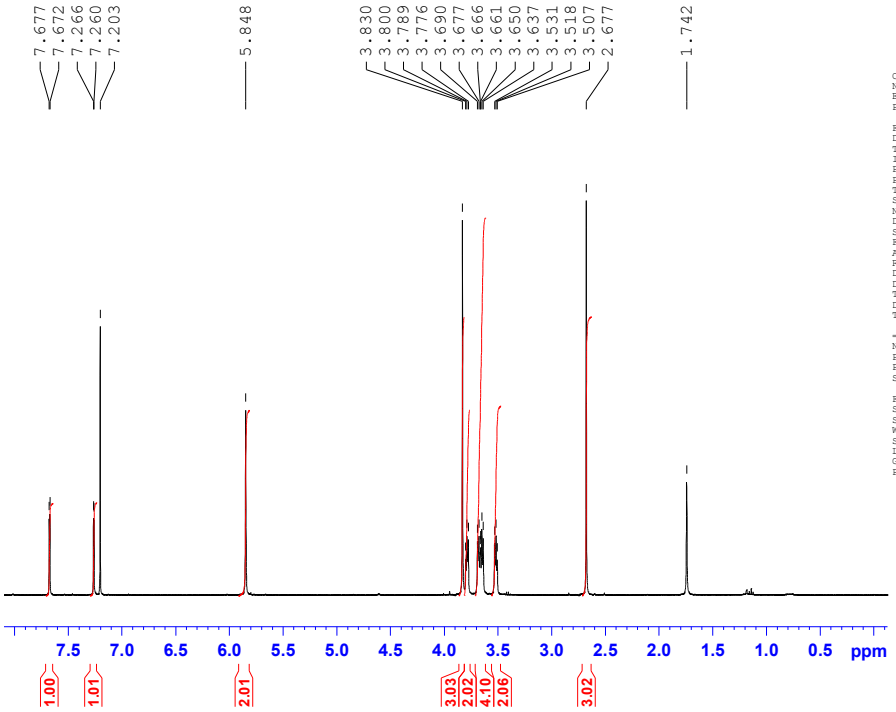
A RB flask was charged with *N*-(bromoacetyl)morpholine (**5**) (1.00 g, 4.80 mmol) and diethyl ether (25 mL) under nitrogen. To this solution was added 1,2-dimethylimidazole (0.466 g, 4.80 mmol). The reaction mixture was stirred vigorously for 24 h. The product precipitated out as a white solid. The product was then washed with diethyl ether (10 x 25 mL). The solvent was removed on the rotary evaporator. The product was dried *in vacuo* for 72 h to give **16** as a white solid at RT in 77% yield (1.12 g, 3.68 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.67 (d, J = 2.0 Hz, 1H), 7.26 (d, J = 2.4 Hz, 1H), 5.85 (s, 2H), 3.83 (s, 3H), 3.79 (dd, J = 5.2, 4.4 Hz, 2H), 3.68 (dd, J = 5.2, 4.4 Hz, 2H), 3.65 (dd, J = 5.2, 4.4 Hz, 2H), 3.52 (dd, J = 5.2, 4.4 Hz, 2H), 2.68 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): 163.12, 146.25, 123.22, 121.51, 66.75, 66.44, 51.04, 45.59, 42.64, 35.78, 11.17

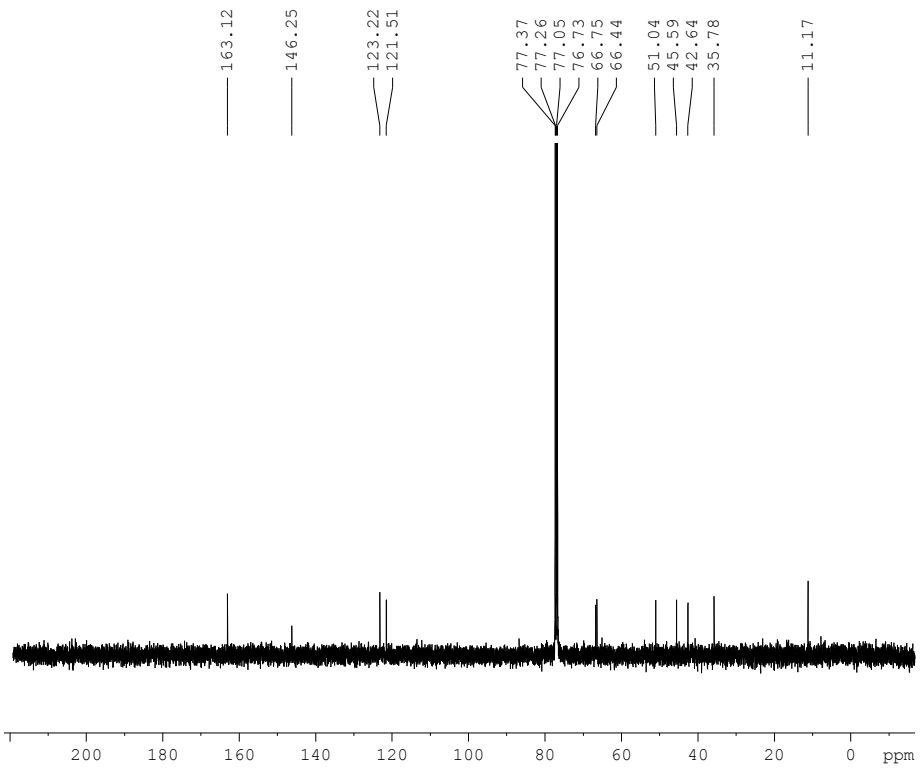
Melting point: 199-200 ºC

ES-MS (+ve) m/z: Found $[M–Br^–]^+$ 224.1395, $C_{11}H_{18}N_3O_2^+$ requires 224.1393



BRUKER

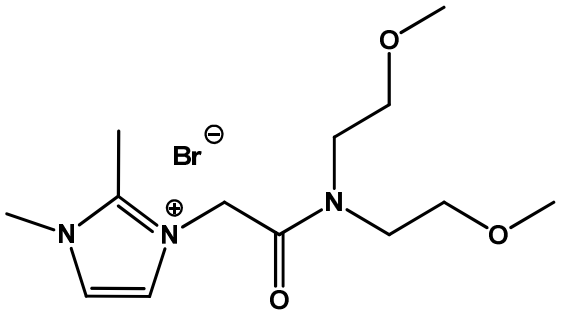
```
Current Data Parameters
NAME                  Nov18-2011
EXPNO                        240
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20111118
Time                       14.21
INSTRUM                    spect
PROBHD  5 mm QNP 1H/13
PULPROG                    zg30
TD                        65536
SOLVENT                   CDCl3
NS                           16
DS                            2
SWH                    8278.146 Hz
FIDRES                 0.126314 Hz
AQ                     3.9584243 sec
RG                         322.5
DW                        60.400 usec
DE                         6.00 usec
TE                        293.2 K
D1                  1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         1H
P1                        12.00 usec
PL1                        0.00 dB
SFO1                400.1324710 MHz

F2 - Processing parameters
SI                        32768
SF                  400.1300323 MHz
WDW                          EM
SSB                           0
LB                         0.30 Hz
GB                            0
PC                         1.00
```



BRUKER

```
Current Data Parameters
NAME                  Nov18-2011
EXPNO                         61
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20111118
Time                       20.43
INSTRUM                    spect
PROBHD  5 mm QNP 1H/13
PULPROG                  zgpg30
TD                        65536
SOLVENT                   CDCl3
NS                         1024
DS                            4
SWH                   23980.814 Hz
FIDRES                 0.365918 Hz
AQ                     1.3664756 sec
RG                         6502
DW                        20.850 usec
DE                         6.00 usec
TE                        293.2 K
D1                  2.00000000 sec
d11                 0.03000000 sec
DELTA               1.89999998 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                        13C
P1                        10.00 usec
PL1                        0.00 dB
SFO1                100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                         1H
PCPD2                     80.00 usec
PL2                       -3.00 dB
PL12                      12.00 dB
PL13                      12.00 dB
SFO2                400.1316005 MHz

F2 - Processing parameters
SI                        32768
SF                  100.6127690 MHz
WDW                          EM
SSB                           0
LB                         1.00 Hz
GB                            0
PC                         1.40
```

1*H*-Imidazolium-1,2-dimethyl-3-[2-[*bis*(2-methoxyethyl)amino]-2-oxoethyl]bromide (17):



Procedure:

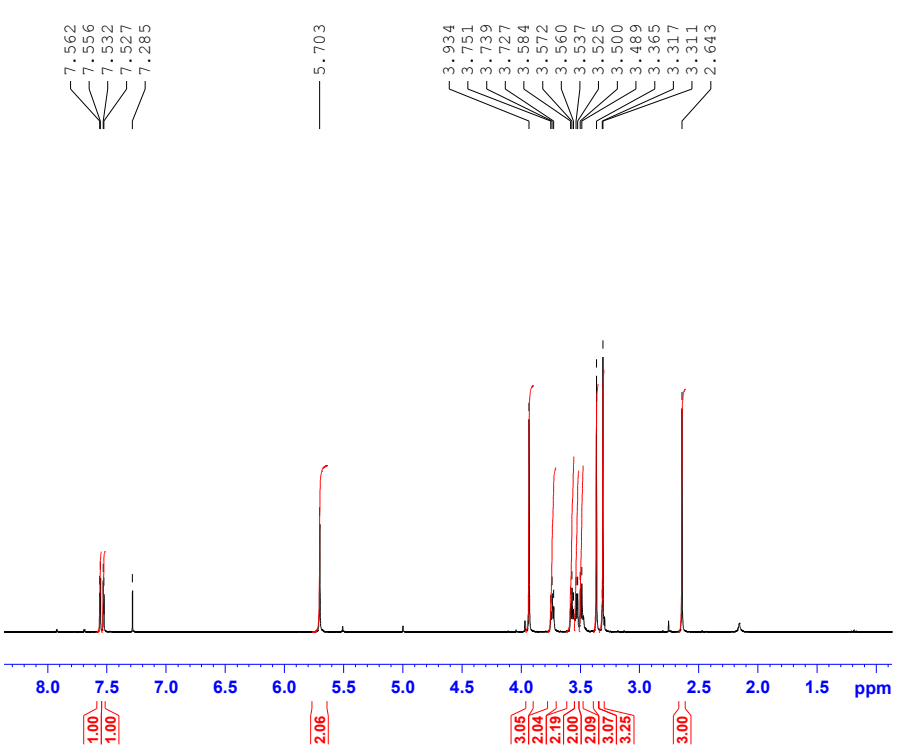
A RB flask was charged with 2-bromo-*N*,*N*-*bis*(2-methoxyethyl)-acetamide (**6**) (1.00 g, 3.93 mmol) and diethyl ether (25 mL) under nitrogen. To this solution was added 1,2-dimethylimidazole (3.78 g, 3.93 mmol). The reaction mixture was stirred vigorously for 24 h. The product precipitated out as a white solid. The product was then washed with diethyl ether (10 x 25 mL). The solvent was removed on the rotary evaporator. The product was dried *in vacuo* for 72 h to give **17** as a white solid at RT in 85% yield (1.17 g, 3.34 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.56 (d, J = 2.4 Hz, 1H), 7.53 (d, J = 2.0 Hz, 1H), 5.70 (s, 2H), 3.93 (s, 3H), 3.74 (t, J = 4.8 Hz, 2H), 3.57 (t, J = 4.8 Hz, 2H), 3.53 (t, J = 4.8 Hz, 2H), 3.49 (t, J = 4.8 Hz, 2H), 3.36 (s, 3H), 3.31 (s, 3H), 2.64 (s, 3H).

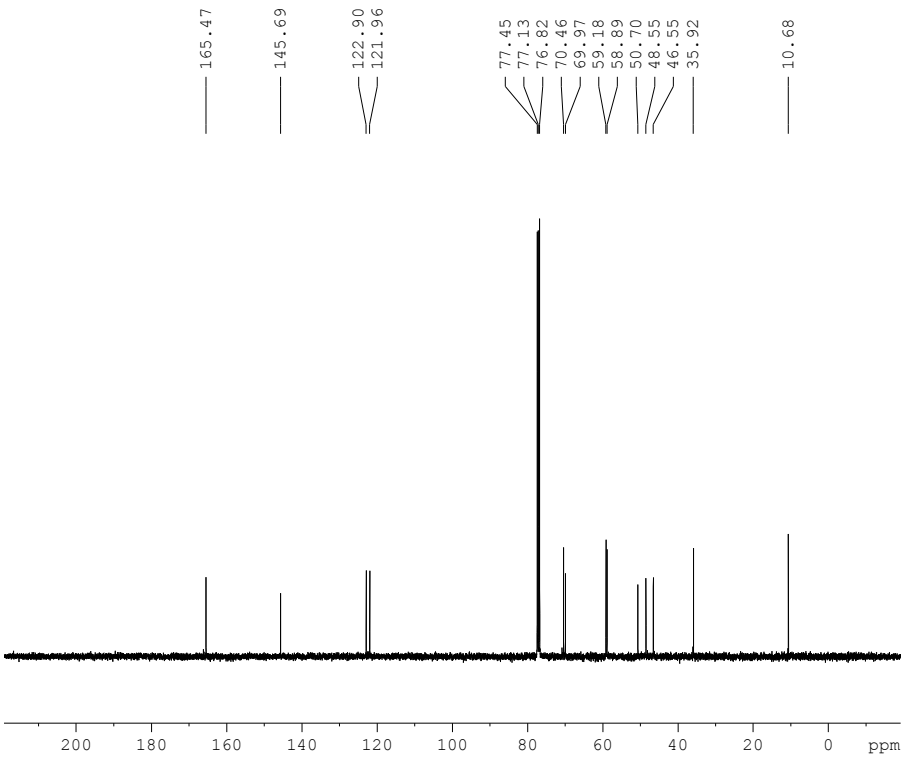
^{13}C-NMR (100 MHz, $CDCl_3$): 165.47, 145.69, 122.90, 121.96, 70.46, 69.97, 59.18, 58.89, 50.70, 48.55, 46.55, 35.93, 10.68

Melting point: 119-120 ºC

ES-MS (+ve) m/z: Found $[M–Br^–]^+$ 270.1816, $C_{13}H_{24}N_3O_3^+$ requires 270.1812

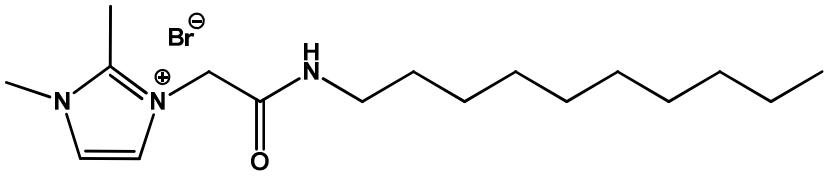


```
Current Data Parameters
NAME                  Nov18-2011
EXPNO                        230
PROCNO                         1

F2 - Acquisition Parameters
Date_                  20111118
Time                      14.13
INSTRUM                   spect
PROBHD  5 mm QNP 1H/13
PULPROG                   zg30
TD                       65536
SOLVENT                  CDCl3
NS                          16
DS                           2
SWH                   8278.146 Hz
FIDRES                0.126314 Hz
AQ                    3.9584243 sec
RG                         114
DW                      60.400 usec
DE                       6.00 usec
TE                      293.2 K
D1                    1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         1H
P1                       12.00 usec
PL1                       0.00 dB
SFO1                400.1324710 MHz

F2 - Processing parameters
SI                         32768
SF                  400.1300000 MHz
WDW                           EM
SSB                            0
LB                        0.30 Hz
GB                             0
PC                          1.00
```



```
Current Data Parameters
NAME                  Nov17-2011
EXPNO                         41
PROCNO                         1

F2 - Acquisition Parameters
Date_                  20111117
Time                      21.08
INSTRUM                   spect
PROBHD  5 mm QNP 1H/13
PULPROG                 zgpg30
TD                       65536
SOLVENT                  CDCl3
NS                         1024
DS                            4
SWH                   23980.814 Hz
FIDRES                0.365918 Hz
AQ                    1.3664756 sec
RG                          4096
DW                      20.850 usec
DE                       6.00 usec
TE                      293.2 K
D1                    2.00000000 sec
d11                   0.03000000 sec
DELTA                 1.89999998 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                        13C
P1                       10.00 usec
PL1                       0.00 dB
SFO1                100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                         1H
PCPD2                    80.00 usec
PL2                      -3.00 dB
PL12                     12.00 dB
PL13                     12.00 dB
SFO2                400.1316005 MHz

F2 - Processing parameters
SI                         32768
SF                  100.6127690 MHz
WDW                           EM
SSB                            0
LB                        1.00 Hz
GB                             0
PC                          1.40
```

1*H*-Imidazolium, 1,2-dimethyl-3-[2-(decylamino)-2-oxoethyl]bromide (18):



Procedure:

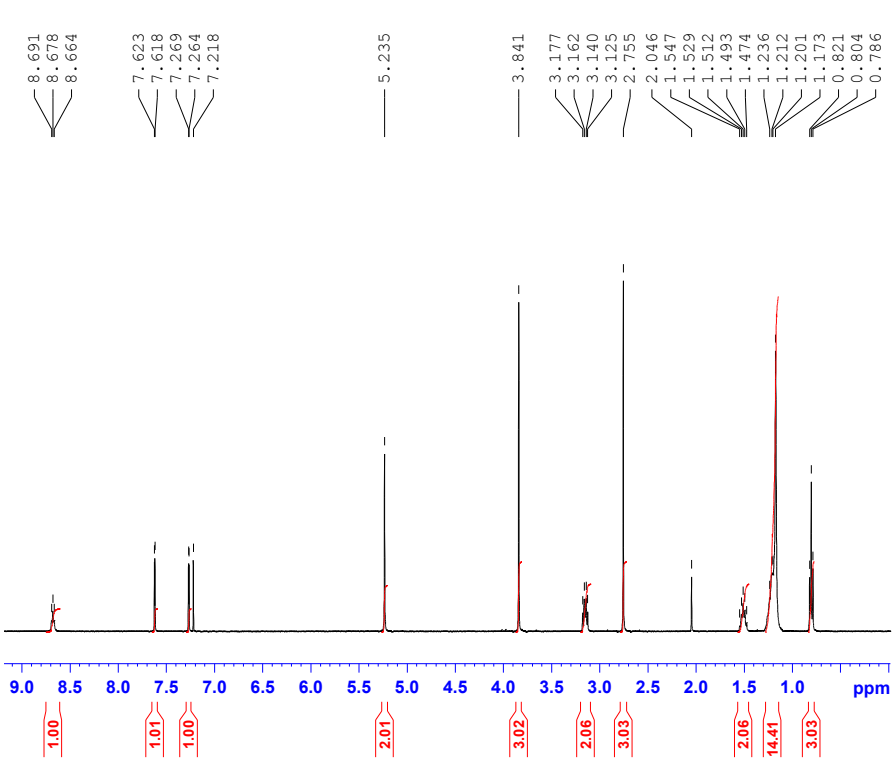
A RB flask was charged with 2-bromo-*N*-decyl-acetamide (**7**) (3.00 g, 10.78 mmol) and diethyl ether (50 mL) under nitrogen. To this solution was added 1,2-dimethylimidazole (1.04 g, 10.78 mmol). The reaction mixture was stirred vigorously for 24 h. The product precipitated out as a white solid. The product was then washed with diethyl ether (10 x 50 mL). The solvent was removed on the rotary evaporator. The product was dried *in vacuo* for 72 h to give **18** as a white solid at RT in 67% yield (2.70 g, 7.21 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$): 8.68 (dd, *J* = 5.6, 5.2 Hz, 1H), 7.62 (d, *J* = 2.4 Hz, 1H), 7.26 (d, *J* = 2.0 Hz, 1H), 5.23 (s, 2H), 3.84 (s, 3H), 3.15 (t, *J* = 6.0 Hz, 2H), 2.75 (s, 3H), 1.55-1.47 (m, 2H), 1.23-1.17 (m, 14H), 0.80 (t, *J* = 6.8 Hz, 3H)

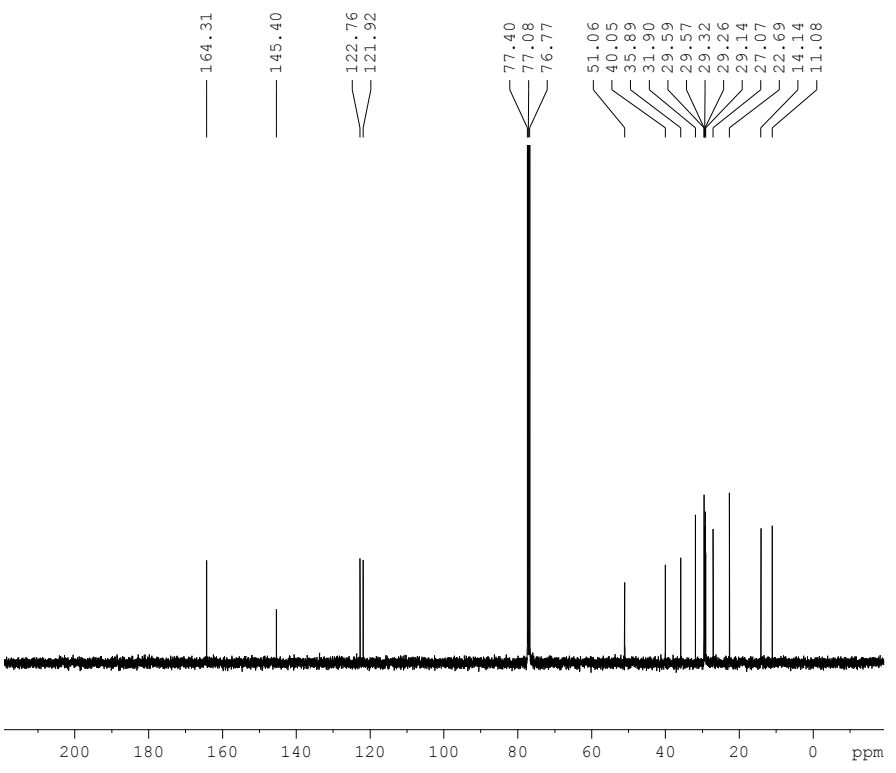
^{13}C-NMR (100 MHz, $CDCl_3$): 164.31, 145.40, 122.76, 121.92, 51.06, 40.05, 35.89, 31.90, 29.59, 29.57, 29.32, 29.26, 29.14, 27.07, 22.69, 14.14, 11.08

Melting point: 95-96 ºC

ES-MS (+ve) m/z: Found $[M–Br^–]^+$ 294.2542, $C_{17}H_{32}N_3O^+$ requires 294.2545

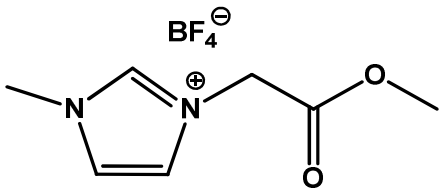


```
Current Data Parameters
NAME                  Nov29-2011
EXPNO                        100
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20111129
Time                       12.45
INSTRUM                    spect
PROBHD      5 mm QNP 1H/13
PULPROG                    zg30
TD                        65536
SOLVENT                   CDCl3
NS                           16
DS                            2
SWH                    8278.146 Hz
FIDRES                 0.126314 Hz
AQ                     3.9584243 sec
RG                          114
DW                       60.400 usec
DE                        6.00 usec
TE                       295.2 K
D1                     1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         1H
P1                       12.00 usec
PL1                       0.00 dB
SFO1                400.1324710 MHz

F2 - Processing parameters
SI                         32768
SF                  400.1300263 MHz
WDW                           EM
SSB                            0
LB                          0.30 Hz
GB                             0
PC                          1.00
```



```
Current Data Parameters
NAME                  Nov30-2011
EXPNO                        101
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20111201
Time                       18.44
INSTRUM                    spect
PROBHD      5 mm QNP 1H/13
PULPROG                  zgpg30
TD                        65536
SOLVENT                   CDCl3
NS                         1024
DS                            4
SWH                   23980.814 Hz
FIDRES                 0.365918 Hz
AQ                     1.3664756 sec
RG                          6502
DW                       20.850 usec
DE                        6.00 usec
TE                       301.2 K
D1                     2.00000000 sec
d11                    0.03000000 sec
DELTA                  1.89999998 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         13C
P1                       10.00 usec
PL1                       0.00 dB
SFO1                100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                  waltz16
NUC2                         1H
PCPD2                    80.00 usec
PL2                      -3.00 dB
PL12                     12.00 dB
PL13                     12.00 dB
SFO2                400.1316005 MHz

F2 - Processing parameters
SI                         32768
SF                  100.6127690 MHz
WDW                           EM
SSB                            0
LB                          1.00 Hz
GB                             0
PC                          1.40
```

1*H*-Imidazolium-3-(2-methoxy-2-oxoethyl)-1-methyl- tetrafluoroborate (20):



Procedure:

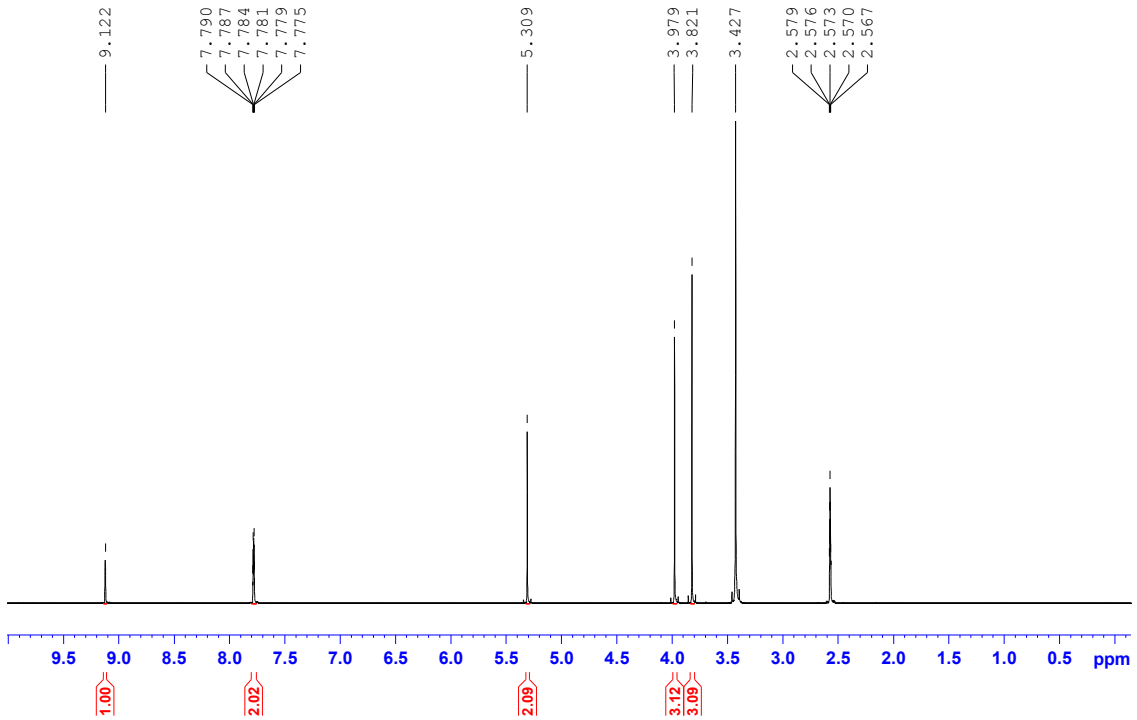
A flask was charged with 3-methyl-1-(methoxycarbonylmethyl)imidazolium bromide (**8**) (500 mg, 2.31 mmol) and acetone (4 mL) under a nitrogen atmosphere. $NaBF_4$ (310 mg, 2.31 mmol) was added in one portion and the suspension was stirred vigorously for 4 days at RT. The fine white precipitate was filtered quickly in air and washed with dry acetone (2 x 4 mL). The filtrate and washings were combined and solvent removed by rotary evaporation, then *in vacuo* for 2 days to give **20** as a white solid in 95 % yield (492 mg, 2.03 mmol).

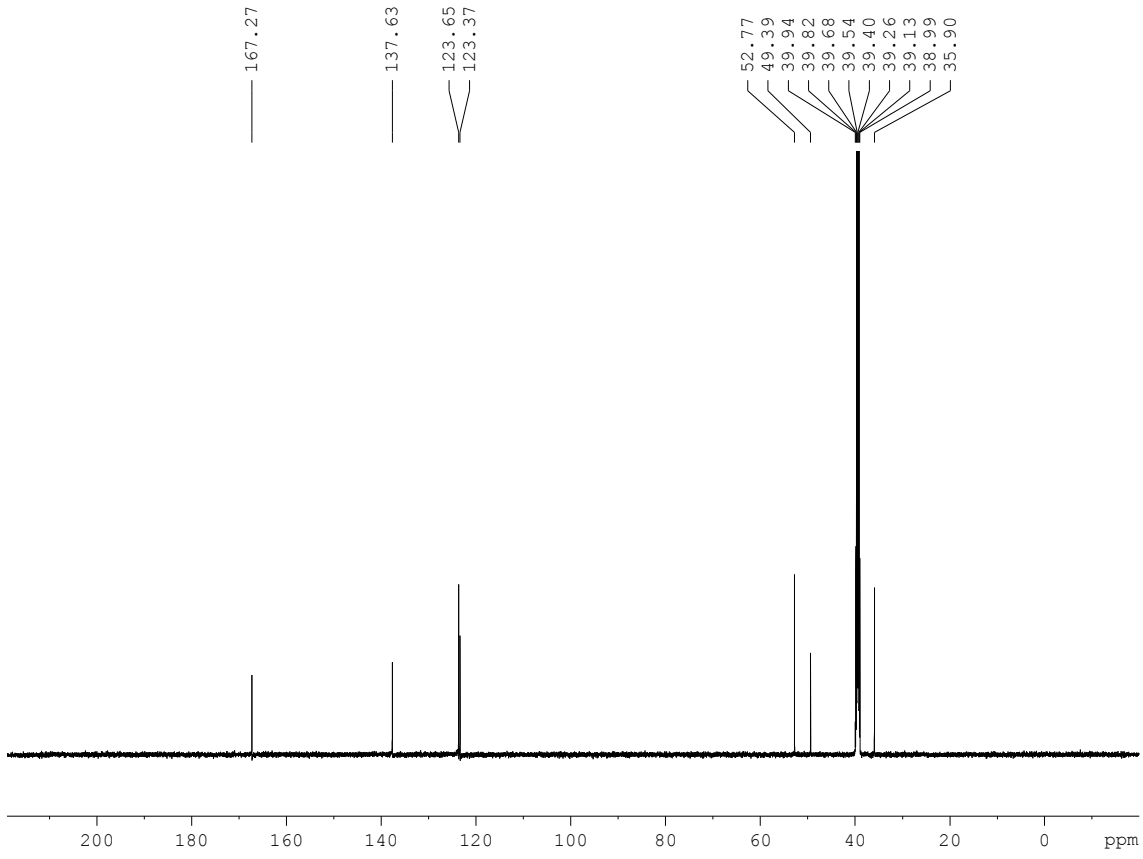
^{1}H NMR (600 MHz, DMSO-d_6) 9.12 (s, 1H), 7.79-7.77 (m, 2H), 5. 31 (s, 2H), 3.97 (s, 3H), 3.82 (s, 3H).

^{13}C NMR (150 MHz, DMSO-d_6) 167.27, 137.63, 123.65, 123.37, 52.77, 49.39, 35.90.

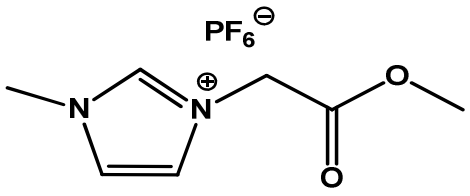
Melting point: 45-47 ºC.

ES-MS (+ve) m/z: Found $[M–BF_4^–]^+$ 155.0821, $C_7H_{11}N_2O_2^+$ requires 155.0815


9.122
7.790
7.787
7.784
7.781
7.779
7.775
5.309
3.979
3.821
3.427
2.579
2.576
2.573
2.570
2.567
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
2.02
2.09
3.12
3.09


167.27
137.63
123.65
123.37
52.77
49.39
39.94
39.82
39.68
39.54
39.40
39.26
39.13
38.99
35.90
200 180 160 140 120 100 80 60 40 20 0 ppm

1*H*-Imidazolium, 3-(2-methoxy-2-oxoethyl)-1-methyl- hexafluorophosphate (21):



Procedure:

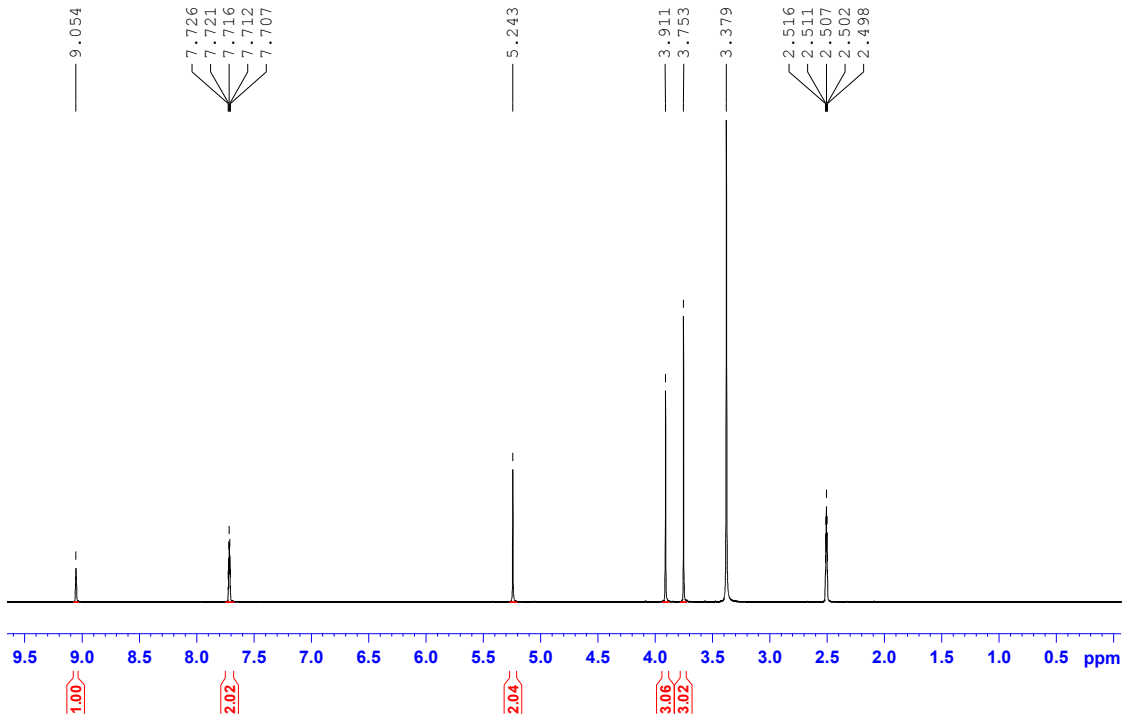
A flask was charged with 3-methyl-1-(ethoxycarbonylmethyl)imidazolium bromide (**8**) (500 mg, 2.13 mmol), and acetone (2 mL). Potassium hexafluorophosphate (600 mg, 3.49 mmol) in acetone (2 mL) was added in one portion and the suspension was stirred vigorously for 4 days under reflux. After 4 days the fine white precipitate was filtered quickly in air and washed with dry acetone (2 x 4 mL). The filtrate and washings were combined, solvent removed by rotary evaporation, then *in vacuo* for 2 days to yield **21** as a white solid at RT in 95 % yield (605 mg, 2.01 mmol).

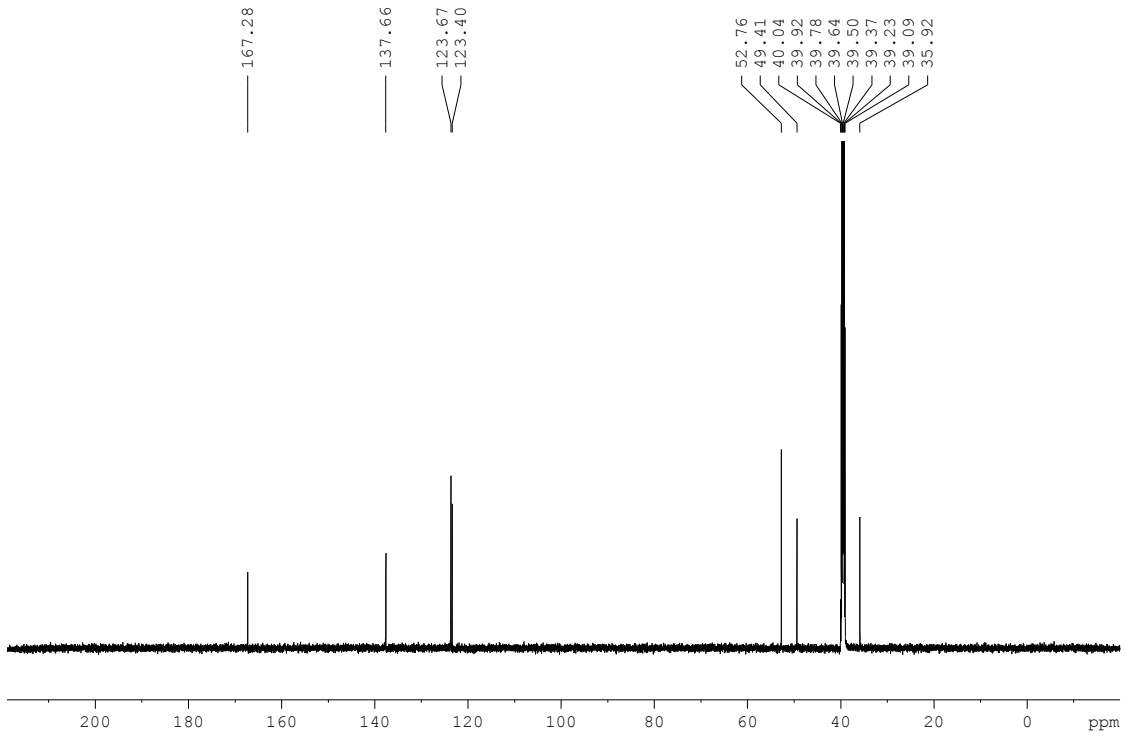
^{1}H NMR (400 MHz, DMSO-d6): 9.05 (s, 1H), 7.72-7.70 (m, 2H), 5.24 (s, 2H), 3.91 (s, 3H), 3.75 (s, 3H)

^{13}C NMR (150 MHz, DMSO-d6): 167.28, 137.66, 123.67, 123.40, 52.76, 49.41, 35.92

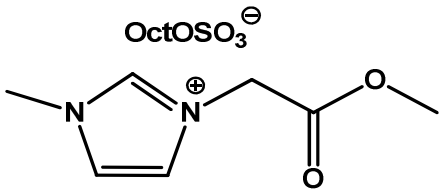
Melting point: 84-86 ºC

ES-MS (+ve) m/z: Found $[M–PF_6^-]^+$ 155.0820, $C_7H_{11}N_2O_2^+$ requires 155.0815


9.054
7.726
7.721
7.716
7.712
7.707
5.243
3.911
3.753
3.379
2.516
2.511
2.507
2.502
2.498
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
2.02
2.04
3.06
3.02


167.28
137.66
123.67
123.40
52.76
49.41
40.04
39.92
39.78
39.64
39.50
39.37
39.23
39.09
35.92
200 180 160 140 120 100 80 60 40 20 0 ppm

1*H*-Imidazolium-3-(2-methoxy-2-oxoethyl)-1-methyl- octyl sulfate (22):



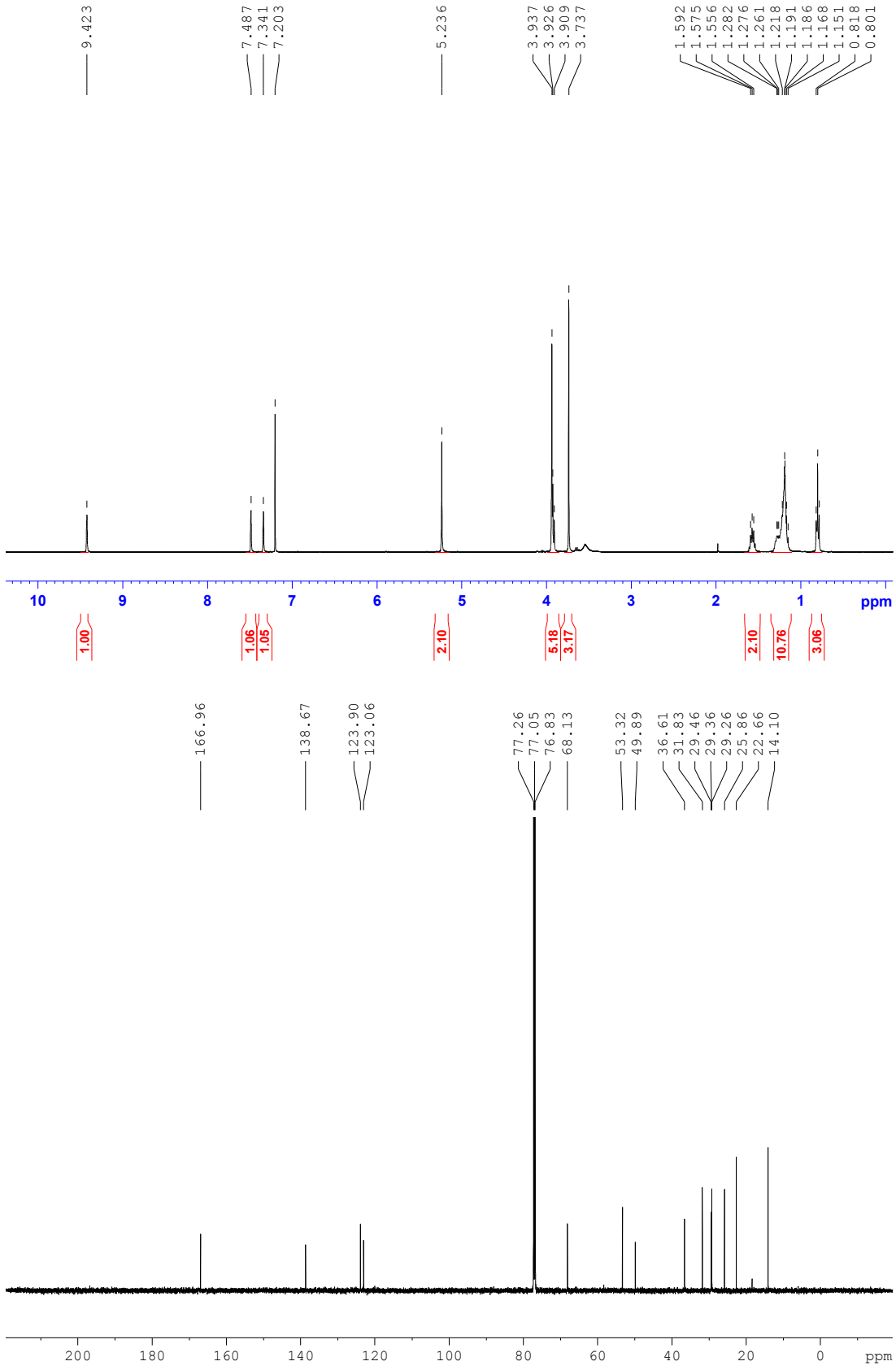
Procedure:

A flask was charged with 3-methyl-1-(methoxycarbonylmethyl)imidazolium bromide (**8**) (2.00 g, 8.51 mmol) and distilled water (7.5 mL). Sodium octylsulfate (1.97 g, 8.51 mmol) in distilled water (7.5 mL) was added in one portion and the suspension was stirred vigorously for 4 h at RT. The water was removed on the rotary evaporator and residue was dissolved in dichloromethane (15 mL) and washed with water. Organic layer was dried over anhydrous magnesium sulphate, filtered and filtrate was evaporated. The product was dried *in vacuo* for 72 h to give **22** as a colourless viscous liquid in 64 % yield (1.91 g, 5.24 mmol).

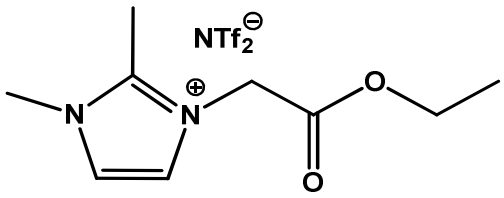
^{1}H NMR (400 MHz, $CDCl_3$): 9.42 (s, 1H), 7.48 (s, 1H), 7.34 (s, 1H), 5.23 (s, 2H), 3.93-3.90 (m, 5H), 3.73 (s, 3H), 1.59-1.55 (m, 2H), 1.28-1.15 (m, 10H), 0.81 (t, J = 6.8 Hz, 3H)

^{13}C NMR (150 MHz, $CDCl_3$): 166.96, 138.67, 123.90, 123.06, 68.13, 53.32, 49.89, 36.61, 31.83, 29.46, 29.36, 29.26, 25.86, 22.66, 14.10.

ES-MS (+ve) m/z: Found $[M–OctOSO_3^-]^+$ 155.0820, $C_7H_{11}N_2O_2^+$ requires 155.0815


9.423
7.487
7.341
7.203
5.236
3.937
3.926
3.909
3.737
1.592
1.575
1.556
1.282
1.276
1.261
1.218
1.191
1.186
1.168
1.151
0.818
0.801
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.06
1.05
2.10
5.18
3.17
2.10
10.76
3.06
166.96
138.67
123.90
123.06
77.26
77.05
76.83
68.13
53.32
49.89
36.61
31.83
29.46
29.36
29.26
25.86
22.66
14.10
200
180
160
140
120
100
80
60
40
20
0
ppm

1*H*-Imidazolium-1,2-dimethyl-3-(2-ethoxy-2-oxoethyl)-1-methyl-*bis*(trifluoromethanesulfonimide) (23):



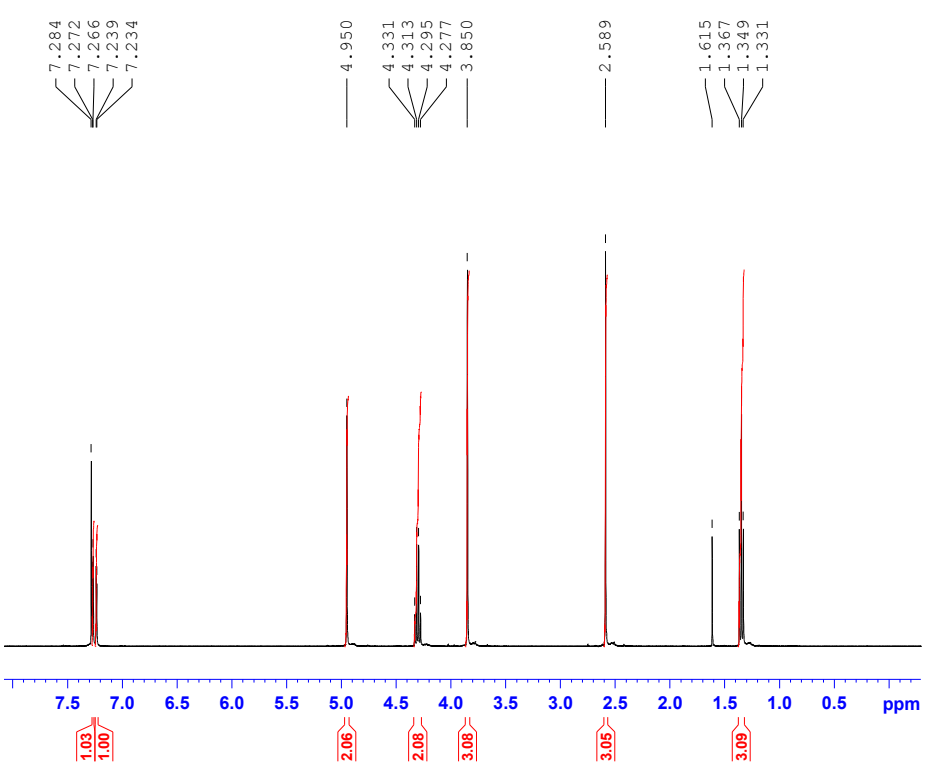
Procedure:

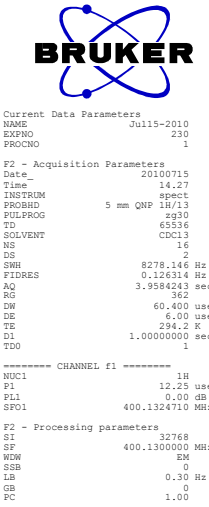
A RB flask was charged with 1*H*-Imidazolium, 1,2-dimethyl-3-(2-butoxy-2-oxoethyl)-1-methyl- bromide (**9**) (1.00 g, 0.38 mmol) and distilled water (5 mL). Lithium *bis*(trifluoromethanesulfonimide) (1.09 g, 0.38 mmol) in distilled water (5 mL) was added in one portion and the suspension was stirred vigorously for 4 h at RT. The aqueous layer was removed and IL washed with water (3 x 10 mL). Water was removed on the rotary evaporator. The product was dried *in vacuo* for 72 h to give **23** as a colourless viscous liquid at RT in 85% yield (1.51 g, 0.326 mmol).

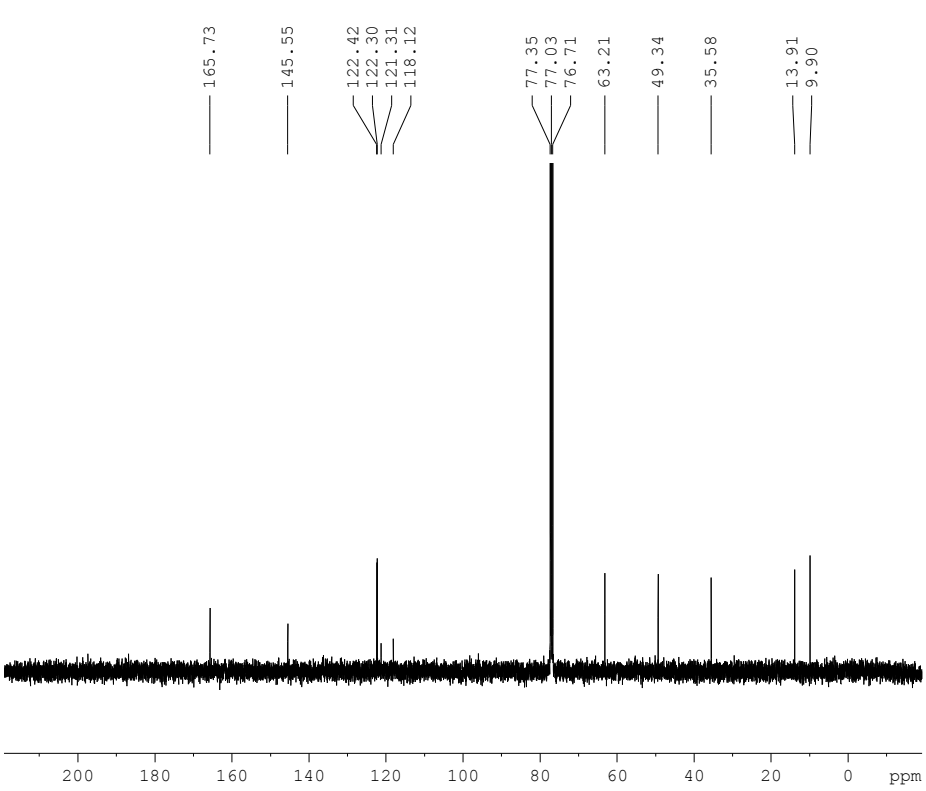
^{1}H-NMR (400 MHz, $CDCl_3$): 7.27 (d, J = 2.4 Hz, 1H), 7.23 (d, J = 2.0 Hz, 1H), 4.95 (s, 2H), 4.30 (q, J = 7.2 Hz, 2H), 3.85 (s, 3H), 2.59 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H)

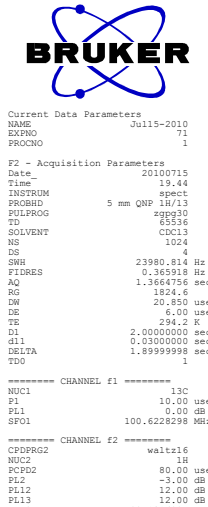
^{13}C-NMR (100 MHz, $CDCl_3$): 165.73, 145.55, 122.42, 122.30, 119.72 (q, J = 320 Hz, 2 CF_3), 63.21, 49.34, 35.58, 13.91, 9.90

ES-MS (+ve) m/z: Found $[M–NTf_2^-]^+$ 183.1130, $C_{11}H_{19}N_2O_2^+$ requires 183.1128

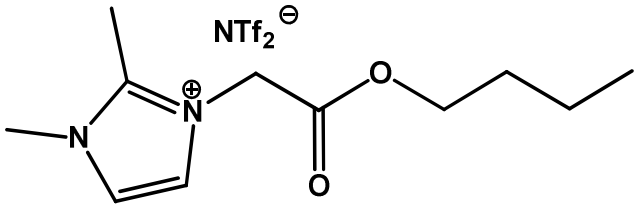

7.284
7.272
7.266
7.239
7.234
4.950
4.331
4.313
4.295
4.277
3.850
2.589
1.615
1.367
1.349
1.331
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.03
1.00
2.06
2.08
3.08
3.05
3.09


Current Data Parameters
NAME Jul15-2010
EXPNO 230
PROCNO 1
F2 - Acquisition Parameters
Date_ 20100715
Time 14.27
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 362
DW 60.400 usec
DE 6.00 usec
TE 294.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 12.25 usec
PL1 0.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00


165.73
145.55
122.42
122.30
121.31
118.12
77.35
77.03
76.71
63.21
49.34
35.58
13.91
9.90
200 180 160 140 120 100 80 60 40 20 0 ppm


Current Data Parameters
NAME Jul15-2010
EXPNO 71
PROCNO 1
F2 - Acquisition Parameters
Date_ 20100715
Time 19.44
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1024
DS 4
SWH 23980.814 Hz
FIDRES 0.365918 Hz
AQ 1.3664756 sec
RG 1824.6
DW 20.850 usec
DE 6.00 usec
TE 294.2 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 10.00 usec
PL1 0.00 dB
SFO1 100.6228298 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -3.00 dB
PL12 12.00 dB
PL13 12.00 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

1*H*-Imidazolium-1,2-dimethyl-3-(2-butoxy-2-oxoethyl)-1-methyl-*bis*(trifluoromethanesulfonimide) (24):



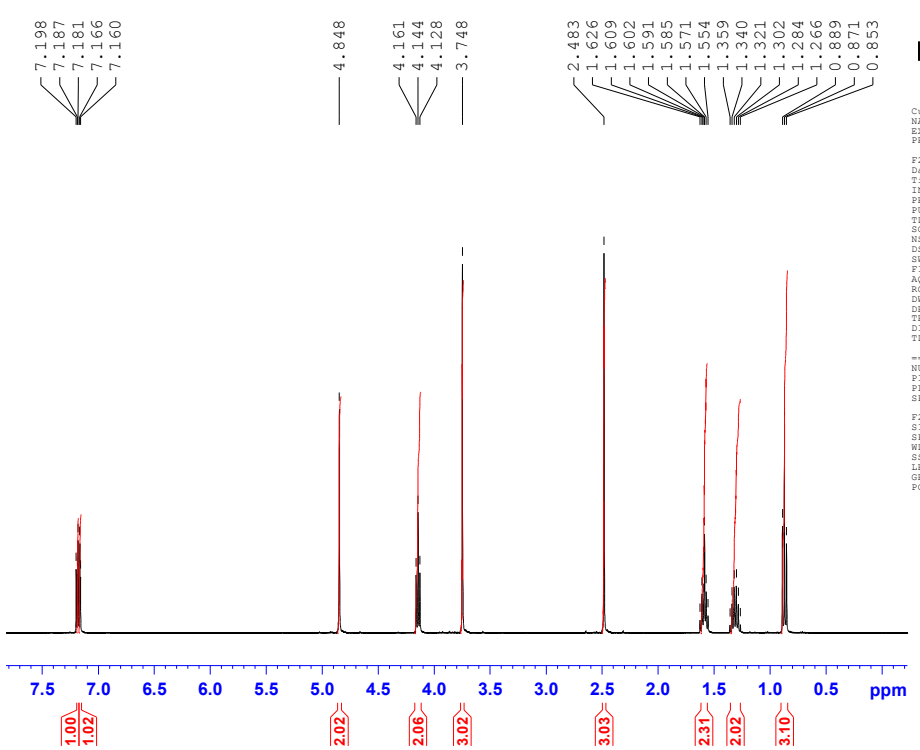
Procedure:

A RB flask was charged with 1*H*-Imidazolium, 1,2-dimethyl-3-(2-butoxy-2-oxoethyl)-1-methyl- bromide (**10**) (3.00 g, 10.3 mmol) and distilled water (15 mL). Lithium *bis*(trifluoromethanesulfonimide) (2.96 g, 10.3 mmol) in distilled water (10 mL) was added in one portion and the suspension was stirred vigorously for 4 h at RT. The aqueous layer was removed and IL washed with water (3 x 40 mL). Water was removed on the rotary evaporator. The product was dried *in vacuo* for 72 h to give **24** as a colourless liquid at RT in 91% yield (4.61 g, 9.39 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.19 (d, J = 2.4 Hz, 1H), 7.16 (d, J = 2.4 Hz, 1H), 4.85 (s, 2H), 4.14 (t, J = 6.6 Hz, 2H), 3.75 (s, 3H), 2.48 (s, 3H), 1.63-1.55 (m, 2H), 1.36-1.26 (m, 2H), 0.87 (t, J = 7.2 Hz, 3H)

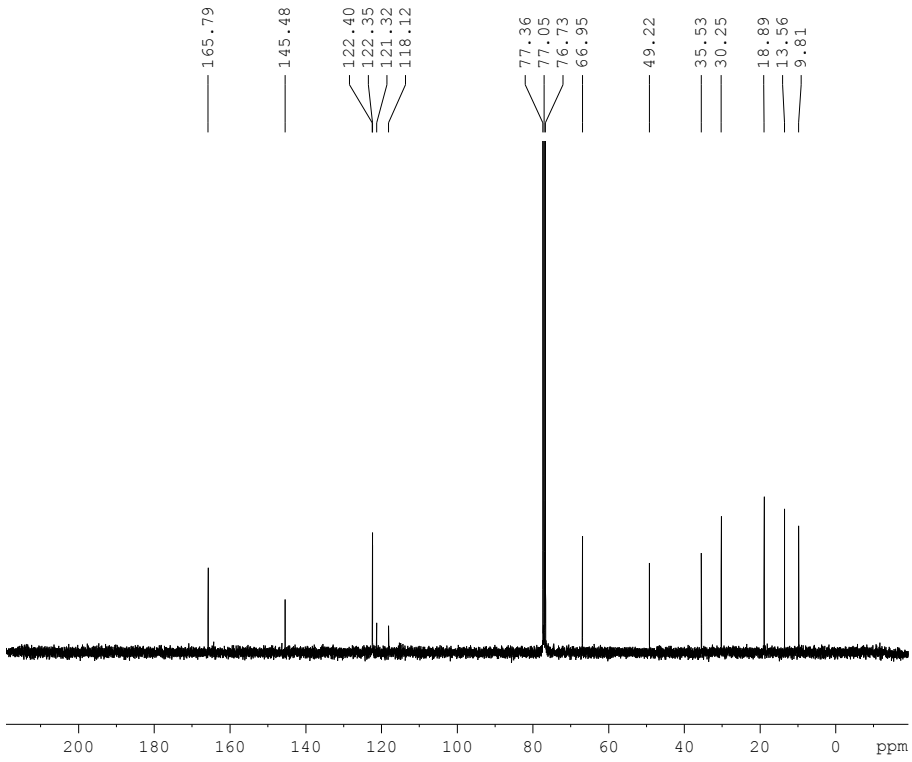
^{13}C-NMR (100 MHz, $CDCl_3$): 165.79, 145.48, 122.40, 122.35, 119.72 (q, J = 320 Hz, 2 CF_3), 66.95, 49.22, 35.53, 30.25, 18.89, 13.56, 9.81

ES-MS (+ve) m/z: Found $[M–NTf_2^-]^+$ 211.1449, $C_{11}H_{19}N_2O_2^+$ requires 211.1441



BRUKER

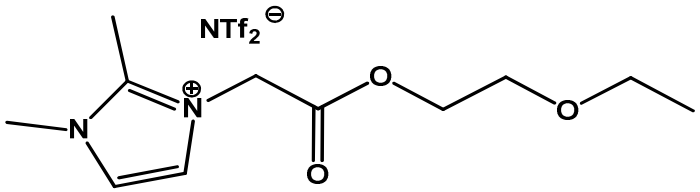
```
Current Data Parameters
NAME                  Oct28-2010
EXPNO                        320
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20101028
Time                       16.49
INSTRUM                    spect
PROBHD      5 mm QNP 1H/13
PULPROG                    zg30
TD                        65536
SOLVENT                   CDCl3
NS                           16
DS                            2
SWH                    8278.146 Hz
FIDRES                 0.126314 Hz
AQ                     3.9584243 sec
RG                          181
DW                       60.400 usec
DE                        6.00 usec
TE                       293.2 K
D1                     1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         1H
P1                       12.25 usec
PL1                       0.00 dB
SFO1                400.1324710 MHz

F2 - Processing parameters
SI                         32768
SF                  400.1300343 MHz
WDW                           EM
SSB                            0
LB                        0.30 Hz
GB                             0
PC                          1.00
```



BRUKER

```
Current Data Parameters
NAME                  Oct28-2010
EXPNO                         41
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20101028
Time                       22.01
INSTRUM                    spect
PROBHD      5 mm QNP 1H/13
PULPROG                  zgpg30
TD                        65536
SOLVENT                   CDCl3
NS                         1024
DS                            4
SWH                   23980.814 Hz
FIDRES                 0.365918 Hz
AQ                     1.3664756 sec
RG                         3251
DW                       20.850 usec
DE                        6.00 usec
TE                       294.2 K
D1                     2.00000000 sec
d11                    0.03000000 sec
DELTA                  1.89999998 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         13C
P1                       10.00 usec
PL1                       0.00 dB
SFO1                100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                  waltz16
NUC2                         1H
PCPD2                    80.00 usec
PL2                      -3.00 dB
PL12                     12.00 dB
PL13                     12.00 dB
SFO2                400.1316005 MHz

F2 - Processing parameters
SI                         32768
SF                  100.6127690 MHz
WDW                           EM
SSB                            0
LB                        1.00 Hz
GB                             0
PC                          1.40
```

1*H*-Imidazolium-1,2-dimethyl-3-[2-(2-ethoxyethoxy)-2-oxoethyl]-1-methyl-*bis*(trifluoromethanesulfonimide) (25):



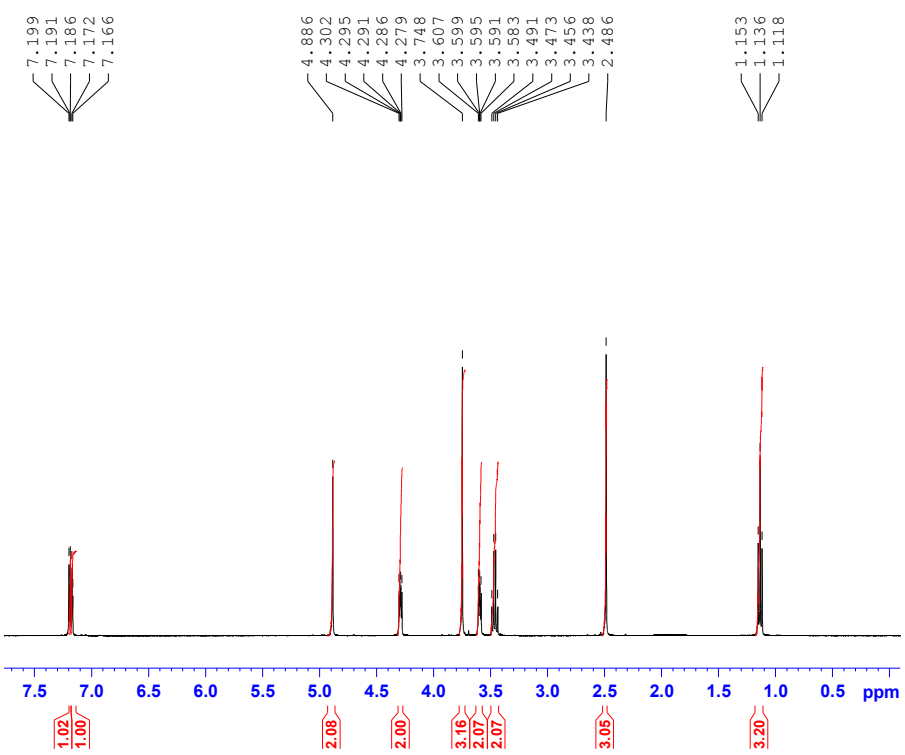
Procedure:

A RB flask was charged with 1*H*-Imidazolium, 1,2-dimethyl-3-[2-(2-ethoxyethoxy)-2-oxoethyl]-1-methyl- bromide (**11**) (2.00 g, 6.5 mmol) and distilled water (9 mL). Lithium *bis*(trifluoromethanesulfonimide) (1.87 g, 6.5 mmol) in distilled water (9 mL) was added in one portion and the suspension was stirred vigorously for 4 h at RT. The aqueous layer was removed, the IL washed with water (3 x 40 mL) to remove LiBr formed. The excess water was removed on the rotary evaporator. The product was dried *in vacuo* for 72 h to give **25** as a colourless liquid at RT in 49% yield (1.605 g, 3.16 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.19 (d, J = 2.0 Hz, 1H), 7.17 (d, J = 2.4 Hz, 1H), 4.88 (s, 2H), 4.29 (m, 2H), 3.75 (s, 3H), 3.60-3.58 (m, 2H), 3.46 (q, J = 7.2 Hz, 1H), 2.49 (s, 3H), 1.14 (t, J = 7.2 Hz, 3H)

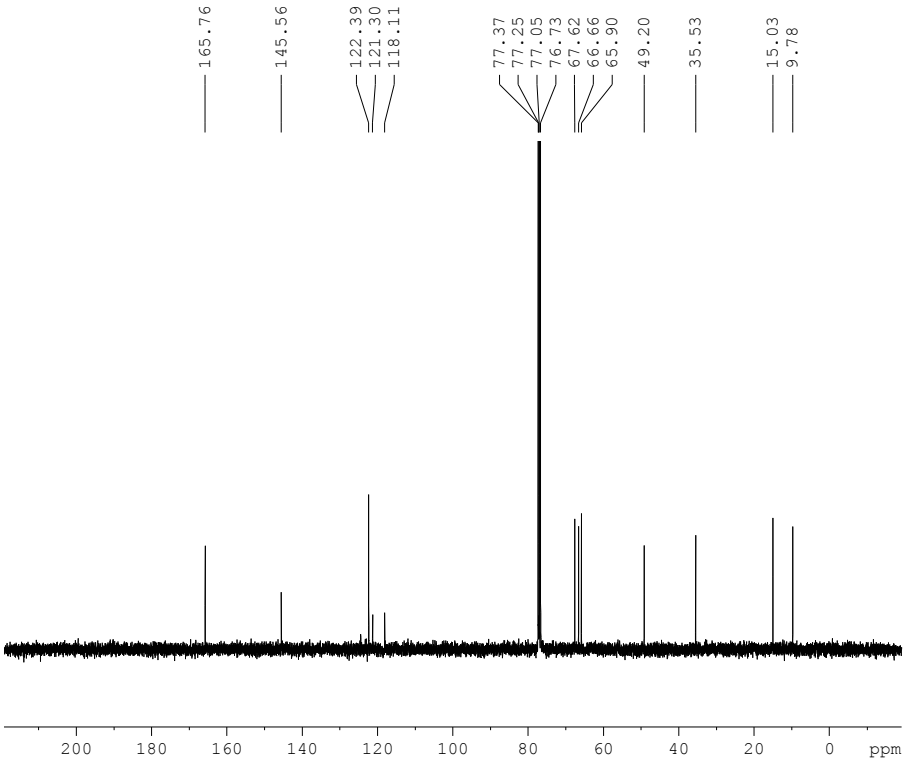
^{13}C-NMR (100 MHz, $CDCl_3$): 165.76, 145.56, 122.39, 122.30, 119.72 (q, J = 320 Hz, 2 CF_3), 67.62, 66.66, 65.90, 49.20, 35.53, 15.03, 9.78

ES-MS (+ve) m/z: Found $[M–NTf_2^-]^+$ 227.1392, $C_{11}H_{19}N_2O_3^+$ requires 227.1390



BRUKER

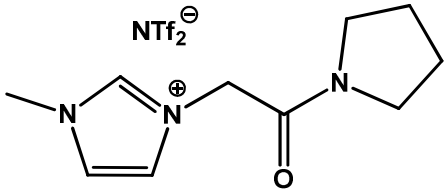
```
Current Data Parameters
NAME                  Oct30-2010
EXPNO                         10
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20101030
Time                       15.55
INSTRUM                    spect
PROBHD  5 mm QNP 1H/13
PULPROG                    zg30
TD                        65536
SOLVENT                   CDCl3
NS                           16
DS                            2
SWH                    8278.146 Hz
FIDRES                 0.126314 Hz
AQ                     3.9584243 sec
RG                          181
DW                        60.400 usec
DE                         6.00 usec
TE                        293.2 K
D1                     1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                          1H
P1                        12.25 usec
PL1                        0.00 dB
SFO1                  400.1324710 MHz

F2 - Processing parameters
SI                            32768
SF                    400.1300338 MHz
WDW                              EM
SSB                               0
LB                             0.30 Hz
GB                                0
PC                             1.00
```



BRUKER

```
Current Data Parameters
NAME                  Nov01-2010
EXPNO                         31
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20101101
Time                       22.38
INSTRUM                    spect
PROBHD  5 mm QNP 1H/13
PULPROG                   zgpg30
TD                        65536
SOLVENT                   CDCl3
NS                         1024
DS                            4
SWH                   23980.814 Hz
FIDRES                 0.365918 Hz
AQ                     1.3664756 sec
RG                        5792.6
DW                        20.850 usec
DE                         6.00 usec
TE                        294.2 K
D1                     2.00000000 sec
d11                    0.03000000 sec
DELTA                  1.89999998 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                          13C
P1                        10.00 usec
PL1                        0.00 dB
SFO1                  100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                   waltz16
NUC2                          1H
PCPD2                     80.00 usec
PL2                       -3.00 dB
PL12                      12.00 dB
PL13                      12.00 dB
SFO2                  400.1316005 MHz

F2 - Processing parameters
SI                            32768
SF                    100.6127690 MHz
WDW                              EM
SSB                               0
LB                             1.00 Hz
GB                                0
PC                             1.40
```

1*H*-Imidazolium,1-methyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl] *bis*(trifluoromethanesulfonimide) (26):



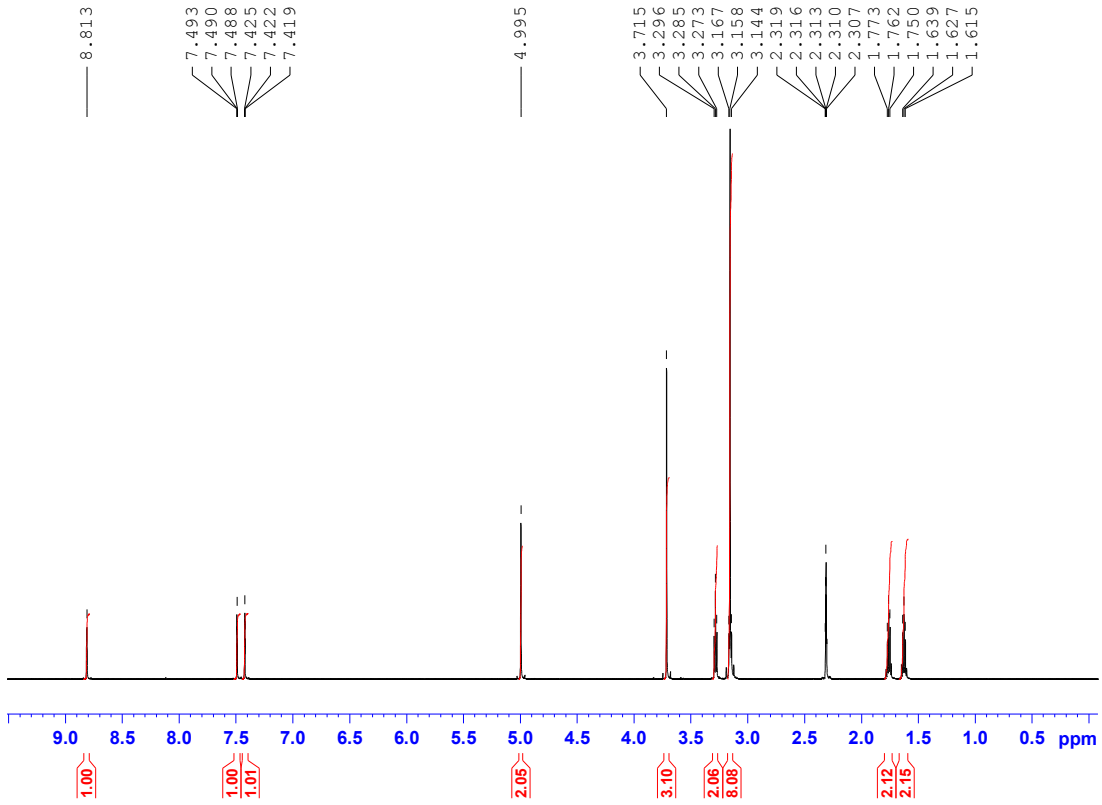
Procedure:

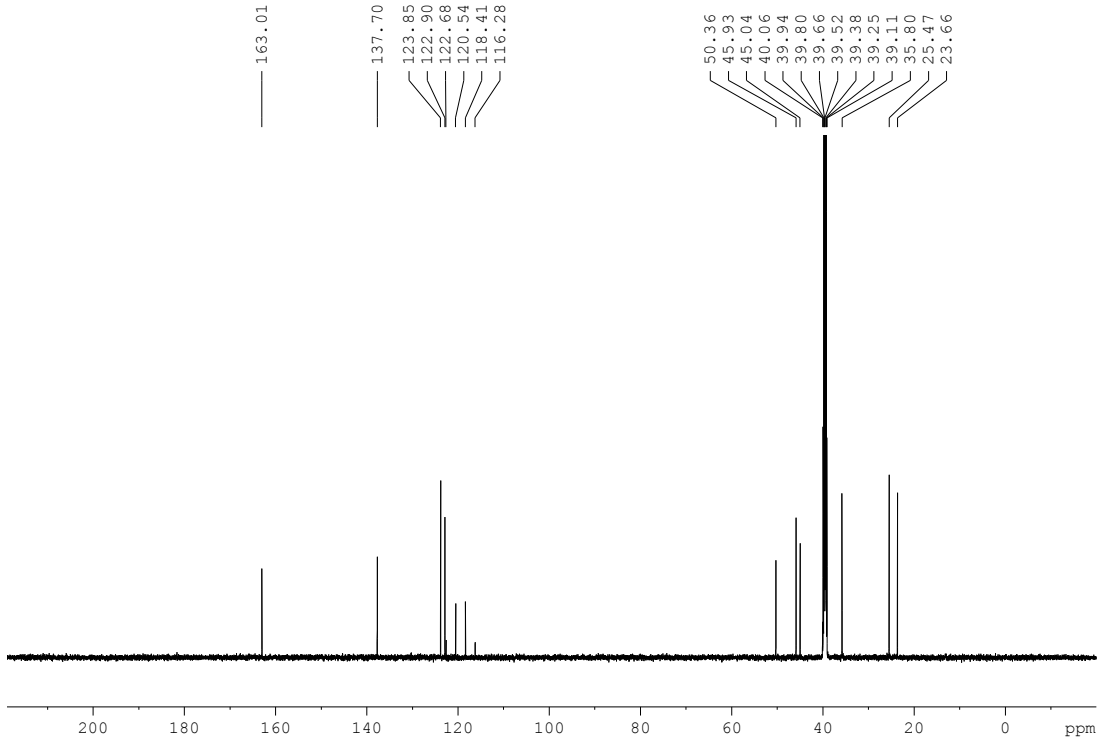
A flask was charged with 3-methyl-1-(pyrrolidinecarbonylmethyl)imidazolium bromide (**12**) (11.00 g, 40.14 mmol) and distilled water (40 mL). Lithium *bis*(trifluoromethanesulfonimide) (11.52 g, 40.14 mmol) in distilled water (40 mL) was added in one portion and the suspension was stirred vigorously for 4 h at RT. The top aqueous layer was removed, the IL washed with water (3 x 40 mL) then the solvent removed on the rotary evaporator. The product was dried *in vacuo* for 72 h to give **26** as a colourless liquid at RT in 69 % yield (13.15 g, 27.72 mmol).

^{1}H NMR (600 MHz, DMSO-d_6): 8.82 (s, 1H), 7.49 (t, J = 1.6 Hz, 1H), 7.42 (t, J = 1.6 Hz, 1H), 4.99 (s, 2H), 3.74 (s, 3H), 3.28 (t, J = 6.8 Hz, 2H), 3.16 (t, J = 6.8 Hz, 2H), 1.77-1.75 (m, 2H), 1.63-1.61 (m, 2H).

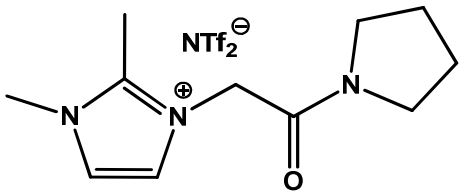
^{13}C NMR (150 MHz, DMSO-d_6): 163.01, 137.70, 123.85, 122.90, 119.47 (q, J = 319.5 Hz, 2 CF_3), 50.36, 45.93, 45.04, 35.80, 25.47, 23.66.

ES-MS (+ve) m/z: Found $[M–NTf_2^-]^+$ 194.1297, $C_{10}H_{16}N_3O^+$ requires 194.1288


8.813
7.493
7.490
7.488
7.425
7.422
7.419
4.995
3.715
3.296
3.285
3.273
3.167
3.158
3.144
2.319
2.316
2.313
2.310
2.307
1.773
1.762
1.750
1.639
1.627
1.615
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
1.00
1.01
2.05
3.10
2.06
8.08
2.12
2.15


163.01
137.70
123.85
122.90
122.68
120.54
118.41
116.28
50.36
45.93
45.04
40.06
39.94
39.80
39.66
39.52
39.38
39.25
39.11
35.80
25.47
23.66
200 180 160 140 120 100 80 60 40 20 0 ppm

1*H*-Imidazolium-1,2-dimethyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl] *bis*(trifluoromethanesulfonimide) (27):



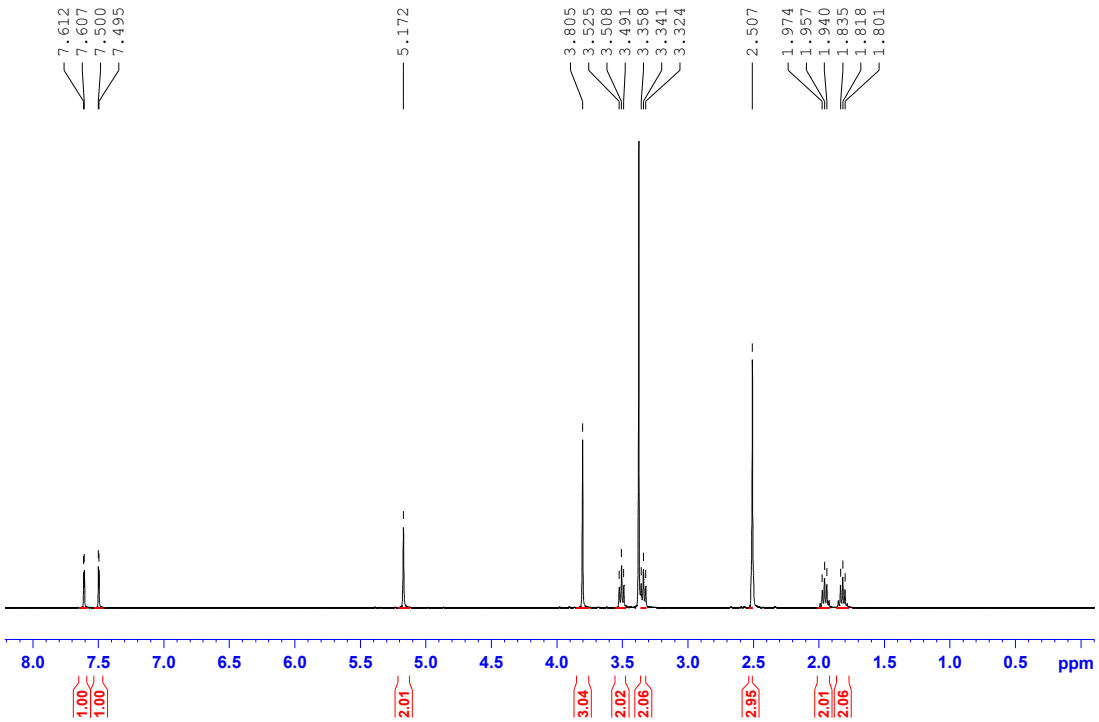
Procedure:

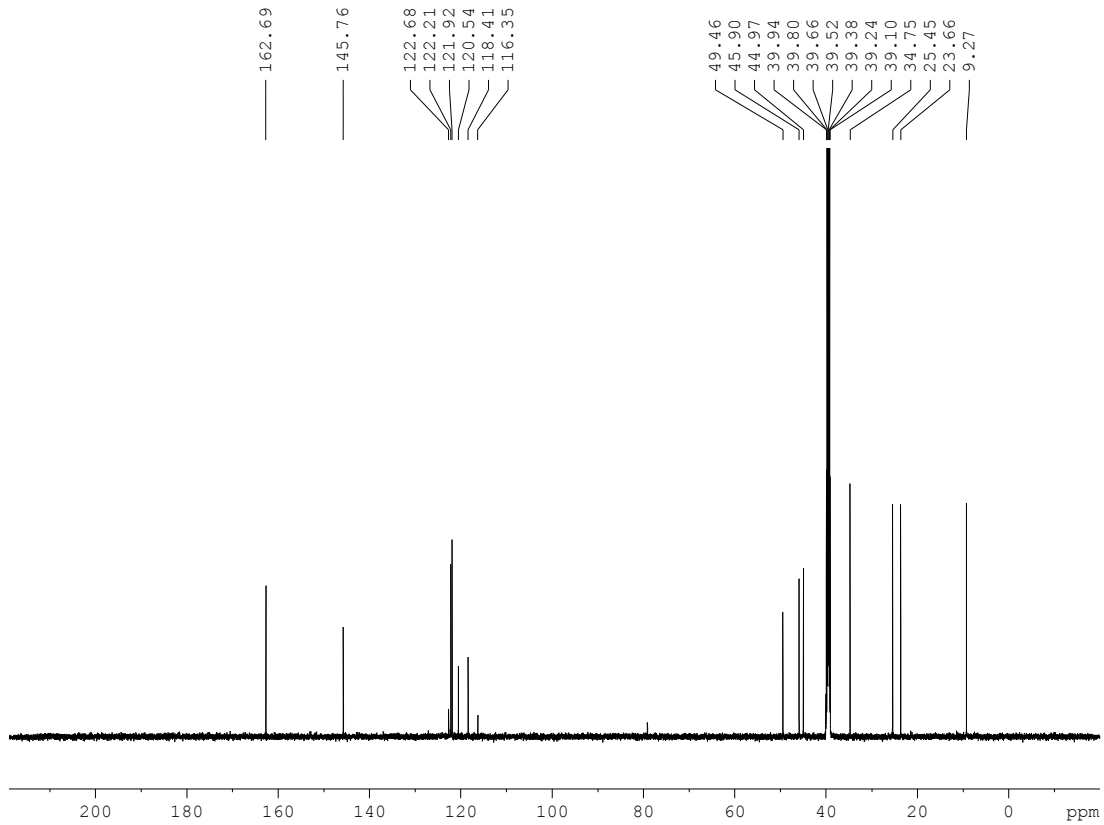
A flask was charged with 2,3-dimethyl-1-(pyrrolidinecarbonylmethyl)imidazolium bromide (**13**) (11.00 g, 38.19 mmol) and distilled water (40 mL). Lithium *bis*(trifluoromethanesulfonimide) (10.96 g, 38.19 mmol) in distilled water (40 mL) was added in one portion and the suspension was stirred vigorously for 4 h at RT. The top aqueous layer was removed, the IL washed with water (3 x 50 mL) then the solvent removed on the rotary evaporator. The product was dried *in vacuo* for 72 h to give **27** as a colourless liquid at RT in 75 % yield (14.13 g, 28.92 mmol).

^{1}H NMR (400 MHz, DMSO-d_6): 7.61 (d, J = 2.0 Hz, 1H), 7.50 (d, J = 2.0 Hz, 1H) 5.17 (s, 2H), 3.80 (s, 3H), 3.50 (t, J = 6.8 Hz, 2H), 3.34 (t, J = 6.8 Hz, 2H), 2.51 (s, 3H), 1.97-1.94 (m, 2H), 1.83-1.80 (m, 2H)

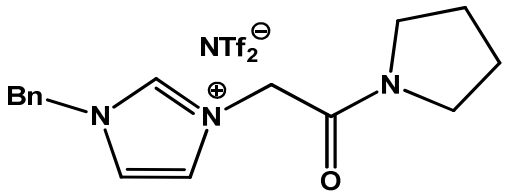
^{13}C NMR (150 MHz, DMSO-d_6): 162.69, 145.76, 122.21, 121.92, 119.47 (q, J = 309 Hz, 2 CF_3), 49.46, 45.90, 44.97, 34.75, 25.45, 23.66, 9.27.

ES-MS (+ve) m/z: Found $[M–NTf_2^-]^+$ 208.1447, $C_{11}H_{18}N_3O^+$ requires 208.1444


7.612
7.607
7.500
7.495
5.172
3.805
3.525
3.508
3.491
3.358
3.341
3.324
2.507
1.974
1.957
1.940
1.835
1.818
1.801
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
1.00
2.01
3.04
2.02
2.06
2.95
2.01
2.06


162.69
145.76
122.68
122.21
121.92
120.54
118.41
116.35
49.46
45.90
44.97
39.94
39.80
39.66
39.52
39.38
39.24
39.10
34.75
25.45
23.66
9.27
200
180
160
140
120
100
80
60
40
20
0
ppm

1*H*-Imidazolium-3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-1-(phenylmethyl)-*bis*(trifluoromethanesulfonimide) (28):



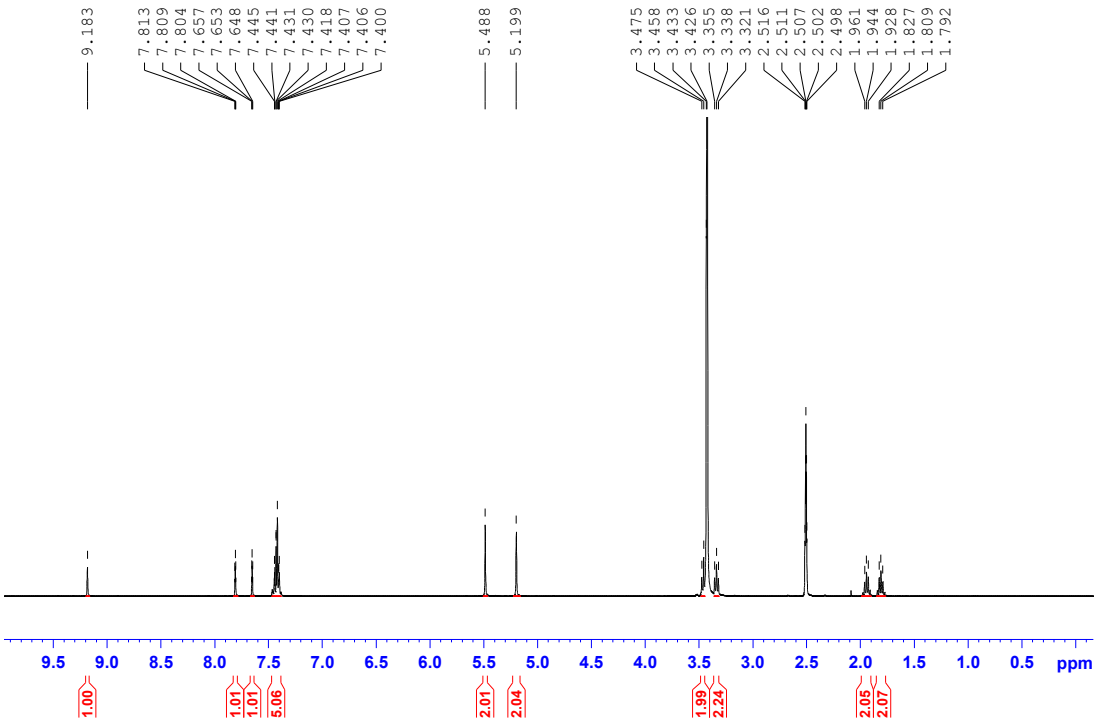
Procedure:

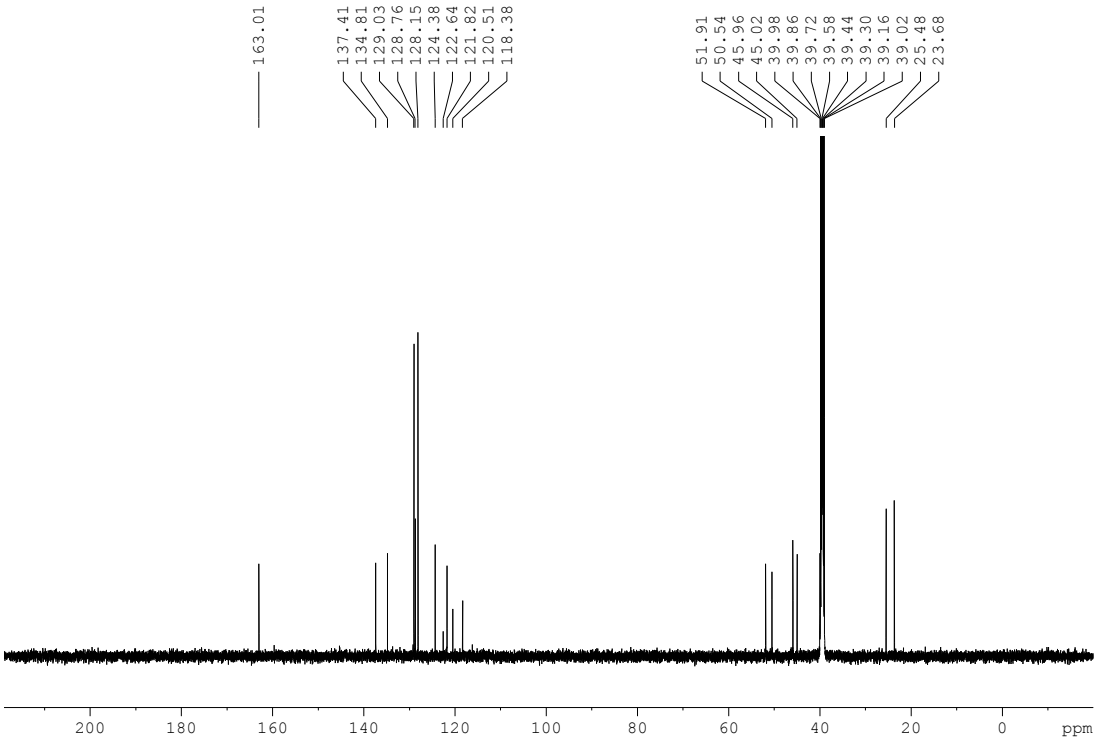
A flask was charged with 3-benzyl-1-(pyrrolidinecarbonylmethyl)imidazolium bromide (**14**) (200 mg, 0.57 mmol) and distilled water (2 mL). Lithium *bis*(trifluoromethanesulfonimide) (163 mg, 0.57 mmol) in distilled water (2 mL) was added in one portion and the suspension was stirred vigorously for 4 h at RT. The top aqueous layer was removed, the IL washed with water (3 x 4 mL) then the solvent removed on the rotary evaporator. The product was dried *in vacuo* for 72 h to give **27** as a colourless liquid at RT in 86 % yield (271 mg, 0.49 mmol).

^{1}H NMR (400 MHz, DMSO-d_6): 9.18 (s, 1H), 7.80 (t, J = 1.6 Hz, 1H), 7.65 (t, J = 1.6 Hz, 1H), 7.44-7.40 (m, 5H), 5.88 (s, 2H), 5.19 (s, 2H), 3.45 (t, J = 6.8 Hz, 2H), 3.29 (t, J = 6.8 Hz, 2H) 1.96-1.92 (m, 2H), 1.82-1.79 (m, 2H).

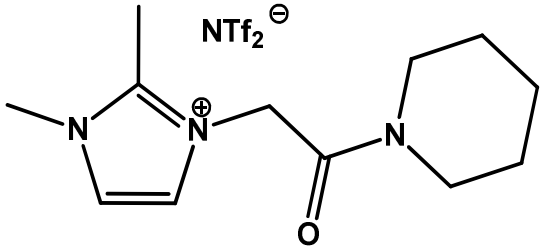
^{13}C NMR (150 MHz, DMSO-d_6) 163.01, 137.41, 134.81, 129.03, 128.76, 128.15, 124.38, 121.82, 119.44 (q, J = 319 Hz, 2 CF_3), 51.91, 50.54, 45.96, 45.02, 25.48, 23.68.

ES-MS (+ve) m/z: Found $[M–NTf_2^-]^+$ 270.1606, $C_{16}H_{20}N_3O^+$ requires 270.1601


9.183
7.813
7.809
7.804
7.657
7.653
7.648
7.445
7.441
7.431
7.430
7.418
7.407
7.406
7.400
5.488
5.199
3.475
3.458
3.433
3.426
3.355
3.338
3.321
2.516
2.511
2.507
2.502
2.498
1.961
1.944
1.928
1.827
1.809
1.792
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
1.01
1.01
5.06
2.01
2.04
1.99
2.24
2.05
2.07


163.01
137.41
134.81
129.03
128.76
128.15
124.38
122.64
121.82
120.51
118.38
51.91
50.54
45.96
45.02
39.98
39.86
39.72
39.58
39.44
39.30
39.16
39.02
25.48
23.68
200 180 160 140 120 100 80 60 40 20 0 ppm

1*H*-Imidazolium-1,2-dimethyl-3-[2-oxo-2-(1-piperidinyl)ethyl] *bis*(trifluoromethanesulfonimide) (29):



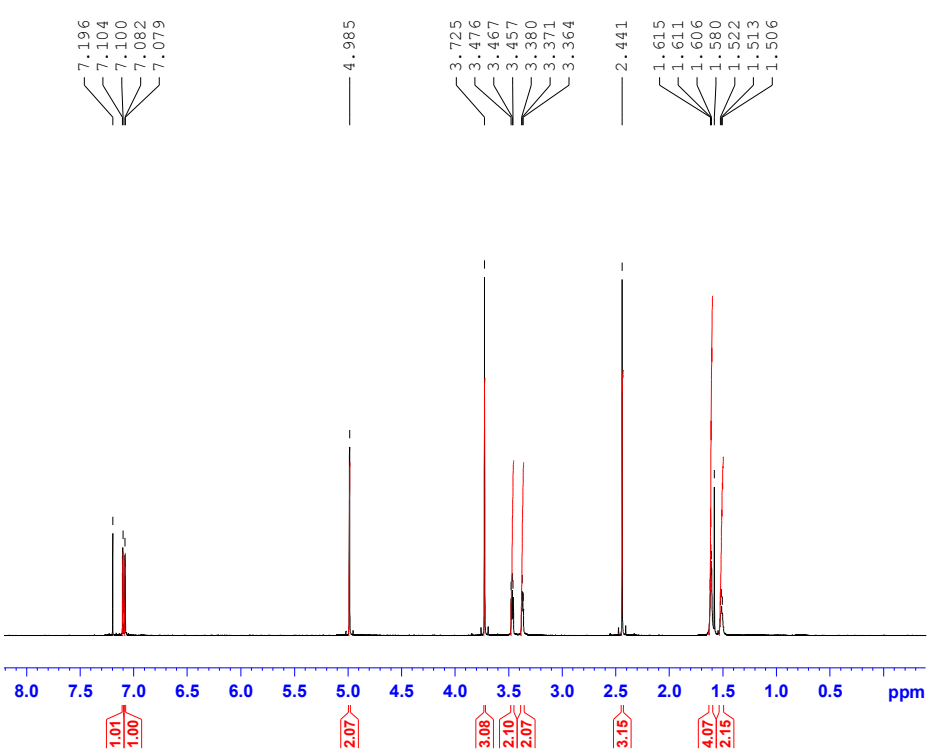
Procedure:

A RB flask was charged with 1*H*-Imidazolium, 1,2-dimethyl-3-[2-oxo-2-(1-piperidinyl)ethyl] bromide (**15**) (0.700 g, 2.30 mmol) and distilled water (4 mL). Lithium *bis*(trifluoromethanesulfonimide) (0.665 g, 2.30 mmol) in distilled water (4 mL) was added in one portion and the suspension was stirred vigorously for 4 h at RT. The top aqueous layer was removed and the IL washed with water (3 x 40 mL). Residual water was removed on the rotary evaporator. The product was dried *in vacuo* for 72 h to give **29** as a colourless liquid at RT in 80% yield (0.93g, 1.85 mmol).

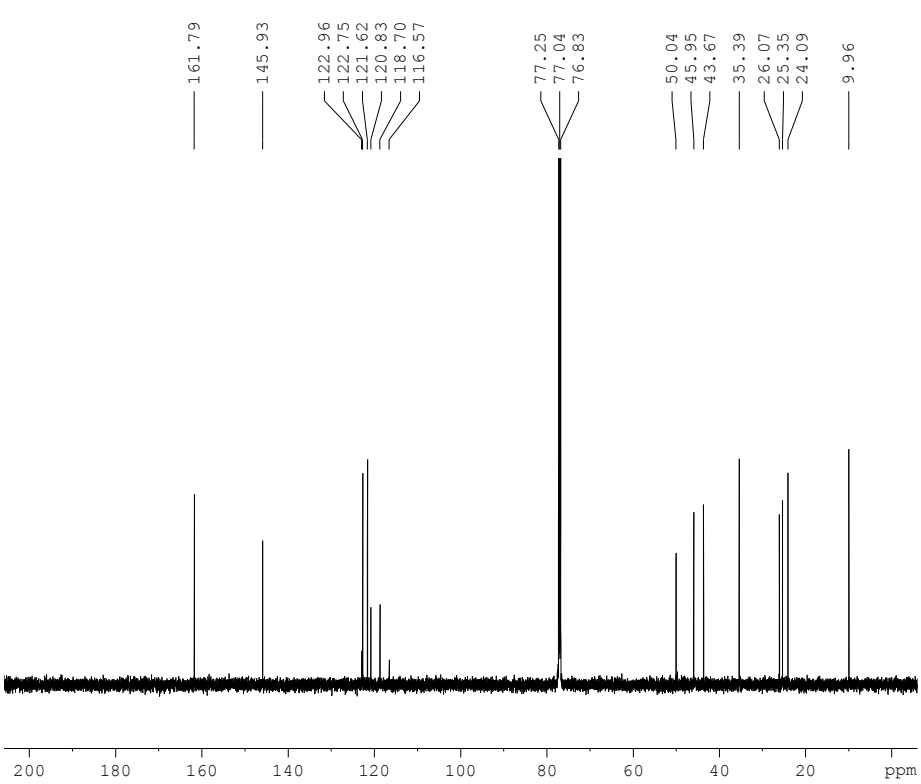
^{1}H-NMR (600 MHz, $CDCl_3$): 7.10 (d, J = 2.4 Hz, 1H), 7.08 (d, J =1.8 Hz, 1H), 4.98 (s, 2H), 3.72 (s, 3H), 3.47 (t, J = 6.0 Hz, 2H), 3.37 (t, J = 5.4 Hz, 2H), 2.44 (s, 3H), 1.61-1.58 (m, 4H), 1.52-1.50 (br m, 2H).

^{13}C-NMR (150 MHz, $CDCl_3$): 161.79, 145.93, 122.96, 122.75, 119.76 (q, J = 319.5 Hz, 2 CF_3), 50.04, 45.95, 43.67, 35.39, 26.07, 25.35, 24.09, 9.96.

ES-MS (+ve) m/z: Found $[M–NTf_2^–]^+$ 222.1609, $C_{12}H_{20}N_3O^+$ requires 222.1601

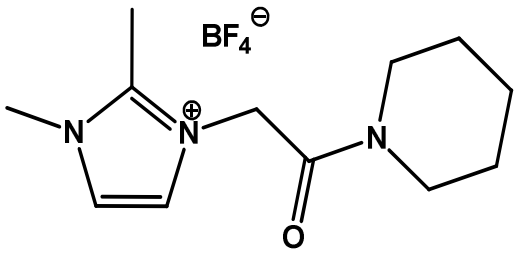


```
Current Data Parameters
NAME                  Aug24-2010
EXPNO                         30
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20100824
Time                       17.13
INSTRUM                    spect
PROBHD      5 mm PABBO BB-
PULPROG                    zg30
TD                        65536
SOLVENT                   CDCl3
NS                            16
DS                             2
SWH                    12335.526 Hz
FIDRES                 0.188225 Hz
AQ                     2.6564426 sec
RG                           256
DW                        40.533 usec
DE                        10.73 usec
TE                        293.6 K
D1                    1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                          1H
P1                        11.65 usec
PL1                       -5.30 dB
PL1W                  25.53414154 W
SFO1                  600.3267072 MHz

F2 - Processing parameters
SI                         32768
SF                    600.3230582 MHz
WDW                           EM
SSB                            0
LB                          0.30 Hz
GB                             0
PC                          1.00
```



```
Current Data Parameters
NAME                  Aug24-2010
EXPNO                         31
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20100824
Time                       18.05
INSTRUM                    spect
PROBHD      5 mm PABBO BB-
PULPROG                  zgpg30
TD                        65536
SOLVENT                   CDCl3
NS                          1024
DS                             4
SWH                    36057.691 Hz
FIDRES                 0.550197 Hz
AQ                     0.9088159 sec
RG                          2050
DW                        13.867 usec
DE                         6.50 usec
TE                        294.3 K
D1                    2.00000000 sec
D11                   0.03000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         13C
P1                         9.71 usec
PL1                        1.50 dB
PL1W                 78.77777863 W
SFO1                 150.9664335 MHz

======== CHANNEL f2 ========
CPDPRG2                  waltz16
NUC2                          1H
PCPD2                     70.00 usec
PL2                       -5.30 dB
PL12                      10.02 dB
PL13                     120.00 dB
PL2W                  25.53414154 W
PL12W                 0.75010353 W
PL13W                 0.00000000 W
SFO2                  600.3254013 MHz

F2 - Processing parameters
SI                         32768
SF                    150.9513390 MHz
WDW                           EM
SSB                            0
LB                          1.00 Hz
GB                             0
PC                          1.40
```

1*H*-Imidazolium, 1,2-dimethyl-3-[2-oxo-2-(1-piperidinyl)ethyl] tetrafluoroborate (30):



Procedure:

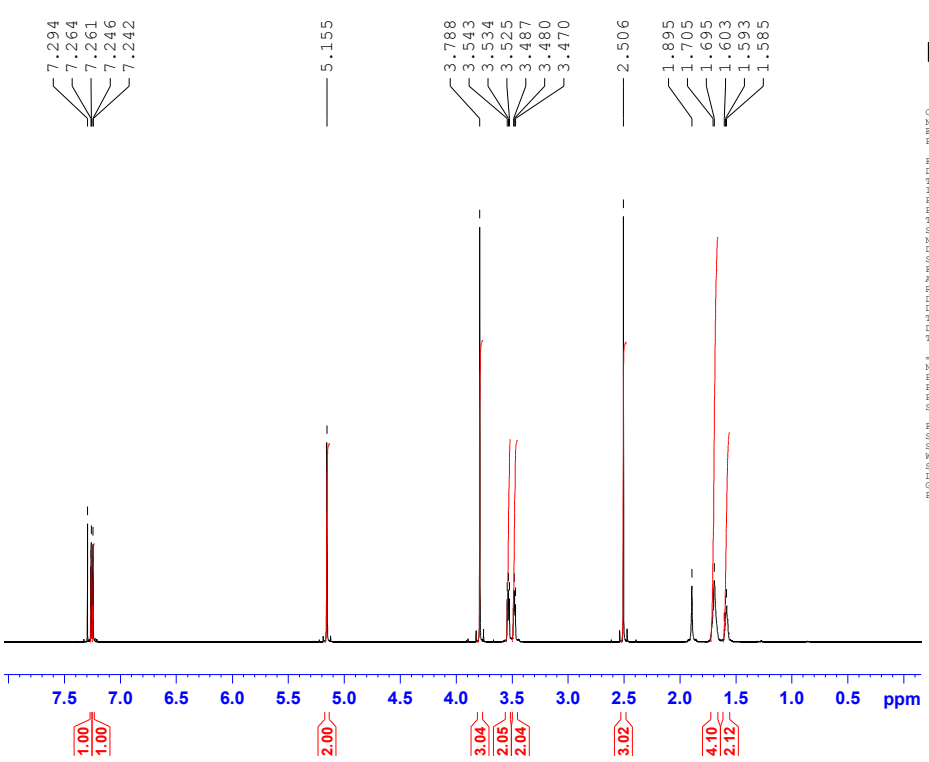
A flask was charged with 1*H*-Imidazolium, 1,2-dimethyl-3-[2-oxo-2-(1-piperidinyl)ethyl] bromide (**15**) (1.00 g, 3.30 mmol) and acetone (10 mL) under a nitrogen atmosphere. Sodium tetrafluoroborate (0.472 g, 4.30 mmol) was added in one portion and the suspension was stirred vigorously for 4 days at RT. The fine white precipitate was filtered quickly in air and washed with dry acetone (2 x 4 mL). The filtrate and washings were combined and solvent removed by rotary evaporation, then *in vacuo* for 2 days to give **30** as a white solid in 100% yield (1.02 g, 3.30 mmol).

^{1}H-NMR (600 MHz, $CDCl_3$): 7.26 (d, J = 1.8 Hz, 1H), 7.24 (d, J = 2.4 Hz, 1H), 5.15 (s, 2H), 3.79 (s, 3H), 3.53 (t, J = 5.4 Hz, 2H), 3.48 (t, J = 6.0 Hz, 2H), 2.51 (s, 3H), 1.70-1.69 (m, 4H), 1.60-1.58 (m, 2H).

^{13}C-NMR (150 MHz, $CDCl_3$): 162.39, 146.00, 122.59, 121.75, 49.60, 45.90, 43.53, 35.19, 25.96, 25.37, 24.16, 9.74.

Melting point: 119-120 ºC

ES-MS (+ve) m/z: Found $[M–BF_4^-]^+$ 222.1597, $C_{12}H_{20}N_3O^+$ requires 222.1601

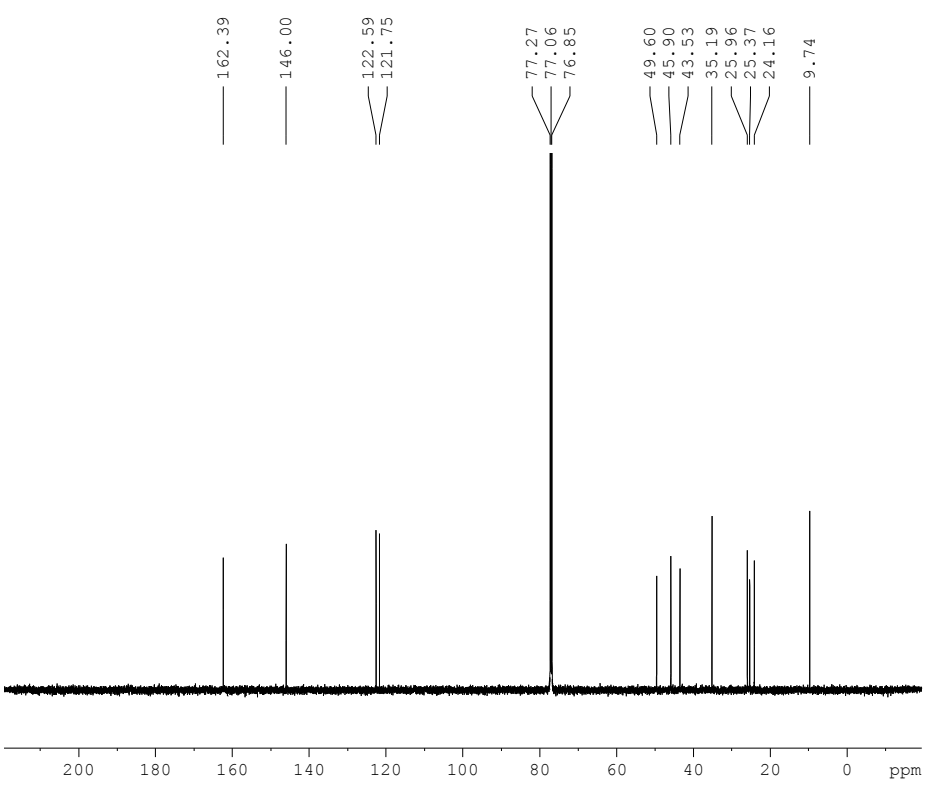


Current Data Parameters
NAME Aug02-2011
EXPNO 90
PROCNO 1

F2 - Acquisition Parameters
Date_ 20110803
Time 18.30
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 12335.526 Hz
FIDRES 0.188225 Hz
AQ 2.6564426 sec
RG 228
DW 40.533 usec
DE 10.73 usec
TE 293.1 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 11.65 usec
PL1 -5.30 dB
PL1W 25.53414154 W
SFO1 600.3267072 MHz

F2 - Processing parameters
SI 32768
SF 600.3230000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



Current Data Parameters
NAME Aug02-2011
EXPNO 91
PROCNO 1

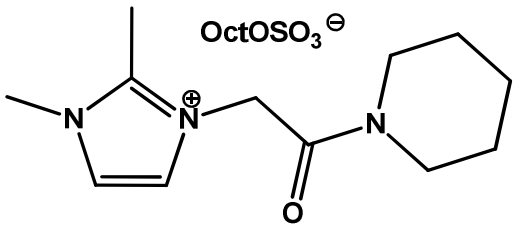
F2 - Acquisition Parameters
Date_ 20110803
Time 19.23
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1024
DS 4
SWH 36057.691 Hz
FIDRES 0.550197 Hz
AQ 0.9088159 sec
RG 2050
DW 13.867 usec
DE 6.50 usec
TE 293.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 9.71 usec
PL1 1.50 dB
PL1W 78.77777863 W
SFO1 150.9664335 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 70.00 usec
PL2 -5.30 dB
PL12 10.02 dB
PL13 120.00 dB
PL2W 25.53414154 W
PL12W 0.75010353 W
PL13W 0.00000000 W
SFO2 600.3254013 MHz

F2 - Processing parameters
SI 32768
SF 150.9513390 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

1*H*-Imidazolium, 1,2-dimethyl-3-[2-oxo-2-(1-piperidinyl)ethyl] octyl sulfate (31):



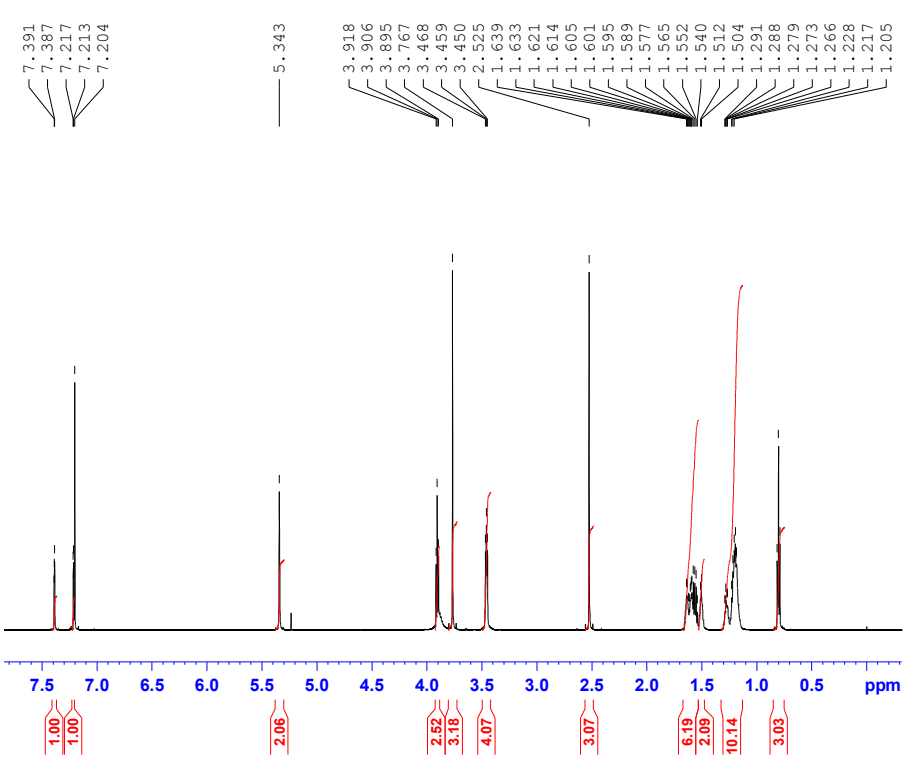
Procedure:

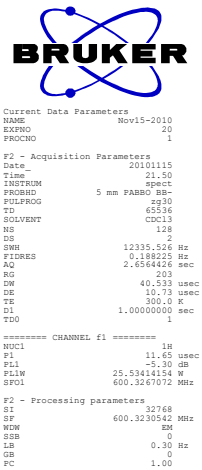
A flask was charged with 1*H*-Imidazolium, 1,2-dimethyl-3-[2-oxo-2-(1-piperidinyl)ethyl] bromide (**15**) (1.00 g, 3.3 mmol) and distilled water (10 mL). Sodium octylsulfate (0.768 g, 3.3 mmol) in distilled water (5 mL) was added in one portion and the suspension was stirred vigorously for 24 h at RT. The water was removed on the rotary evaporator and residue was dissolved in chloroform (10 mL) and washed with water. Organic layer was dried over anhydrous magnesium sulphate, filtered and filtrate was evaporated. The product was dried *in vacuo* for 72 h to give **31** as a white sticky solid in 79% yield (1.12 g, 2.6 mmol).

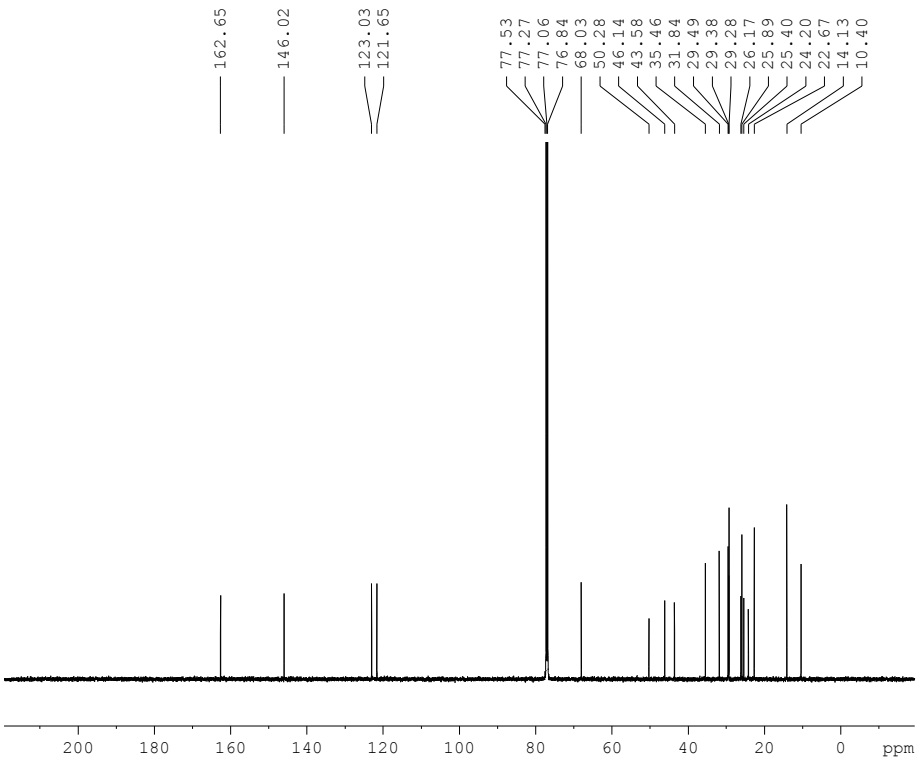
^{1}H-NMR (600 MHz, $CDCl_3$): 7.39 (d, J = 2.4 Hz, 1H), 7.21 (d, J = 2.4 Hz, 1H), 5.34 (s, 2H), 3.91 (t, J = 6.0 Hz, 2H), 3.77 (s, 3H), 3.46 (t, J = 6.0 Hz, 4H), 2,52 (s, 3H), 2.44 (s, 3H), 1.64-1.50 (m, 8H), 1.29-1.20 (m, 10H).

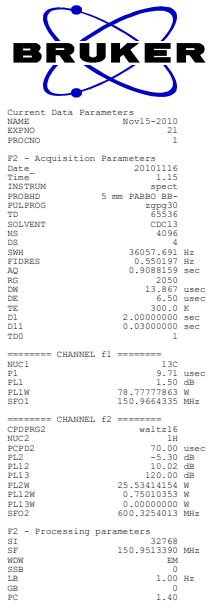
^{13}C-NMR (150 MHz, $CDCl_3$): 162.65, 146.02, 123.03, 121.65, 68.03, 50.28, 46.14, 43.58, 35.46, 31.84, 29.49, 29.38, 29.28, 26.17, 25.89, 25.40, 24.20, 22.67, 14.13, 10.40.

ES-MS (+ve) m/z: Found $[M–OctOSO_3^-]^+$ 222.1602, $C_{12}H_{20}N_3O^+$ requires 222.1601

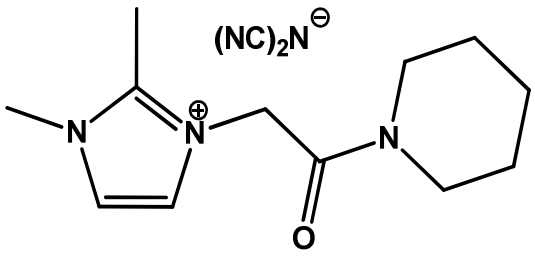

7.391
7.387
7.217
7.213
7.204
5.343
3.918
3.906
3.895
3.767
3.468
3.459
3.450
2.525
1.639
1.633
1.621
1.614
1.605
1.601
1.595
1.589
1.577
1.565
1.552
1.540
1.512
1.504
1.291
1.288
1.279
1.273
1.266
1.228
1.217
1.205
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
1.00
2.06
2.52
3.18
4.07
3.07
6.19
2.09
10.14
3.03


BRUKER
Current Data Parameters
NAME Nov15-2010
EXPNO 20
PROCNO 1
F2 - Acquisition Parameters
Date_ 20101115
Time 21.50
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 128
DS 2
SWH 12335.526 Hz
FIDRES 0.188225 Hz
AQ 2.6564426 sec
RG 203
DW 40.533 usec
DE 10.73 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 11.65 usec
PL1 -5.30 dB
PL1W 25.53414154 W
SFO1 600.3267072 MHz
F2 - Processing parameters
SI 32768
SF 600.3230542 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00


162.65
146.02
123.03
121.65
77.53
77.27
77.06
76.84
68.03
50.28
46.14
43.58
35.46
31.84
29.49
29.38
29.28
26.17
25.89
25.40
24.20
22.67
14.13
10.40
200 180 160 140 120 100 80 60 40 20 0 ppm


BRUKER
Current Data Parameters
NAME Nov15-2010
EXPNO 21
PROCNO 1
F2 - Acquisition Parameters
Date_ 20101116
Time 1.15
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 4096
DS 4
SWH 36057.691 Hz
FIDRES 0.550197 Hz
AQ 0.9088159 sec
RG 2050
DW 13.867 usec
DE 6.50 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.71 usec
PL1 1.50 dB
PL1W 78.77777863 W
SFO1 150.9664335 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 70.00 usec
PL2 -5.30 dB
PL12 10.02 dB
PL13 120.00 dB
PL2W 25.53414154 W
PL12W 0.75010353 W
PL13W 0.00000000 W
SFO2 600.3254013 MHz
F2 - Processing parameters
SI 32768
SF 150.9513390 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

1*H*-Imidazolium, 1,2-dimethyl-3-[2-oxo-2-(1-piperidinyl)ethyl] dicynamide (32):



Procedure:

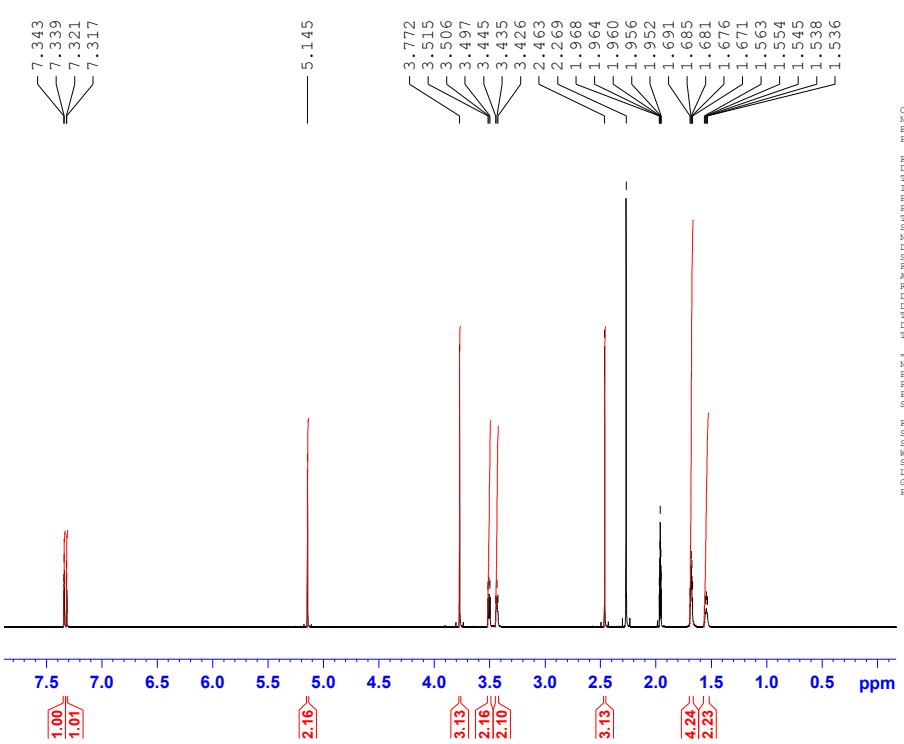
A flask was charged with 1*H*-Imidazolium, 1,2-dimethyl-3-[2-oxo-2-(1-piperidinyl)ethyl] bromide (**15**) (1.00 g, 3.3 mmol) and acetone (5 mL) under a nitrogen atmosphere. Sodium dicyanamide (0.442 g, 4.96 mmol) was added in one portion and the suspension was stirred vigorously for 4 days at RT. The fine white precipitate was filtered quickly in air and washed with dry acetonitrile (2 x 4 mL). The filtrate and washings were combined and solvent removed by rotary evaporation, then *in vacuo* for 2 days to give **32** as a white solid in 99% yield (0.950 g, 3.2 mmol).

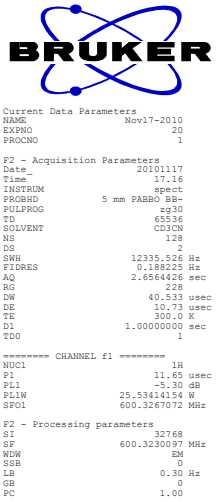
^{1}H-NMR (600 MHz, CD_3CN): 7.34 (d, J = 2.4 Hz, 1H), 7.32 (d, J = 2.4 Hz, 1H), 5.14 (s, 2H), 3.77 (s, 3H), 3.51 (t, J = 5.4 Hz, 2H), 3.43 (t, J = 6.0 Hz, 2H), 2.46 (s, 3H), 1.69-1.67 (m, 4H), 1.56-1.54 (m, 2H).

^{13}C-NMR (150 MHz, CD_3CN): 163.48, 147.84, 123.90, 123.45, 121.20, 47.16, 44.63, 36.62, 27.38, 26.79, 25.49, 10.98.

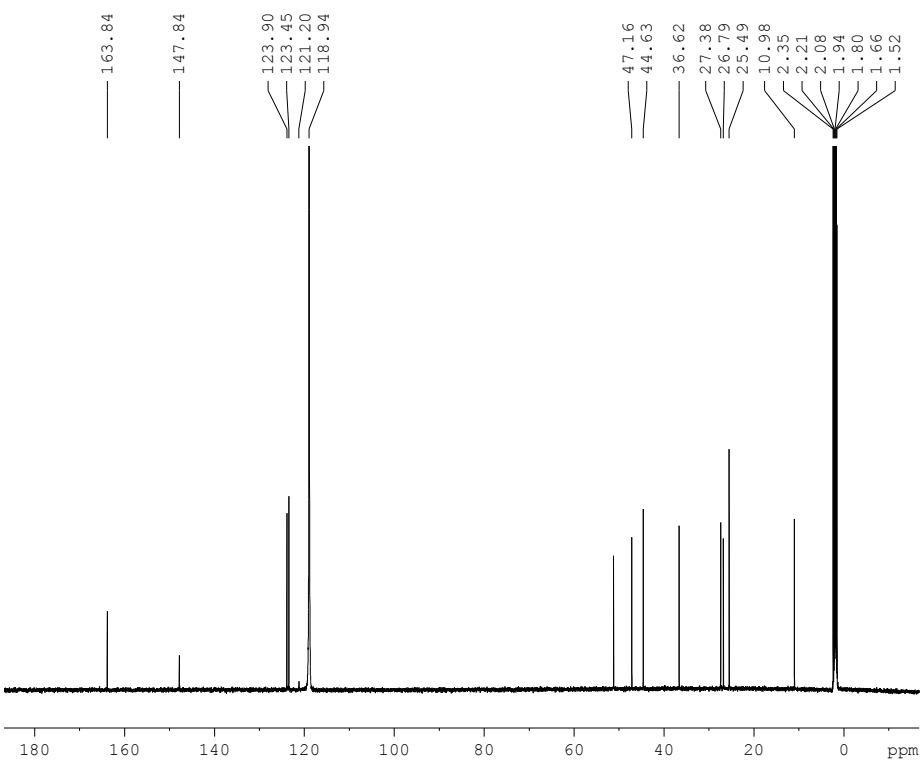
Melting point: 84-85 ºC

ES-MS (+ve) m/z: Found $[M–N(CN)_2^–]^+$ 222.1616, $C_{12}H_{20}N_3O^+$ requires 222.1601



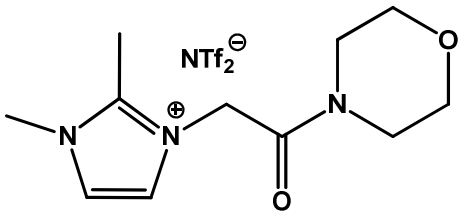


```
Current Data Parameters
NAME                  Nov17-2010
EXPNO                         20
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20101117
Time                       17.16
INSTRUM                    spect
PROBHD      5 mm PABBO BB-
PULPROG                    zg30
TD                        65536
SOLVENT                   CD3CN
NS                          128
DS                            2
SWH                   12335.526 Hz
FIDRES                0.188225 Hz
AQ                    2.6564426 sec
RG                          228
DW                       40.533 usec
DE                       10.73 usec
TE                       300.0 K
D1                    1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                          1H
P1                       11.65 usec
PL1                      -5.30 dB
PL1W                25.53414154 W
SFO1               600.3267072 MHz

F2 - Processing parameters
SI                         32768
SF                600.3230097 MHz
WDW                           EM
SSB                            0
LB                        0.30 Hz
GB                             0
PC                          1.00
```



```
Current Data Parameters
NAME                  Nov17-2010
EXPNO                         21
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20101117
Time                       20.41
INSTRUM                    spect
PROBHD      5 mm PABBO BB-
PULPROG                  zgpg30
TD                        65536
SOLVENT                   CD3CN
NS                         4096
DS                            4
SWH                   36057.691 Hz
FIDRES                0.550197 Hz
AQ                    0.9088159 sec
RG                         2050
DW                       13.867 usec
DE                        6.50 usec
TE                       300.0 K
D1                    2.00000000 sec
D11                   0.03000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                          13C
P1                        9.71 usec
PL1                       1.50 dB
PL1W                78.77777863 W
SFO1               150.9664335 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                          1H
PCPD2                    70.00 usec
PL2                      -5.30 dB
PL12                     10.02 dB
PL13                    120.00 dB
PL2W                25.53414154 W
PL12W                0.75010353 W
PL13W                0.00000000 W
SFO2               600.3254013 MHz

F2 - Processing parameters
SI                         32768
SF                150.9511014 MHz
WDW                           EM
SSB                            0
LB                        1.00 Hz
GB                             0
PC                          1.40
```

1*H*-Imidazolium-1,2-dimethyl-3-[2-oxo-2-(1-morpholinyl)ethyl] *bis*(trifluoromethanesulfonimide) (33):



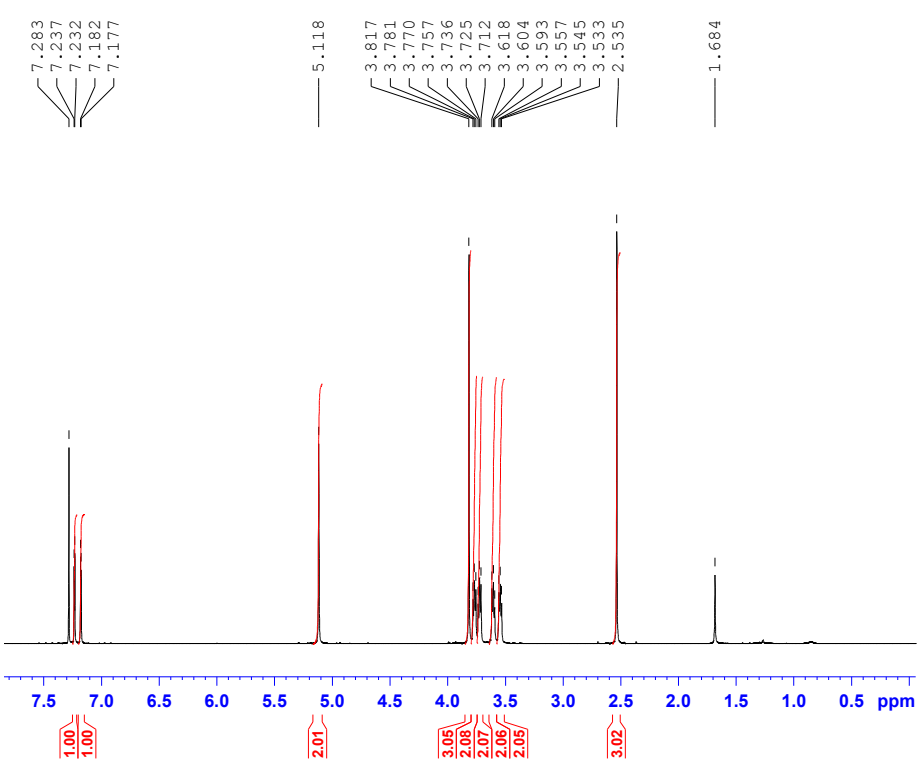
Procedure:

A RB flask was charged with 1*H*-Imidazolium,1,2-dimethyl-3-[2-oxo-2-(1-morpholinyl)ethyl] bromide (**16**) (1.10 g, 3.62 mmol) and distilled water (4 mL). Lithium *bis*(trifluoromethane) sulfonamide (1.04 g, 3.62 mmol) in distilled water (4 mL) was added in one portion and the suspension was stirred vigorously for 4 h at RT. The top aqueous layer was removed; the IL washed with water (3 x 4 mL) and residual water was removed on the rotary evaporator. The product was dried *in vacuo* for 72 h to give **33** as a colourless liquid at RT in 85% yield (1.56 g, 3.09 mmol).

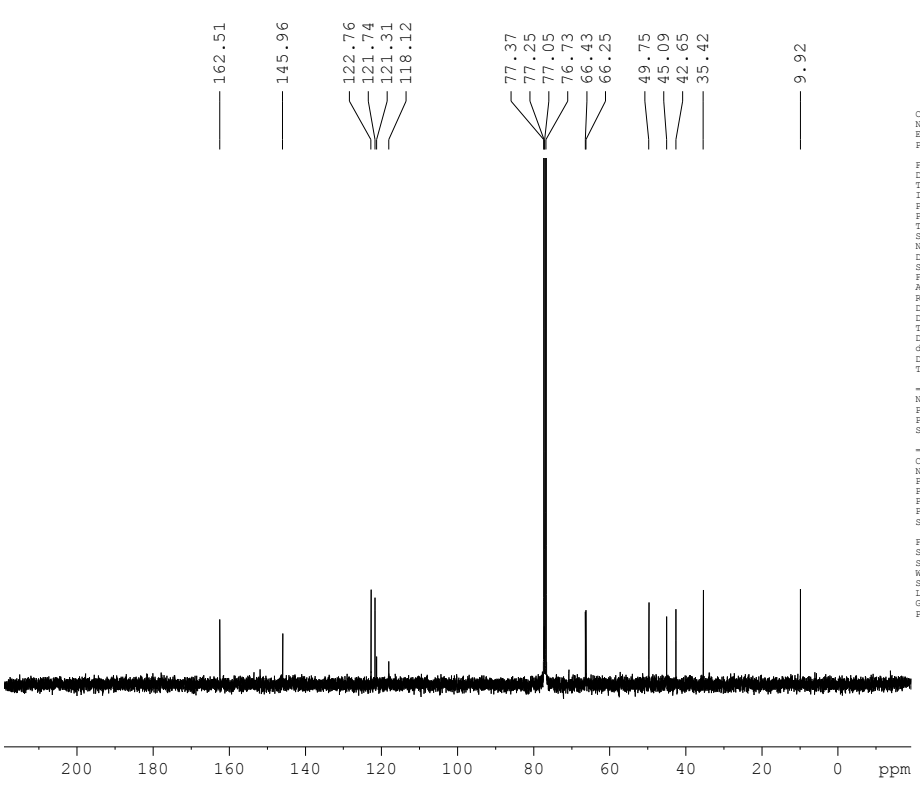
^{1}H-NMR (400 MHz, $CDCl_3$): 7.23 (d, J = 2.0 Hz, 1H), 7.18 (d, J = 2.0 Hz, 1H), 5.11 (s, 2H), 3.82 (s, 3H), 3.77 (dd, J = 5.2, 4.4 Hz, 2H), 3.72 (dd, J = 5.2, 4.4 Hz, 2H), 3.60 (dd, J = 5.2, 4.4 Hz, 2H), 3.54 (dd, J = 5.2, 4.4 Hz, 2H), 2.53 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): 162.51, 145.96, 122.76, 121.74, 119.71 (q, J = 319 Hz, 2 CF_3), 66.43, 66.25, 49.75, 45.09, 42.65, 35.42, 9.92

ES-MS (+ve) m/z: Found $[M–NTf_2^-]^+$ 224.1389, $C_{12}H_{20}N_3O^+$ requires 224.1393

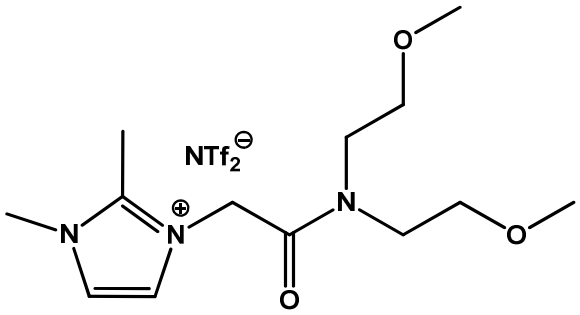



```
Current Data Parameters
NAME                  Nov21-2011
EXPNO                         10
PROCNO                         1

F2 - Acquisition Parameters
Date_                  20111121
Time                       9.49
INSTRUM                   spect
PROBHD  5 mm QNP 1H/13
PULPROG                   zg30
TD                       65536
SOLVENT                  CDCl3
NS                          16
DS                           2
SWH                 8278.146 Hz
FIDRES              0.126314 Hz
AQ                  3.9584243 sec
RG                       322.5
DW                    60.400 usec
DE                     6.00 usec
TE                     292.2 K
D1                 1.00000000 sec
TD0                          1

======== CHANNEL f1 ========
NUC1                       1H
P1                     12.00 usec
PL1                     0.00 dB
SFO1              400.1324710 MHz

F2 - Processing parameters
SI                       32768
SF                400.1300000 MHz
WDW                         EM
SSB                          0
LB                      0.30 Hz
GB                           0
PC                        1.00
```




```
Current Data Parameters
NAME                  Nov21-2011
EXPNO                         11
PROCNO                         1

F2 - Acquisition Parameters
Date_                  20111121
Time                      18.44
INSTRUM                   spect
PROBHD  5 mm QNP 1H/13
PULPROG                 zgpg30
TD                       65536
SOLVENT                  CDCl3
NS                        1024
DS                           4
SWH                23980.814 Hz
FIDRES              0.365918 Hz
AQ                  1.3664756 sec
RG                        6502
DW                    20.850 usec
DE                     6.00 usec
TE                     324.2 K
D1                 2.00000000 sec
d11                0.03000000 sec
DELTA              1.89999998 sec
TD0                          1

======== CHANNEL f1 ========
NUC1                      13C
P1                     10.00 usec
PL1                     0.00 dB
SFO1              100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                  80.00 usec
PL2                    -3.00 dB
PL12                   12.00 dB
PL13                   12.00 dB
SFO2              400.1316005 MHz

F2 - Processing parameters
SI                       32768
SF                100.6127690 MHz
WDW                         EM
SSB                          0
LB                      1.00 Hz
GB                           0
PC                        1.40
```

1*H*-Imidazolium-1,2-dimethyl-3-[2-[*bis*(2-methoxyethyl)amino]-2-oxoethyl]-*bis*(trifluoromethanesulfonimide) (34):



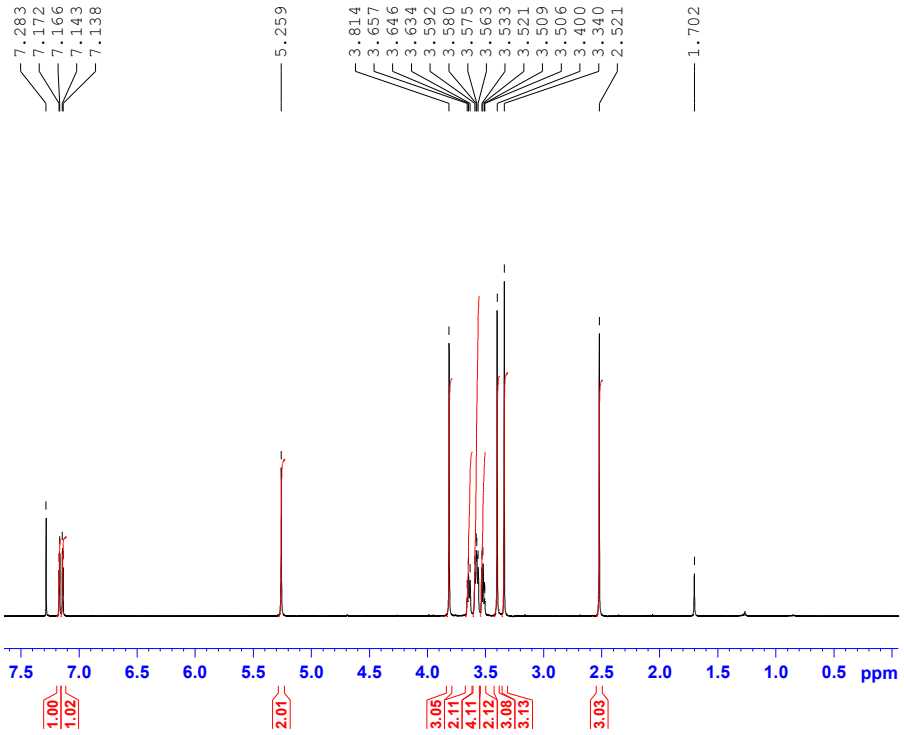
Procedure:

A RB flask was charged with 1*H*-Imidazolium, 1,2-dimethyl-3-[2-[*bis*(2-methoxyethyl)amino]-2-oxoethyl] bromide (**17**) (1.00 g, 2.85 mmol) and distilled water (4 mL). Lithium *bis*(trifluoromethanesulfonimide) (0.819 g, 2.85 mmol) in distilled water (4 mL) was added in one portion and the suspension was stirred vigorously for 4 h at RT. The top aqueous layer was removed and the IL washed with water (3 x 4 mL) and residual water was removed on the rotary evaporator. The product was dried *in vacuo* for 72 h to give **34** as a colourless liquid at RT in 68% yield (1.07 g, 1.94 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.17 (d, J = 2.4 Hz, 1H), 7.14 (d, J = 2.0 Hz, 1H), 5.26 (s, 2H), 3.81 (s, 3H), 3.65 (dd, J = 4.8, 4.4 Hz, 2H), 3.59-3.56 (m, 4H), 3.53-3.50 (m, 2H), 3.40 (s, 3H), 3.34 (s, 3H), 2.52 (s, 3H).

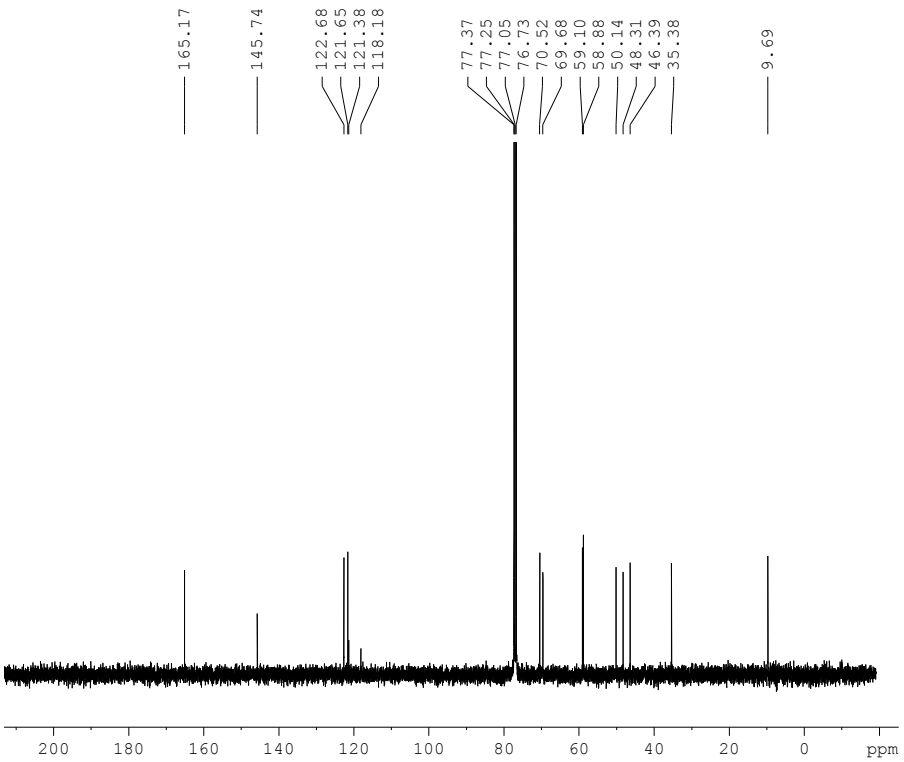
^{13}C-NMR (100 MHz, $CDCl_3$): 165.17, 145.74, 122.68, 121.65, 119.76 (q, J = 320 Hz, 2 CF_3), 70.52, 69.68, 59.10, 58.88, 50.14, 48.31, 46.39, 35.38, 9.69

ES-MS (+ve) m/z: Found $[M–NTf_2^-]^+$ 270.1823, $C_{12}H_{20}N_3O^+$ requires 270.1812



BRUKER

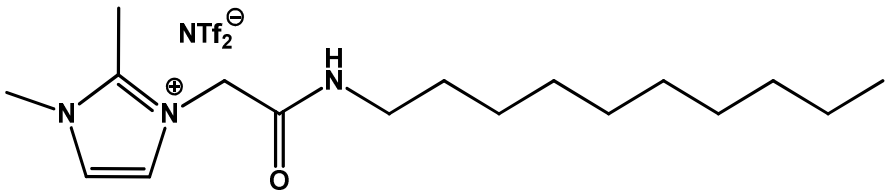
```
Current Data Parameters
NAME                  Nov18-2011
EXPNO                        280
PROCNO                         1

F2 - Acquisition Parameters
Date_                  20111118
Time                      16.16
INSTRUM                   spect
PROBHD  5 mm QNP 1H/13
PULPROG                   zg30
TD                       65536
SOLVENT                  CDCl3
NS                          16
DS                           2
SWH                   8278.146 Hz
FIDRES                0.126314 Hz
AQ                    3.9584243 sec
RG                        161.3
DW                       60.400 usec
DE                        6.00 usec
TE                       293.2 K
D1                    1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         1H
P1                       12.00 usec
PL1                       0.00 dB
SFO1                  400.1324710 MHz

F2 - Processing parameters
SI                           32768
SF                    400.1300000 MHz
WDW                             EM
SSB                              0
LB                            0.30 Hz
GB                               0
PC                            1.00
```



BRUKER

```
Current Data Parameters
NAME                  Nov18-2011
EXPNO                         71
PROCNO                         1

F2 - Acquisition Parameters
Date_                  20111118
Time                      23.16
INSTRUM                   spect
PROBHD  5 mm QNP 1H/13
PULPROG                 zgpg30
TD                       65536
SOLVENT                  CDCl3
NS                        1024
DS                           4
SWH                  23980.814 Hz
FIDRES                0.365918 Hz
AQ                    1.3664756 sec
RG                         6502
DW                       20.850 usec
DE                        6.00 usec
TE                       293.2 K
D1                    2.00000000 sec
d11                   0.03000000 sec
DELTA                 1.89999998 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                        13C
P1                       10.00 usec
PL1                       0.00 dB
SFO1                  100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                         1H
PCPD2                    80.00 usec
PL2                      -3.00 dB
PL12                     12.00 dB
PL13                     12.00 dB
SFO2                  400.1316005 MHz

F2 - Processing parameters
SI                           32768
SF                    100.6127690 MHz
WDW                             EM
SSB                              0
LB                            1.00 Hz
GB                               0
PC                            1.40
```

1*H*-Imidazolium-1,2-dimethyl-3-[2-(decylamino)-2-oxoethyl] *bis*(trifluoromethanesulfonimide) (35):



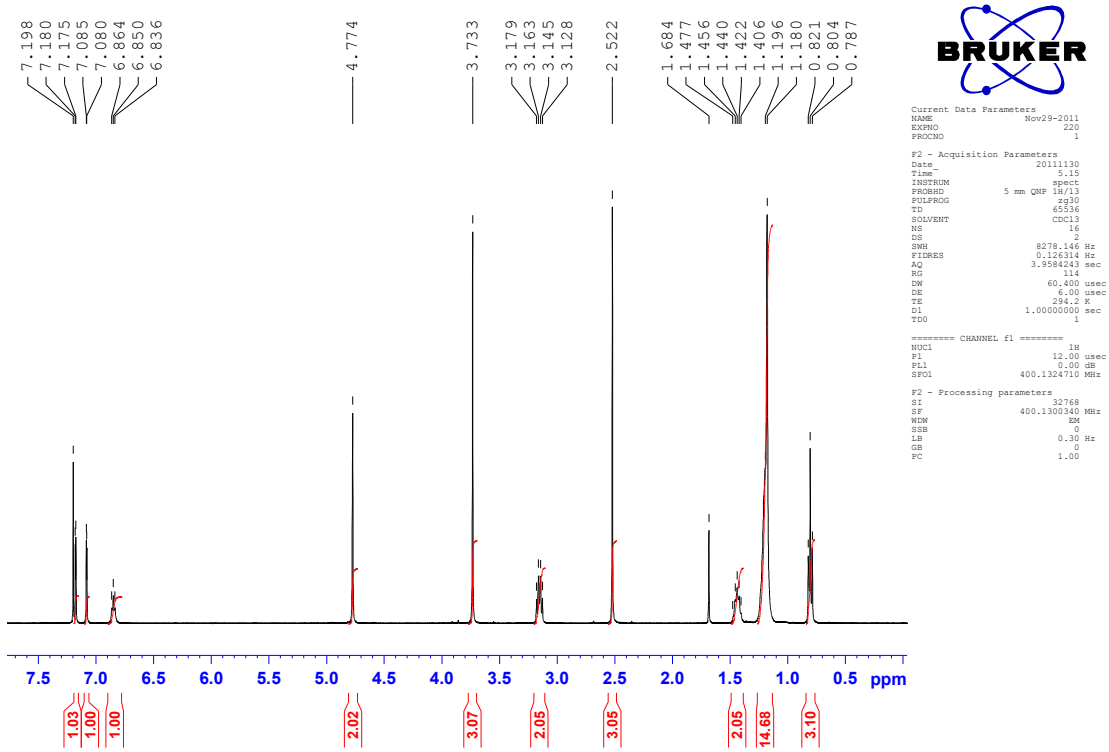
Procedure:

A RB flask was charged with 1*H*-Imidazolium, 1,2-dimethyl-3-[2-(decylamino)-2-oxoethyl] bromide (**18**) (0.600 g, 1.60 mmol) and distilled water (4 mL). Lithium *bis*(trifluoromethane-sulfonimide) (0.460 g, 1.60 mmol) in distilled water (4 mL) was added in one portion and the suspension was stirred vigorously for 4 h at RT. The top aqueous layer was removed and the IL washed with water (3 x 4 mL) and residual water was removed on the rotary evaporator. The product was dried *in vacuo* for 72 h to give **35** as a colourless liquid at RT in 94% yield (0.867 g, 1.51 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.17 (d, J = 2.4 Hz, 1H), 7.08 (d, J = 2.0 Hz, 1H), 6.85 (t, J = 5.6 Hz, 1H), 4.77 (s, 2H), 3.73 (s, 3H), 3.18-3.12 (m, 2H), 2.52 (s, 3H), 1.48-1.40 (m, 2H), 1.19-1.18 (br m, 14H), 0.80 (t, J = 7.8 Hz, 3H)

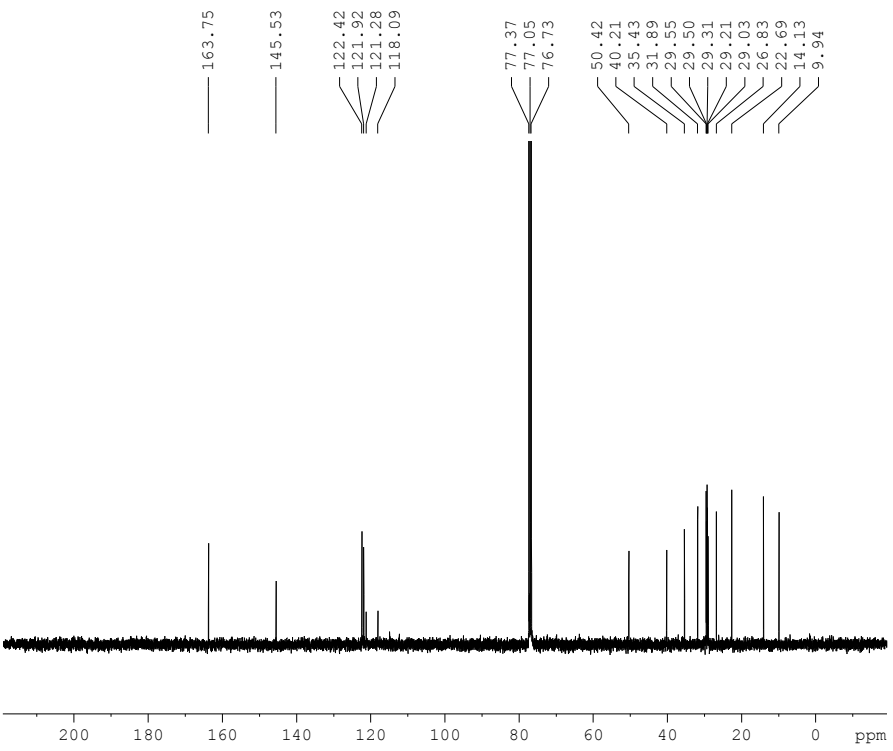
^{13}C-NMR (100 MHz, $CDCl_3$): 163.75, 145.53, 122.42, 121.92, 119.78 (q, J = 319 Hz, 2 CF_3), 50.42, 40.21, 35.43, 31.89, 29.55, 29.50, 29.31, 29.21, 29.03, 26.83, 22.69, 14.13, 9.94

ES-MS (+ve) m/z: Found $[M–NTf_2^–]^+$ 294.2531, $C_{12}H_{20}N_3O^+$ requires 294.2545



BRUKER

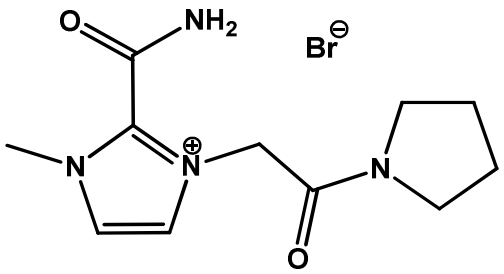
```
Current Data Parameters
NAME                  Nov29-2011
EXPNO                        220
PROCNO                         1

F2 - Acquisition Parameters
Date_                 20111130
Time                      5.15
INSTRUM                  spect
PROBHD  5 mm QNP 1H/13
PULPROG                  zg30
TD                      65536
SOLVENT                  CDCl3
NS                          16
DS                           2
SWH                 8278.146 Hz
FIDRES              0.126314 Hz
AQ                  3.9584243 sec
RG                         114
DW                    60.400 usec
DE                     6.00 usec
TE                     294.2 K
D1                 1.00000000 sec
TD0                          1

======== CHANNEL f1 ========
NUC1                         1H
P1                    12.00 usec
PL1                    0.00 dB
SFO1              400.1324710 MHz

F2 - Processing parameters
SI                       32768
SF                400.1300340 MHz
WDW                         EM
SSB                          0
LB                      0.30 Hz
GB                           0
PC                        1.00
```



BRUKER

```
Current Data Parameters
NAME                  Nov30-2011
EXPNO                        111
PROCNO                         1

F2 - Acquisition Parameters
Date_                 20111201
Time                     21.17
INSTRUM                  spect
PROBHD  5 mm QNP 1H/13
PULPROG                zgpg30
TD                      65536
SOLVENT                  CDCl3
NS                        1024
DS                           4
SWH                23980.814 Hz
FIDRES              0.365918 Hz
AQ                  1.3664756 sec
RG                         650
DW                    20.850 usec
DE                     6.00 usec
TE                     297.2 K
D1                 2.00000000 sec
d11                0.03000000 sec
DELTA              1.89999998 sec
TD0                          1

======== CHANNEL f1 ========
NUC1                        13C
P1                    10.00 usec
PL1                    0.00 dB
SFO1              100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                         1H
PCPD2                 80.00 usec
PL2                   -3.00 dB
PL12                  12.00 dB
PL13                  12.00 dB
SFO2              400.1316005 MHz

F2 - Processing parameters
SI                       32768
SF                100.6127690 MHz
WDW                         EM
SSB                          0
LB                      1.00 Hz
GB                           0
PC                        1.40
```

1*H*-Imidazolium-2-carboxamide, 1-methyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl] bromide (40):



Procedure:

A RB flask was charged with 1-methyl-1*H*-imidazole-2-carboxamide (**38**) (2.00 g, 16.00 mmol) and THF (100 mL) under nitrogen. To this solution was added 2-bromo-1-(pyrrolidin-1-yl)ethanone (3.07 g, 16.00 mmol). The reaction mixture was refluxed for 2 days with vigorous stirring. The product precipitated as a white solid, was then washed with THF (5 x 50 mL). The solvent was removed on the rotary evaporator and the product was dried *in vacuo* for 72 h to give **40** as a white solid at RT in 47% yield (2.35 g, 7.43 mmol).

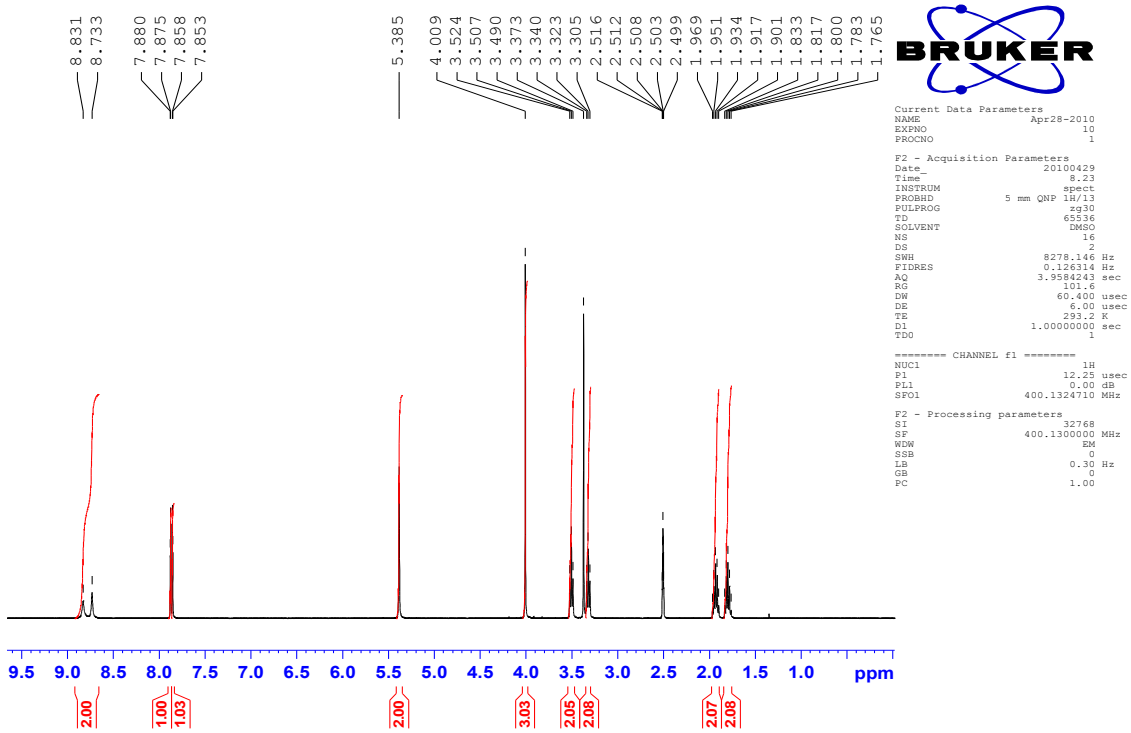
^{1}H-NMR (400 MHz, DMSO-d_6): 8.83 (bs, 1H), 8.73 (bs, 1H), 7.88 (d, J = 2.0 Hz, 1H), 7.85 (d, J = 2.0 Hz, 1H), 5.38 (s, 2H), 4.01 (s, 3H), 3.51 (t, J = 6.8 Hz, 2H), 3.28 (t, J = 6.8 Hz, 2H), 1.97-1.90 (m, 2H), 1.83-1.76 (m, 2H)

^{13}C-NMR (150 MHz, DMSO-d_6): 162.42, 154.60, 138.97, 124.13, 123.40, 50.75, 45.99, 45.15, 36.86, 25.45, 23.67.

IR (neat) (cm^{-1}): 3500, 3255, 3101, 2880, 1704, 1638, 1541, 1421, 786.

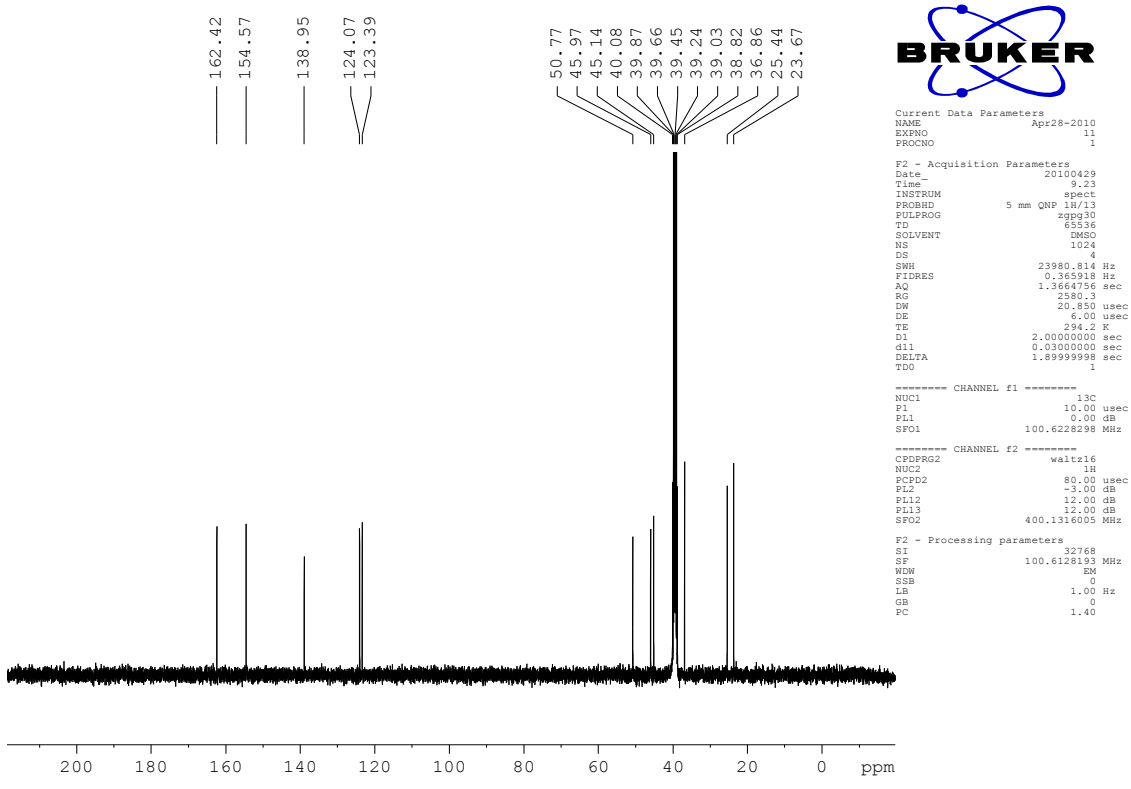
Melting Point: 197-198 °C

ES-MS (+ve) m/z: Found $[M–Br^–]^+$ 237.1361, $C_{11}H_{17}N_4O_2^+$ requires 237.1346



BRUKER

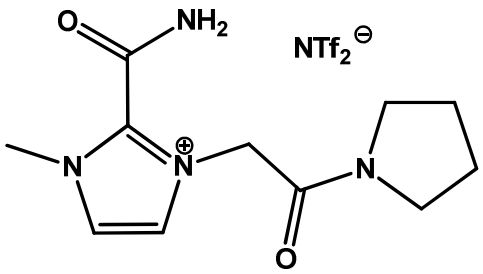
```
Current Data Parameters
NAME                  Apr28-2010
EXPNO                         10
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20100429
Time                        8.23
INSTRUM                    spect
PROBHD      5 mm QNP 1H/13 
PULPROG                    zg30
TD                        65536
SOLVENT                    DMSO
NS                            16
DS                             2
SWH                  8278.146 Hz
FIDRES               0.126314 Hz
AQ                   3.9584243 sec
RG                        101.6
DW                       60.400 usec
DE                        6.00 usec
TE                       293.2 K
D1                   1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                          1H
P1                         12.25 usec
PL1                         0.00 dB
SFO1           400.1324710 MHz

F2 - Processing parameters
SI                         32768
SF             400.1300000 MHz
WDW                           EM
SSB                            0
LB                          0.30 Hz
GB                             0
PC                          1.00
```



BRUKER

```
Current Data Parameters
NAME                  Apr28-2010
EXPNO                         11
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20100429
Time                        9.23
INSTRUM                    spect
PROBHD      5 mm QNP 1H/13 
PULPROG                  zgpg30
TD                        65536
SOLVENT                    DMSO
NS                          1024
DS                             4
SWH                  23980.814 Hz
FIDRES               0.365918 Hz
AQ                   1.3664756 sec
RG                       2580.3
DW                       20.850 usec
DE                        6.00 usec
TE                       294.2 K
D1                   2.00000000 sec
d11                  0.03000000 sec
DELTA                1.89999998 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         13C
P1                         10.00 usec
PL1                         0.00 dB
SFO1           100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                  waltz16
NUC2                          1H
PCPD2                      80.00 usec
PL2                        -3.00 dB
PL12                       12.00 dB
PL13                       12.00 dB
SFO2           400.1316005 MHz

F2 - Processing parameters
SI                         32768
SF             100.6128193 MHz
WDW                           EM
SSB                            0
LB                          1.00 Hz
GB                             0
PC                          1.40
```

1*H*-Imidazolium-2-carboxamide-1-methyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl] *bis*(trifluoromethanesulfonimide) (41):



Procedure:

A RB flask was charged with 1*H*-Imidazolium-2-carboxamide, 1-methyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl] bromide (**40**) (1.00 g, 3.15 mmol) and distilled water (5 mL). Lithium *bis*(trifluoromethanesulfonimide) (0.905 g, 3.15 mmol) in distilled water (5 mL) was added in one portion and the suspension was stirred vigorously for 4 h at RT. The product precipitated as a white solid. The aqueous layer was removed, and the IL washed with water (3 x 40 mL). The solvent was removed on the rotary evaporator and the product was dried *in vacuo* for 72 h to give **41** as a colorless solid at RT in 73% yield (1.205 g, 2.33 mmol).

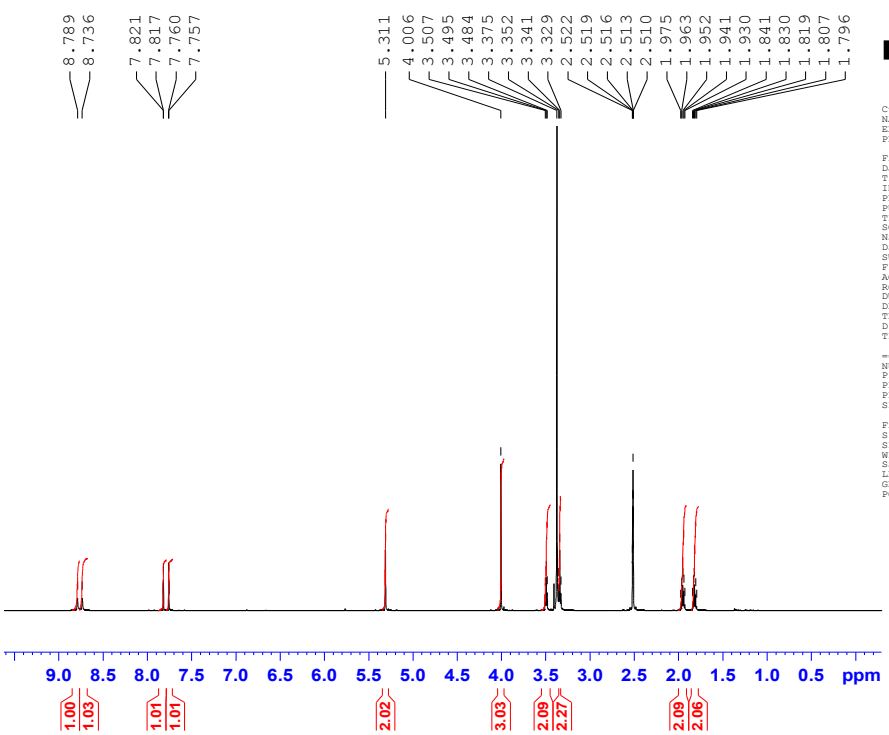
^{1}H-NMR (600 MHz, DMSO-d_6): 8.83 (bs, 1H), 8.73 (bs, 1H), 7.82 (d, *J* = 2.4 Hz, 1H), 7.76 (d, *J* = 1.8 Hz, 1H), 4.00 (s, 3H), 5.31 (s, 2H), 3.49 (t, J = 7.2 Hz, 2H), 3.34 (t, J = 7.2 Hz, 2H), 1.97-1.93 (m, 2H), 1.84-1.79 (m, 2H)

^{13}C-NMR (150 MHz, DMSO-d_6): 162.42, 154.62, 138.97, 124.17, 123.39, 119.44 (q, *J* = 319 Hz, 2 CF_3), 50.71, 45.99, 45.14, 36.85, 25.44, 23.66

IR (neat) (cm^{-1}): 3407, 3151, 2984, 1708, 1646, 1536, 1459, 1354, 1178, 1046, 606

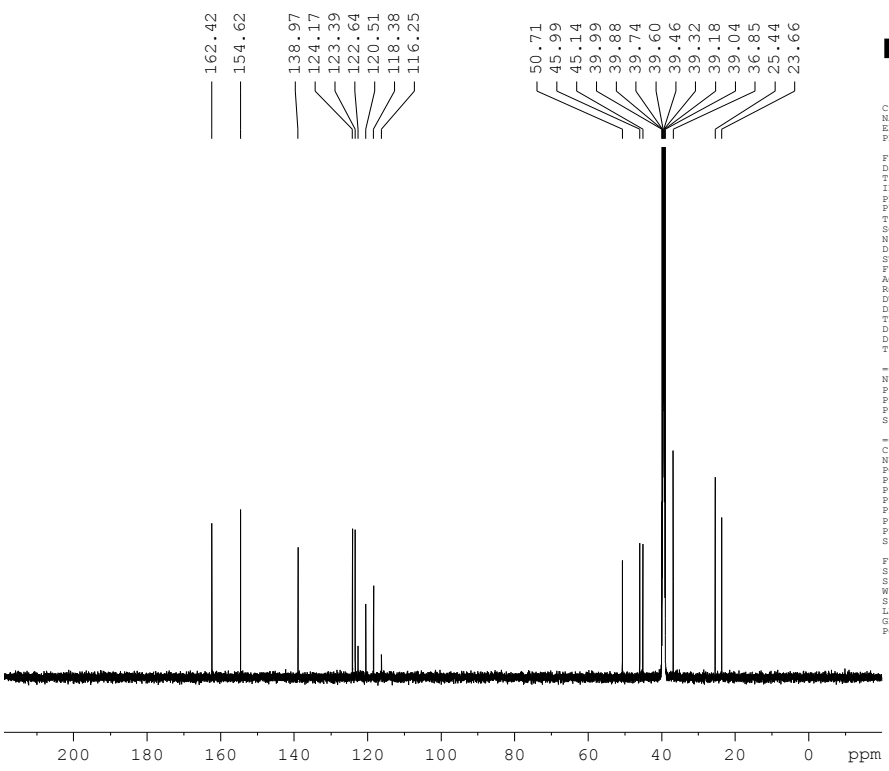
Melting Point: 79-81 °C

ES-MS (+ve) m/z: Found $[M– NTf_2^–]^+$ 237.1348, $C_{11}H_{17}N_4O_2^+$ requires 237.1346



BRUKER

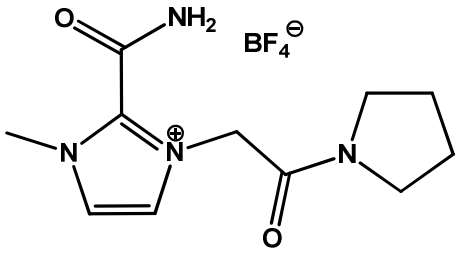
```
Current Data Parameters
NAME                  Feb05-2010
EXPNO                         10
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20100205
Time                       17.41
INSTRUM                    spect
PROBHD  5 mm PABBO BB-
PULPROG                    zg30
TD                        65536
SOLVENT                    DMSO
NS                          512
DS                            2
SWH                   12335.526 Hz
FIDRES                0.188225 Hz
AQ                    2.6564426 sec
RG                          181
DW                     40.533 usec
DE                     10.55 usec
TE                        292.7 K
D1                    1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                          1H
P1                        12.50 usec
PL1                        -5.30 dB
PL1W                  25.53414154 W
SFO1                  600.3267072 MHz

F2 - Processing parameters
SI                            32768
SF                    600.3230000 MHz
WDW                              EM
SSB                               0
LB                             0.30 Hz
GB                                0
PC                             1.00
```



BRUKER

```
Current Data Parameters
NAME                  Feb05-2010
EXPNO                         11
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20100205
Time                       21.05
INSTRUM                    spect
PROBHD  5 mm PABBO BB-
PULPROG                  zgpg30
TD                        65536
SOLVENT                    DMSO
NS                          4096
DS                             4
SWH                   36057.691 Hz
FIDRES                0.550197 Hz
AQ                    0.9088159 sec
RG                          2050
DW                     13.867 usec
DE                      6.50 usec
TE                        293.7 K
D1                    2.00000000 sec
D11                   0.03000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         13C
P1                         8.00 usec
PL1                        1.50 dB
PL1W                  78.77777863 W
SFO1                  150.9664335 MHz

======== CHANNEL f2 ========
CPDPRG2                  waltz16
NUC2                          1H
PCPD2                     70.00 usec
PL2                        -5.30 dB
PL12                       10.02 dB
PL13                      120.00 dB
PL2W                  25.53414154 W
PL12W                 0.75010353 W
PL13W                 0.00000000 W
SFO2                  600.3254013 MHz

F2 - Processing parameters
SI                            32768
SF                    150.9514145 MHz
WDW                              EM
SSB                               0
LB                             1.00 Hz
GB                                0
PC                             1.40
```

1*H*-Imidazolium-2-carboxamide,1-methyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl] tetrafluoroborate (42):



Procedure:

A flask was charged with 1*H*-Imidazolium-2-carboxamide, 1-methyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl] bromide (**40**) (1.20 g, 3.78 mmol) and ethanol (60 mL) under a nitrogen atmosphere. Sodium tetrafluoroborate (0.415 g, 3.78 mmol) was added in one portion and the suspension was stirred vigorously for 24 hours at RT. The fine white precipitate was filtered quickly in air and washed with ethanol. The filtrate and washings were combined and solvent removed by rotary evaporation, then *in vacuo* for 2 days to give **42** as a pale pink solid in 62% yield (0.764 g, 2.36 mmol).

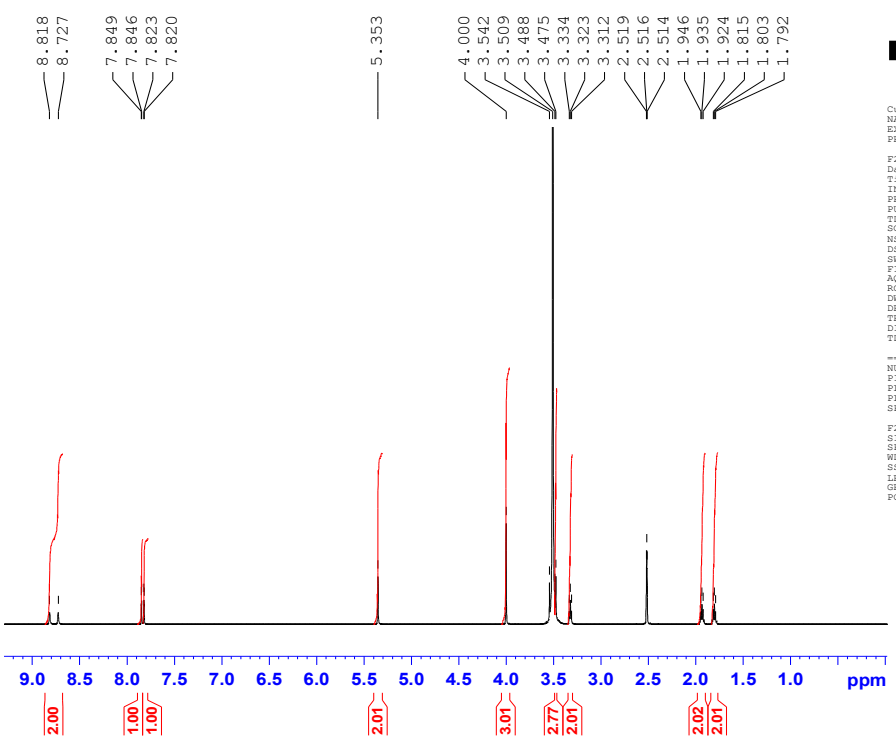
^{1}H-NMR (600 MHz, DMSO-d_6): 8.82 (bs, 1H), 8.73 (bs, 1H), 7.84 (d, J = 1.8 Hz, 1H), 7.82 (d, J = 1.8 Hz, 1H), 5.35 (s, 2H), 4.00 (s, 3H), 3.54-3.48 (m, 2H), 3.32 (t, J = 6.6 Hz, 2H), 1.92-1.95 (m, 2H), 1.79-1.82 (m, 2H)

^{13}C-NMR (150 MHz, DMSO-d_6): 162.42, 154.58, 138.92, 124.08, 123.38, 50.77, 46.00, 45.17, 36.83, 25.42, 23.64.

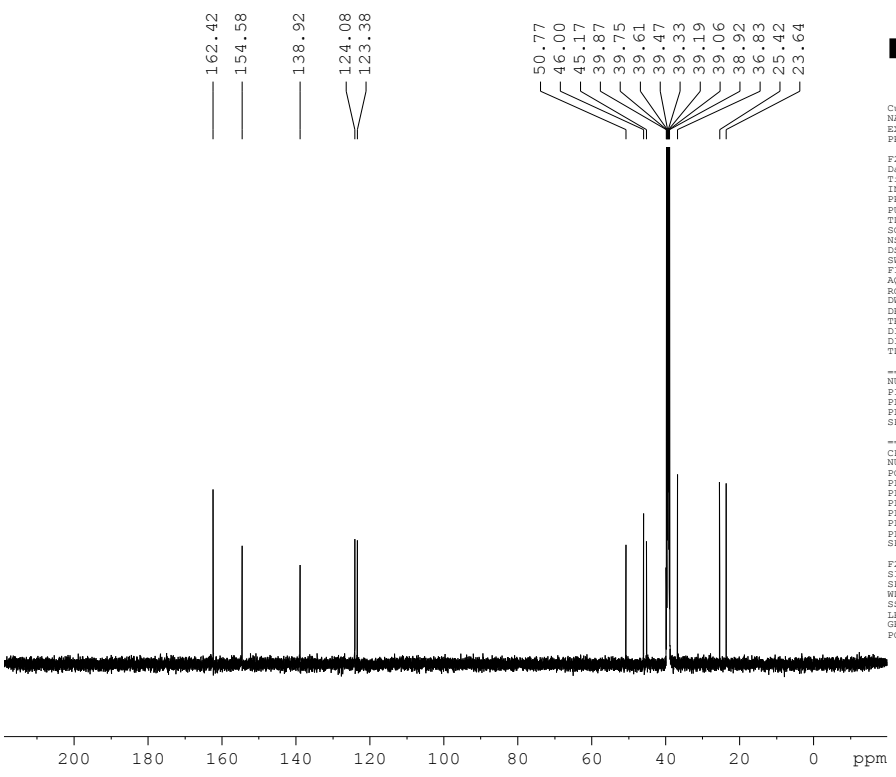
IR (neat) (cm^{-1}): 3178 (br), 1709, 1643, 1434, 1191, 707.

Melting point: 145-147 °C

ES-MS (+ve) m/z: Found $[M–BF_4^–]^+$ 237.1355, $C_{11}H_{17}N_4O_2^+$ requires 237.1346

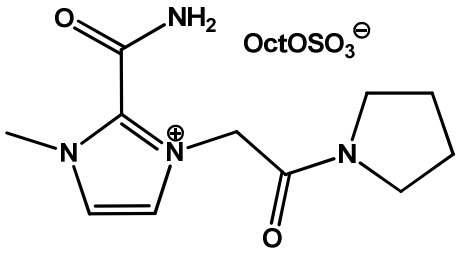



```
Current Data Parameters
NAME                  Nov04-2010
EXPNO                        110
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20101104
Time                       17.27
INSTRUM                    spect
PROBHD      5 mm PABBO BB-
PULPROG                    zg30
TD                        65536
SOLVENT                    DMSO
NS                           16
DS                            2
SWH                   12335.526 Hz
FIDRES                0.188225 Hz
AQ                    2.6564426 sec
RG                         80.6
DW                       40.533 usec
DE                       10.73 usec
TE                       300.0 K
D1                    1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         1H
P1                       11.65 usec
PL1                       -5.30 dB
PL1W                25.53414154 W
SFO1                600.3267072 MHz

F2 - Processing parameters
SI                         32768
SF                  600.3230000 MHz
WDW                           EM
SSB                            0
LB                        0.30 Hz
GB                             0
PC                          1.00
```




```
Current Data Parameters
NAME                  Nov04-2010
EXPNO                        111
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20101104
Time                       18.19
INSTRUM                    spect
PROBHD      5 mm PABBO BB-
PULPROG                  zgpg30
TD                        65536
SOLVENT                    DMSO
NS                         1024
DS                            4
SWH                   36057.691 Hz
FIDRES                0.550197 Hz
AQ                    0.9088159 sec
RG                         2050
DW                       13.867 usec
DE                        6.50 usec
TE                       300.0 K
D1                    2.00000000 sec
D11                   0.03000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         13C
P1                        9.71 usec
PL1                       1.50 dB
PL1W                78.77777863 W
SFO1                150.9664335 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                         1H
PCPD2                    70.00 usec
PL2                       -5.30 dB
PL12                      10.02 dB
PL13                     120.00 dB
PL2W                25.53414154 W
PL12W                0.75010353 W
PL13W                0.00000000 W
SFO2                600.3254013 MHz

F2 - Processing parameters
SI                         32768
SF                  150.9514145 MHz
WDW                           EM
SSB                            0
LB                        1.00 Hz
GB                             0
PC                          1.40
```

1*H*-Imidazolium-2-carboxamide, 1-methyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl] octyl sulfate (43):



Procedure:

A flask was charged with 1*H*-Imidazolium-2-carboxamide, 1-methyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl] bromide (**40**) (1.00 g, 3.15 mmol) and distilled water (10 mL). Sodium octylsulfate (0.731 g, 3.15 mmol) in distilled water (10 mL) was added in one portion and the suspension was stirred vigorously for 24 h at RT. The water was removed on the rotary evaporator and residue was dissolved in dichloromethane (20 mL) and washed with water. Organic layer was dried over anhydrous magnesium sulphate, filtered and solvent removed by rotary evaporation. The product was dried *in vacuo* for 72 h to give **43** as a white solid in 46% yield (0.649 g, 1.45 mmol).

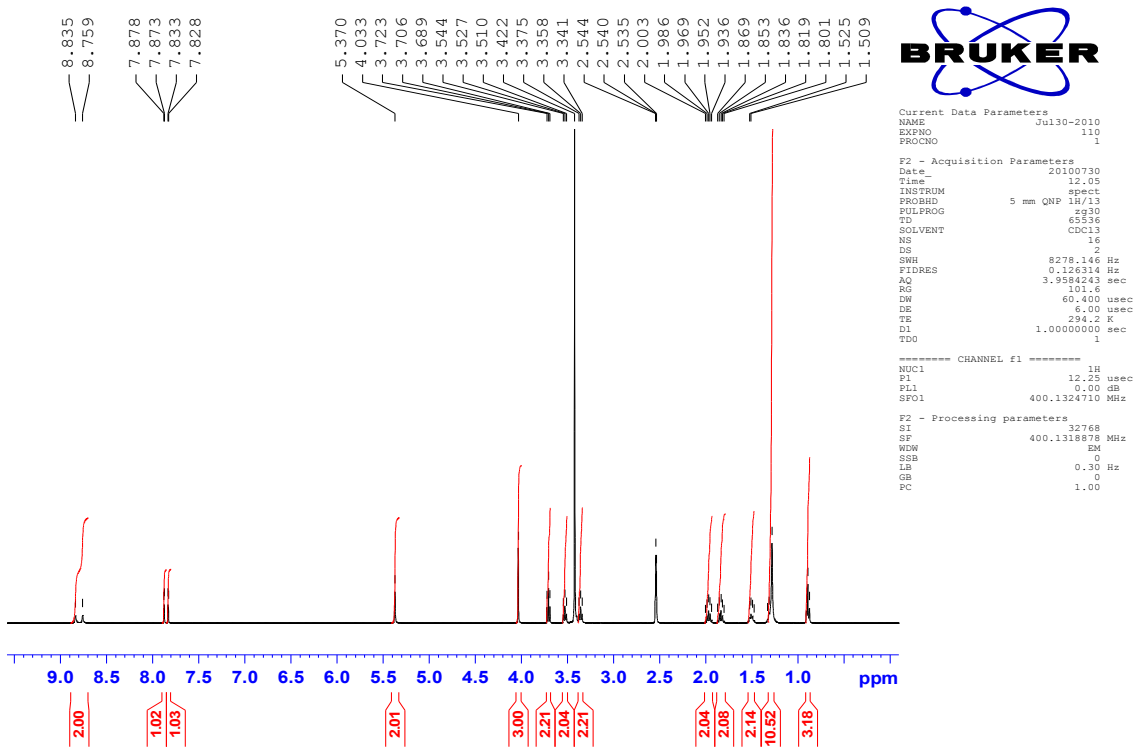
^{1}H-NMR (400 MHz, DMSO-d_6): 8.76 (bs, 1H), 8.83 (bs, 1H), 7.87 (d, *J* = 2.0 Hz, 1H), 7.83 (d, *J* = 2.0 Hz, 1H), 5.37 (s, 2H), 4.03 (s, 3H), 3.70 (t, *J* = 6.8 Hz, 2H), 3.52 (t, *J* = 6.8 Hz, 2H), 3.36 (t, *J* = 6.8 Hz, 2H), 2.00-1.94 (m, 2H), 1.87-1.82 (m, 2H), 1.47-1.54 (m, 2H), 1.31-1.33 (m, 10H), 0.89 (t, *J* = 7.2 Hz, 3H)

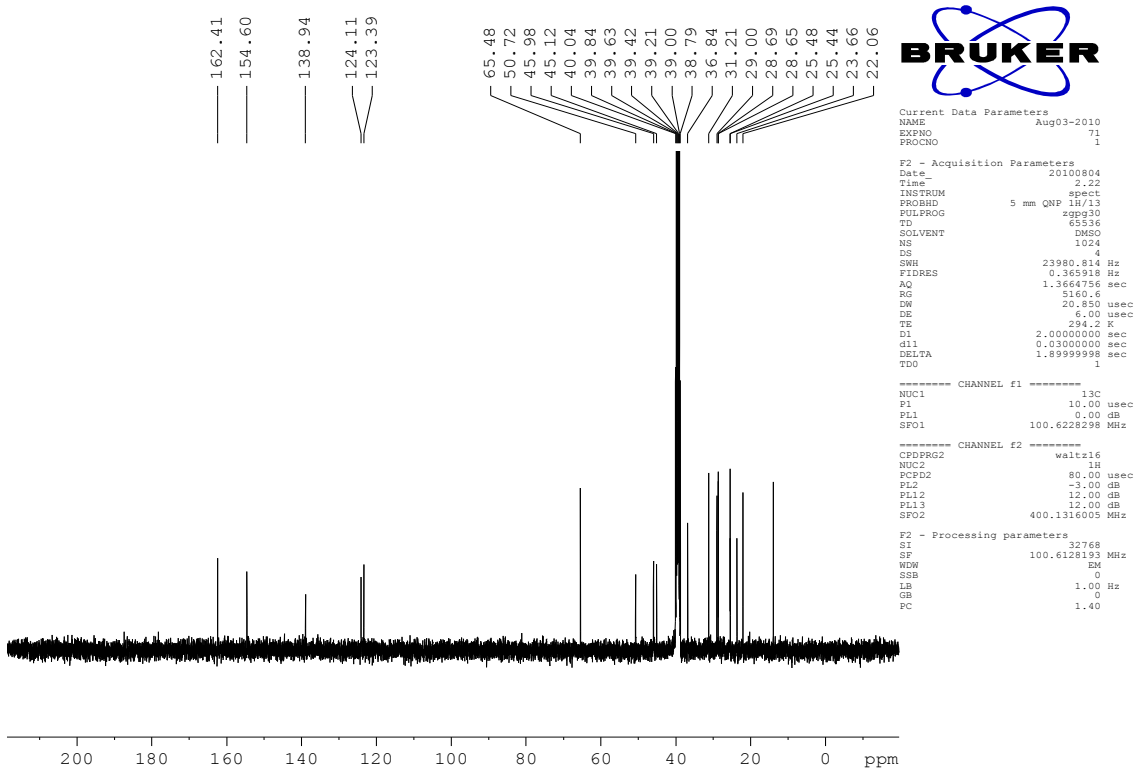
^{13}C-NMR (100 MHz, DMSO-d_6): 162.41, 154.60, 138.94, 124.11, 123.39, 65.48, 50.72, 45.98, 45.12, 36.84, 31.21, 29.00, 28.69, 28.65, 25.48, 25.44, 23.66, 22.06, 13.93.

IR (neat) (cm^{-1}): 3499, 3259, 3109, 2920, 1708, 1640, 1541, 1247, 1215, 1082, 786.

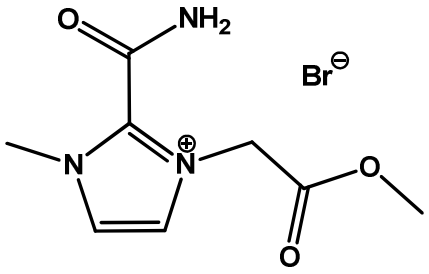
Melting Point: 122-124 °C

ES-MS (+ve) m/z: Found $[M–OctOSO_3^–]^+$ 237.1356, $C_{11}H_{17}N_4O_2^+$ requires 237.1346


8.835
8.759
7.878
7.873
7.833
7.828
5.370
4.033
3.723
3.706
3.689
3.544
3.527
3.510
3.422
3.375
3.358
3.341
2.544
2.540
2.535
2.003
1.986
1.969
1.952
1.936
1.869
1.853
1.836
1.819
1.801
1.525
1.509
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
2.00
1.02
1.03
2.01
3.00
2.21
2.04
2.21
2.04
2.08
2.14
10.52
3.18
BRUKER
Current Data Parameters
NAME Jul30-2010
EXPNO 110
PROCNO 1
F2 - Acquisition Parameters
Date_ 20100730
Time 12.05
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 101.6
DW 60.400 usec
DE 6.00 usec
TE 294.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 12.25 usec
PL1 0.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1318878 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00


162.41
154.60
138.94
124.11
123.39
65.48
50.72
45.98
45.12
40.04
39.84
39.63
39.42
39.21
39.00
38.79
36.84
31.21
29.00
28.69
28.65
25.48
25.44
23.66
22.06
200 180 160 140 120 100 80 60 40 20 0 ppm
BRUKER
Current Data Parameters
NAME Aug03-2010
EXPNO 71
PROCNO 1
F2 - Acquisition Parameters
Date_ 20100804
Time 2.22
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 1024
DS 4
SWH 23980.814 Hz
FIDRES 0.365918 Hz
AQ 1.3664756 sec
RG 5160.6
DW 20.850 usec
DE 6.00 usec
TE 294.2 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 10.00 usec
PL1 0.00 dB
SFO1 100.6228298 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -3.00 dB
PL12 12.00 dB
PL13 12.00 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6128193 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

1*H*-Imidazolium-2-carboxamide, 1-methyl-3-(methoxycarbonylmethyl) bromide (44):



Procedure:

A RB flask was charged with 1-methyl-1*H*-imidazole-2-carboxamide (**38**) (0.500 g, 4.0 mmol) and THF under nitrogen. To this solution was added methyl bromoacetate (0.612 g, 4.0 mmol). The reaction mixture was refluxed for 4 days with vigorous stirring. The product precipitated as a pink colored solid and was then washed with THF (5 x 50 mL). The solvent was removed on the rotary evaporator and the product was dried *in vacuo* for 48 h to give **44** as a pink colored solid at RT in 17% yield (0.189 g, 0.68 mmol).

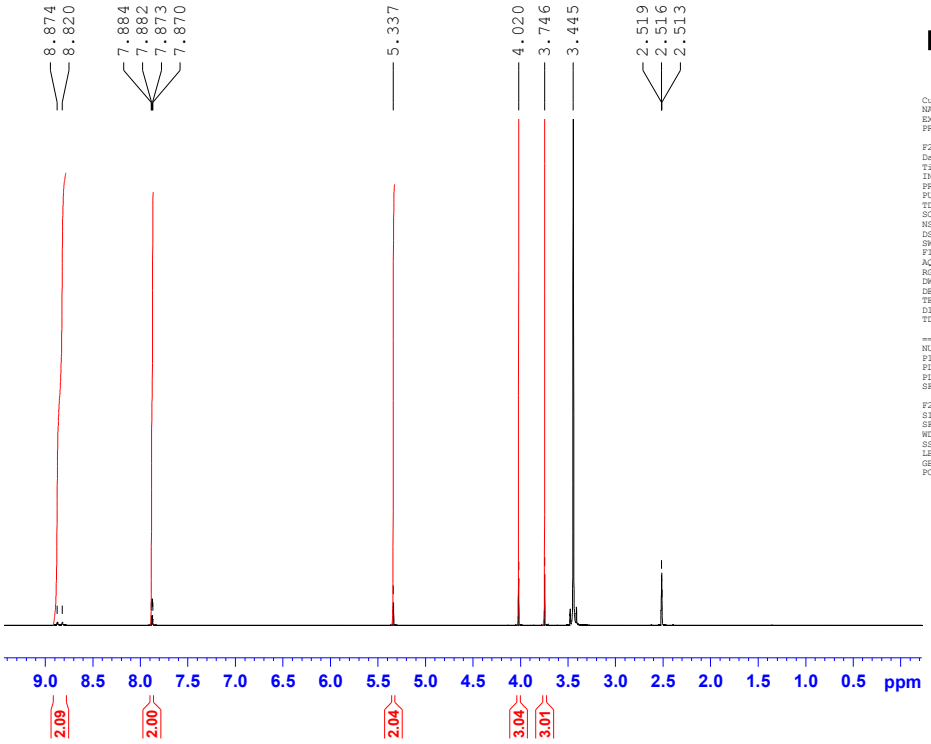
^{1}H-NMR (600 MHz, DMSO-d_6): 8.87 (bs, 1H), 8.82 (bs, 1H), 7.88 (d, J = 1.2 Hz, 1H), 8.87 (d, J = 1.8 Hz, 1H), 5.34 (s, 2H), 4.02 (s, 3H), 3.75 (s, 3H).

^{13}C-NMR (150 MHz, DMSO-d_6): 166.76, 154.32, 138.37, 124.30, 123.87, 52.92, 49.88, 37.00.

IR (neat) (cm^{-1}): 3297, 3070, 1745, 1691, 1522, 1454, 1231, 730.

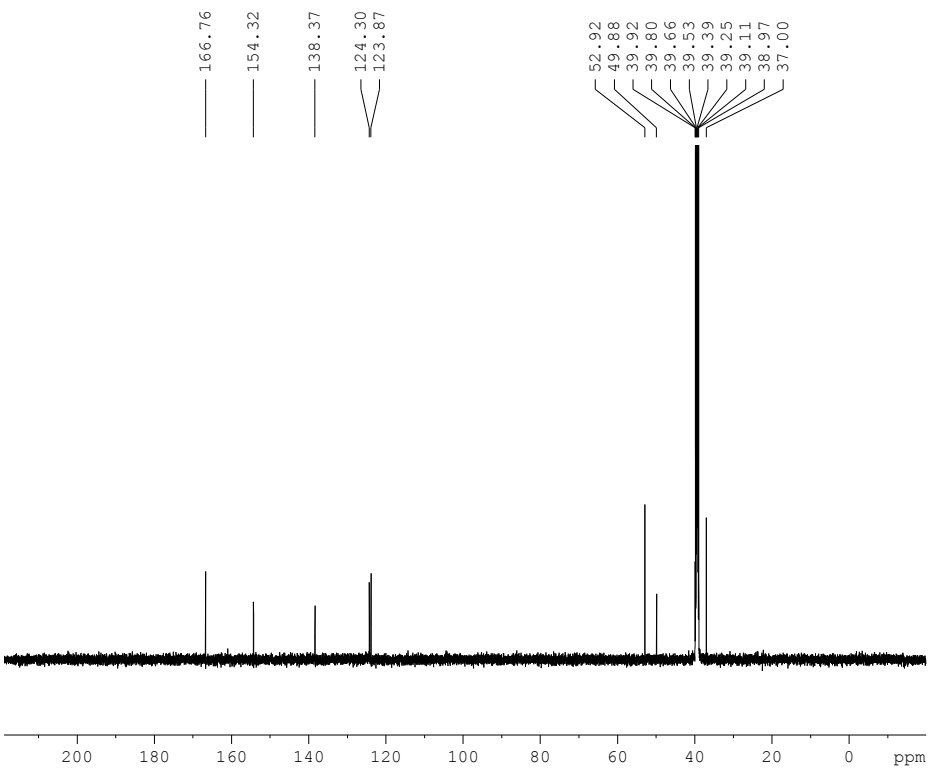
Melting Point: 200 °C (decomposed)

ES-MS (+ve) m/z: Found $[M–Br^–]^+$ 237.1356, $C_8H_{12}N_3O_3^+$ requires 237.1346.



BRUKER

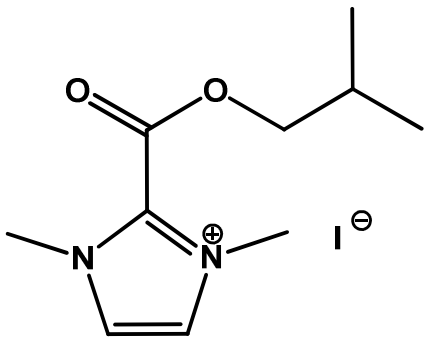
```
Current Data Parameters
NAME                  Dec04-2009
EXPNO                         20
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20091204
Time                       13.47
INSTRUM                    spect
PROBHD  5 mm PABBO BB-
PULPROG                    zg30
TD                        65536
SOLVENT                    DMSO
NS                           16
DS                            2
SWH                   12335.526 Hz
FIDRES                 0.188225 Hz
AQ                    2.6564426 sec
RG                          101
DW                       40.533 usec
DE                       10.55 usec
TE                       292.5 K
D1                    1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         1H
P1                       12.50 usec
PL1                      -5.30 dB
PL1W                25.53414154 W
SFO1               600.3267072 MHz

F2 - Processing parameters
SI                         32768
SF                 600.3230000 MHz
WDW                           EM
SSB                            0
LB                          0.30 Hz
GB                             0
PC                          1.00
```



BRUKER

```
Current Data Parameters
NAME                  Dec04-2009
EXPNO                         21
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20091204
Time                       15.02
INSTRUM                    spect
PROBHD  5 mm PABBO BB-
PULPROG                  zgpg30
TD                        65536
SOLVENT                    DMSO
NS                         1024
DS                            4
SWH                   36057.691 Hz
FIDRES                 0.550197 Hz
AQ                    0.9088159 sec
RG                         2050
DW                       13.867 usec
DE                        6.50 usec
TE                       294.2 K
D1                    2.00000000 sec
D11                   0.03000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         13C
P1                        8.00 usec
PL1                       1.50 dB
PL1W                78.77777863 W
SFO1               150.9664335 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                         1H
PCPD2                    70.00 usec
PL2                      -5.30 dB
PL12                     10.02 dB
PL13                    120.00 dB
PL2W                25.53414154 W
PL12W                0.75010353 W
PL13W                0.00000000 W
SFO2               600.3254013 MHz

F2 - Processing parameters
SI                         32768
SF                 150.9514145 MHz
WDW                           EM
SSB                            0
LB                          1.00 Hz
GB                             0
PC                          1.40
```

2-(isobutoxycarbonyl)-1,3-dimethyl-1*H*-imidazol-3-ium iodide (45):



Procedure:

A RB flask was charged with Isobutyl 1-methyl-1*H*-imidazole-2-carboxylate (**39**) (2.00 g, 10.9 mmol) and diethyl ether (100 mL) under nitrogen. To this solution was added methyl iodide (6.24 g, 43.9 mmol) in one portion. The reaction mixture was refluxed for 2 days with vigorous stirring. The product precipitated as a light yellow solid, was filtered then washed with diethyl ether (5 x 50 mL). The residual solvent was removed on the rotary evaporator. The product was dried *in vacuo* for 24 h to give **45** as a light yellow solid at RT in 62% yield (2.21 g, 6.82 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$): 8.24 (s, 2H), 4.31 (d, J = 6.4 Hz, 2H), 4.30 (s, 6H), 2.16 (sept*, J = 6.8, 6.4 Hz, 1H), 1.05 (d, J = 6.8 Hz, 6H).

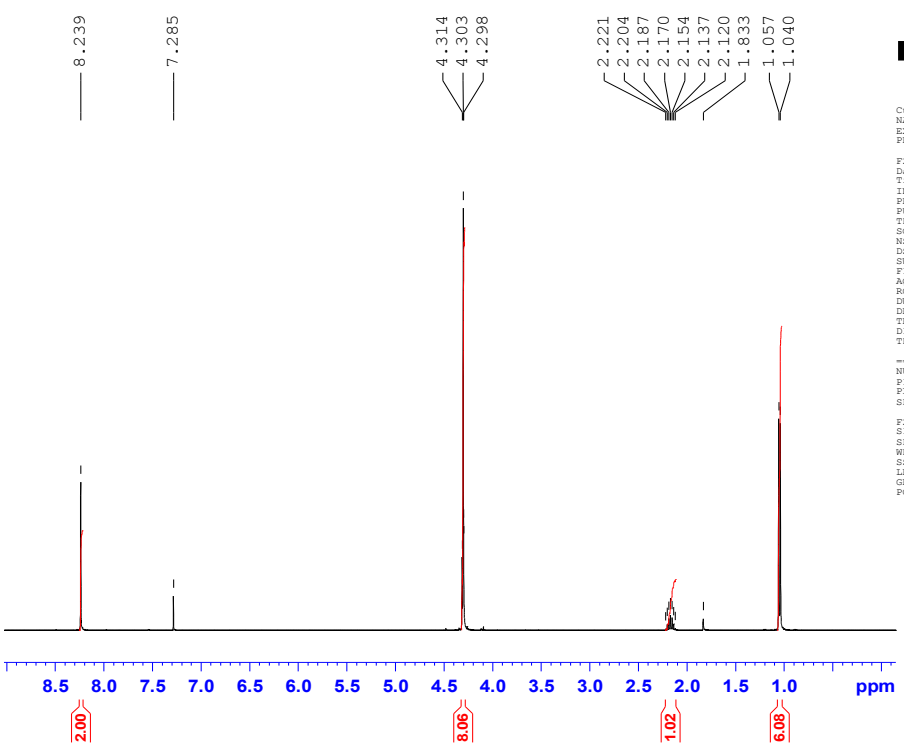
^{13}C-NMR (100 MHz, $CDCl_3$): 148.70, 127.13, 121.77, 69.21, 35.07, 22.26, 14.02.

IR (neat) (cm^{-1}): 3075, 2957, 1726, 1526, 1441, 635.

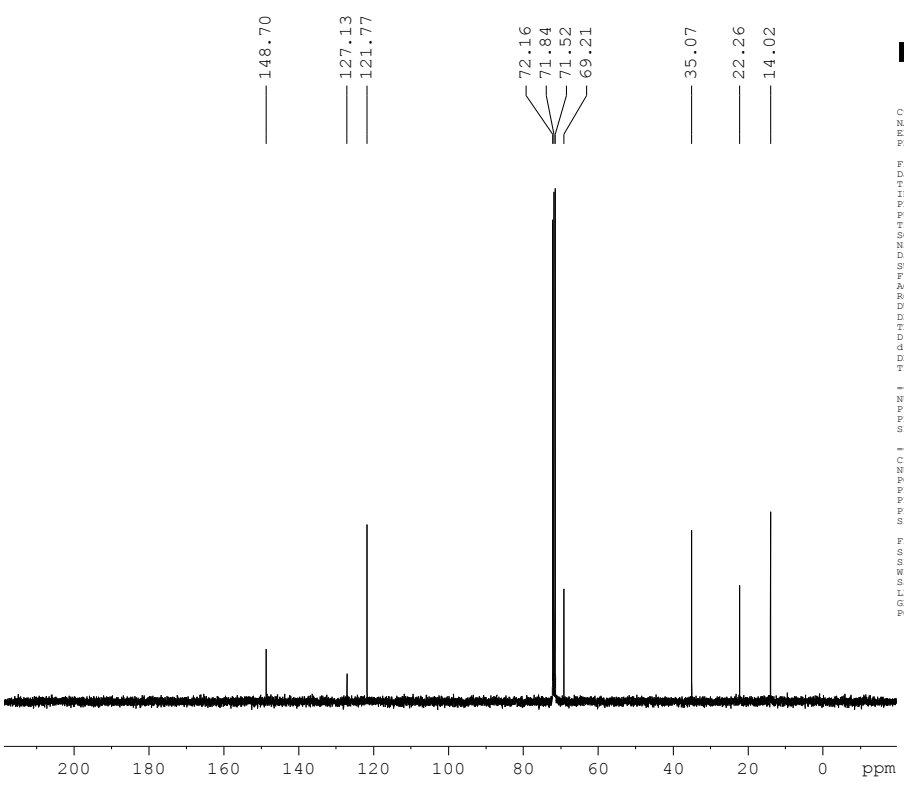
Melting Point: 116-117 °C

ES-MS (+ve) m/z: Found $[M–I^–]^+$ 197.1296, $C_{10}H_{17}N_2O_2^+$ requires 197.1284

* Septet of triplets

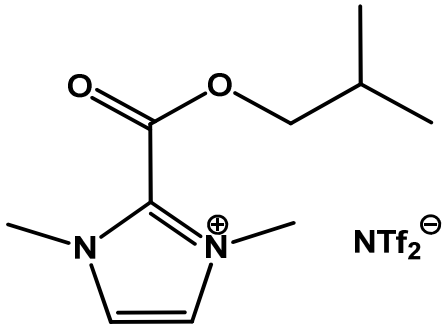



```
Current Data Parameters
NAME                  May26-2010
EXPNO                        120
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20100526
Time                       14.54
INSTRUM                    spect
PROBHD  5 mm QNP 1H/13
PULPROG                    zg30
TD                        65536
SOLVENT                   CDCl3
NS                           16
DS                            2
SWH                    8278.146 Hz
FIDRES                 0.126314 Hz
AQ                     3.9584243 sec
RG                          181
DW                       60.400 usec
DE                        6.00 usec
TE                       293.2 K
D1                    1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         1H
P1                       12.25 usec
PL1                       0.00 dB
SFO1                  400.1324710 MHz

F2 - Processing parameters
SI                         32768
SF                    400.1300000 MHz
WDW                           EM
SSB                            0
LB                          0.30 Hz
GB                             0
PC                          1.00
```




```
Current Data Parameters
NAME                  May26-2010
EXPNO                         81
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20100527
Time                       0.48
INSTRUM                    spect
PROBHD  5 mm QNP 1H/13
PULPROG                  zgpg30
TD                        65536
SOLVENT                    DMSO
NS                          1024
DS                             4
SWH                    23980.814 Hz
FIDRES                 0.365918 Hz
AQ                     1.3664756 sec
RG                         2896.3
DW                       20.850 usec
DE                        6.00 usec
TE                       294.2 K
D1                    2.00000000 sec
d11                   0.03000000 sec
DELTA                 1.89999998 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         13C
P1                       10.00 usec
PL1                       0.00 dB
SFO1                  100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                  waltz16
NUC2                         1H
PCPD2                    80.00 usec
PL2                       -3.00 dB
PL12                      12.00 dB
PL13                      12.00 dB
SFO2                  400.1316005 MHz

F2 - Processing parameters
SI                         32768
SF                    100.6128193 MHz
WDW                           EM
SSB                            0
LB                          1.00 Hz
GB                             0
PC                          1.40
```

2-(isobutoxycarbonyl)-1,3-dimethyl-1*H*-imidazol-3-ium-*bis*(trifluoromethanesulfonimide) (46):



Procedure:

A RB flask was charged with 2-(isobutoxycarbonyl)-1,3-dimethyl-1*H*-imidazol-3-ium iodide (**45**) (0.500 g, 1.54 mmol) and distilled water (2 mL). Lithium *bis*(trifluoromethane) sulfonamide (0.443g, 1.54 mmol) in distilled water (2 mL) was added in one portion and the suspension was stirred vigorously for 4 h at RT. The product precipitated as a light yellow solid. The aqueous layer was removed, and the IL washed with water (3 x 40 mL) then the solvent removed on the rotary evaporator. The product was dried *in vacuo* for 48 h to give **46** as a pale yellow solid at RT in 86% yield (0.630 g, 1.32 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.54 (s, 2H), 4.32 (d, J = 6.4 Hz, 2H), 4.19 (s, 6H), 2.16 (sept*, J = 6.8, 6.4 Hz, 1H), 1.07 (d, J = 6.8 Hz, 6H)

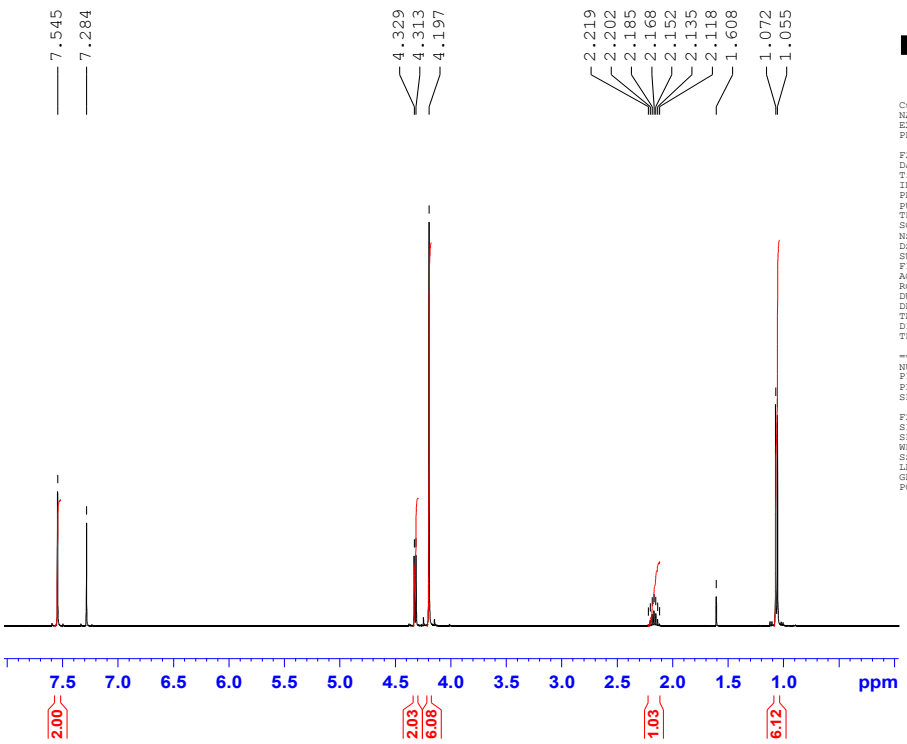
^{13}C-NMR (100 MHz, $CDCl_3$): 153.64, 132.27, 126.53, 119.72(q, J = 320 Hz, 2 CF_3), 74.58, 39.61, 27.48, 19.05

IR (neat) (cm^{-1}): 3138, 2977, 1732, 1531, 1441, 1350, 1166, 567

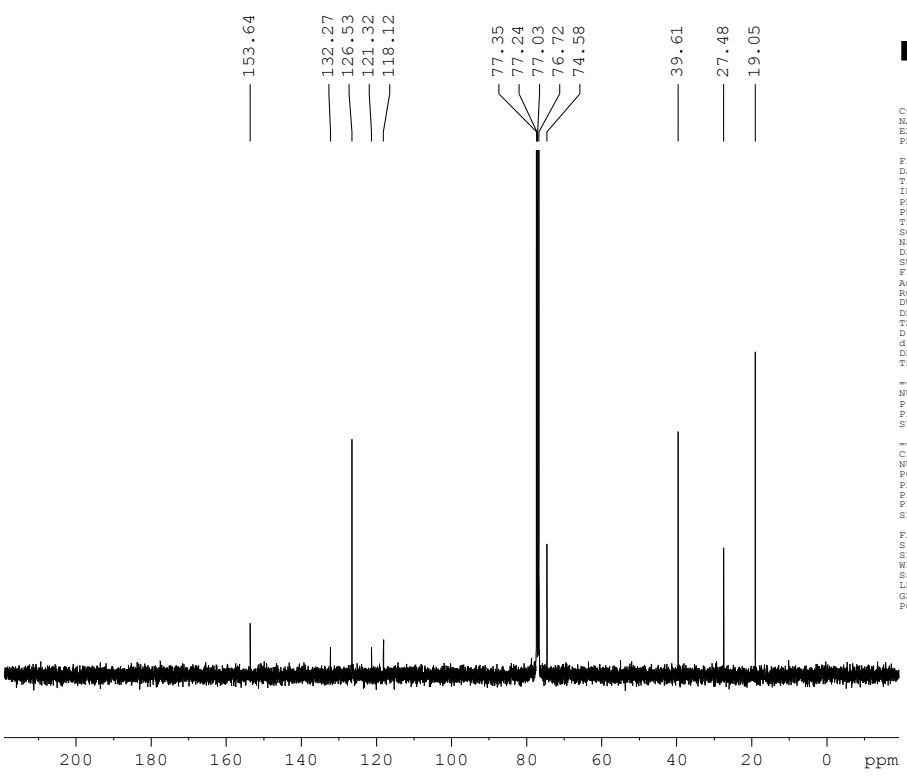
Melting Point: 45-46 °C

ES-MS (+ve) m/z: Found $[M–NTf_2^-]^+$ 197.1283, $C_{10}H_{17}N_2O_2^+$ requires 197.1284

* Septet of triplets

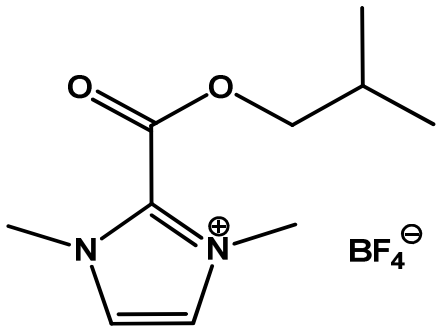



```
Current Data Parameters
NAME                  Jul23-2010
EXPNO                        130
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20100723
Time                       16.28
INSTRUM                    spect
PROBHD  5 mm QNP 1H/13
PULPROG                    zg30
TD                        65536
SOLVENT                   CDCl3
NS                           16
DS                            2
SWH                    8278.146 Hz
FIDRES                 0.126314 Hz
AQ                     3.9584243 sec
RG                          362
DW                       60.400 usec
DE                        6.00 usec
TE                       294.2 K
D1                    1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                         1H
P1                       12.25 usec
PL1                       0.00 dB
SFO1                400.1324710 MHz

F2 - Processing parameters
SI                        32768
SF                  400.1300000 MHz
WDW                          EM
SSB                           0
LB                         0.30 Hz
GB                            0
PC                         1.00
```




```
Current Data Parameters
NAME                  Jul23-2010
EXPNO                         71
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20100724
Time                       9.43
INSTRUM                    spect
PROBHD  5 mm QNP 1H/13
PULPROG                  zgpg30
TD                        65536
SOLVENT                   CDCl3
NS                         3000
DS                            4
SWH                   23980.814 Hz
FIDRES                 0.365918 Hz
AQ                     1.3664756 sec
RG                         1448.2
DW                       20.850 usec
DE                        6.00 usec
TE                       294.2 K
D1                    2.00000000 sec
d11                   0.03000000 sec
DELTA                 1.89999998 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                        13C
P1                       10.00 usec
PL1                       0.00 dB
SFO1                100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                         1H
PCPD2                    80.00 usec
PL2                      -3.00 dB
PL12                     12.00 dB
PL13                     12.00 dB
SFO2                400.1316005 MHz

F2 - Processing parameters
SI                        32768
SF                  100.6127690 MHz
WDW                          EM
SSB                           0
LB                         1.00 Hz
GB                            0
PC                         1.40
```

2-(isobutoxycarbonyl)-1,3-dimethyl-1*H*-imidazol-3-ium- tetrafluoroborate (47):



Procedure:

A RB flask was charged with isobutyl 1-methyl-1H-imidazole-2-carboxylate (**39**) (0.200 g, 1.10 mmol) and dry diethyl ether (10 mL) under nitrogen. To this solution was added trimethyloxonium tetrafluoroborate (0.162 g, 1.10 mmol) quickly. The reaction mixture was stirred vigorously for 24 h. The product precipitated as a white solid, was filtered, and then washed with diethyl ether (2 x 50 mL). The solvent was removed on the rotary evaporator. The product was dried *in vacuo* for 24 h to give **47** as a white solid at RT in 97% yield (0.302 g, 1.06 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$): 7.65 (s, 2H), 4.29 (d, J = 6.4 Hz, 2H), 4.16 (s, 6H), 2.14 (sept*, J = 6.8, 6.4 Hz, 1H), 1.05 (d, J = 6.8 Hz, 6H)

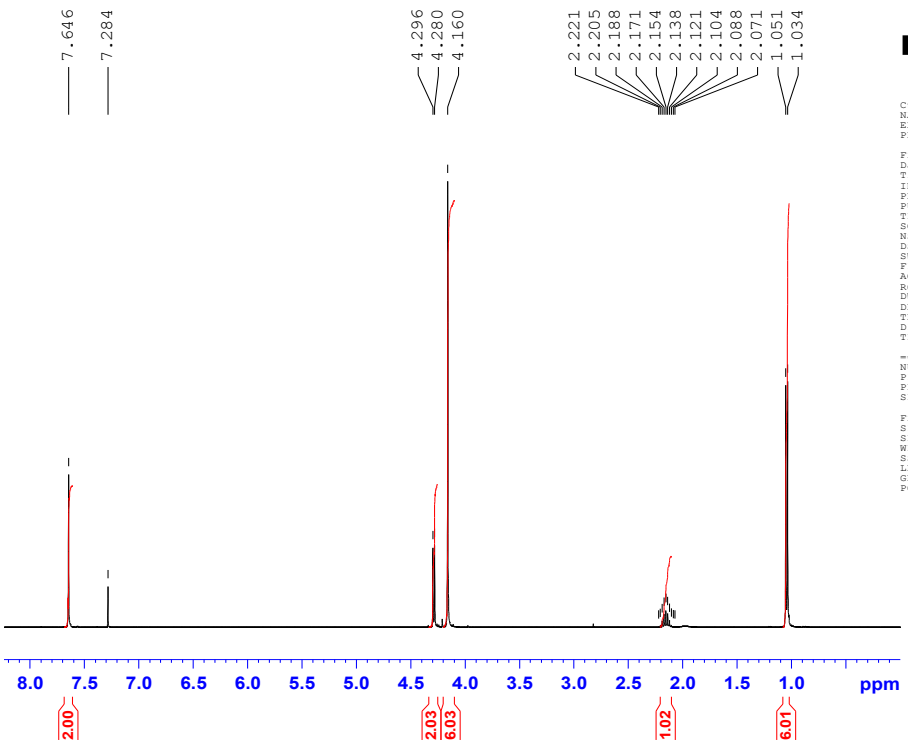
^{13}C-NMR (100 MHz, $CDCl_3$): 153.92, 132.23, 126.65, 74.15, 39.26, 27.45, 19.11

IR (neat) (cm^{-1}): 3153, 2971, 1733, 1532, 1447, 1006, 649

Melting Point: 64-65 °C

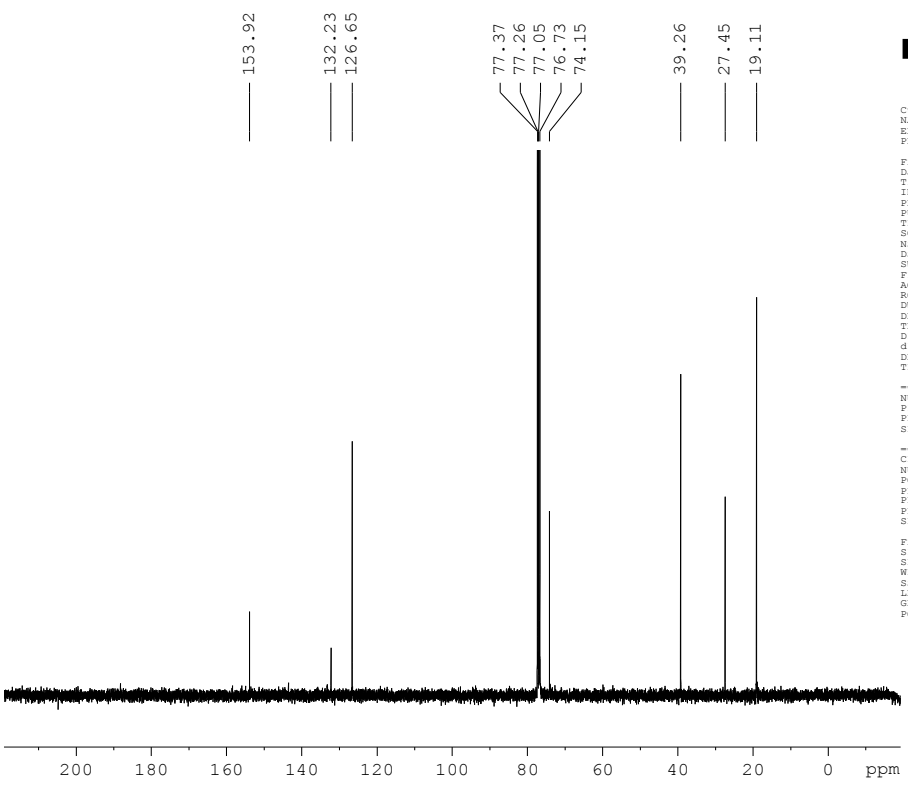
ES-MS (+ve) m/z: Found $[M–BF_4^-]^+$ 197.1295, $C_{10}H_{17}N_2O_2^+$ requires 197.1284

* Septet of triplets



BRUKER

```
Current Data Parameters
NAME                  May28-2010
EXPNO                         70
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20100528
Time                       23.05
INSTRUM                    spect
PROBHD      5 mm QNP 1H/13
PULPROG                    zg30
TD                        65536
SOLVENT                   CDCl3
NS                           16
DS                            2
SWH                    8278.146 Hz
FIDRES                 0.126314 Hz
AQ                     3.9584243 sec
RG                         161.3
DW                        60.400 usec
DE                         6.00 usec
TE                        294.2 K
D1                     1.00000000 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                          1H
P1                         12.25 usec
PL1                         0.00 dB
SFO1                400.1324710 MHz

F2 - Processing parameters
SI                        32768
SF                  400.1300000 MHz
WDW                          EM
SSB                           0
LB                         0.30 Hz
GB                            0
PC                         1.00
```



BRUKER

```
Current Data Parameters
NAME                  May28-2010
EXPNO                         71
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20100529
Time                        0.05
INSTRUM                    spect
PROBHD      5 mm QNP 1H/13
PULPROG                   zppg30
TD                        65536
SOLVENT                   CDCl3
NS                         1024
DS                            4
SWH                   23980.814 Hz
FIDRES                 0.365918 Hz
AQ                     1.3664756 sec
RG                         5792.6
DW                        20.850 usec
DE                         6.00 usec
TE                        294.2 K
D1                     2.00000000 sec
d11                    0.03000000 sec
DELTA                  1.89999998 sec
TD0                            1

======== CHANNEL f1 ========
NUC1                          13C
P1                         10.00 usec
PL1                         0.00 dB
SFO1                100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                   waltz16
NUC2                          1H
PCPD2                      80.00 usec
PL2                        -3.00 dB
PL12                       12.00 dB
PL13                       12.00 dB
SFO2                400.1316005 MHz

F2 - Processing parameters
SI                        32768
SF                  100.6127690 MHz
WDW                          EM
SSB                           0
LB                         1.00 Hz
GB                            0
PC                         1.40
```

9.3 Applications of ILs in Acetalisation Reaction

9.3.1 General Procedure of Acetalisation of benzaldehyde

A 20 mL reaction flask was fitted with a magnetic stirring bar, charged with catalyst (0.08 mmol), fitted with a septum and flushed with argon. Benzaldehyde (170 μL, 1.67 mmol) was added followed by dry methanol (3.4 mL) *via* syringe. The solution was then stirred under argon at room temperature for 24 h. When conversion was judged to be either complete or >95% (by ^{1}H NMR spectroscopic analysis) the reaction was quenched with $PhNHNH_2$ and the solvent was removed *in vacuo*. The crude product was then purified by flash-chromatography on SiO_2 or yield was calculated by ^{1}H NMR spectroscopy using an internal standard.

Benzaldehyde dimethyl acetal (73): The ^{1}H NMR and ^{13}C NMR of the product were consistent with the reported data.[5]

9.4 Applications of ILs in Asymmetric Carbonyl-Ene Reaction of Phenylglyoxal

9.4.1 General procedure of enantioselective catalytic carbonyl-ene reactions in ILs

To a solution of (*R*)-BINAP-$PdCl_2$ (10.00 mg, 0.0125 mmol) in CH_2Cl_2 (2 mL) was added silver hexafluoroantimonate ($AgSbF_6$) (9.40 mg, 0.0275 mmol) under argon atmosphere. After the mixture was stirred at room temperature for 30 min, the *in situ* activated catalyst solution in dichloromethane was transferred through a small filter into a small flask which was already charged with ionic liquid (0.5 or 1 mmol) and phenylglyoxal **81** (38.04 mg, 0.25 mmol). After removing the dichloromethane under vacuum, *α*-methylstyrene (32.5 μL, 0.25 mmol) was added to the mixture. The reaction mixture was stirred at room temperature for 1 hour. Then the reaction mixture was extracted with ether (2 mL x 3). Removal of the ether gave a residue which was loaded onto a silica gel column and eluted with hexane/ethyl acetate (5/1) to give the *ene* product as a colourless oil. The isolated material was checked by ^{1}H-NMR ($CDCl_3$, 400 MHz) and ^{13}C-NMR ($CDCl_3$, 100 MHz). The enantiomeric excess was determined by GC or HPLC with a chiral column.

Recycle Procedure

Following extraction of the products from the ionic liquid, the IL (containing the catalyst) was dried under vacuum to remove the residual solvent. Fresh substrates were then added to the system and the reactions recommenced as described.

2-Hydroxy-1,4-diphenyl-4-penten-1-one (82): The ^{1}H NMR and ^{13}C NMR of the product were consistent with the reported data.[2] The enantiomeric excess was determined by HPLC [column, Lux Cellulose 2, elution with a mixture of hexane/isopropanol 80/20, flow rate 1 mL/min, (*R*)-enantiomer rt_1:7.72 min. (minor), (*S*)-enantiomer rt_2: 11.14 min. (major), λ = 258 nm]

3-(1-Cyclohexenyl)-2-hydroxy-1-phenyl-1-propanone (86): The ^{1}H NMR and ^{13}C NMR of the product were consistent with the reported data.[2] The enantiomeric excess was determined by HPLC [column Lux Cellulose 1, elution with a mixture of hexane/isopropanol 80/20, flow rate 1 mL/min, (*R*)-enantiomer rt_1:7.05 min. (minor), (*S*)-enantiomer rt_2: 11.67 min. (major), λ = 254 nm]

3-(1-Cyclopentenyl)-2-hydroxy-1-phenyl-1-propanone (87): ^{1}H-NMR: 7.85-7.83 (m, 2H), 7.57-7.53 (m, 1H), 7.46-7.42 (m, 2H), 5.38 (s, 1H), 5.17-5.12 (m, 1H), 3.65 (d, *J* = 6.4 Hz, 1H), 2.58 (d, *J* = 15.2 Hz, 1H), 2.33-2.21 (m, 5H), 1.88-1.75 (m, 2H). ^{13}C-NMR: 201.76, 139.53, 133.96, 133.75, 128.89, 128.59, 127.55, 72.34, 37.78, 35.44, 32.48, 23.46. ES-MS (+ve) m/z: Found [M+Na] 239.1038, $C_{13}H_{24}N_3O_3Na^+$ requires 239.1047. The enantiomeric excess was determined by HPLC [column Lux Cellulose 1, elution with a mixture of hexane/isopropanol 80/20, flow rate 1 mL/min, (*R*)-enantiomer rt_1:6.98 min. (minor), (*S*)-enantiomer rt_2: 11.79 min. (major), λ = 258 nm]

2-Hydroxy-5,5-dimethyl-4-methylene-1-phenyl-1-hexanone (88): The ^{1}H NMR and ^{13}C NMR of the product were consistent with the reported data.[2] The enantiomeric excess was determined by HPLC [column Lux Cellulose 2, elution with a mixture of hexane/isopropanol 80/20, flow rate 1 mL/min, (*R*)-enantiomer rt_1:5.87 min. (minor), (*S*)-enantiomer rt_2: 8.35 min. (major), λ = 254 nm]

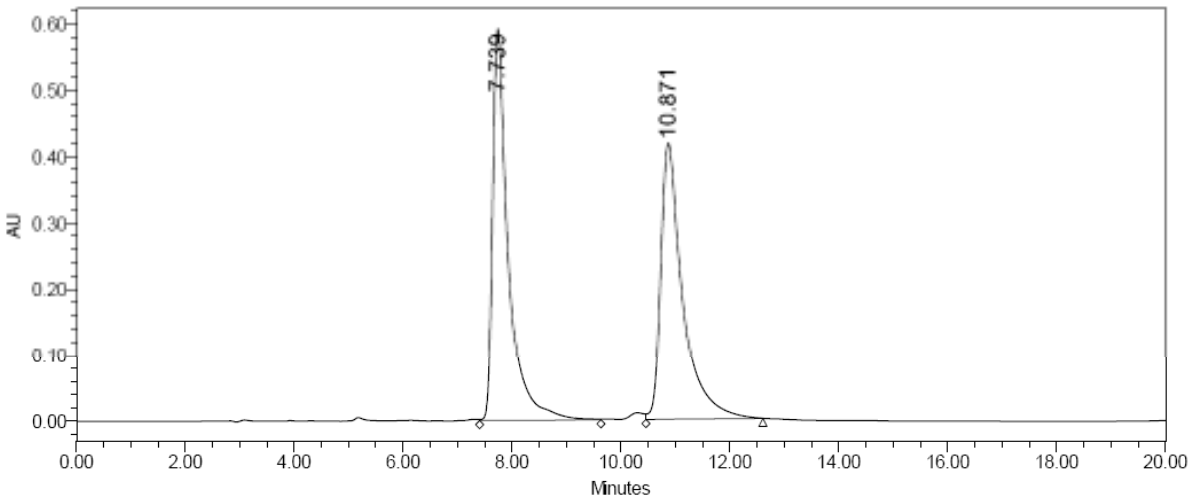
Compound 82 (racemic)

Empower 2 software

Injection Summary Report

SAMPLE INFORMATION

Sample Name:	KT33C2	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	KT33C2
Vial:	33	Acq. Method Set:	damien
Injection #:	1	Processing Method	RG
Injection Volume:	20.00 ul	Channel Name:	486
Run Time:	20.0 Minutes	Proc. Chnl. Descr.:	
Date Acquired:	8/21/2010 4:18:26 AM IST		
Date Processed:	7/9/2012 12:39:47 AM IST		



Channel: 486 ; Processed Channel: ; Result Id: 4954; Processing Method: RG

Processed Channel Descr.:

	RT	Area	% Area	Height
1	7.739	11864297	50.38	591493
2	10.871	11684256	49.62	417140

Reported by User: System
Report Method: Injection Summary Report
Report Method ID 1005
Page: 1 of 1

Project Name: Defaults\Damien
Date Printed:
7/9/2012
12:39:48 AM Europe/Dublin

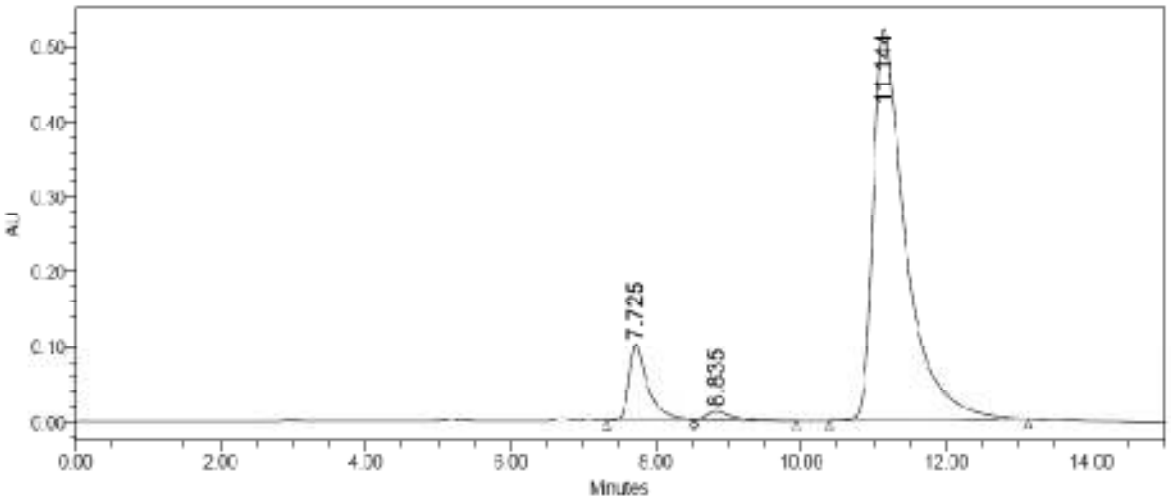
Compound 82

Empower 2 software

Injection Summary Report

SAMPLE INFORMATION

Sample Name:	KT68	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	KT68
Vial:	31	Acq. Method Set:	damien
Injection #:	1	Processing Method	RG
Injection Volume:	15.00 ul	Channel Name:	486
Run Time:	15.0 Minutes	Proc. Chnl. Descr.:	
Date Acquired:	9/8/2010 6:21:43 AM IST		
Date Processed:	7/9/2012 12:44:01 AM IST		



Channel: 486 ; Processed Channel: ; Result Id: 4956; Processing Method: RG

Processed Channel Descr.:

	RT	Area	% Area	Height
1	7.725	1882704	10.15	101538
2	6.835	341874	1.84	13193
3	11.144	16327363	88.01	524128

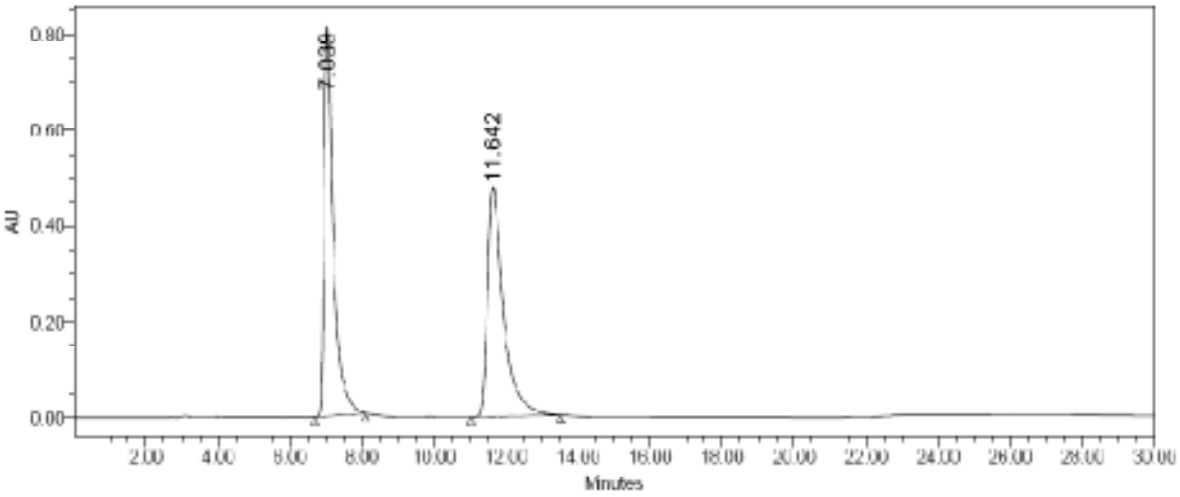
Compound 86 (racemic)

Empower 2 software

Injection Summary Report

SAMPLE INFORMATION

Sample Name:	RG - 390	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	RG 390
Vial:	25	Acq. Method Set:	Shelly
Injection #:	1	Processing Method	Rohitkumar
Injection Volume:	20.00 ul	Channel Name:	2487Channel 1
Run Time:	30.0 Minutes	Proc. Chnl. Descr.:	
Date Acquired:	9/21/2011 3:23:18 AM IST		
Date Processed:	3/30/2012 5:40:59 AM IST		



Channel: 2487Channel 1; Processed Channel: ; Result Id: 1293; Processing Method: Rohitkumar

Processed Channel Descr.:

	RT	Area	% Area	Height
1	7.039	14473001	49.55	813785
2	11.642	14737015	50.45	479259

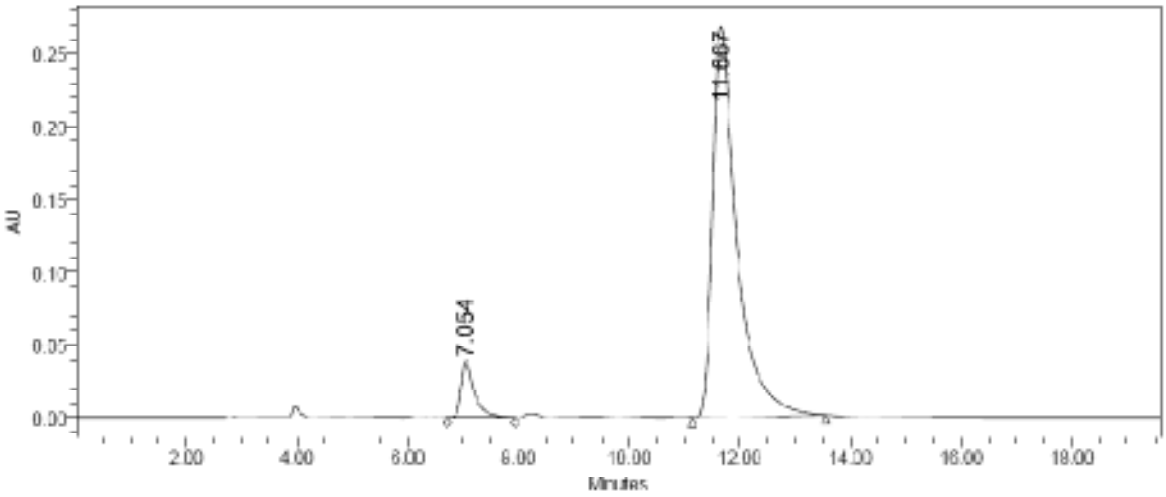
Compound 86

Empower 2 software

Injection Summary Report

SAMPLE INFORMATION

Sample Name:	RG - 392	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	RG 392
Vial:	15	Acq. Method Set:	Shelly
Injection #:	1	Processing Method	Rohitkumar
Injection Volume:	20.00 ul	Channel Name:	2487Channel 1
Run Time:	30.0 Minutes	Proc. Chnl. Descr.:	
Date Acquired:	9/21/2011 6:13:20 AM IST		
Date Processed:	3/30/2012 5:42:02 AM IST		



Channel: 2487Channel 1; Processed Channel: ; Result Id: 1295; Processing Method: Rohitkumar

Processed Channel Descr.:

	RT	Area	% Area	Height
1	7.054	679664	7.68	39217
2	11.667	8166686	92.32	268259

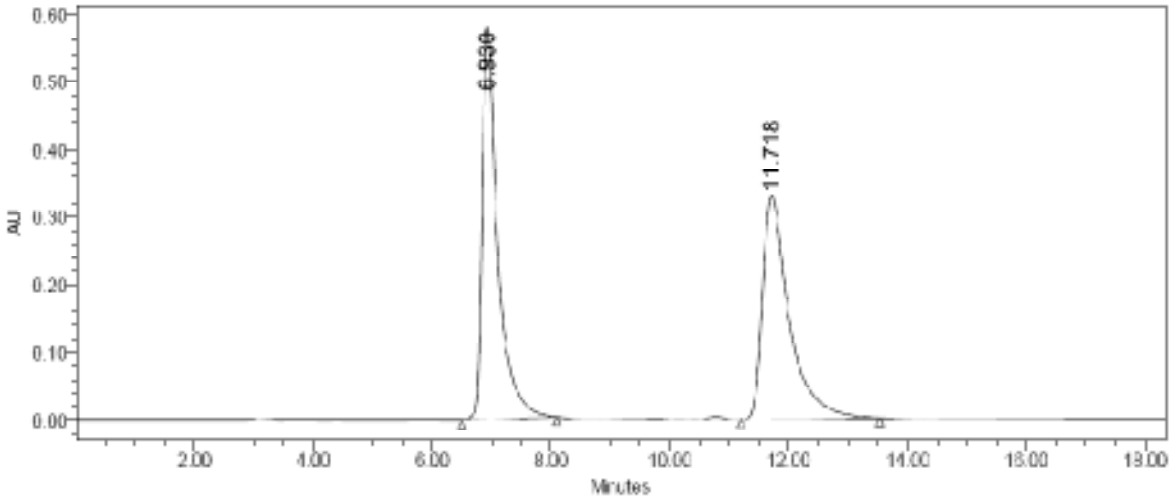
Compound 87 (racemic)

Empower2 software

Injection Summary Report

SAMPLE INFORMATION

Sample Name:	RG 391	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	RG 391
Vial:	24	Acq. Method Set:	Rohit
Injection #:	1	Processing Method	Rohitkumar
Injection Volume:	15.00 ul	Channel Name:	2487Channel 1
Run Time:	30.0 Minutes	Proc. Chnl. Descr.:	
Date Acquired:	9/21/2011 1:15:52 AM IST		
Date Processed:	3/30/2012 5:43:09 AM IST		



Channel: 2487Channel 1: Processed Channel: ; Result Id: 1297; Processing Method: Rohitkumar

Processed Channel Descr.:

	RT	Area	% Area	Height
1	6.930	10427776	50.41	579756
2	11.718	10257397	49.59	329530

Reported by User: System
Report Method: Injection Summary Report
Report Method ID 1005
Page: 1 of 1

Project Name: Defaults\Shell 14.09.11
Date Printed:
3/30/2012
5:43:09 AM Europe/Dublin

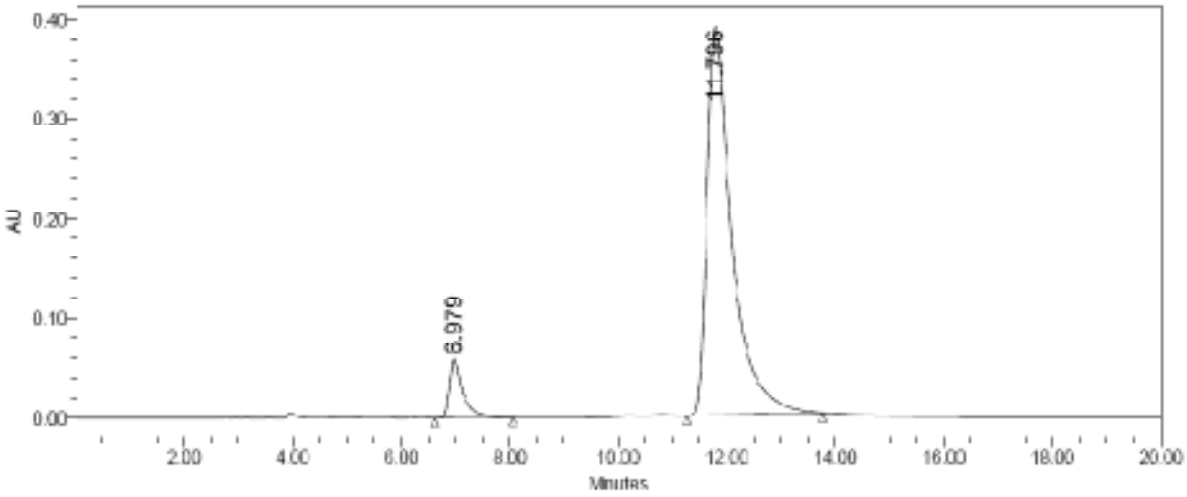
Compound 87

Empower 2

Injection Summary Report

SAMPLE INFORMATION

Sample Name:	RG - 393	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	RG 393
Vial:	16	Acq. Method Set:	Rohit
Injection #:	1	Processing Method	Rohitkumar
Injection Volume:	20.00 ul	Channel Name:	2487Channel 1
Run Time:	20.0 Minutes	Proc. Chnl. Descr.:	
Date Acquired:	9/21/2011 6:36:02 AM IST		
Date Processed:	3/30/2012 5:44:03 AM IST		



Channel: 2487Channel 1; Processed Channel: ; Result Id: 1299; Processing Method: Rohitkumar

Processed Channel Descr.:

	RT	Area	% Area	Height
1	6.979	992900	7.38	59326
2	11.796	12456673	92.62	390922

Reported by User: System
Report Method: Injection Summary Report
Report Method ID 1005
Page: 1 of 1

Project Name: Defaults\Shell 14.09.11
Date Printed:
3/30/2012
5:44:03 AM Europe/Dublin

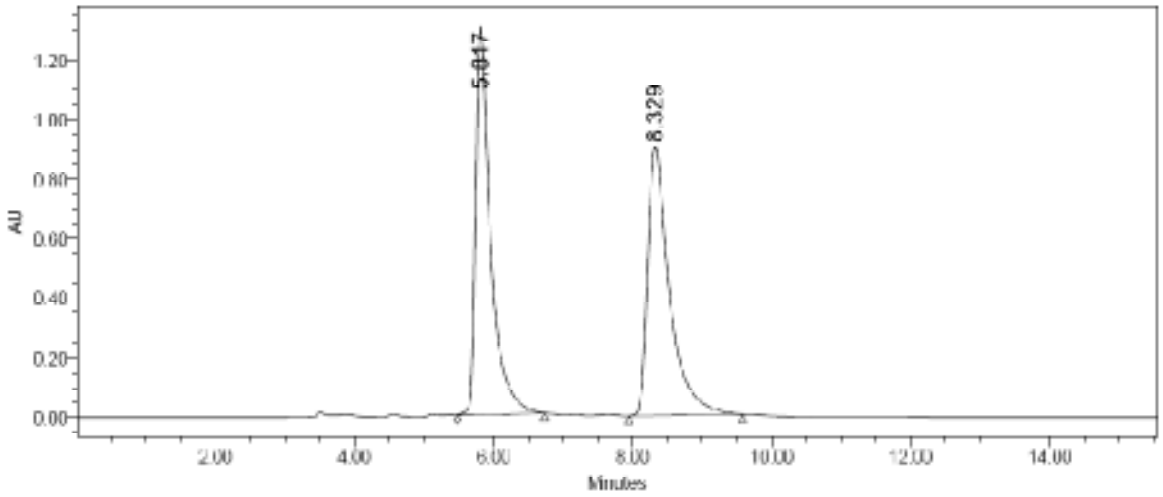
Compound 88 (racemic)

Empower 2 software

Injection Summary Report

SAMPLE INFORMATION

Sample Name:	RG - 395.2	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	RG 395_2
Vial:	34	Acq. Method Set:	Shelly
Injection #:	1	Processing Method	Rohitkumar
Injection Volume:	15.00 ul	Channel Name:	2487Channel 1
Run Time:	30.0 Minutes	Proc. Chnl. Descr.:	
Date Acquired:	9/29/2011 2:59:20 AM IST		
Date Processed:	3/30/2012 5:45:46 AM IST		



Channel: 2487Channel 1; Processed Channel: ; Result Id: 1301; Processing Method: Rohitkumar

Processed Channel Descr.:

	RT	Area	% Area	Height
1	5.817	19576545	49.89	1302475
2	8.329	19661493	50.11	903341

Reported by User: System
Report Method: Injection Summary Report
Report Method ID 1005
Page: 1 of 1

Project Name: Defaults\Shell 14.09.11
Date Printed:
3/30/2012
5:45:47 AM Europe/Dublin

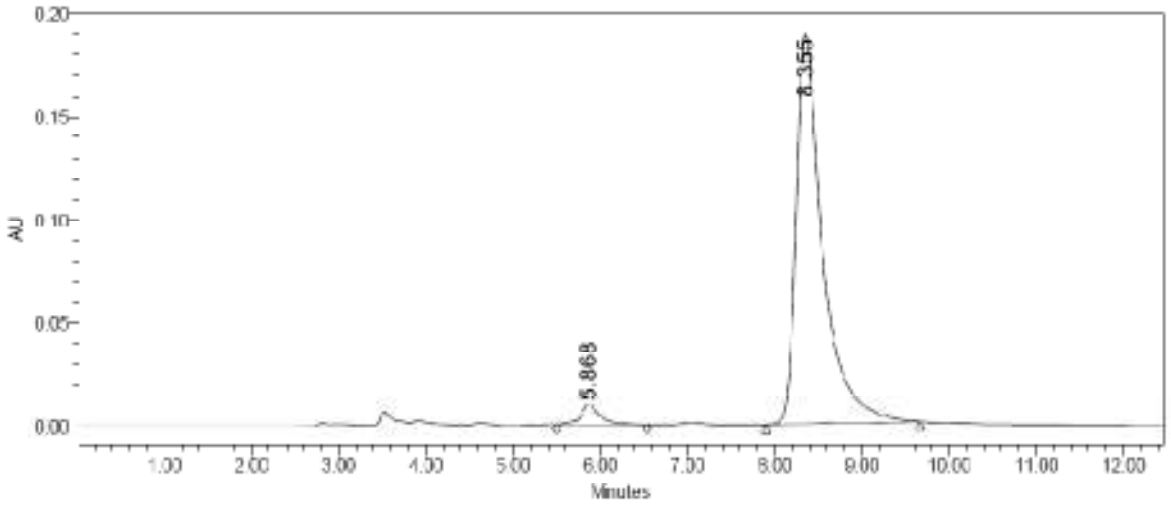
Compound 88

Empower 2 software

Injection Summary Report

SAMPLE INFORMATION

Sample Name:	RG - 396	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	RG 396
Vial:	24	Acq. Method Set:	Shelly
Injection #:	1	Processing Method	Rohitkumar
Injection Volume:	20.00 ul	Channel Name:	2487Channel 1
Run Time:	20.0 Minutes	Proc. Chnl. Descr.:	
Date Acquired:	9/30/2011 5:34:23 AM IST		
Date Processed:	3/30/2012 5:49:28 AM IST		



Channel: 2487Channel 1; Processed Channel: ; Result Id: 1311; Processing Method: Rohitkumar

Processed Channel Descr.:

	RT	Area	% Area	Height
1	5.868	159018	3.81	9924
2	8.355	3985150	96.19	189549

Reported by User: System
Report Method: Injection Summary Report
Report Method ID 1005
Page: 1 of 1

Project Name: Defaults\Shell 14.09.11
Date Printed:
3/30/2012
5:49:28 AM Europe/Dublin

9.5 Applications of ILs in Asymmetric Carbonyl-Ene Reaction of Ethyl Trifluoropyruvate

9.5.1 General procedure of enantioselective catalytic carbonyl-ene reactions in ILs

To a solution of (*R*)-BINAP-$PdCl_2$ (10 mg, 0.0125 mmol) in CH_2Cl_2 (2 mL) was added silver hexafluoroantimonate ($AgSbF_6$) (9.4 mg, 0.0275 mmol) under argon atmosphere. After the mixture was stirred at room temperature for 30 min, the *in situ* activated catalyst solution in dichloromethane was transferred through a small filter into small flask which was already charged with ionic liquid (0.5 or 1 mmol). After removing the dichloromethane under vacuum, ethyl trifluoropyruvate **89** (50 μL, 0.375 mmol) and methylenecyclohexane (30 μL, 0.25 mmol) were added to the mixture. The reaction mixture was stirred at room temperature for 30 minutes. Then the reaction mixture was extracted with ether (2 mL x 3). Removal of the ether gave a residue which was loaded onto a silica gel column and eluted with hexane/ethyl acetate (5/1) to give the *ene* product as a colourless oil. The isolated material was checked with ^{1}H-NMR ($CDCl_3$, 400 MHz) and ^{13}C-NMR ($CDCl_3$, 100 MHz). The enantiomeric excess was determined by GC or HPLC with a chiral column.

Recycle Procedure

Following extraction of the products from the ionic liquid, the IL (containing the catalyst) was dried under vacuum to remove the residual. Fresh substrates were then added to the system and the reactions recommenced as described.

Ethyl 2-(Cyclohexenylmethyl)-3,3,3-trifluoro-2-hydroxypropanoate (90): The ^{1}H NMR and ^{13}C NMR of the product were consistent with the reported data.[3] The enantiomeric excess was determined by chiral GC [column, CP-Cyclodextrin-beta-2,3,6-M-19, i.d. 0.25mm· 25 m, VARIANT; carrier gas, Helium 1mL/min.; column, 120^{o}C; injection temp, 150^{o}C, Detector: 230^{o}C), (*R*)-enantiomer rt_1: 11.04 min. (minor), (*S*)-enantiomer rt_2: 11.40 min. (major).

Ethyl 2-(Cyclopentenylmethyl)-3,3,3-trifluoro-2-hydroxypropanoate (92): The ^{1}H NMR and ^{13}C NMR of the product were consistent with the reported data.[4] The enantiomeric excess was determined by chiral GC [column, CP-Cyclodextrin-beta-2,3,6-M-19, i.d. 0.25mm· 25 m, VARIANT; carrier gas, Helium 1mL/min.; column, 110^{o}C; injection temp, 150^{o}C, Detector: 230^{o}C), (*R*)-enantiomer rt_1: 7.26 min. (minor), (*S*)-enantiomer rt_2: 7.50 min. (major).

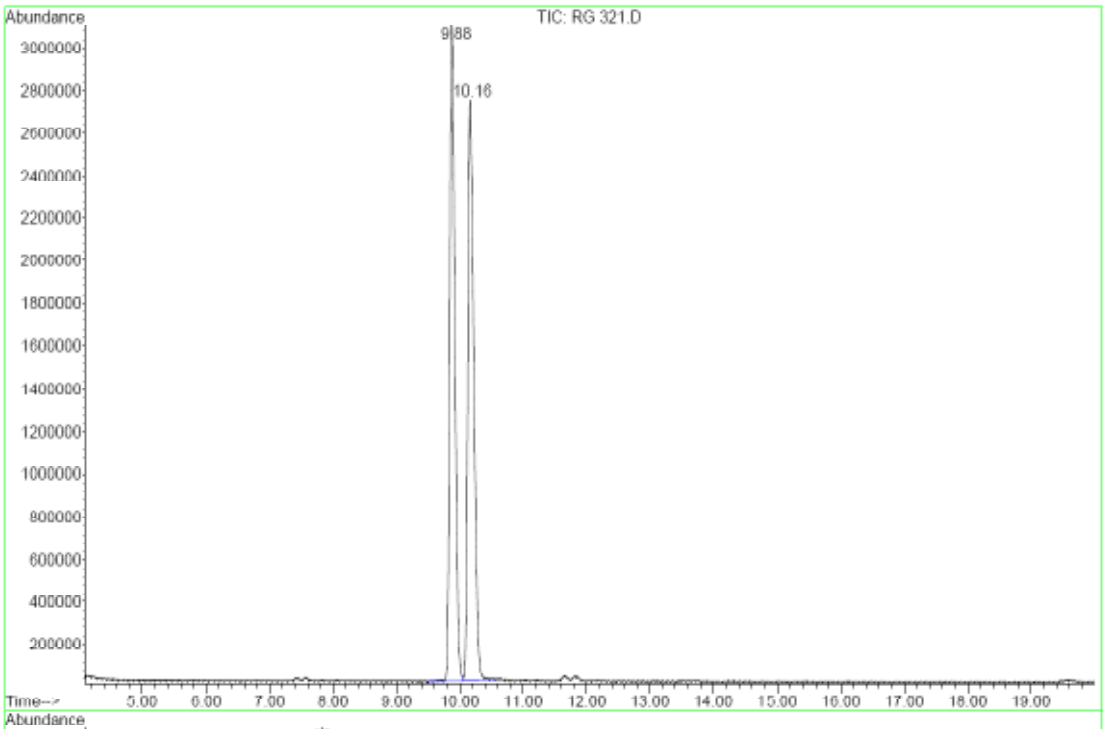
Ethyl 2-Hydroxy-5-methyl-4-methylene-2-(trifluoromethyl)- hexanoate (93a) and Ethyl 2-Hydroxy-4,5- dimethyl-2-(trifluoromethyl)-4-hexenoate (93a'): The ^{1}H NMR and ^{13}C NMR of the product were consistent with the reported data.[2] The enantiomeric excess was determined by chiral GC column, CP-Cyclodextrin-beta-2,3,6-M-19, i.d. 0.25mm· 25 m, VARIANT; carrier gas, Helium 1mL/min.; column, 70^{o}C; injection temp, 150^{o}C, Detector: 230^{o}C), **93a** rt_1: 23.63 min. (minor), rt_2: 24.22 min. (major), **93a'** rt_1: 36.83 min. (minor), rt_2: 39.05 min. (major).

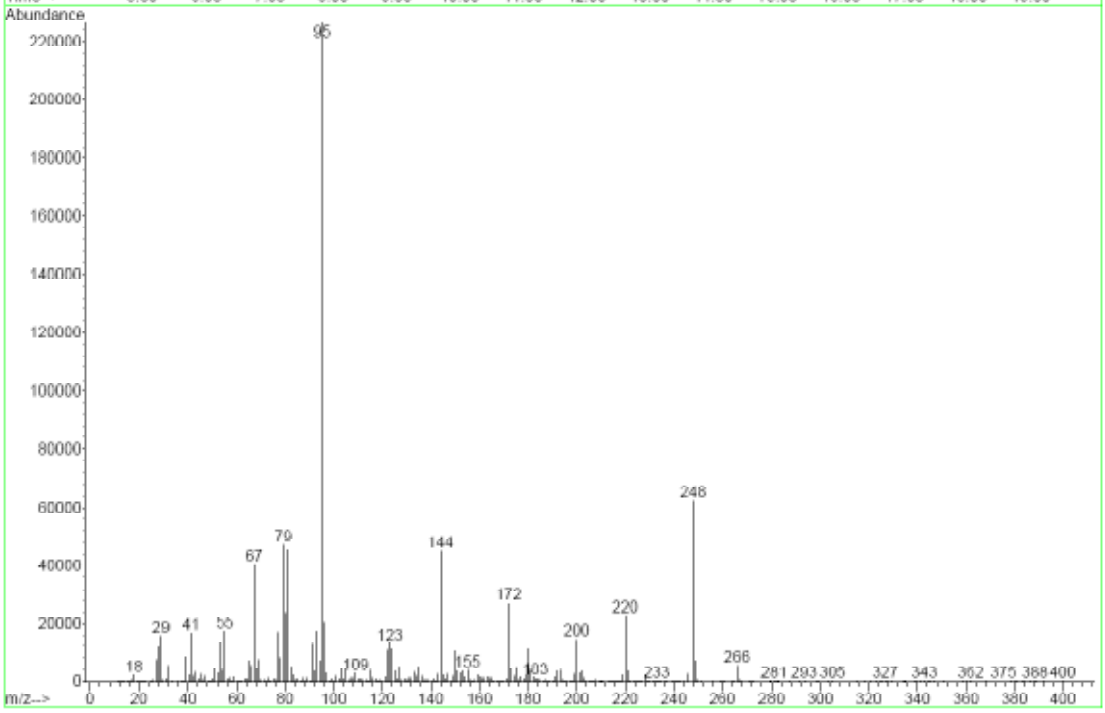
Ethyl 2-Hydroxy-5,5-dimethyl-4-methylene-2-(trifluoromethyl)- hexanoate (94): The ^{1}H NMR and ^{13}C NMR of the product were consistent with the reported data.[2] The enantiomeric excess was determined by chiral GC (column, CP-Cyclodextrin-beta-2,3,6-M-19, i.d. 0.25mm· 25 m, VARIANT; carrier gas, Helium 1mL/min.; column, 100^{o}C; injection temp, 150^{o}C, Detector: 230^{o}C), (*R*)-enantiomer rt_1: 8.48 min. (minor), (*S*)-enantiomer rt_2: 8.77 min. (major).

Ethyl 2-Hydroxy-4-phenyl-2-(trifluoromethyl)pent-4-enoate (95): The ^{1}H NMR and ^{13}C NMR of the product were consistent with the reported data.[2] The enantiomeric excess was determined by HPLC with a Chiralpak AS column (1% 2-propanol in hexane, flow 0.5 mL/min, (*R*)-enantiomer rt_1: 9.37 min. (minor), (*S*)-enantiomer rt_2: 10.16 min. (major).

Compound 90 (racemic)

```
File       :D:\Rohit\GC\RG 321.D
Operator   : Rohit
Acquired   : 26 Jan 2011  18:12     using AcqMethod CP7500 ENE 1 RG
Instrument :    Instrumen
Sample Name: RG 321
Misc Info  : in Diethylether
Vial Number: 3
```

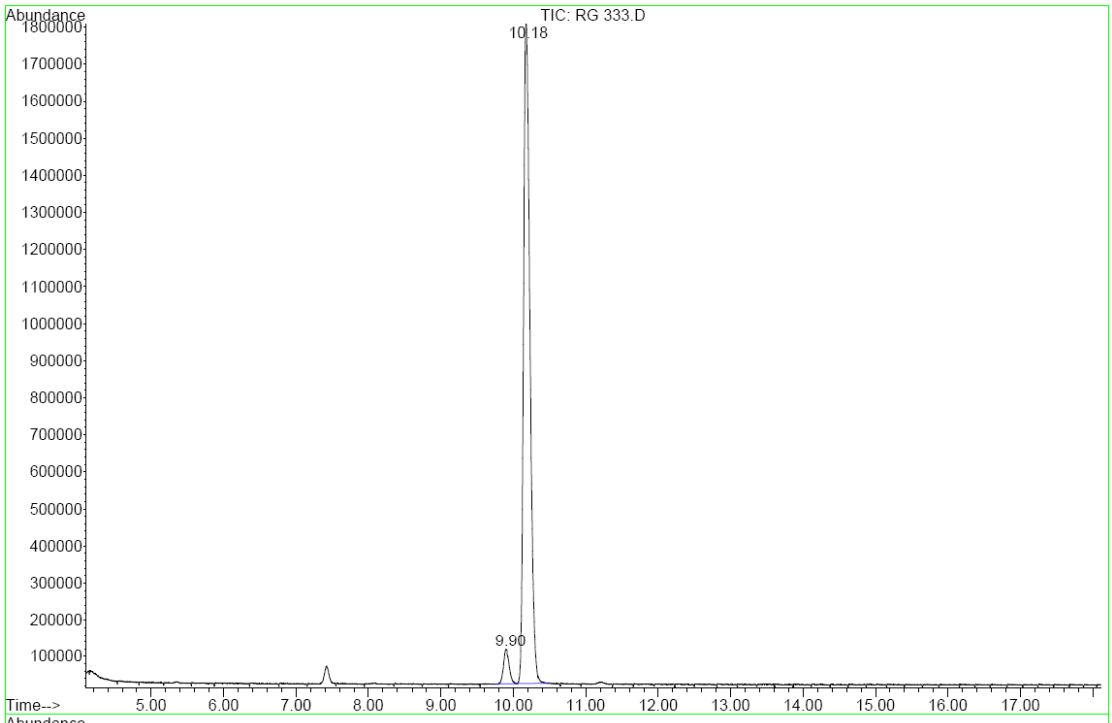


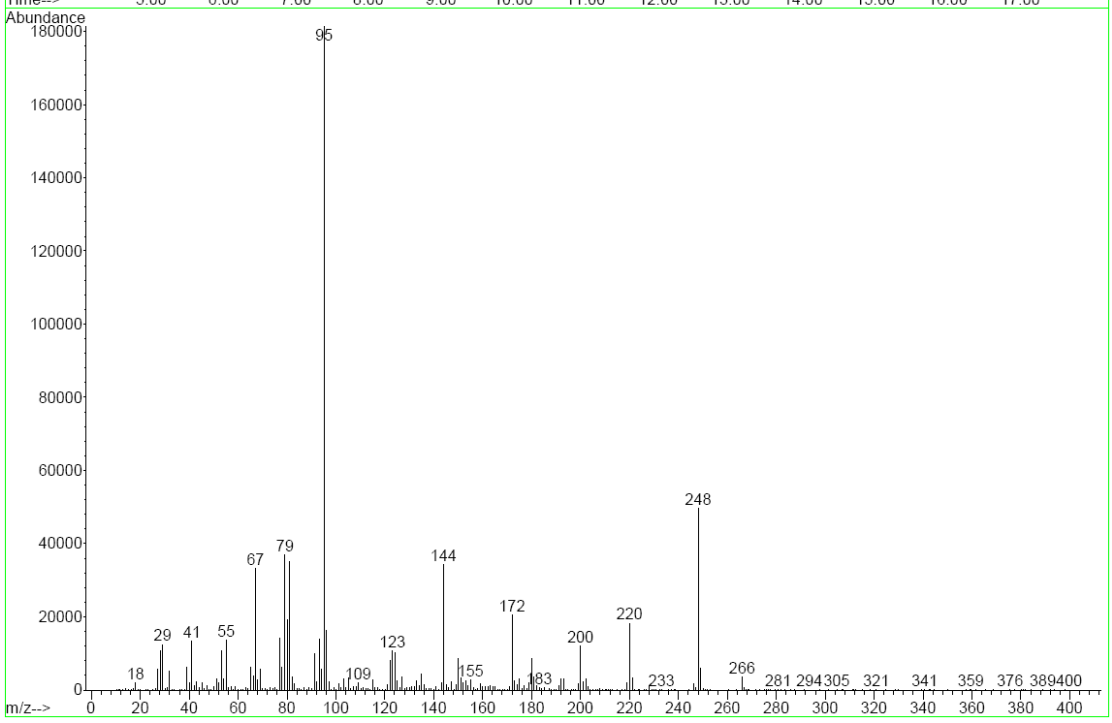


peak #	R.T. min	first scan	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	9.875	1193	1274	1312	BV 2	3069890	176358772	98.48%	49.616%
2	10.161	1312	1337	1422	VB 2	2725853	179085820	100.00%	50.384%

Compound 90

```
File       :D:\Rohit\GC\RG 333.D
Operator   : Rohit
Acquired   :  3 Feb 2011  17:31     using AcqMethod CP7500 ENE 1 RG
Instrument :     Instrumen
Sample Name: RG 333
Misc Info  : in Diethylether
Vial Number: 3
```

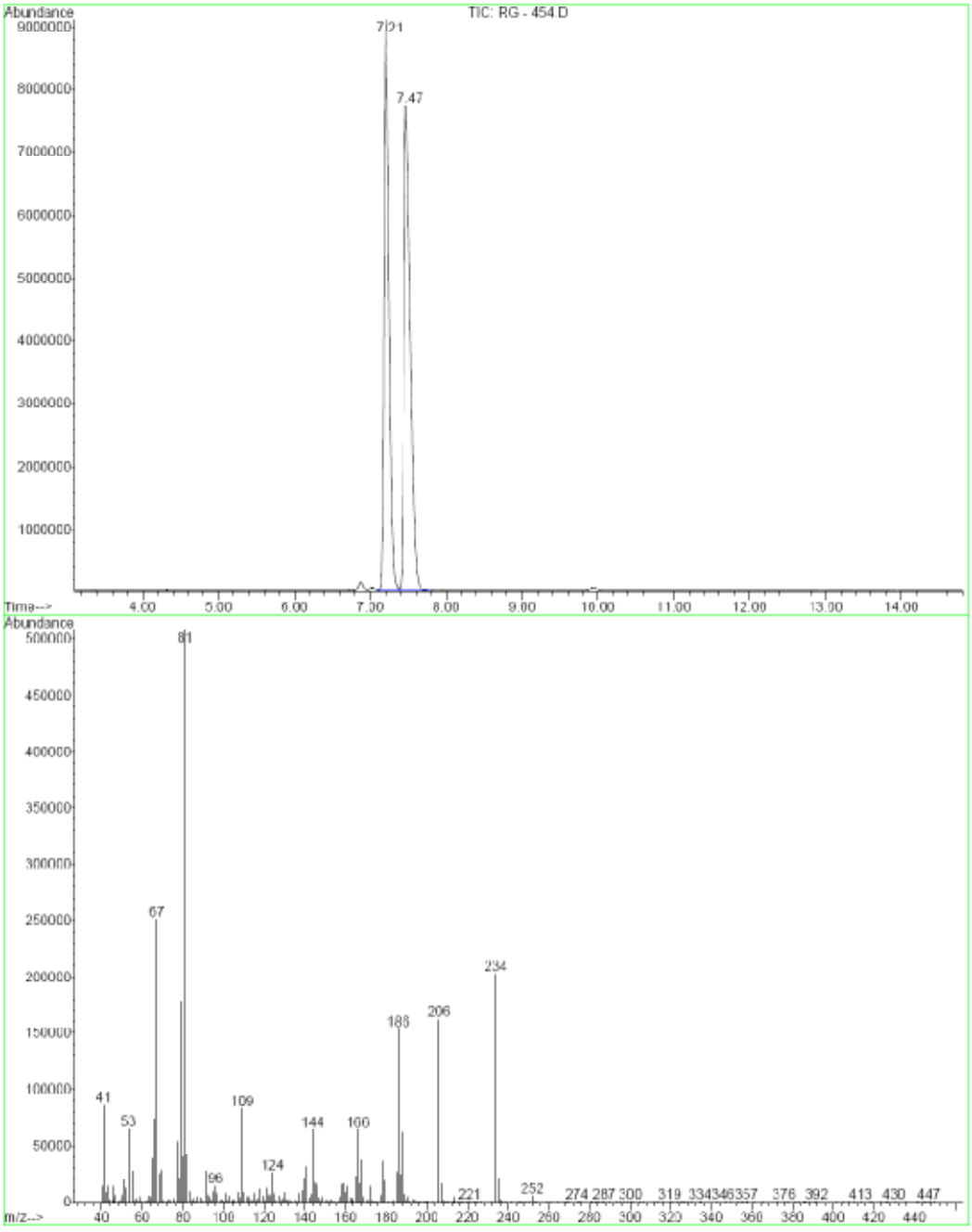




peak #	R.T. min	first scan	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	9.902	1247	1280	1311	BV 3	92710	4998492	4.55%	4.355%
2	10.179	1311	1341	1405	PB 2	1783267	109781945	100.00%	95.645%

Compound 92 (racemic)

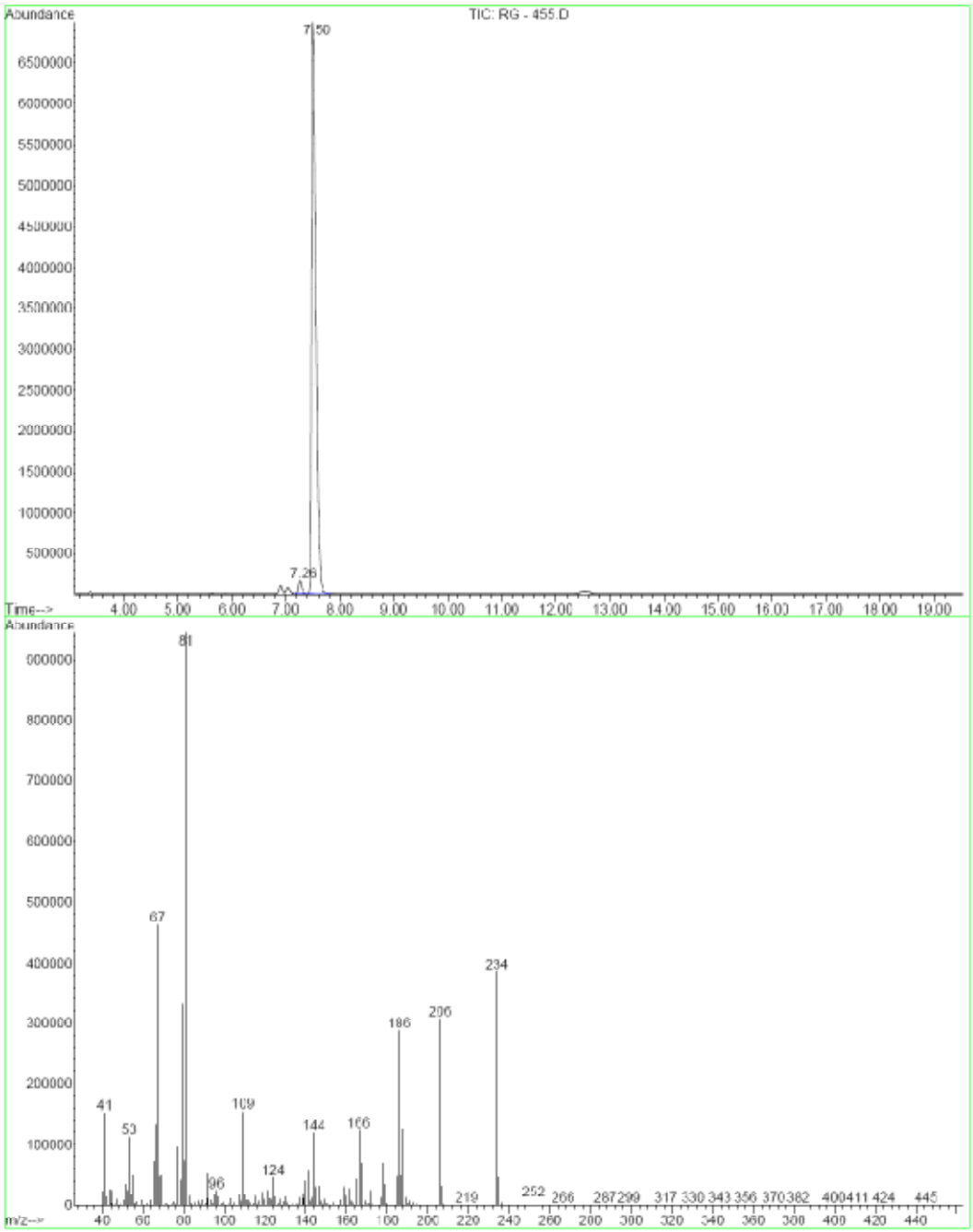
```
File       :D:\Rchit\GC\RG - 454.D
Operator   :
Acquired   : 20 Feb 2012  18:01     using AcqMethod CP7500  ENE110
Instrument :    Instrumen
Sample Name:
Misc Info  :
Vial Number: 1
```



peak #	R.T. min	first scan	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	7.208	843	866	902	VV 2	9071247	433370107	96.82%	49.191%
2	7.469	902	921	990	VB	7680435	447619546	100.00%	50.809%

Compound 92

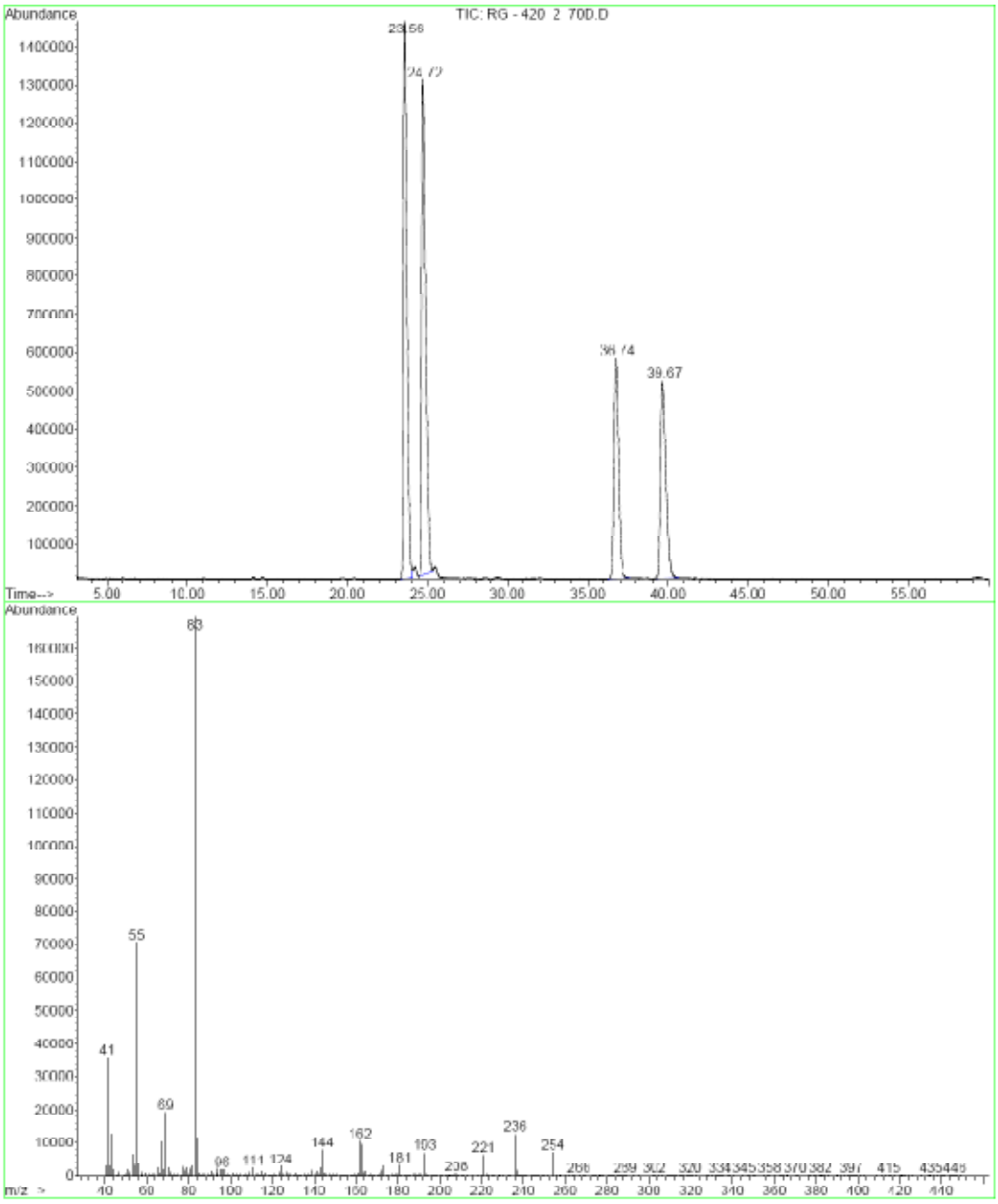
```
File       :D:\Rohit\GC\RG - 455.D
Operator   :
Acquired   : 20 Feb 2012  18:17     using AcqMethod CP7500  ENE110
Instrument :    Instrumen
Sample Name:
Misc Info  :
Vial Number: 1
```



peak #	R.T. min	first scan	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	7.262	858	877	904	BB 5	154656	6596629	1.80%	1.771%
2	7.504	908	928	991	BB 2	6938387	365901719	100.00%	98.229%

Compound 93a/93a' (racemic)

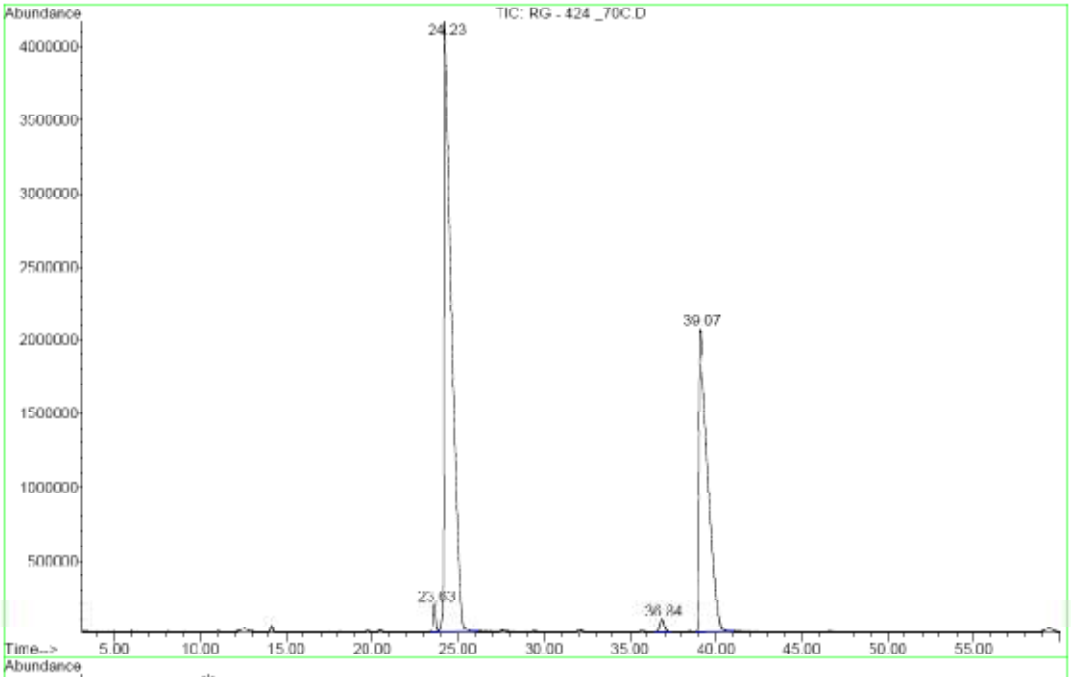
```
File       :D:\Rohit\GC\RG - 420_2_70D.D
Operator   :
Acquired   :  6 Mar 2012  19:26     using AcqMethod CP7500  ENE 70
Instrument :     Instrumen
Sample Name:
Misc Info  :
Vial Number: 1
```

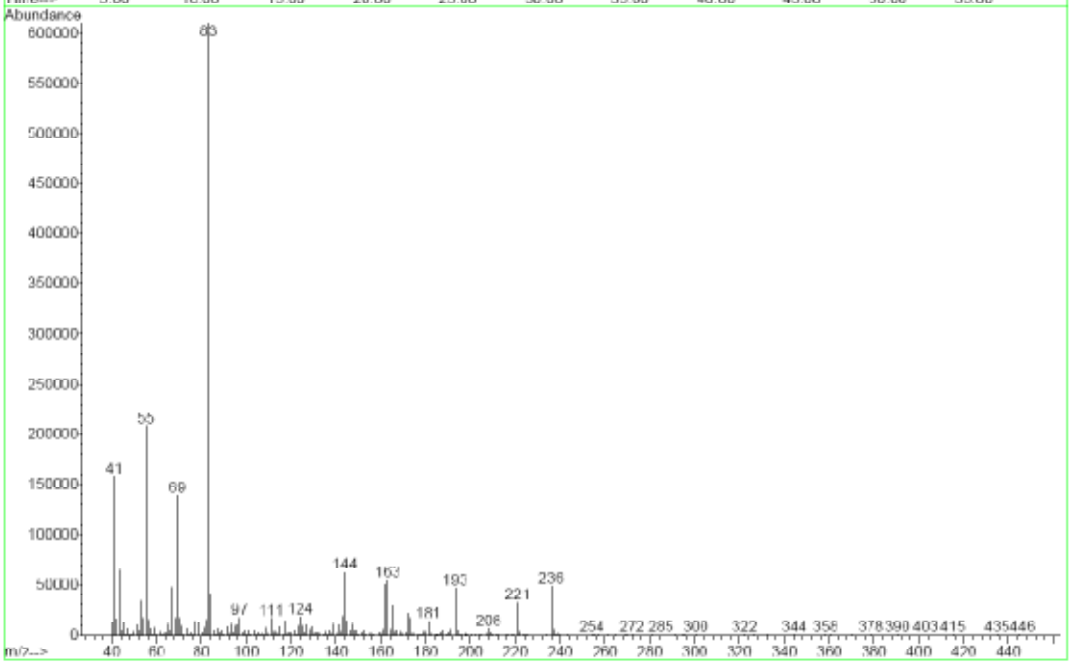


peak #	R.T. min	first scan	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	23.561	4255	4305	4407	BV 4	1449817	206341235	95.01%	31.411%
2	24.717	4499	4548	4674	BV 3	1290250	217188383	100.00%	33.062%
3	36.739	6980	7076	7255	BB 3	571153	114327844	52.64%	17.404%
4	39.668	7604	7692	7899	BB 3	514037	119056699	54.82%	18.124%

Compound 93a/93a’

```
File       :D:\Rohit\GC\RG - 424 _70C.D
Operator   :
Acquired   : 28 Feb 2012  12:55     using AcqMethod CP7500  ENE 70
Instrument :    Instrumen
Sample Name:
Misc Info  :
Vial Number: 1
```

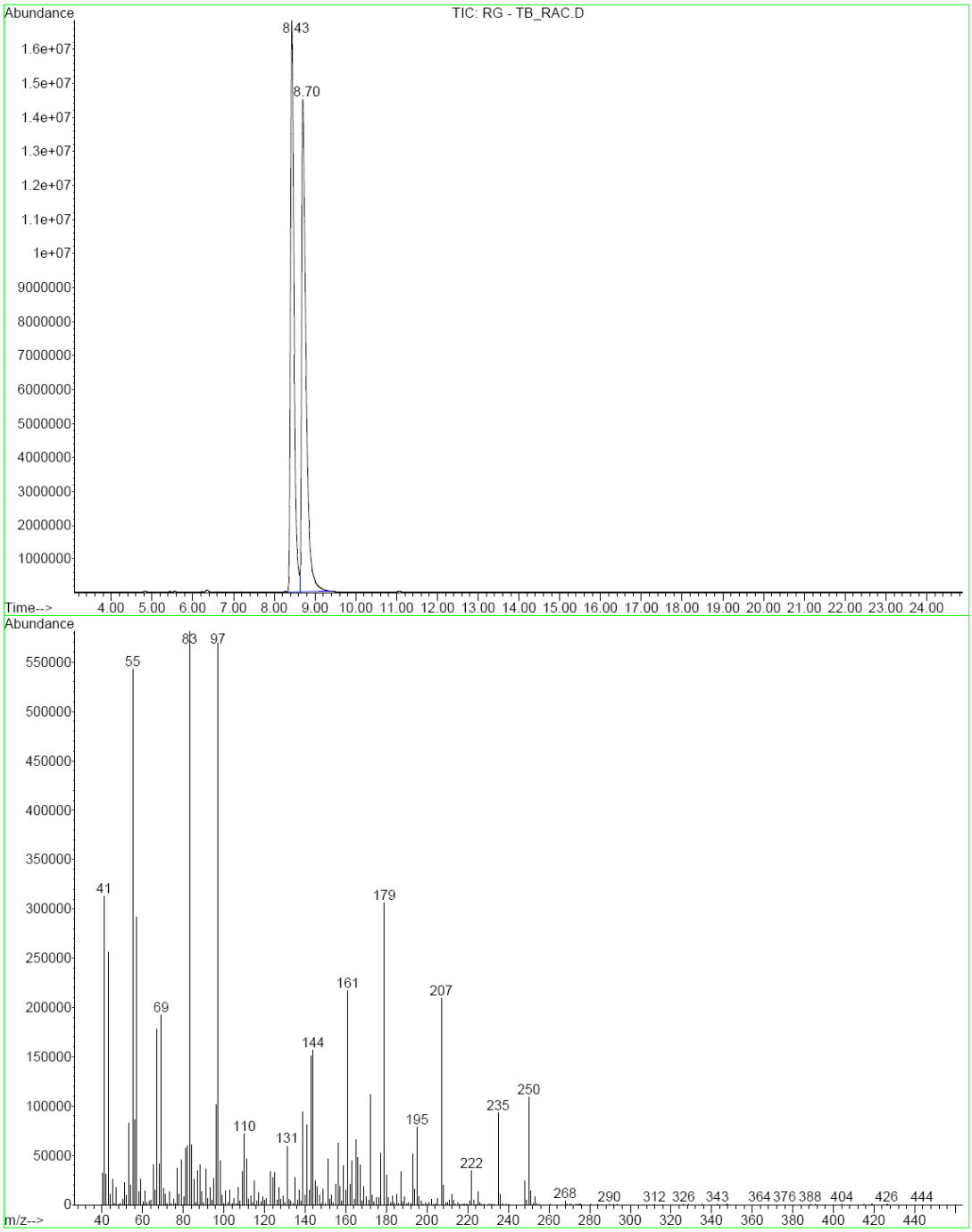




peak #	R.T. min	first scan	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	23.633	4270	4320	4372	BV 3	106947	19570300	1.64%	0.989%
2	24.232	4372	4446	4847	VB 3	4105768	1194146835	100.00%	60.370%
3	36.839	7009	7097	7209	BB 3	92634	15491173	1.30%	0.783%
4	39.069	7513	7566	7970	BB 3	2043459	748839315	62.71%	37.857%

Compound 94 (racemic)

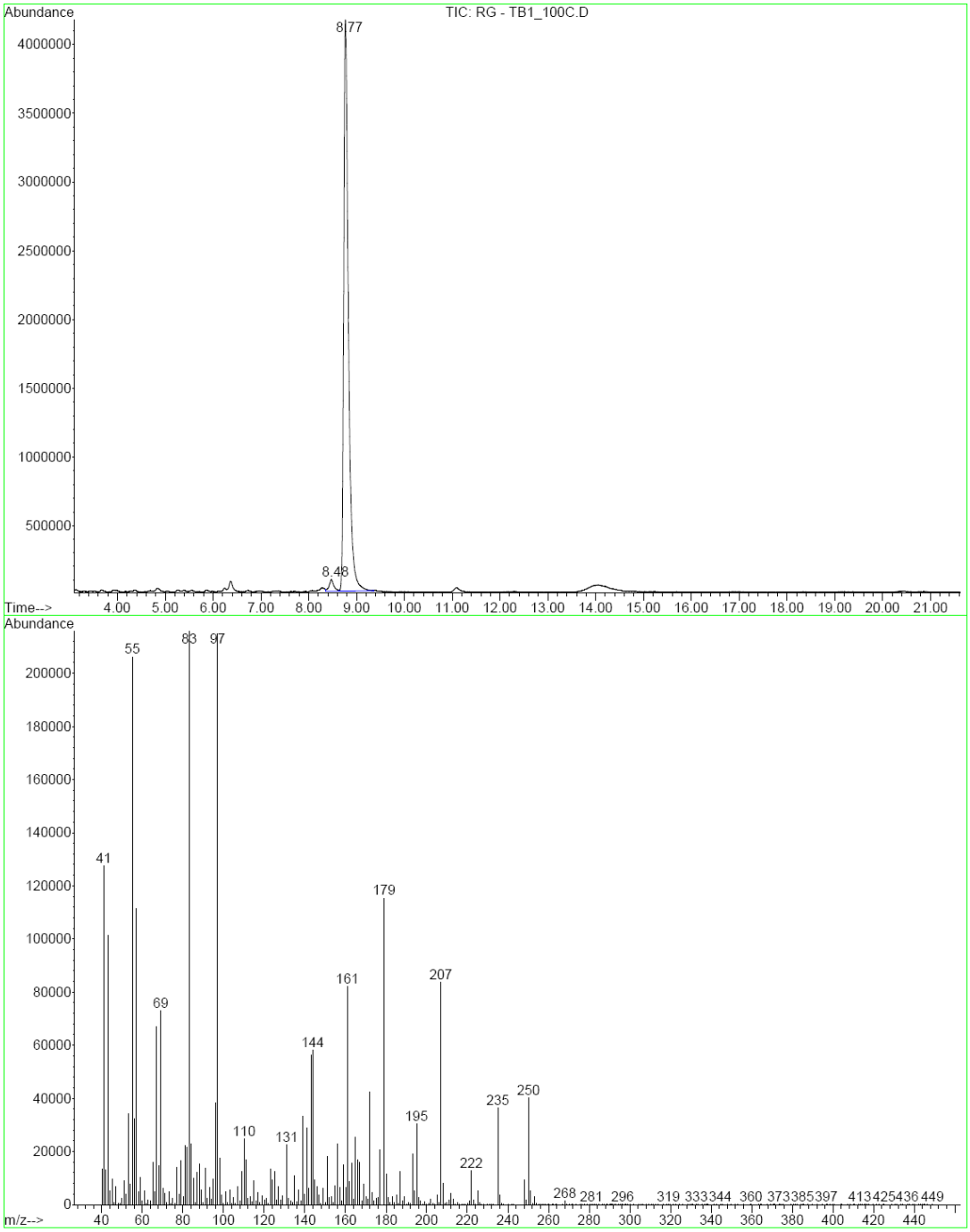
```
File       :D:\Rohit\GC\RG - TB_RAC.D
Operator   :
Acquired   :  2 Mar 2012  15:50     using AcqMethod CP7500  ENE 100
Instrument :    Instrumen
Sample Name:
Misc Info  :
Vial Number: 1
```



peak #	R.T. min	first scan	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	8.432	1097	1123	1163	BV 4	16735163	1018162592	93.86%	48.416%
2	8.703	1163	1180	1315	VB 2	14459509	1084778971	100.00%	51.584%

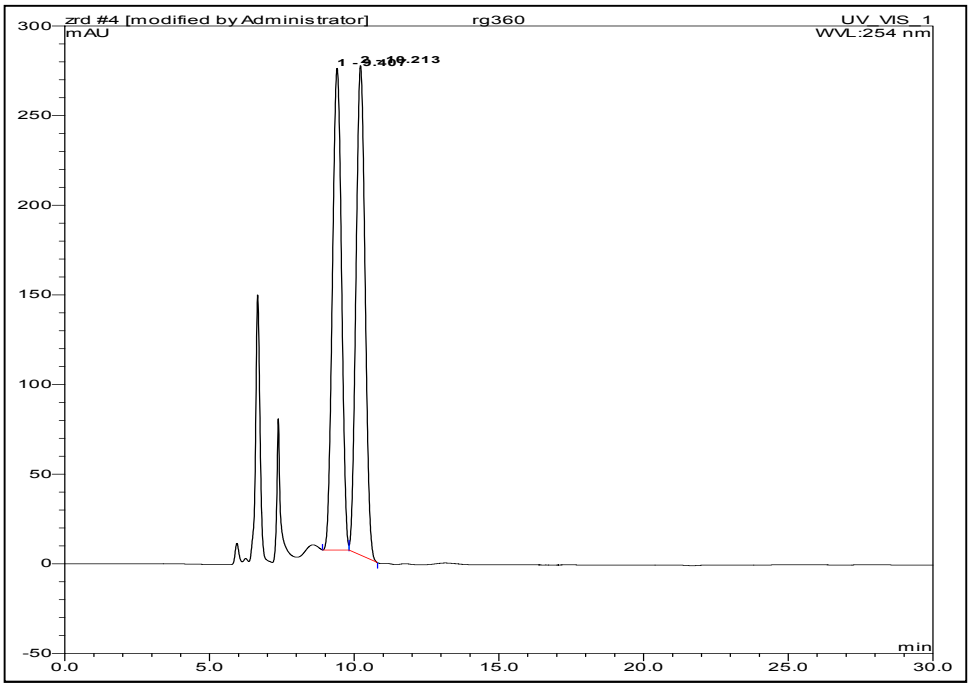
Compound 94

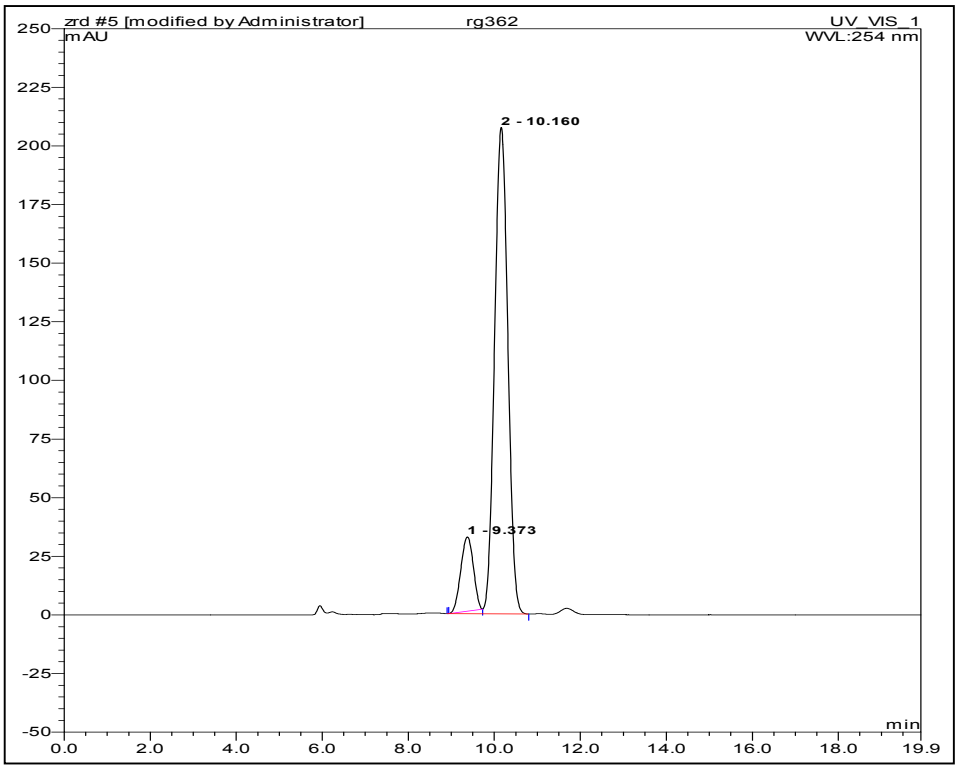
```
File       :D:\Rohit\GC\RG - TB1_100C.D
Operator   :
Acquired   : 28 Feb 2012  15:22     using AcqMethod CP7500  ENE 100
Instrument :    Instrumen
Sample Name:
Misc Info  :
Vial Number: 1
```



peak #	R.T. min	first scan	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	8.478	1107	1133	1168	VV 8	84399	5902419	2.07%	2.032%
2	8.773	1168	1195	1319	VB 3	4157153	284577092	100.00%	97.968%

Compound 95 (racemic)





No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	9.37	n.a.	31.634	10.685	12.45	n.a.	Ru
2	10.16	n.a.	207.485	75.132	87.55	n.a.	BMB*
Total:			239.119	85.817	100.00	0.000	

9.6 Toxicity study of ionic liquids:

9.6.1 Antifungal activity:

In vitro antifungal activities of the compounds were evaluated on a panel of four ATCC strains (*Candida albicans* ATCC 44859, *Candida albicans* ATCC 90028, *Candida parapsilosis* ATCC 22019, *Candida krusei* ATCC 6258) and eight clinical isolates of yeasts (*Candida krusei* E28, *Candida tropicalis* 156, *Candida glabrata* 20/I, *Candida lusitaniae* 2446/I, *Trichosporon asahii* 1188) and filamentous fungi (*Aspergillus fumigatus* 231, *Absidia corymbifera* 272, *Trichophyton mentagrophytes* 445) from the collection of fungal strains deposited at the Department of Biological and Medical Sciences, Faculty of Pharmacy, Charles University, Hradec Králové, Czech Republic. Three ATCC strains were used as the quality control strains. All the isolates were maintained on Sabouraud dextrose agar prior to being tested.

Minimum inhibitory concentrations (MICs) were determined by modified CLSI standard of microdilution format of the M27-A3 and M38-A2 documents.[6,7] Dimethyl sulfoxide (100 %) served as a diluent for all compounds, the final concentration of which did not exceed 2 %. RPMI 1640 (Sevapharma, Prague) medium supplemented with *L*-glutamine and buffered with 0.165 M morpholinepropanesulfonic acid (Serva) to pH 7.0 by 10 M NaOH was used as the test medium. The wells of the microdilution tray contained 200 µl of the RPMI 1640 medium with 2-fold serial dilutions of the compounds (2000 to 0.488 µmol/l for the new compounds) and 10 µl of inoculum suspension. Fungal inoculum in RPMI 1640 was prepared to give a final concentration of $5 \times 10^3 \pm 0.2$ cfu.ml^{-1}. The trays were incubated at 35°C and MICs were read visually after 24 h and 48 h. The MIC values for the dermatophytic strain (*T. mentagrophytes*) were determined after 72 h and 120 h. The MICs were defined as 80 % inhibition (IC_{80}) of the growth of control for yeasts and as 50 % inhibition (IC_{50}) of the growth of control for filamentous fungi. MICs were determined twice and in duplicate. The deviations from the usually obtained values were no higher than the nearest concentration value up and down the dilution scale.

9.6.2 Antibacterial activity:

In vitro antibacterial activity[8] of the compounds were evaluated on a panel of three ATCC strains (*Staphylococcus aureus* ATCC 6538, *Escherichia coli* ATCC 8739, *Pseudomonas aeruginosa* ATCC 9027) and five clinical isolates (*Staphylococcus aureus* MRSA HK5996/08, *Staphylococcus epidermidis* HK6966/08, *Enterococcus* sp.

HK14365/08, *Klebsiella pneumoniae* HK11750/08, *Klebsiella pneumoniae* ESBL HK14368/08) from the collection of bacterial strains deposited at the Department of Biological and Medical Sciences, Faculty of Pharmacy, Charles University, Hradec Králové, Czech Republic. The above-mentioned ATCC strains also served as the quality control strains. All the isolates were maintained on Mueller-Hinton agar prior to being tested.

Dimethyl sulfoxide (100 %) served as a diluent for all compounds, the final concentration did not exceed 2 %. Mueller-Hinton agar (MH, HiMedia, Čadersky-Envitek, Czech Republic) buffered to *p*H 7.4 (±0.2) was used as the test medium. The wells of the microdilution tray contained 200 µl of the Mueller-Hinton medium with 2-fold serial dilutions of the compounds (2000 to 0.488 µmol/l) and 10 µl of inoculum suspension. Inoculum in MH medium was prepared to give a final concentration of 0.5 McFarland scale (1.5×10^8 cfu.ml^{-1}). The trays were incubated at 37°C and MICs were read visually after 24 h and 48 h. The MICs were defined as 95 % inhibition of the growth of control. MICs were determined twice and in duplicate. The deviations from the usually obtained values were no higher than the nearest concentration value up and down the dilution scale.

9.6.3 Anti-bacterial studies in DCU:

Test strains were grown in nutrient broth at 30 °C overnight. Next day, cultures were centrifuged at 5000 rpm for 10 minutes. The pellet formed was washed twice with 10 ml of 0.01 M sodium phosphate buffer (pH 7.0). Optical density of cultures was adjusted to give an optical density of 0.07 at 660 nm. The compound solution and 96 well plates were ready before the cultures were adjusted to the desired optical density. For the stock solution of chemical, the ionic liquid was dissolved in 1 ml of sterile water or organic solvents such as methanol and DMSO, dependant on compound solubility.

For microplate preparation, 190 µl of Müeller-hinton broth was dispensed into wells in column 1. 100 µl of Müeller-hinton broth was dispensed into all wells from column 2 to column 12. 10 µl of the compound solution was pipetted into wells in column 1 (far left of plate). The compound was mixed into the wells in column 1 by pipetting up and down 6-8 times. 100 µl was withdrawn from column 1 and added to column 2. This made column 2 a two-fold dilution of column 1. This was mixed up and down 6-8 times. 100 µl was transferred to column 3. This procedure was repeated down to column 10 only. 100 µl was discarded from column 10 rather than putting it in column 11. 5 µl of the strain to be tested was dispensed into wells in columns 11 to 1 in that order.

Column 11 was used as a growth control and column 12 was the sterility control. The plates were incubated at 30 °C overnight. Growth on the plates was noted and optical density measured after 24 hours.

9.7 Biodegradation of ionic liquids

9.7.1 CO_2 Headspace test:

To evaluate the biodegradability of the test ionic liquids, the "CO_2 Headspace" test (ISO 14593) was applied.[9] There are several biodegradation study methods (Table 1.1, Chapter 1) but the CO_2 Headspace test was chosen as it is better suited for charged, volatile and water soluble compounds. Also, this method allows for the evaluation of the ultimate aerobic biodegradability of an organic compound in an aqueous medium at a given concentration of microorganism, by analysis of the inorganic carbon produced. The test ionic liquid, as the only source of carbon and energy, was added to a buffer/mineral salts medium which had been inoculated with a mixed population of microorganisms derived from activated sludge collected from a sewage treatment plant located in Manresa (Barcelona), to give a final organic carbon concentration of 20 mg/L. These solutions were incubated in sealed vessels with a "headspace" of air, which provided a reservoir of oxygen for aerobic biodegradation. The volume of activated sludge used for inoculation was that which gave a concentration of 4 mg/L suspended solids in the final mixture. Based on experience, the use of this inoculum concentration in this test is suitable to give a population (102-105 colony-forming units in the final mixture) which offers adequate biodegradative activity and degrades the reference substance by the stipulated percentage.

Sample preparation

- Water-soluble substances. Stock solutions were prepared in water
- Poorly water-soluble test compounds. Stock solutions were prepared in methanol (HPLC, LIChrosolvR, Merck KGaA, >99,8%) or in ethyl acetate (PAC-ACS-ISO, Panreac, >99.5%)

Biodegradation (mineralization to carbon dioxide) was determined by measuring the net increase in total inorganic carbon (TIC) levels over time compared to unamended blanks. Sodium n-dodecyl sulfate (SDS) was used as a reference substance. The test ran for 28 days. The extent of biodegradation was expressed as a percentage of the

theoretical amount of inorganic carbon (ThID) based on the amount of IL added initially. Assuming 100% mineralization of the test ionic liquid, the theoretical amount of inorganic carbon (ThID), in excess of that produced in the blank controls, equals the amount of total organic carbon (TOC) added as the test compound to each vessel at the start of the test, that is: (ThIC=TOC)

Percentage biodegradation Dt in each case is given by:

$$D_t = \frac{(\mathrm{TIC_t} - \mathrm{TIC_b})}{\mathrm{TOC_i}} \mathrm{x100}$$

where:

TICt is the TIC, in milligrams, in test vessel at time t,
TICb is the mean TIC, in milligrams, in blank control vessels at time t
TOCi is the TOC, in milligrams, initially added to the test vessel

The measured data of the last day of the test (28 days) were used to calculate the mean biodegradation value and the precision with which the percentage of biodegradation was determined. To know the precision with which percentage of biodegradation was determined, four replicate test vessels and the same number of blanks control vessels on the 28th day were analysed:

- the mean total inorganic carbon in the blank vessels and the percentage of biodegradation for each individual vessel was calculated
- the mean of the separate degradation values and their standard deviation was calculated
- and finally the confidence limits for the mean value of biodegradation was evaluated as

  $\pm \frac{t.s}{\sqrt{n}}$

  where t is the Student's t value for (n-1) degrees of freedom at the 95% probability level, s is the standard deviation and n is the number of individual values used to determine the biodegradation percentage.

References:

1. (a) N. Gathergood and P. J. Scammells, *Aus.J. Chem.*, 2002, **55**, 557-560. (b) N. Gathergood M. T. Garcia, P. J. Scammells, *Green Chem*., 2004, **6**, 166-175, (c) S. Morrissey, B. Pegot, D. Coleman, M. T. Garcia, D. Ferguson, B. Quilty, N. Gathergood, *Green Chem.*, 2009, **11**, 475-483, (d) S. Morrissey, Thesis - '*Environmentally-Benign Imidazolium Based Ionic Liquids: Synthesis, Characterisation and Applications in Hydrogenation Reactions*', Dublin City University, 2008
2. H.-K. Luo, Y-L. Woo, H. Schumann, C. Jacob, M. V. Meurs, H.-Y. Yang, Y-T. Tan, *Adv. Synth. Catal.*, 2010, **352**, 1356-1364
3. K. Aikawa, S. Kainuma, M. Hatano, K. Mikami, *Tetrahedron Lett.*, 2004, **45**, 183-185
4. S. Doherty, J. G. Knight, C. H. Smyth, R. W. Harrington, W. Clegg, *J. Org. Chem.*, 2006, **71**, 9751-9764
5. B. Hatano, K. Nagahashi, S. Habaue, *Chem. Lett.*, 2007, **36**, 1418-1419
6. Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts. Approved standard. Document M27-A3. Clinical Laboratory Standard Institute, Wayne, PA, **2008**
7. Reference Method for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi. Approved standard. Document M38-A2. Clinical Laboratory Standard Institute, Wayne, PA, **2008**
8. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically. Approved Standard - Seventh Edition. Document M07-A7. Clinical Laboratory Standard Institute, Wayne, PA, **2006**
9. ISO 14593: Water quality, Evaluation of ultimate aerobic biodegradability of organic compounds in aqueous medium. Method by analysis of inorganic carbon in sealed vessels 'CO_2 headspace' test

Appendix 1: Toxicity Data of Ionic Liquids

Table A1.1: MIC_{80} values of bromide salts of ester and amide side chain ionic liquids (**8**, **10-16**) in anti-fungal screening

Strain	Time (h)	**MIC_{80} Values of Ionic Liquids (Concentration in µM)**				
		Ester Side chain			**Amide side chain**	
		8	**10**	**11**	**12-15**	**16**
Candida albicans ATCC 44859	24h	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000
Candida albicans ATCC 90028	24h	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000
Candida parapsilosis ATCC 22019	24h	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000
Candida krusei ATCC 6258	24h	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000
Candida krusei E28	24h	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000
Candida tropicalis 156	24h	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000
Candida glabrata 20/I	24h	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000
Candida lusitaniae 2446/I	24h	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000
Trichosporon beigelii 1188	24h	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000
Aspergillus fumigatus 231*	24h	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000
Absidia corymbifera 272*	24h	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000
Trichophyton mentagrophytes 445*	72h	>2000	>2000	>2000	>2000	>2000
	120h	>2000	>2000	>2000	>2000	>2000

* MIC_{50} values

Table A1.2: MIC_{95} values of bromide salts of ester and amide side chain ionic liquids (**8**, **10-16**) in anti-bacterial screening

Strain	Time (h)	**MIC_{95} Values of Ionic Liquids (Concentration in µM)**				
		Ester Side chain			**Amide side chain**	
		8	**10**	**11**	**12-15**	**16**
Staphylococcus aureus, ATCC 6538	24h	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000
Staphylococcus aureus, HK 5996/08	24h	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000
Staphylococcus epidermidis, HK 6966/08	24h	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000
Enterococcus sp. HK 14365/08	24h	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000
Escherichia coli, ATCC 8739	24h	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000
Klebsiella pneumonia, HK 11750/08	24h	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000
Klebsiella pneumonia, ESBL HK 14368/08	24h	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000
Pseudomonas aeruginosa, ATCC 9027	24h	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000

Table A1.3: MIC_{80} values of ester and amide side chain ionic liquids (**19-33**) in anti-fungal screening

Strain	Time (h)	**MIC_{80} Values of Ionic Liquids (Concentration in µM)**				
		Ester Side chain			**Amide side chain**	
		19-22	**23**	**24-25**	**26-32**	**33**
Candida albicans ATCC 44859	24h	>2000	**1000**	>2000	>2000	>2000
	48h	>2000	>1000	>2000	>2000	>2000
Candida albicans ATCC 90028	24h	>2000	**1000**	>2000	>2000	>2000
	48h	>2000	>1000	>2000	>2000	>2000
Candida parapsilosis ATCC 22019	24h	>2000	>1000	>2000	>2000	>2000
	48h	>2000	>1000	>2000	>2000	>2000
Candida krusei ATCC 6258	24h	>2000	>1000	>2000	>2000	>2000
	48h	>2000	>1000	>2000	>2000	>2000
Candida krusei E28	24h	>2000	>1000	>2000	>2000	>2000
	48h	>2000	>1000	>2000	>2000	>2000
Candida tropicalis 156	24h	>2000	>1000	>2000	>2000	>2000
	48h	>2000	>1000	>2000	>2000	>2000
Candida glabrata 20/I	24h	>2000	>1000	>2000	>2000	>2000
	48h	>2000	>1000	>2000	>2000	>2000
Candida lusitaniae 2446/I	24h	>2000	>1000	>2000	>2000	>2000
	48h	>2000	>1000	>2000	>2000	>2000
Trichosporon beigelii 1188	24h	>2000	>1000	>2000	>2000	>2000
	48h	>2000	>1000	>2000	>2000	>2000
Aspergillus fumigatus 231*	24h	>2000	>1000	>2000	>2000	>2000
	48h	>2000	>1000	>2000	>2000	>2000
Absidia corymbifera 272*	24h	>2000	>1000	>2000	>2000	>2000
	48h	>2000	>1000	>2000	>2000	>2000
Trichophyton mentagrophytes 445*	72h	>2000	>1000	>2000	>2000	>2000
	120h	>2000	>1000	>2000	>2000	>2000

* MIC_{50} values

Table A1.4: MIC_{95} values of ester and amide side chain ionic liquids (**19-33**) in anti-bacterial screening

Strain	Time (h)	**MIC_{95} Values of Ionic Liquids (Concentration in µM)**				
		Ester Side chain			**Amide side chain**	
		19-22	**23**	**24-25**	**26-32**	**33**
Staphylococcus aureus, ATCC 6538	24h	>2000	>1000	>2000	>2000	>2000
	48h	>2000	>1000	>2000	>2000	>2000
Staphylococcus aureus, HK 5996/08	24h	>2000	>1000	>2000	>2000	>2000
	48h	>2000	>1000	>2000	>2000	>2000
Staphylococcus epidermidis, HK 6966/08	24h	>2000	>1000	>2000	>2000	>2000
	48h	>2000	>1000	>2000	>2000	>2000
Enterococcus sp. HK 14365/08	24h	>2000	>1000	>2000	>2000	>2000
	48h	>2000	>1000	>2000	>2000	>2000
Escherichia coli, ATCC 8739	24h	>2000	>1000	>2000	>2000	>2000
	48h	>2000	>1000	>2000	>2000	>2000
Klebsiella pneumonia, HK 11750/08	24h	>2000	>1000	>2000	>2000	>2000
	48h	>2000	>1000	>2000	>2000	>2000
Klebsiella pneumonia, ESBL HK 14368/08	24h	>2000	>1000	>2000	>2000	>2000
	48h	>2000	>1000	>2000	>2000	>2000
Pseudomonas aeruginosa, ATCC 9027	24h	>2000	>1000	>2000	>2000	>2000
	48h	>2000	>1000	>2000	>2000	>2000

Table A1.5: MIC_{80} values of C-2 substituted imidazolium ionic liquids (**40-47**) in anti-fungal screening

Strain	Time (h)	**MIC_{80} Values of Ionic Liquids (Concentration in µM)**					
		Amide substitution			**Ester substitution**		
		40	**41-43**	**44**	**45**	**46**	**47**
Candida albicans ATCC 44859	24h	>2000	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000	>2000
Candida albicans ATCC 90028	24h	>2000	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000	>2000
Candida parapsilosis ATCC 22019	24h	>2000	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000	>2000
Candida krusei ATCC 6258	24h	>2000	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000	>2000
Candida krusei E28	24h	>2000	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000	>2000
Candida tropicalis 156	24h	>2000	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000	>2000
Candida glabrata 20/I	24h	>2000	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000	>2000
Candida lusitaniae 2446/I	24h	>2000	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000	>2000
Trichosporon beigelii 1188	24h	>2000	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000	>2000
Aspergillus fumigatus 231*	24h	>2000	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000	>2000
Absidia corymbifera 272*	24h	>2000	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000	>2000
Trichophyton mentagrophytes 445*	72h	>2000	>2000	>2000	>2000	>2000	>2000
	120h	>2000	>2000	>2000	>2000	>2000	>2000

* MIC_{50} values

Table A1.6: MIC_{95} values of C-2 substituted imidazolium ionic liquids (**40-47**) in anti-bacterial screening

Strain	Time (h)	**MIC_{95} Values of Ionic Liquids (Concentration in µM)**					
		Amide substitution			**Ester substitution**		
		40	**41-43**	**44**	**45**	**46**	**47**
Staphylococcus aureus, ATCC 6538	24h	>2000	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000	>2000
Staphylococcus aureus, HK 5996/08	24h	>2000	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000	>2000
Staphylococcus epidermidis, HK 6966/08	24h	>2000	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000	>2000
Enterococcus sp. HK 14365/08	24h	>2000	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000	>2000
Escherichia coli, ATCC 8739	24h	>2000	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000	>2000
Klebsiella pneumonia, HK 11750/08	24h	>2000	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000	>2000
Klebsiella pneumonia, ESBL HK 14368/08	24h	>2000	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000	>2000
Pseudomonas aeruginosa, ATCC 9027	24h	>2000	>2000	>2000	>2000	>2000	>2000
	48h	>2000	>2000	>2000	>2000	>2000	>2000

Appendix 2: Green Chemistry Metrics

SYNFLOW

Green metrics Lab Book V2.0

User guide

Patrice Ribiere, 25/07/2011

Introduction

The Green Metrics Lab Book is a Microsoft Excel® spreadsheet aimed to automatise reagent and solvent charges calculations and a subsequent set of green metrics.

Quick overview

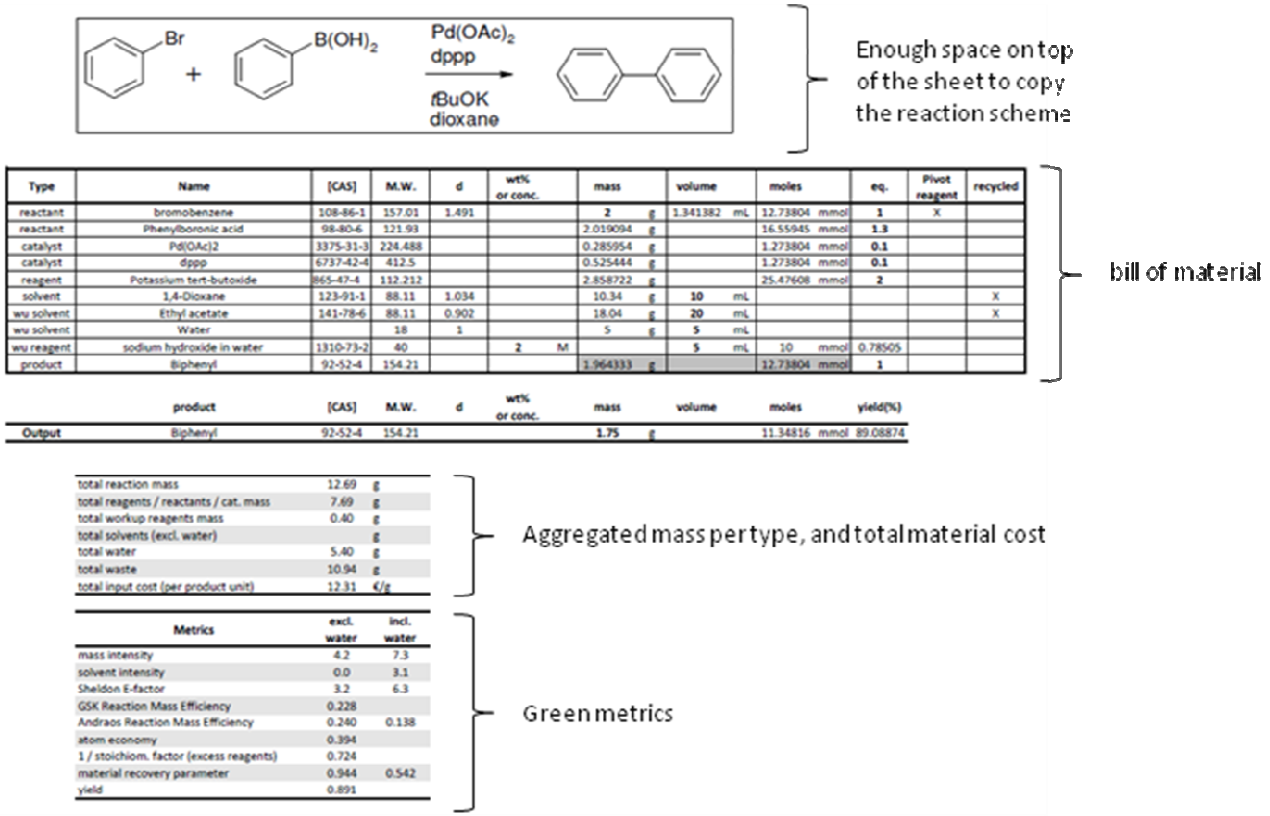
Structure of the Excel file:

The Excel file contains 2 different types of spreadsheets:

- A series of experiment sheets, each one storing data from a single reaction. An experiment is composed of 3 tables: a bill of the materials used in the reaction, a table aggregating the mass of these materials according to their type (reagents, solvents, water, waste...), and a green metrics summary for the reaction. (see picture next page).
- a single sheet called “Chemicals” which can be considered as basic chemical database. (see header next page).

The idea for using an excel file is to be able

- to share easily between partners both the data for an experiment (by copying the sheet of interest) and the chemical database (by merging two “Chemicals” tables together).
- to use macro programming to make automatic and speed-up calculations.



Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
reactant	bromobenzene	108-86-1	157.01	1.491		2 g	1.341382 mL	12.73804 mmol	1	X	
reactant	Phenylboronic acid	98-80-6	121.93			2.019094 g		16.55945 mmol	1.3		
catalyst	Pd(OAc)2	3375-31-3	224.488			0.285954 g		1.273804 mmol	0.1		
catalyst	dppp	6737-42-4	412.5			0.525444 g		1.273804 mmol	0.1		
reagent	Potassium tert-butoxide	865-47-4	112.212			2.858722 g		25.47608 mmol	2		
solvent	1,4-Dioxane	123-91-1	88.11	1.034		10.34 g	10 mL				X
wu solvent	Ethyl acetate	141-78-6	88.11	0.902		18.04 g	20 mL				X
wu solvent	Water		18	1		5 g	5 mL				
wu reagent	sodium hydroxide in water	1310-73-2	40		2 M		5 mL	10 mmol	0.78505		
product	Biphenyl	92-52-4	154.21			1.964333 g		12.73804 mmol	1		

	product	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	yield(%)
Output	Biphenyl	92-52-4	154.21			1.75 g		11.34816 mmol	89.08874

total reaction mass	12.69	g
total reagents / reactants / cat. mass	7.69	g
total workup reagents mass	0.40	g
total solvents (excl. water)		g
total water	5.40	g
total waste	10.94	g
total input cost (per product unit)	12.31	€/g

Metrics	excl. water	incl. water
mass intensity	4.2	7.3
solvent intensity	0.0	3.1
Sheldon E-factor	3.2	6.3
GSK Reaction Mass Efficiency	0.228	
Andraos Reaction Mass Efficiency	0.240	0.138
atom economy	0.394	
1 / stoichiom. factor (excess reagents)	0.724	
material recovery parameter	0.944	0.542
yield	0.891	

Final aspect of an experiment sheet

Name	[CAS]	M.W. (g/mol)	d	wt% or conc.	unit	solvent name	Price (€/unit)	unit	COSHH	Bp	Mp	Fp	...

Header of the “Chemicals” sheet

Create new Experiment:

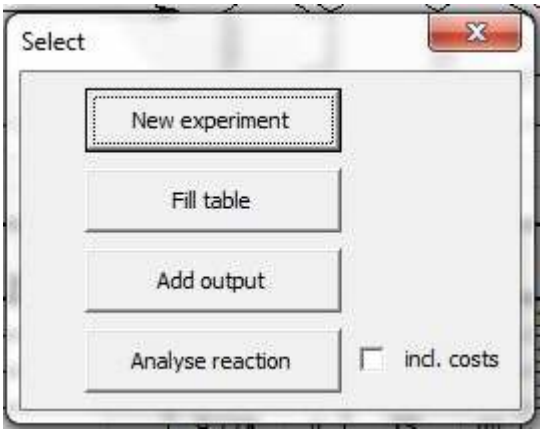
1) Open the "Lab book and Green Metrics" excel file and choose "**enable macro**" (clicking "**option**" in the bar above the worksheet).

2) Each experiment sheet name should have the following format:

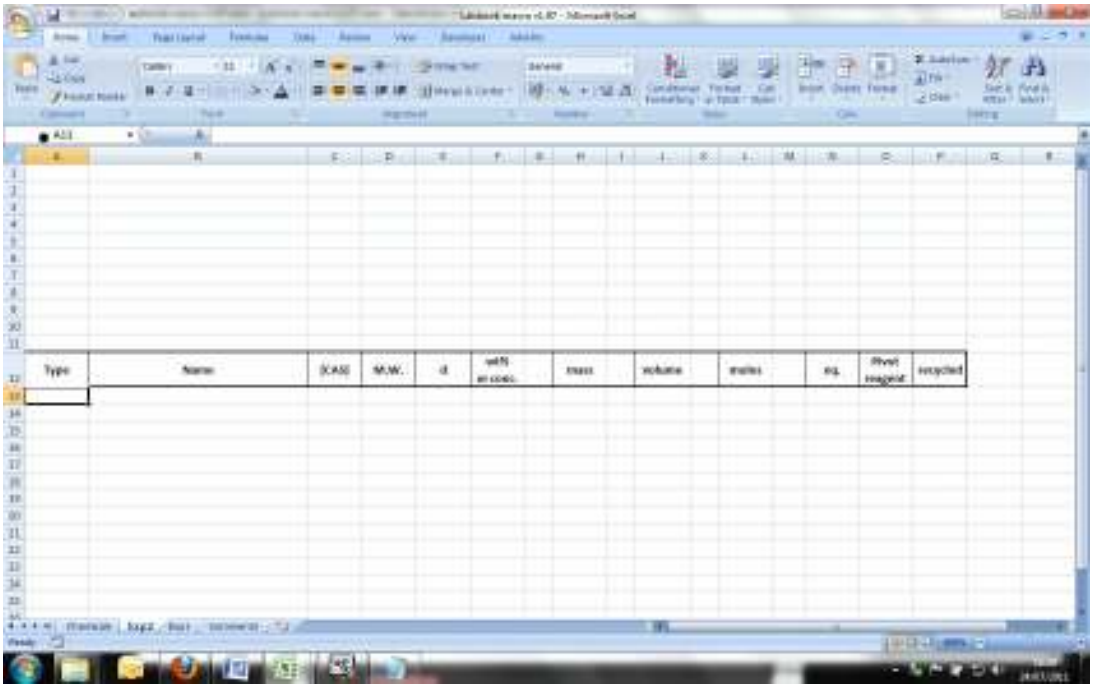
"experimentator's name" followed by the experiment number

e.g. "Exp 01" or "JD 112" or "John Doe25"

Press **Crtl + "M"** to launch the menu window (the macro will work on the current activated spreadsheet)

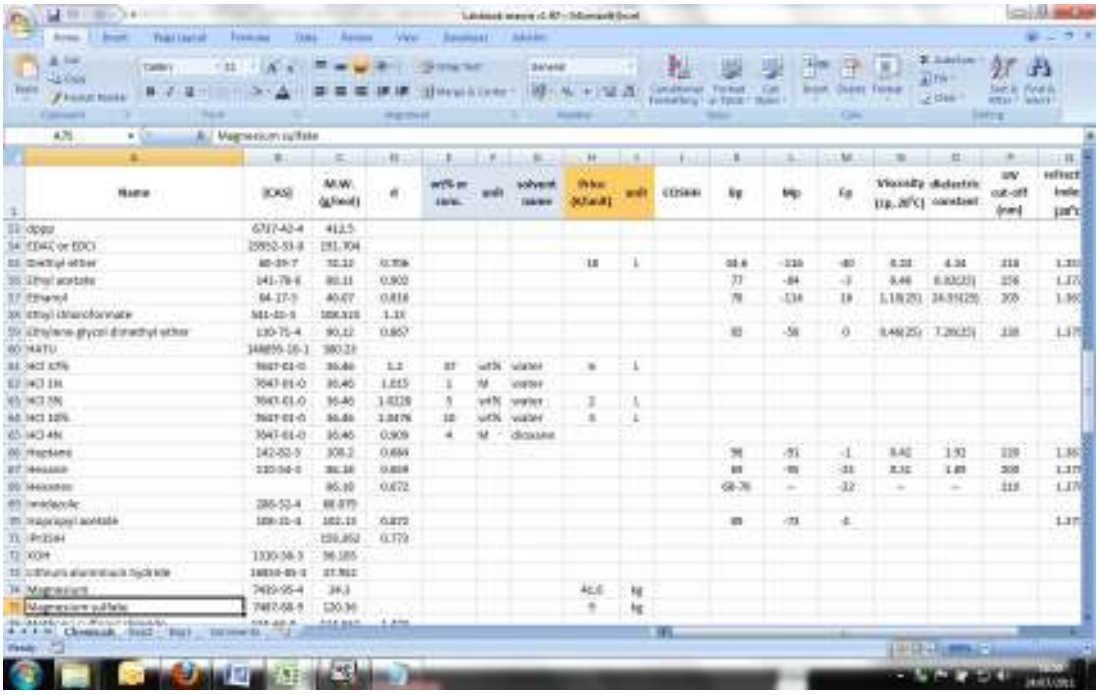


3) Select "New Experiment": a new spreadsheet will be created next to "chemicals" with a name having an incremented experiment number (e.g. "Exp 02" or "JD 113" or "John Doe26"), and the header of the bill of material.



The top of the sheet (row 1 to 11) are left empty to allow space for copying a reaction scheme. **Please remember: the header of the bill of material should always be at the 12th row** (do not insert row above it).

4) In "**Chemicals**", select the reagents, solvents and target product for your reaction. Hold the **Ctrl** key for multiple selection.



The "Chemicals" table can record solutions (e.g. HCl 5wt% in water or HCl 0.5M in MeOH). Please confer to the blue headed columns (enter the concentration value, select the unit –either wt% or M – from the drop-down menu, enter the solvent name).

5) Press **Crtl + "M"** : the selected chemicals will automatically be transferred to the experiment sheet with the highest experiment number.

Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
	1,4-Dioxane	123-91-1	88.11	1.034							
	bromobenzene	108-86-1	157.01	1.491							
	Biphenyl	92-52-4	154.21								
	dppp	6737-42-4	412.5								
	Pd(OAc)2	3375-31-3	224.488								
	Phenylboronic acid	98-80-6	121.93								
	Potassium tert-butoxide	865-47-4	112.212								
	Ethyl acetate	141-78-6	88.11	0.902							
	Water		18	1							

You can modify the order of the materials in the table: to move one material a row up, select this material and press **Crtl + "L"**.

You can also add more chemicals to the table simply by going again through **4)-5)**.

A solution transferred to the table will have the following name:

"chemicals" in "solvent" (e.g. "HCl in water" or "HCl in MeOH").

Fill the table:

1) Back to the new experiment sheet, fill the following information in the table:

- Type of chemicals (from the drop down list): reagent (a molecule for which no part remains in the product of the reaction), reactant (a molecule for which a part remains in the product), catalyst, solvent, wu reagent (work-up reagent), wu solvent (work-up solvent) or product (the product of interest in the reaction).
- For each material: either a charge (mass, volume, number of mole) **or** a number of equivalent (for reagents/reactants/catalysts/wu reagents). Select the corresponding units from the drop-down lists.
- For the **pivot reagent** or reactant (i.e. the material upon which all the other calculations are based), enter a charge **and** the number of equivalent. Enter "**X**" in the corresponding row of the "Pivot reagent" column.
- For the **product**, enter the number of expected equivalent (100% yield) compare to the pivot reagent. (most of the time, it will be equal to 1, but it would be equal to 0.5 for a dimerisation, or to 2 for the ozonolysis of a symmetrical alkene for example).

Type	Name	[CAS]	M.W.	d	wt% or conc.		mass		volume		moles	eq.	Pivot reagent	recycled
reactant	bromobenzene	108-86-1	157.01	1.491			2	g				1	X	
reactant	Phenylboronic acid	98-80-6	121.93									1.3		
catalyst	Pd(OAc)2	3375-31-3	224.488									0.1		
catalyst	dppp	6737-42-4	412.5									0.1		
reagent	Potassium tert-butoxide	865-47-4	112.212									2		
solvent	1,4-Dioxane	123-91-1	88.11	1.034					10	mL				
wu solvent	Ethyl acetate	141-78-6	88.11	0.902					20	mL				
wu solvent	Water		18	1					5	mL				
wu reagent	sodium hydroxide in water	1310-73-2	40		2	M			5	mL				
product	Biphenyl	92-52-4	154.21									1		

Please remember: Values of mass and volume represent what is actually charged, i.e. if the concentration is given, the mass and volume values will be for the solution to be charged, not for the pure material. Same wise, in this case the density value is expected to be for the mixture not the pure product.

2) Press **Crtl + "M"** to launch the menu window, and select "**Fill table**". The rest of the values in the table will be automatically calculated. Their units will be initially selected by default, but the user can choose in advance a specific unit from the drop-down menu prior to the calculations.

Type	Name	[CAS]	M.W.	d	wt% or conc.		mass		volume		moles		eq.	Pivot reagent	recycled
reactant	bromobenzene	108-86-1	157.01	1.491			2	g	1.341382	mL	12.73804	mmol	1	X	
reactant	Phenylboronic acid	98-80-6	121.93				2.019094	g			16.55945	mmol	1.3		
catalyst	Pd(OAc)2	3375-31-3	224.488				0.285954	g			1.273804	mmol	0.1		
catalyst	dppp	6737-42-4	412.5				0.525444	g			1.273804	mmol	0.1		
reagent	Potassium tert-butoxide	865-47-4	112.212				2.858722	g			25.47608	mmol	2		
solvent	1,4-Dioxane	123-91-1	88.11	1.034			10.34	g	10	mL					
wu solvent	Ethyl acetate	141-78-6	88.11	0.902			18.04	g	20	mL					
wu solvent	Water		18	1			5	g	5	mL					
wu reagent	sodium hydroxide in water	1310-73-2	40		2	M			5	mL	10	mmol	0.78505		
product	Biphenyl	92-52-4	154.21				1.964333	g			12.73804	mmol	1		

The charge or equivalent values entered by the user will now be in bold. As the rest of the values are calculated through excel formula system, the user can change his own (bold) data, and the rest of the calculation will change accordingly.

Please remember: Values (in grey) for the product are maximum output (100% yield).

Add Output:

1) Press **Crtl + "M"** to launch the menu window, and select "**Add output**". A new row is created.

Type	Name	[CAS]	M.W.	d	wt% or conc.		mass		volume		moles		eq.	Pivot reagent	recycled
reactant	bromobenzene	108-86-1	157.01	1.491			2	g	1.341382	mL	12.73804	mmol	1	X	
reactant	Phenylboronic acid	98-80-6	121.93				2.019094	g			16.55945	mmol	1.3		
catalyst	Pd(OAc)2	3375-31-3	224.488				0.285954	g			1.273804	mmol	0.1		
catalyst	dppp	6737-42-4	412.5				0.525444	g			1.273804	mmol	0.1		
reagent	Potassium tert-butoxide	865-47-4	112.212				2.858722	g			25.47608	mmol	2		
solvent	1,4-Dioxane	123-91-1	88.11	1.034			10.34	g	10	mL					
wu solvent	Ethyl acetate	141-78-6	88.11	0.902			18.04	g	20	mL					
wu solvent	Water		18	1			5	g	5	mL					
wu reagent	sodium hydroxide in water	1310-73-2	40		2	M			5	mL	10	mmol	0.78505		
product	Biphenyl	92-52-4	154.21				1.964333	g			12.73804	mmol	1		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		yield(%)
Output	Biphenyl	92-52-4	154.21				g				mmol	

2) Enter a discharge value (mass, volume or mole).

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		yield(%)
Output	Biphenyl	92-52-4	154.21			1.75	g				mmol	

It is possible to have the product as a solution (a concentration input is then needed).

Analysis the reaction:

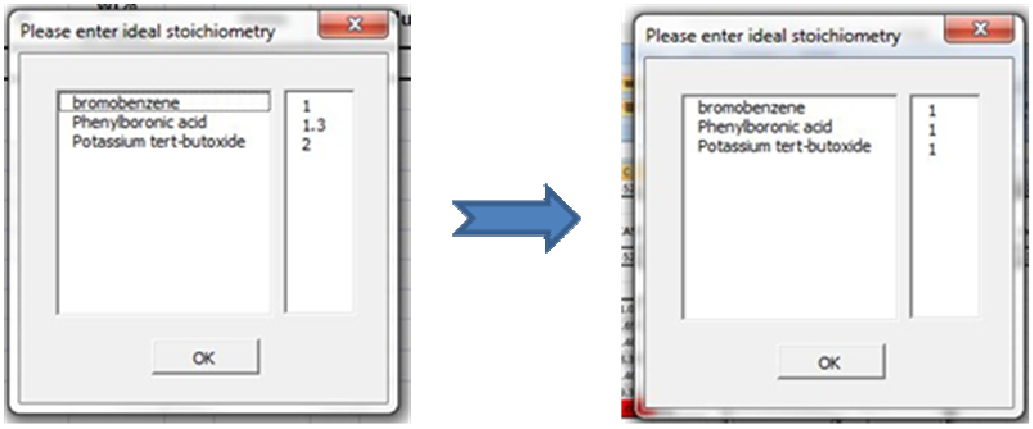
1) If any material is recycled, enter "X" in the corresponding cell of the "recycled" column of the bill of material. This material won't be taken into account for the following calculations (mass, cost, metrics).

	Type	Name	[CAS]	M.W.	d	wt% or conc.		mass		volume		moles		eq.	Pivot reagent	recycled
12																
13	reactant	bromobenzene	108-86-1	157.01	1.491			2	g	1.341382	mL	12.73804	mmol	1	X	
14	reactant	Phenylboronic acid	98-80-6	121.93				2.019094	g			16.55945	mmol	1.3		
15	catalyst	Pd(OAc)2	3375-31-3	224.488				0.285954	g			1.273804	mmol	0.1		
16	catalyst	dppp	6737-42-4	412.5				0.525444	g			1.273804	mmol	0.1		
17	reagent	Potassium tert-butoxide	865-47-4	112.212				2.858722	g			25.47608	mmol	2		
18	solvent	1,4-Dioxane	123-91-1	88.11	1.034			10.34	g	10	mL					X
19	wu solvent	Ethyl acetate	141-78-6	88.11	0.902			18.04	g	20	mL					X
20	wu solvent	Water		18	1			5	g	5	mL					
21	wu reagent	sodium hydroxide in water	1310-73-2	40		2	M			5	mL	10	mmol	0.78505		
22	product	Biphenyl	92-52-4	154.21				1.964333	g			12.73804	mmol	1		

2) Press **Crtl + "M"** to launch the menu window, and select "**Analyse reaction**" from the menu.

The user can include the calculation of raw material cost in the analysis. If the program cannot find a material, its concentration, or its cost in the "Chemical" sheet, a window will list the missing chemicals and the reason why it was excluded of the cost calculation. In that case the cost result cell will be coloured in red.

3) Enter the ideal stoichiometry of the reaction in the new window.



Original stoichiometry (reagents used in excess from the bill of material)

ideal stoichiometry

This data from this window will be used in the calculation of two of the green metrics: the atom economy, and the stoichiometric factor.

4) Two new tables will be added. The first one will extract and aggregate the mass of materials according to different categories.

- total reaction mass
- total reagents / reactants / cat. mass

- total workup reagents mass
- total solvents (excl. water)
- total water
- total waste
- total raw material cost (€/mass unit)

5) The second table will provide the following green metrics:

- **Mass intensity** (both excluding and including water):

$$Mass\ intensity = \frac{total\ mass\ of\ raw\ materials\ (incl.\ workup)}{mass\ of\ product\ recovered}$$

- **Solvent intensity** (both excluding and including water):

$$Solvent\ intensity = \frac{total\ mass\ of\ solvents\ (incl.\ workup)}{mass\ of\ product\ recovered}$$

- **Sheldon Environmental impact factor, E-Factor** (both excluding and including water):

$$E - Factor = \frac{total\ mass\ of\ wastes}{mass\ of\ product\ recovered}$$

$$E - Factor = \frac{total\ mass\ of\ raw\ materials - mass\ of\ product\ recovered}{mass\ of\ product\ recovered}$$

- **GSK Reaction Mass Efficiency**:

$$GSK\ RME = \frac{mass\ of\ product\ recovered}{total\ mass\ of\ reagents/reactants/catalysts}$$

- **Andraos Reaction Mass Efficiency**:

$$Andraos\ RME = \frac{mass\ of\ product\ recovered}{total\ mass\ of\ raw\ materials} = \frac{1}{mass\ intensity}$$

$$Andraos\ RME = \frac{1}{1 + E - factor}$$

$$Andraos\ RME = \frac{yield\ \times Atom\ Economy\ \times material\ recovery\ parameter}{Stoichiometric\ Factor}$$

- **Atom Economy**:

$$AE = \frac{eq_{product} \times MW_{product}}{\sum(eq_i^0 \times MW_i)}$$

where eq_i^0 is the ideal stoichiometry of reagent i for the reaction, and MW_i is the molecular weight of reagent i.

- **Stoichiometric Factor**:

$$SF = \frac{\sum mass_{total\ reagents}}{\sum mass_{stoichiometric\ reagents}} = 1 + \frac{\sum mass_{excess\ reagents}}{\sum mass_{stoichiometric\ reagents}}$$

and calculated as:

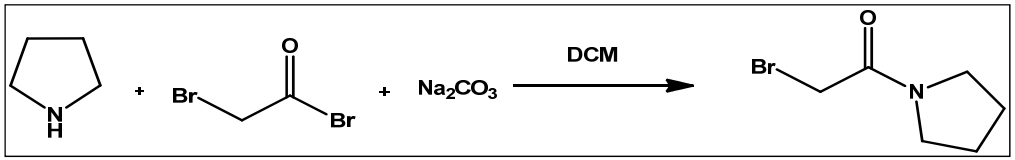
$$SF = \frac{\sum(eq_i \times MW_i)}{\sum(eq_i^0 \times MW_i)}$$

where eq_i is the stoichiometry of reagent i in the current reaction.

- **Material recovery parameter**:

$$material\ recovery\ parameter = \frac{Andraos\ RME\ \times Stoichiometric\ Factor}{yield\ \times Atom\ Economy}$$

- **Yield**.

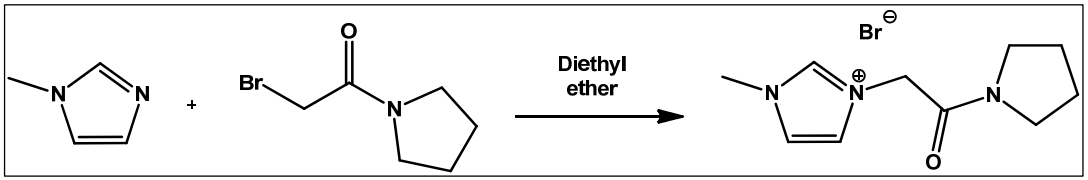


Type	Name	[CAS]	M.W.	d	wt% or conc.		mass		volume		moles		eq.	Pivot reagent	recycled
reactant	bromoacetyl bromide	598-21-0	201.84	2.317			**28.46**	g	12.28312	mL	141.0028	mmol	1.0028117		
reactant	pyrrolidine	123-75-1	71.12	0.852			**10**	g	11.73709	mL	140.6074	mmol	**1**	X	
reagent	sodium carbonate	497-19-8	105.99				**14.94**	g			140.9567	mmol	1.002484		
solvent	Dichloromethane	75-09-2	84.93	1.325			159	g	**120**	mL					
wu solvent	Water		18	1			100	g	**100**	mL					
product	N-(Bromoacetyl)pyrrolidine	90892-09-4	192.05				27.00366	g			140.6074	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	N-(Bromoacetyl)pyrrolidine	90892-09-4	192.05			**10.51**	g		54.72533	mmol	38.920656

total reaction mass	312.40	g
total reagents / reactants / cat. mass	53.40	g
total workup reagents mass		g
total solvents (excl. water)	159.00	g
total water	100.00	g
total waste	301.89	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	20.2	29.7
solvent intensity	15.1	24.6
Sheldon E-factor	19.2	28.7
GSK Reaction Mass Efficiency	0.197	
Andraos Reaction Mass Efficiency	0.049	0.034
atom economy	0.506	
1 / stoichiom. factor (excess reagents)	1.000	
material recovery parameter	0.251	0.171
yield	0.389	

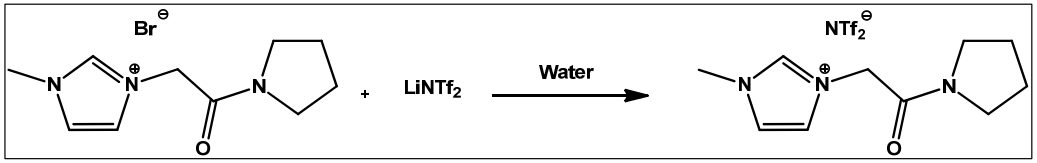


Type	Name	[CAS]	M.W.	d	wt% or conc.		mass		volume		moles		eq.	Pivot reagent	recycled
reactant	N-Methylimidazole	616-47-7	82.105	1.04			**6.4**	g	6.153846	mL	77.94897	mmol	0.998007		
reactant	N-(Bromoacetyl)pyrrolidine	90892-09-4	192.05				**15**	g			78.10466	mmol	**1**	X	
solvent	Diethyl ether	60-29-7	74.12	0.706			282.4	g	**400**	mL					
wu solvent	Diethyl ether	60-29-7	74.12	0.706			353	g	**500**	mL					
product	1H-Imidazolium, 1-methyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-, bromide	1188502-49-9	274.157				21.41294	g			78.10466	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	1H-Imidazolium, 1-methyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-, bromide	1188502-49-9	274.157			**17.32**	g		63.17548	mmol	80.88567

total reaction mass	656.80	g
total reagents / reactants / cat. mass	21.40	g
total workup reagents mass		g
total solvents (excl. water)	635.40	g
total water		g
total waste	639.48	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	37.9	37.9
solvent intensity	36.7	36.7
Sheldon E-factor	36.9	36.9
GSK Reaction Mass Efficiency	0.809	
Andraos Reaction Mass Efficiency	0.026	0.026
atom economy	1.000	
1 / stoichiom. factor (excess reagents)	1.001	
material recovery parameter	0.033	0.033
yield	0.809	

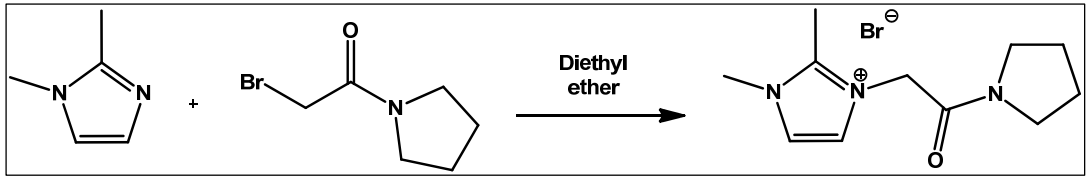


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
reactant	1H-Imidazolium, 1-methyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-, bromide	1188502-49-9	274.157			**11**	g			40.123	mmol	**1**	X	
reactant	Lithium bis(trifluoromethanesulfonimide)	90076-65-6	287.09			11.51891	g			40.123	mmol	**1**		
solvent	Water		18					**40**	mL					
wu solvent	Water		18	1		120	g	**120**	mL					
product	1*H* -Imidazolium, 1-methyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-, bis(trifluoromethanesulfonimide)	1239486-27-1	474.399			19.03431	g			40.123	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	ım, 1-methyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-, bis(trifluoromethane	1239486-27-1	474.399			**13.15**	g		27.71928	mmol	69.08578

total reaction mass	142.52	g
total reagents / reactants / cat. mass	22.52	g
total workup reagents mass		g
total solvents (excl. water)		g
total water	120.00	g
total waste	129.37	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	1.7	10.8
solvent intensity	0.0	9.1
Sheldon E-factor	0.7	9.8
GSK Reaction Mass Efficiency	0.584	
Andraos Reaction Mass Efficiency	0.584	0.092
atom economy	0.845	
1 / stoichiom. factor (excess reagents)	1.000	
material recovery parameter	1.000	0.158
yield	0.691	

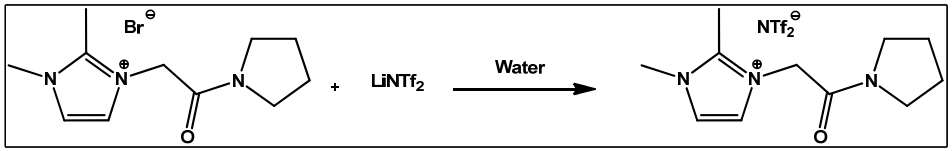


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
reactant	1,2-Dimethylimidazole	1739-84-0	96.13			**3.84**	g			39.94591	mmol	**1**	X	
reactant	N-(Bromoacetyl)pyrrolidine	90892-09-4	192.05			**8.06**	g			41.96824	mmol	1.050627		
solvent	Diethyl ether	60-29-7	74.12	0.706		70.6	g	**100**	mL					
wu solvent	Diethyl ether	60-29-7	74.12	0.706		141.2	g	**200**	mL					
product	1*H* -Imidazolium, 1,2-dimethyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-, bromide	1188502-55-7	288.184			11.51177	g			39.94591	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	1H-Imidazolium, 1,2-dimethyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-, bromide	1188502-55-7	288.184			**9.41**	g		32.65275	mmol	81.74242

total reaction mass	223.70	g
total reagents / reactants / cat. mass	11.90	g
total workup reagents mass		g
total solvents (excl. water)	211.80	g
total water		g
total waste	214.29	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	23.8	23.8
solvent intensity	22.5	22.5
Sheldon E-factor	22.8	22.8
GSK Reaction Mass Efficiency	0.791	
Andraos Reaction Mass Efficiency	0.042	0.042
atom economy	1.000	
1 / stoichiom. factor (excess reagents)	0.967	
material recovery parameter	0.053	0.053
yield	0.817	

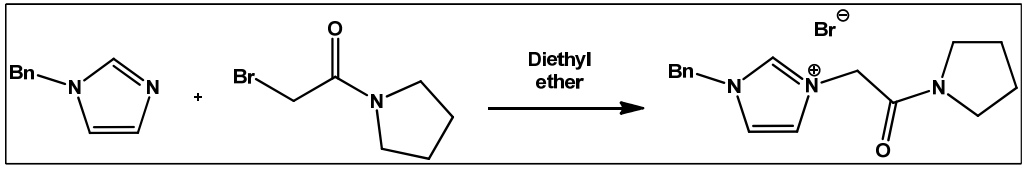


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
reactant	1H-Imidazolium, 1,2-dimethyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-, bromide	1188502-55-7	288.184			**11**	g			38.17006	mmol	**1**	X	
reactant	Lithium bis(trifluoromethanesulfonimide)	90076-65-6	287.09			10.95824	g			38.17006	mmol	**1**		
solvent	Water		18	1		40	g	**40**	mL					
wu solvent	Water		18	1		150	g	**150**	mL					
product	1H-Imidazolium, 1,2-dimethyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-, bis(trifluoromethanesulfonimide)	1239486-32-8	488.426			18.64325	g			38.17006	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	1H-Imidazolium, 1,2-dimethyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-, bis(trifluoromethanesulfonimide)	1239486-32-8	488.426			**14.13**	g		28.92966	mmol	75.79151

total reaction mass	211.96	g
total reagents / reactants / cat. mass	21.96	g
total workup reagents mass		g
total solvents (excl. water)		g
total water	190.00	g
total waste	197.83	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	1.6	15.0
solvent intensity	0.0	13.4
Sheldon E-factor	0.6	14.0
GSK Reaction Mass Efficiency	0.643	
Andraos Reaction Mass Efficiency	0.643	0.067
atom economy	0.849	
1 / stoichiom. factor (excess reagents)	1.000	
material recovery parameter	1.000	0.104
yield	0.758	

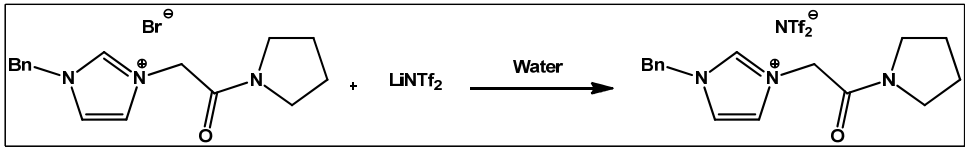


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
reactant	1-Benzylimidazole	4238-71-5	158.2			**2**	g			12.64223	mmol	**1**	X	
reactant	N-(Bromoacetyl)pyrrolidine	90892-09-4	192.05			2.427939	g			12.64223	mmol	**1**		
solvent	Diethyl ether	60-29-7	74.12	0.706		70.6	g	**100**	mL					
wu solvent	Diethyl ether	60-29-7	74.12	0.706		176.5	g	**250**	mL					
product	1*H* -Imidazolium, 3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-1-(phenylmethyl)-, bromide	1239486-29-3	350.25			4.427939	g			12.64223	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	1*H* -Imidazolium, 3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-1-(phenylmethyl)-, bromide	1239486-29-3	350.25			**2.78**	g		7.937188	mmol	62.78315

total reaction mass	251.53	g
total reagents / reactants / cat. mass	4.43	g
total workup reagents mass		g
total solvents (excl. water)	247.10	g
total water		g
total waste	248.75	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	90.5	90.5
solvent intensity	88.9	88.9
Sheldon E-factor	89.5	89.5
GSK Reaction Mass Efficiency	0.628	
Andraos Reaction Mass Efficiency	0.011	0.011
atom economy	1.000	
1 / stoichiom. factor (excess reagents)	1.000	
material recovery parameter	0.018	0.018
yield	0.628	

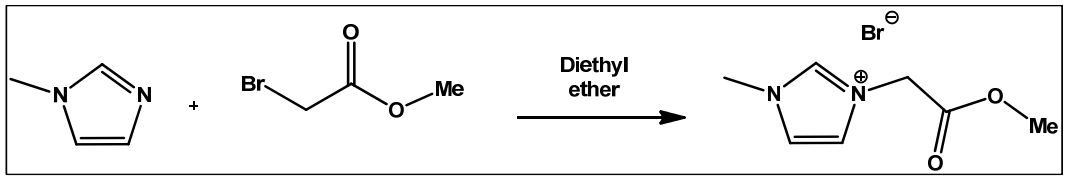


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
reactant	1H-Imidazolium, 3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-1-(phenylmethyl)-, bromide	1239486-29-3	350.25			**200** mg		0.571021 mmol	**1**	X	
reactant	Lithium bis(trifluoromethanesulfonimide)	90076-65-6	287.09			163.9343 mg		0.571021 mmol	**1**		
solvent	Water		18	1		4000 mg	**4** mL				
wu solvent	Water		18	1		12000 mg	**12** mL				
product	1H-Imidazolium, 3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-1-(phenylmethyl)-, bis(trifluoromethanesulfonimide)	1239486-31-7	550.078			314.1059 mg		0.571021 mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	yield(%)
Output	1H-Imidazolium, 3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-1-(phenylmethyl)-, bis(trifluoromethanesulfonimide)	1239486-31-7	550.078			**271** mg		0.492657 mmol	86.27663

total reaction mass	16363.93	mg
total reagents / reactants / cat. mass	363.93	mg
total workup reagents mass		mg
total solvents (excl. water)		mg
total water	16000.00	mg
total waste	16092.93	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	1.3	60.4
solvent intensity	0.0	59.0
Sheldon E-factor	0.3	59.4
GSK Reaction Mass Efficiency	0.745	
Andraos Reaction Mass Efficiency	0.745	0.017
atom economy	0.863	
1 / stoichiom. factor (excess reagents)	1.000	
material recovery parameter	1.000	0.022
yield	0.863	

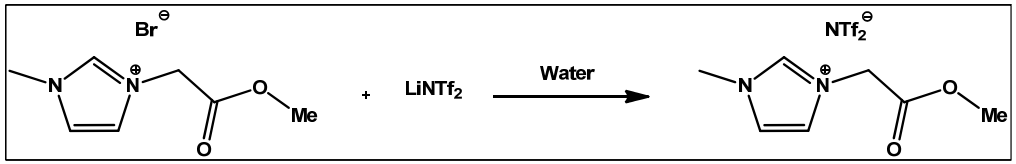


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
reactant	N-Methylimidazole	616-47-7	82.105	1.04		5.152697	g	4.954516	mL	62.7574	mmol	**1.2**		
reactant	Methyl bromoacetate	96-32-2	152.97	1.616		**8**	g	4.950495	mL	52.29784	mmol	**1**	X	
solvent	Diethyl ether	60-29-7	74.12	0.706		35.3	g	**50**	mL					
wu solvent	Diethyl ether	60-29-7	74.12	0.706		141.2	g	**200**	mL					
product	1H-Imidazolium, 3-(2-methoxy-2-oxoethyl)-1-methyl-, bromide	109833-17-2	235.078			12.29407	g			52.29784	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	1H-Imidazolium, 3-(2-methoxy-2-oxoethyl)-1-methyl-, bromide	109833-17-2	235.078			**11.8**	g		50.19611	mmol	95.98123

total reaction mass	189.65	g
total reagents / reactants / cat. mass	13.15	g
total workup reagents mass		**g**
total solvents (excl. water)	176.50	g
total water		g
total waste	177.85	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	16.1	16.1
solvent intensity	15.0	15.0
Sheldon E-factor	15.1	15.1
GSK Reaction Mass Efficiency	0.897	
Andraos Reaction Mass Efficiency	0.062	0.062
atom economy	1.000	
1 / stoichiom. factor (excess reagents)	0.935	
material recovery parameter	0.069	0.069
yield	0.960	



Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
reactant	1H-Imidazolium, 3-(2-methoxy-2-oxoethyl)-1-methyl-, bromide	109833-17-2	235.078			**500** mg		2.126954 mmol	**1**	X	
reactant	Lithium bis(trifluoromethanesulfonimide)	90076-65-6	287.09			732.7525 mg		2.552344 mmol	**1.2**		
solvent	Water		18	1		4000 mg	**4** mL				
wu solvent	Water		18	1		9000 mg	**9** mL				
product	1H-Imidazolium, 3-(2-methoxy-2-oxoethyl)-1-methyl-, bis(trifluoromethanesulfonimide)	503439-61-0	435.32			925.9054 mg		2.126954 mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	yield(%)
Output	1H-Imidazolium, 3-(2-methoxy-2-oxoethyl)-1-methyl-, bis(trifluoromethanesulfonimide)	503439-61-0	435.32			**650** mg		1.493154 mmol	70.20155

total reaction mass	14232.75	mg
total reagents / reactants / cat. mass	1232.75	mg
total workup reagents mass		mg
total solvents (excl. water)		mg
total water	13000.00	mg
total waste	13582.75	mg
total raw material cost		

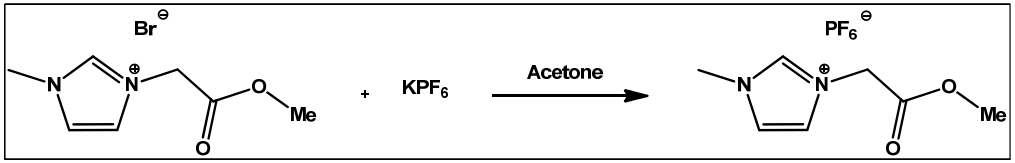
Metrics	excl. water	incl. water
mass intensity	1.9	21.9
solvent intensity	0.0	20.0
Sheldon E-factor	0.9	20.9
GSK Reaction Mass Efficiency	0.527	
Andraos Reaction Mass Efficiency	0.527	0.046
atom economy	0.834	
1 / stoichiom. factor (excess reagents)	0.901	
material recovery parameter	1.000	0.087
yield	0.702	

Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
reactant	1*H* -Imidazolium, 3-(2-methoxy-2-oxoethyl)-1-methyl-, bromide	109833-17-2	235.078			**500** mg		2.126954 mmol	**1**	X	
reactant	Sodium tetrafluoroborate	13755-29-8	109.79			233.5182 mg		2.126954 mmol	**1**		
solvent	Acetone	67-64-1	58.08	0.791		3164 mg	**4** mL				
wu solvent	Acetone	67-64-1	58.08	0.791		6328 mg	**8** mL				
product	1*H* -Imidazolium, 3-(2-methoxy-2-oxoethyl)-1-methyl-, tetrafluoroborate	503439-28-9	241.979			514.6781 mg		2.126954 mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	yield(%)
Output	1*H* -Imidazolium, 3-(2-methoxy-2-oxoethyl)-1-methyl-, tetrafluoroborate	503439-28-9	241.979			**492** mg		2.033234 mmol	95.59373

total reaction mass	10225.52	mg
total reagents / reactants / cat. mass	733.52	mg
total workup reagents mass		mg
total solvents (excl. water)	9492.00	mg
total water		mg
total waste	9733.52	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	20.8	20.8
solvent intensity	19.3	19.3
Sheldon E-factor	19.8	19.8
GSK Reaction Mass Efficiency	0.671	
Andraos Reaction Mass Efficiency	0.048	0.048
atom economy	0.702	
1 / stoichiom. factor (excess reagents)	1.000	
material recovery parameter	0.072	0.072
yield	0.956	

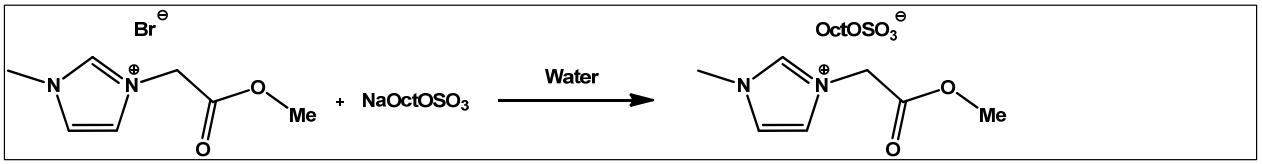


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
reactant	1H-Imidazolium, 3-(2-methoxy-2-oxoethyl)-1-methyl-, bromide	109833-17-2	235.078			**500**	mg			2.126954	mmol	**1**	X	
reactant	Potassium hexafluorophosphate	17084-13-8	184.06			**600**	mg			3.259807	mmol	1.532618		
solvent	Acetone	67-64-1	58.08	0.791		3164	mg	**4**	mL					
wu solvent	Acetone	67-64-1	58.08	0.791		6328	mg	**8**	mL					
product	1H-Imidazolium, 3-(2-methoxy-2-oxoethyl)-1-methyl-, hexafluorophosphate	503439-48-3	300.14			638.3839	mg			2.126954	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	1H-Imidazolium, 3-(2-methoxy-2-oxoethyl)-1-methyl-, hexafluorophosphate	503439-48-3	300.14			**605**	mg		2.015726	mmol	94.77057

total reaction mass	10592.00	mg
total reagents / reactants / cat. mass	1100.00	mg
total workup reagents mass		mg
total solvents (excl. water)	9492.00	mg
total water		mg
total waste	9987.00	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	17.5	17.5
solvent intensity	15.7	15.7
Sheldon E-factor	16.5	16.5
GSK Reaction Mass Efficiency	0.550	
Andraos Reaction Mass Efficiency	0.057	0.057
atom economy	0.716	
1 / stoichiom. factor (excess reagents)	0.810	
material recovery parameter	0.104	0.104
yield	0.948	

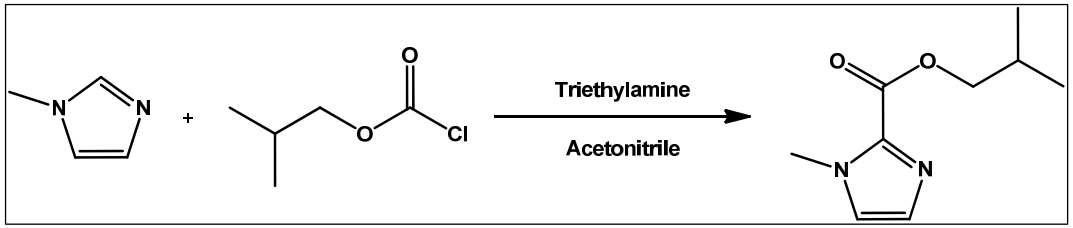


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
reactant	1H-Imidazolium, 3-(2-methoxy-2-oxoethyl)-1-methyl-, bromide	109833-17-2	235.078			**2**	g			8.507814	mmol	**1**	X	
reactant	Sodium octyl sulfate	142-31-4	232.27			1.97611	g			8.507814	mmol	**1**		
solvent	Water		18	1		15	g	**15**	mL					
wu solvent	Dichloromethane	75-09-2	84.93	1.325		19.875	g	**15**	mL					
product	1H-Imidazolium, 3-(2-methoxy-2-oxoethyl)-1-methyl-, octyl sulfate	1239486-26-0	364.46			3.100758	g			8.507814	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	1H-Imidazolium, 3-(2-methoxy-2-oxoethyl)-1-methyl-, octyl sulfate	1239486-26-0	364.46			**1.91**	g		5.24063	mmol	61.59784

total reaction mass	38.85	g
total reagents / reactants / cat. mass	3.98	g
total workup reagents mass		g
total solvents (excl. water)	19.88	g
total water	15.00	g
total waste	36.94	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	12.5	20.3
solvent intensity	10.4	18.3
Sheldon E-factor	11.5	19.3
GSK Reaction Mass Efficiency	0.480	
Andraos Reaction Mass Efficiency	0.080	0.049
atom economy	0.780	
1 / stoichiom. factor (excess reagents)	1.000	
material recovery parameter	0.167	0.102
yield	0.616	

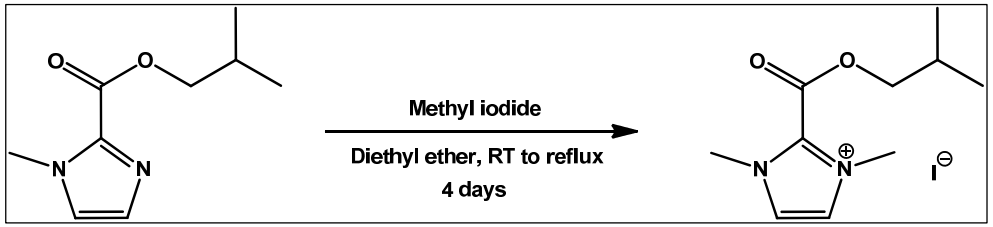


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
reactant	1-Methylimidazole	616-47-7	82.105	1.04		**3.3**	g	3.173077	mL	40.19244	mmol	**1**	X	
reactant	Isobutyl chloroformate	543-27-1	136.58	1.053		10.15554	g	9.644391	mL	74.35601	mmol	**1.85**		
reagent	Triethylamine	121-44-8	101.2	0.726		7.240105	g	9.972596	mL	71.54254	mmol	**1.78**		
solvent	Acetonitrile	75-05-8	41.05	0.786		23.58	g	**30**	mL					
wu solvent	Water		18	1		30	g	**30**	mL					
product	Isobutyl 1-methylimidazole-2-carboxylate	154475-19-1	182.22	1.1		7.323866	g	6.65806	mL	40.19244	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		yield(%)
Output	Isobutyl 1-methylimidazole-2-carboxylate	154475-19-1	182.22	1.1		**3.99**	g	3.627273	mL	21.89661	mmol	54.47943

total reaction mass	74.28	g
total reagents / reactants / cat. mass	20.70	g
total workup reagents mass		g
total solvents (excl. water)	23.58	g
total water	30.00	g
total waste	70.29	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	11.1	18.6
solvent intensity	5.9	13.4
Sheldon E-factor	10.1	17.6
GSK Reaction Mass Efficiency	0.193	
Andraos Reaction Mass Efficiency	0.090	0.054
atom economy	0.570	
1 / stoichiom. factor (excess reagents)	0.621	
material recovery parameter	0.467	0.279
yield	0.545	

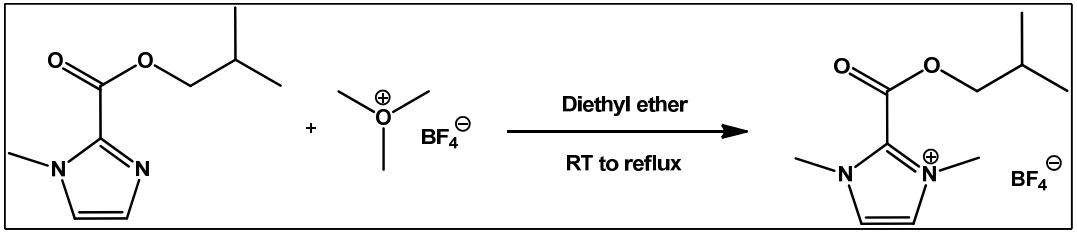


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
reactant	Isobutyl 1-methylimidazole-2-carboxylate	154475-19-1	182.22	1.1		**2**	g	1.818182	mL	10.97574	mmol	**1**	X	
reactant	Iodomethane	74-88-4	141.94	2.28		**6.24**	g	2.736842	mL	43.96224	mmol	4.005399		
solvent	Diethyl ether	60-29-7	74.12	0.706		70.6	g	**100**	mL					
wu solvent	Diethyl ether	60-29-7	74.12	0.706		70.6	g	**100**	mL					
product	1H-Imidazolium, 1,3-dimethyl-2-[(2-methylpropoxy)carbonyl]-, Iodide		324.16			3.557897	g			10.97574	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		yield(%)
Output	idazolium, 1,3-dimethyl-2-[(2-methylpropoxy)carbonyl]-, Iodide		324.16			**2.21**	g			6.817621	mmol	62.11534

total reaction mass	149.44	g
total reagents / reactants / cat. mass	8.24	g
total workup reagents mass		g
total solvents (excl. water)	141.20	g
total water		g
total waste	147.23	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	67.6	67.6
solvent intensity	63.9	63.9
Sheldon E-factor	66.6	66.6
GSK Reaction Mass Efficiency	0.268	
Andraos Reaction Mass Efficiency	0.015	0.015
atom economy	1.000	
1 / stoichiom. factor (excess reagents)	0.432	
material recovery parameter	0.055	0.055
yield	0.621	

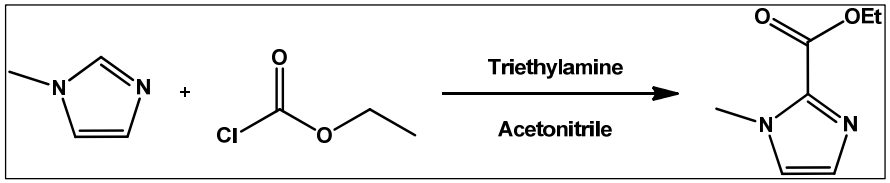


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
reactant	Isobutyl 1-methylimidazole-2-carboxylate	154475-19-1	182.22	1.1		**200**	mg	0.181818	mL	1.097574	mmol	**1**	X	
reactant	Trimethyloxonium tetrafluoroborate	420-37-1	147.91			**162**	mg			1.095261	mmol	0.997892		
solvent	Diethyl ether	60-29-7	74.12	0.706		7060	mg	**10**	mL					
wu solvent	Diethyl ether	60-29-7	74.12	0.706		14120	mg	**20**	mL					
product	1H-Imidazolium, 1,3-dimethyl-2-[(2-methylpropoxy)carbonyl]-, tetrafluoroborate		284.06			311.777	mg			1.097574	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	1H-Imidazolium, 1,3-dimethyl-2-[(2-methylpropoxy)carbonyl]-, tetrafluoroborate		284.06			**302**	mg		1.063156	mmol	96.86411

total reaction mass	21542.00	mg
total reagents / reactants / cat. mass	362.00	mg
total workup reagents mass		**mg**
total solvents (excl. water)	21180.00	mg
total water		mg
total waste	21240.00	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	71.3	71.3
solvent intensity	70.1	70.1
Sheldon E-factor	70.3	70.3
GSK Reaction Mass Efficiency	0.834	
Andraos Reaction Mass Efficiency	0.014	0.014
atom economy	0.860	
1 / stoichiom. factor (excess reagents)	1.001	
material recovery parameter	0.017	0.017
yield	0.969	

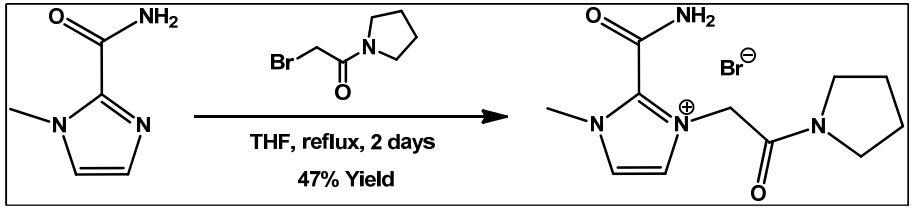


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
reactant	1-Methylimidazole	616-47-7	82.105	1.04		**10**	g	9.615385	mL	121.7953	mmol	**1**	X	
reactant	Ethyl chloroformate	541-41-3	108.523	1.13		24.45254	g	21.63941	mL	225.3212	mmol	**1.85**		
reagent	Triethylamine	121-44-8	101.2	0.726		21.93971	g	30.21999	mL	216.7956	mmol	**1.78**		
solvent	Acetonitrile	75-05-8	41.05	0.786		78.6	g	**100**	mL					
wu solvent	Water		18	1		100	g	**100**	mL					
wu solvent	Chloroform	67-66-3	119.38	1.492		149.2	g	**100**	mL					
product	1*H* -Imidazole-2-carboxylic acid, 1-methyl-, ethyl ester	30148-21-1	154.17	1.14		18.77718	g	16.47121	mL	121.7953	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		yield(%)
Output	1H-Imidazole-2-carboxylic acid, 1-methyl-, ethyl ester	30148-21-1	154.17	1.14		**9.82**	g	8.614035	mL	63.69592	mmol	52.29754

total reaction mass	384.19	g
total reagents / reactants / cat. mass	56.39	g
total workup reagents mass		g
total solvents (excl. water)	227.80	g
total water	100.00	g
total waste	374.37	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	28.9	39.1
solvent intensity	23.2	33.4
Sheldon E-factor	27.9	38.1
GSK Reaction Mass Efficiency	0.174	
Andraos Reaction Mass Efficiency	0.035	0.026
atom economy	0.528	
1 / stoichiom. factor (excess reagents)	0.630	
material recovery parameter	0.198	0.147
yield	0.523	

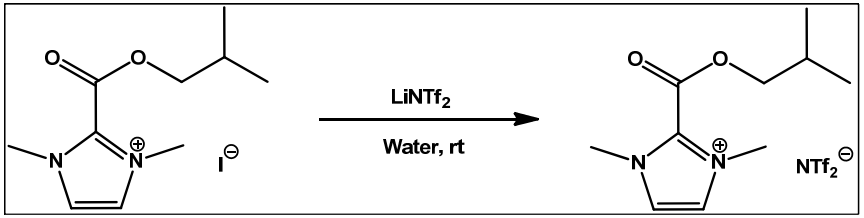


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
reactant	1H-Imidazole-2-carboxamide, 1-methyl-	20062-51-5	125.13			**2**	g			15.98338	mmol	**1**	X	
reactant	N-(Bromoacetyl)pyrrolidine	90892-09-4	192.05			**3.07**	g			15.98542	mmol	1.000128		
solvent	Tetrahydrofuran	109-99-9	72.11	0.889		88.9	g	**100**	mL					
wu solvent	Tetrahydrofuran	109-99-9	72.11	0.889		222.25	g	**250**	mL					
product	1H-Imidazolium-2-carboxamide, 1-methyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-, Bromide		317.18			5.069608	g			15.98338	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	1H-Imidazolium-2-carboxamide, 1-methyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-, Bromide		317.18			**2.35**	g		7.409042	mmol	46.35467

total reaction mass	316.22	g
total reagents / reactants / cat. mass	5.07	g
total workup reagents mass		**g**
total solvents (excl. water)	311.15	g
total water		g
total waste	313.87	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	134.6	134.6
solvent intensity	132.4	132.4
Sheldon E-factor	133.6	133.6
GSK Reaction Mass Efficiency	0.464	
Andraos Reaction Mass Efficiency	0.007	0.007
atom economy	1.000	
1 / stoichiom. factor (excess reagents)	1.000	
material recovery parameter	0.016	0.016
yield	0.464	

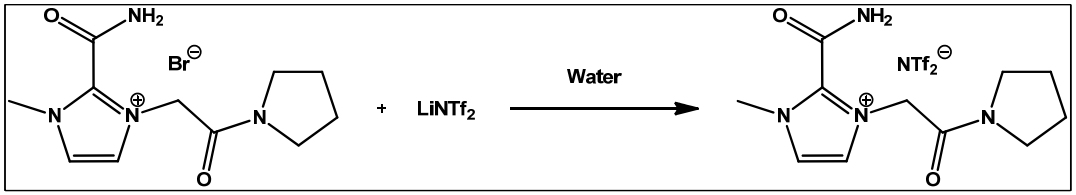


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
reactant	1H-Imidazolium, 1,3-dimethyl-2-[(2-methylpropoxy)carbonyl]-, Iodide		324.16			**500** mg		1.542448 mmol	**1**	X	
reactant	Lithium bis(trifluoromethanesulfonimide)	90076-65-6	287.09			**443** mg		1.54307 mmol	1.000403		
solvent	Water		18	1		4000 mg	**4** mL				
wu solvent	Water		18	1		12000 mg	**12** mL				
product	1H-Imidazolium, 1,3-dimethyl-2-[(2-methylpropoxy)carbonyl]-, bis(trifluoromethanesulfonimide)		477.4			736.3648 mg		1.542448 mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	yield(%)
Output	1H-Imidazolium, 1,3-dimethyl-2-[(2-methylpropoxy)carbonyl]-, bis(trifluoromethanesulfonimide)		477.4			**630** mg		1.319648 mmol	85.55543

total reaction mass	16943.00	mg
total reagents / reactants / cat. mass	943.00	mg
total workup reagents mass		mg
total solvents (excl. water)		mg
total water	16000.00	mg
total waste	16313.00	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	1.5	26.9
solvent intensity	0.0	25.4
Sheldon E-factor	0.5	25.9
GSK Reaction Mass Efficiency	0.668	
Andraos Reaction Mass Efficiency	0.668	0.037
atom economy	0.781	
1 / stoichiom. factor (excess reagents)	1.000	
material recovery parameter	1.000	0.056
yield	0.856	

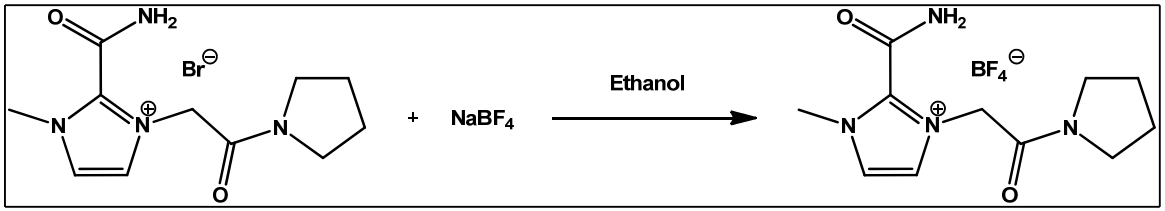


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
reactant	1H-Imidazolium-2-carboxamide, 1-methyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-, Bromide		317.18			**1**	g			3.152784	mmol	**1**	X	
reactant	Lithium bis(trifluoromethanesulfonimide)	90076-65-6	287.09			0.905133	g			3.152784	mmol	**1**		
solvent	Water		18	1		10	g	**10**	mL					
wu solvent	Water		18	1		30	g	**30**	mL					
product	1H-Imidazolium-2-carboxamide, 1-methyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-, bis(trifluoromethanesulfonimide)		517.42			1.631313	g			3.152784	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		yield(%)
Output	1H-Imidazolium-2-carboxamide, 1-methyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-, bis(trifluoromethanesulfonimide)		517.42			**1.205**	g			2.328862	mmol	73.86686

total reaction mass	41.91	g
total reagents / reactants / cat. mass	1.91	g
total workup reagents mass		g
total solvents (excl. water)		g
total water	40.00	g
total waste	40.70	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	1.6	34.8
solvent intensity	0.0	33.2
Sheldon E-factor	0.6	33.8
GSK Reaction Mass Efficiency	0.633	
Andraos Reaction Mass Efficiency	0.633	0.029
atom economy	0.856	
1 / stoichiom. factor (excess reagents)	1.000	
material recovery parameter	1.000	0.045
yield	0.739	

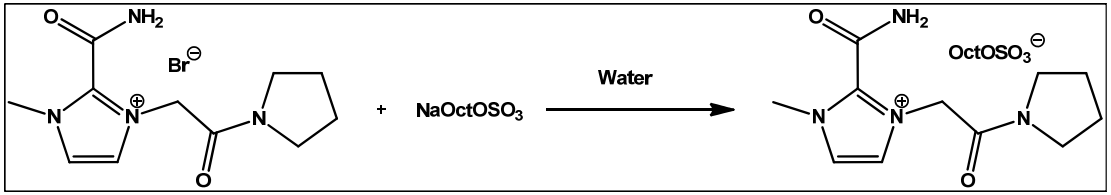


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
reactant	1H-Imidazolium-2-carboxamide, 1-methyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-, Bromide		317.18			**1.2** g		3.783341 mmol	**1**	X	
reactant	Sodium tetrafluoroborate	13755-29-8	109.79			0.415373 g		3.783341 mmol	**1**		
solvent	Ethanol	64-17-5	46.07	0.816		48.96 g	**60** mL				
product	1H-Imidazolium-2-carboxamide, 1-methyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-, tetrafluoroborate		324.08			1.226105 g		3.783341 mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	yield(%)
Output	1H-Imidazolium-2-carboxamide, 1-methyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-, tetrafluoroborate		324.08			**0.764** g		2.357443 mmol	62.31114

total reaction mass	50.58	g
total reagents / reactants / cat. mass	1.62	g
total workup reagents mass		g
total solvents (excl. water)	48.96	g
total water		g
total waste	49.81	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	66.2	66.2
solvent intensity	64.1	64.1
Sheldon E-factor	65.2	65.2
GSK Reaction Mass Efficiency	0.473	
Andraos Reaction Mass Efficiency	0.015	0.015
atom economy	0.759	
1 / stoichiom. factor (excess reagents)	1.000	
material recovery parameter	0.032	0.032
yield	0.623	

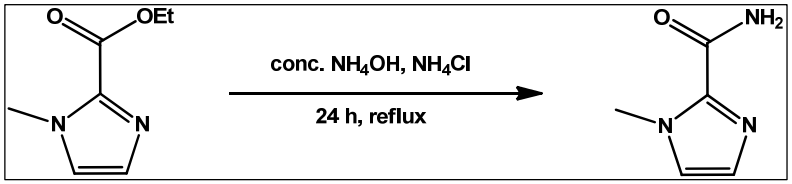


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
reactant	1H-Imidazolium-2-carboxamide, 1-methyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-, Bromide		317.18			**1**	g			3.152784	mmol	**1**	X	
reactant	Sodium octyl sulfate	142-31-4	232.27			**0.731**	g			3.147199	mmol	0.998229		
solvent	Water		18	1		20	g	**20**	mL					
wu solvent	Dichloromethane	75-09-2	84.93	1.325		26.5	g	**20**	mL					
product	1H-Imidazolium-2-carboxamide, 1-methyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-, octylsulfate		446.56			1.407907	g			3.152784	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	1H-Imidazolium-2-carboxamide, 1-methyl-3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-, octylsulfate		446.56			**0.649**	g		1.453332	mmol	46.09679

total reaction mass	48.23	g
total reagents / reactants / cat. mass	1.73	g
total workup reagents mass		g
total solvents (excl. water)	26.50	g
total water	20.00	g
total waste	47.58	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	43.5	74.3
solvent intensity	40.8	71.6
Sheldon E-factor	42.5	73.3
GSK Reaction Mass Efficiency	0.375	
Andraos Reaction Mass Efficiency	0.023	0.013
atom economy	0.813	
1 / stoichiom. factor (excess reagents)	1.001	
material recovery parameter	0.061	0.036
yield	0.461	

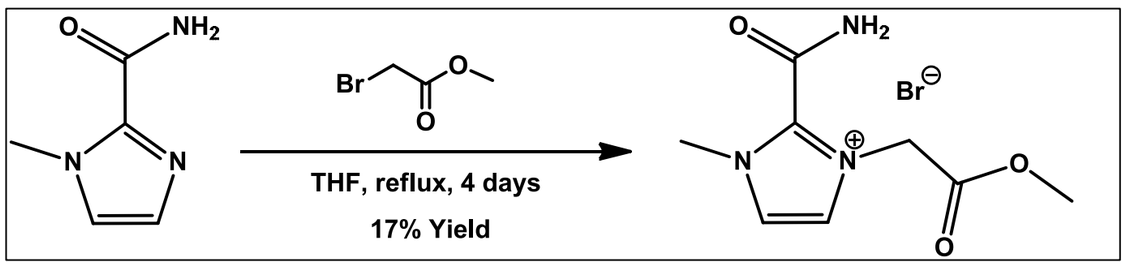


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
reactant	1H-Imidazole-2-carboxylic acid, 1-methyl-, ethyl ester	30148-21-1	154.17	1.14		**6** g	5.263158 mL	38.91808 mmol	**1**	X	
reactant	Ammonium hydroxide solution in Water	1336-21-6	35.05	0.88	**30** wt%	88 g	**100** mL	753.2097 mmol	19.35372		
catalyst	Ammonium chloride	12125-02-9	53.49			**0.2** g		3.739017 mmol	0.096074		
product	1H-Imidazole-2-carboxamide, 1-methyl-	20062-51-5	125.13			4.869819 g		38.91808 mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	yield(%)
Output	1H-Imidazole-2-carboxamide, 1-methyl-	20062-51-5	125.13			**3.21** g		25.65332 mmol	65.91621

total reaction mass	94.20	g
total reagents / reactants / cat. mass	32.60	g
total workup reagents mass		g
total solvents (excl. water)		g
total water	61.60	g
total waste	90.99	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	10.2	29.3
solvent intensity	0.0	19.2
Sheldon E-factor	9.2	28.3
GSK Reaction Mass Efficiency	0.098	
Andraos Reaction Mass Efficiency	0.098	0.034
atom economy	0.661	
1 / stoichiom. factor (excess reagents)	0.227	
material recovery parameter	0.994	0.344
yield	0.659	



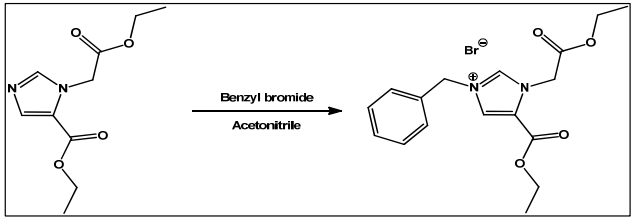
Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
reactant	1H-Imidazole-2-carboxamide, 1-methyl-	20062-51-5	125.13			**500** mg		3.995844 mmol	**1**	X	
reactant	Methyl bromoacetate	96-32-2	152.97	1.616		**612** mg	0.378713 mL	4.000784 mmol	1.001236		
solvent	Tetrahydrofuran	109-99-9	72.11	0.889		17780 mg	**20** mL				
wu solvent	Tetrahydrofuran	109-99-9	72.11	0.889		17780 mg	**20** mL				
product	1H-Imidazolium-2-carboxamide,3-(2-methoxy-2-oxoethyl)-1-methyl-, Bromide		278.1			1111.244 mg		3.995844 mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	yield(%)
Output	1H-Imidazolium-2-carboxamide,3-(2-methoxy-2-oxoethyl)-1-methyl-, Bromide		278.1			**189** mg		0.679612 mmol	17.00796

total reaction mass	36672.00	mg
total reagents / reactants / cat. mass	1112.00	mg
total workup reagents mass		mg
total solvents (excl. water)	35560.00	mg
total water		mg
total waste	36483.00	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	194.0	194.0
solvent intensity	188.1	188.1
Sheldon E-factor	193.0	193.0
GSK Reaction Mass Efficiency	0.170	
Andraos Reaction Mass Efficiency	0.005	0.005
atom economy	1.000	
1 / stoichiom. factor (excess reagents)	0.999	
material recovery parameter	0.030	0.030
yield	0.170	

14



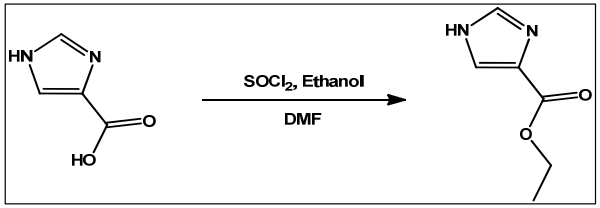
Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
reactant	Diethyl 1H-imidazole-1,5-dicarboxylate (14b)		226.23			**150**	mg			0.663042	mmol	**1**	X	
reactant	Benzyl bromide	100-39-0	171.03	1.438		461.598	mg	**321**	µL	2.69893	mmol	4.070526		
solvent	Acetonitrile	75-05-8	41.05	0.786		1572	mg	**2**	mL					
wu solvent	Diethyl ether	60-29-7	74.12	0.706		14120	mg	**20**	mL					
product	3-benzyl-1,5-bis(ethoxycarbonyl)-1H-imidazol-3-ium, bromide (14)		397.26			263.4001	mg			0.663042	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	3-benzyl-1,5-bis(ethoxycarbonyl)-1H-imidazol-3-ium, bromide (14)		397.26			**174**	mg		0.438	mmol	66.05921

total reaction mass	16303.60	mg
total reagents / reactants / cat. mass	611.60	mg
total workup reagents mass		mg
total solvents (excl. water)	15692.00	mg
total water		mg
total waste	16129.60	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	93.7	93.7
solvent intensity	90.2	90.2
Sheldon E-factor	92.7	92.7
GSK Reaction Mass Efficiency	0.285	
Andraos Reaction Mass Efficiency	0.011	0.011
atom economy	1.000	
1 / stoichiom. factor (excess reagents)	0.431	
material recovery parameter	0.038	0.038
yield	0.661	

14a



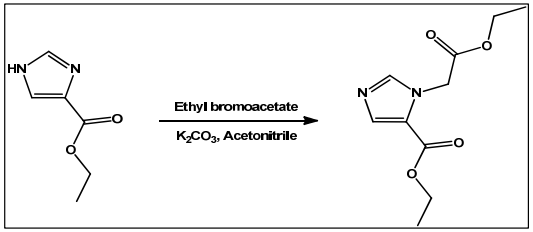
Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
reactant	4-Imidazolecarboxylic acid	1072-84-0	112.09			**250** mg		2.230351 mmol	**1**	X	
reagent	Thionyl Chloride	7719-09-7	118.971	1.373		803.205 mg	**585** µL	6.751267 mmol	3.026998		
reactant	Ethanol	64-17-5	46.07	0.816		4080 mg	**5** mL	88.56089 mmol	39.70716		
catalyst	N,N-Dimethylformamide (DMF)	68-12-2	73.09	0.944		18.88 mg	**20** µL	0.258312 mmol	0.115817		
wu reagent	Sodium hydroxide in water	1310-73-2	40	1.1	**2** M	3300 mg	**3** mL	6 mmol	2.69016		
wu solvent	Ethyl acetate	141-78-6	88.11	0.902		18040 mg	**20** mL				
wu solvent	Water		18	1		30000 mg	**30** mL				
product	Ethyl 1H-imidazole-4-carboxylate (14a)	23785-21-9	140.14			312.5613 mg		2.230351 mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	yield(%)
Output	Ethyl 1H-imidazole-4-carboxylate (14a)	23785-21-9	140.14			**155** mg		1.106037 mmol	49.59027

total reaction mass	56492.09	mg
total reagents / reactants / cat. mass	5152.09	mg
total workup reagents mass	240.00	mg
total solvents (excl. water)	18040.00	mg
total water	33060.00	mg
total waste	56337.09	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	151.2	364.5
solvent intensity	116.4	329.7
Sheldon E-factor	150.2	363.5
GSK Reaction Mass Efficiency	0.030	
Andraos Reaction Mass Efficiency	0.007	0.003
atom economy	0.531	
1 / stoichiom. factor (excess reagents)	0.115	
material recovery parameter	0.219	0.091
yield	0.496	

14b



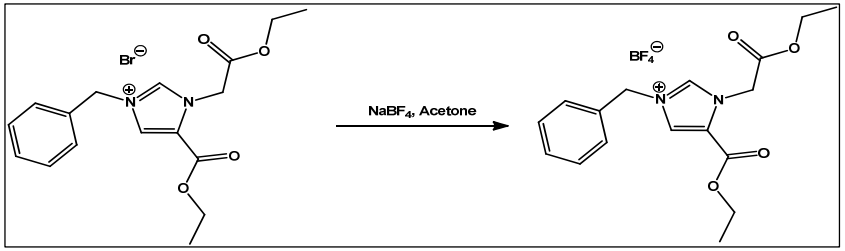
Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
reactant	Ethyl 1H-imidazole-4-carboxylate (14a)	23785-21-9	140.14			**150**	mg			1.070358	mmol	**1**	X	
reactant	Ethyl bromoacetate	105-36-2	167	1.506		323.79	mg	**215**	µL	1.938862	mmol	1.811414		
reagent	Potassium carbonate	584-08-7	138.204			**145**	mg			1.049174	mmol	0.980208		
solvent	Acetonitrile	75-05-8	41.05	0.786		1572	mg	**2**	mL					
wu solvent	Dichloromethane	75-09-2	84.93	1.325		26500	mg	**20**	mL					
wu solvent	Water		18	1		15000	mg	**15**	mL					
wu solvent	Diethyl ether	60-29-7	74.12	0.706		14120	mg	**20**	mL					
wu solvent	Methanol	67-56-1	32.04	0.791		23730	mg	**30**	mL					
wu solvent	Chloroform	67-66-3	119.38	1.492		402840	mg	**270**	mL					
product	Diethyl 1H-imidazole-1,5-dicarboxylate (14b)		226.23			242.1471	mg			1.070358	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	Diethyl 1H-imidazole-1,5-dicarboxylate (14b)		226.23			**161**	mg		0.711665	mmol	66.4885

total reaction mass	484380.79	mg
total reagents / reactants / cat. mass	618.79	mg
total workup reagents mass		mg
total solvents (excl. water)	468762.00	mg
total water	15000.00	mg
total waste	484219.79	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	2915.4	3008.6
solvent intensity	2911.6	3004.7
Sheldon E-factor	2914.4	3007.6
GSK Reaction Mass Efficiency	0.260	
Andraos Reaction Mass Efficiency	0.000	0.000
atom economy	0.508	
1 / stoichiom. factor (excess reagents)	0.770	
material recovery parameter	0.001	0.001
yield	0.665	

15



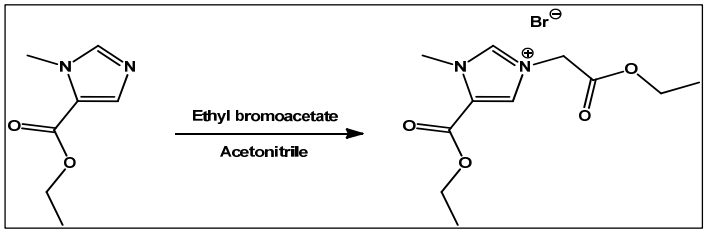
Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
reactant	3-benzyl-1,5-bis(ethoxycarbonyl)-1H-imidazol-3-ium, bromide (14)		397.26			**150** mg		0.377586 mmol	**1**	X	
reactant	Sodium tetrafluoroborate	13755-29-8	109.79			**75** mg		0.683122 mmol	1.809181		
solvent	Acetone	67-64-1	58.08	0.791		7910 mg	**10** mL				
wu solvent	Acetone	67-64-1	58.08	0.791		7910 mg	**10** mL				
product	3-benzyl-1,5-bis(ethoxycarbonyl)-1H-imidazol-3-ium, tetrafluoroborate (15)		404.16			152.6053 mg		0.377586 mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	yield(%)
Output	3-benzyl-1,5-bis(ethoxycarbonyl)-1H-imidazol-3-ium, tetrafluoroborate (15)		404.16			**146** mg		0.361243 mmol	95.67162

total reaction mass	16045.00	mg
total reagents / reactants / cat. mass	225.00	mg
total workup reagents mass		mg
total solvents (excl. water)	15820.00	mg
total water		mg
total waste	15899.00	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	109.9	109.9
solvent intensity	108.4	108.4
Sheldon E-factor	108.9	108.9
GSK Reaction Mass Efficiency	0.649	
Andraos Reaction Mass Efficiency	0.009	0.009
atom economy	0.797	
1 / stoichiom. factor (excess reagents)	0.851	
material recovery parameter	0.014	0.014
yield	0.957	

16

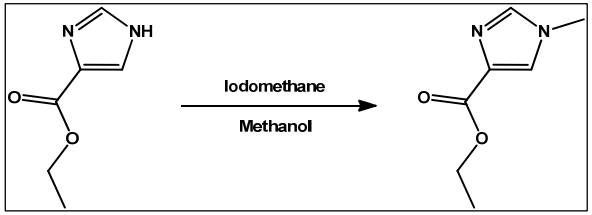


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
reactant	Ethyl 1-methyl-1H-imidazole-5-carboxylate (16a)		154.17			**200**	mg			1.297269	mmol	**1**	X	
reactant	Ethyl bromoacetate	105-36-2	167	1.506		481.92	mg	**320**	µL	2.885749	mmol	2.224479		
solvent	Acetonitrile	75-05-8	41.05	0.786		1572	mg	**2**	mL					
wu solvent	Diethyl ether	60-29-7	74.12	0.706		21180	mg	**30**	mL					
product	3,5-bis(ethoxycarbonyl)-1-methyl-1H-imidazol-3-ium, bromide (16)		321.17			416.644	mg			1.297269	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	3,5-bis(ethoxycarbonyl)-1-methyl-1H-imidazol-3-ium, bromide (16)		321.17			**370**	mg		1.152038	mmol	88.80484

total reaction mass	23433.92	mg
total reagents / reactants / cat. mass	681.92	mg
total workup reagents mass		mg
total solvents (excl. water)	22752.00	mg
total water		mg
total waste	23063.92	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	63.3	63.3
solvent intensity	61.5	61.5
Sheldon E-factor	62.3	62.3
GSK Reaction Mass Efficiency	0.543	
Andraos Reaction Mass Efficiency	0.016	0.016
atom economy	1.000	
1 / stoichiom. factor (excess reagents)	0.611	
material recovery parameter	0.029	0.029
yield	0.888	

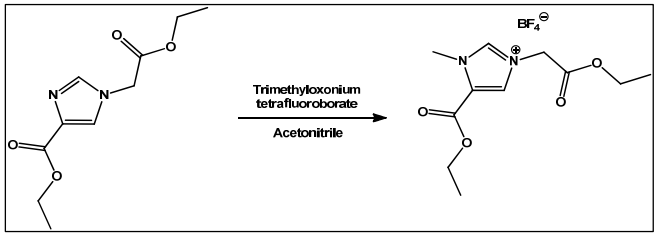


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
reactant	Ethyl 1H-imidazole-4-carboxylate (14a)	23785-21-9	140.14			**120**	mg			0.856287	mmol	**1**	X	
reactant	Iodomethane	74-88-4	141.94	2.28		360.24	mg	**158**	µL	2.537974	mmol	2.96393		
solvent	Methanol	67-56-1	32.04	0.791		7830.9	mg	**9.9**	mL					
wu solvent	Methanol	67-56-1	32.04	0.791		3559.5	mg	**4.5**	mL					
wu solvent	Chloroform	67-66-3	119.38	1.492		440886	mg	**295.5**	mL					
product	Ethyl 1-methyl-1H-imidazole-5-carboxylate (16a)		154.17			132.0137	mg			0.856287	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	Ethyl 1-methyl-1H-imidazole-5-carboxylate (16a)		154.17			**87**	mg		0.564312	mmol	65.90225

total reaction mass	452756.64	mg
total reagents / reactants / cat. mass	480.24	mg
total workup reagents mass		mg
total solvents (excl. water)	452276.40	mg
total water		mg
total waste	452669.64	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	5204.1	5204.1
solvent intensity	5198.6	5198.6
Sheldon E-factor	5203.1	5203.1
GSK Reaction Mass Efficiency	0.181	
Andraos Reaction Mass Efficiency	0.000	0.000
atom economy	0.547	
1 / stoichiom. factor (excess reagents)	0.503	
material recovery parameter	0.001	0.001
yield	0.659	

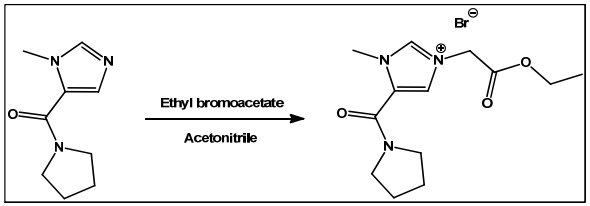


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
reactant	Diethyl 1H-imidazole-1,5-dicarboxylate (14b)		226.23			**150** mg		0.663042 mmol	**1**	X	
reactant	Trimethyloxonium tetrafluoroborate	420-37-1	147.91			**103** mg		0.696369 mmol	1.050264		
solvent	Acetonitrile	75-05-8	41.05	0.786		1572 mg	**2** mL				
product	3,5-bis(ethoxycarbonyl)-1-methyl-1H-imidazol-3-ium, tetrafluoroborate (17)		328.07			217.5242 mg		0.663042 mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	yield(%)
Output	is(ethoxycarbonyl)-1-methyl-1H-imidazol-3-ium, tetrafluoroborate (17)		328.07			**197** mg		0.600482 mmol	90.56464

total reaction mass	1825.00	mg
total reagents / reactants / cat. mass	253.00	mg
total workup reagents mass		mg
total solvents (excl. water)	1572.00	mg
total water		mg
total waste	1628.00	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	9.3	9.3
solvent intensity	8.0	8.0
Sheldon E-factor	8.3	8.3
GSK Reaction Mass Efficiency	0.779	
Andraos Reaction Mass Efficiency	0.108	0.108
atom economy	0.877	
1 / stoichiom. factor (excess reagents)	0.981	
material recovery parameter	0.139	0.139
yield	0.906	



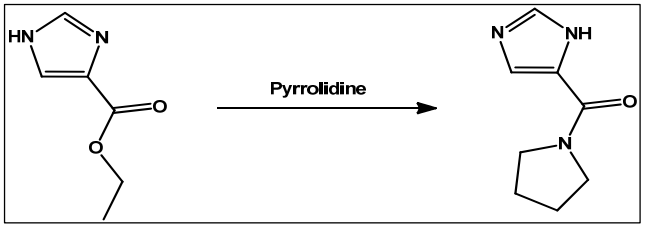
Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
reactant	(1-methyl-1H-imidazol-5-yl)(pyrrolidin-1-yl)methanone (18b)		179.22			**100**	mg			0.557973	mmol	**1**	X	
reactant	Ethyl bromoacetate	105-36-2	167	1.506		371.982	mg	**247**	µL	2.227437	mmol	3.992013		
solvent	Acetonitrile	75-05-8	41.05	0.786		1572	mg	**2**	mL					
wu solvent	Diethyl ether	60-29-7	74.12	0.706		21180	mg	**30**	mL					
product	3-(ethoxycarbonyl)-1-methyl-5-(pyrrolidine-1-carbonyl)-1H-imidazol-3-ium, bromide (18)		346.22			193.1816	mg			0.557973	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	3-(ethoxycarbonyl)-1-methyl-5-(pyrrolidine-1-carbonyl)-1H-imidazol-3-ium, bromide (18)		346.22			**133**	mg		0.384149	mmol	68.84715

total reaction mass	23223.98	mg
total reagents / reactants / cat. mass	471.98	mg
total workup reagents mass		mg
total solvents (excl. water)	22752.00	mg
total water		mg
total waste	23090.98	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	174.6	174.6
solvent intensity	171.1	171.1
Sheldon E-factor	173.6	173.6
GSK Reaction Mass Efficiency	0.282	
Andraos Reaction Mass Efficiency	0.006	0.006
atom economy	1.000	
1 / stoichiom. factor (excess reagents)	0.409	
material recovery parameter	0.020	0.020
yield	0.688	

18a

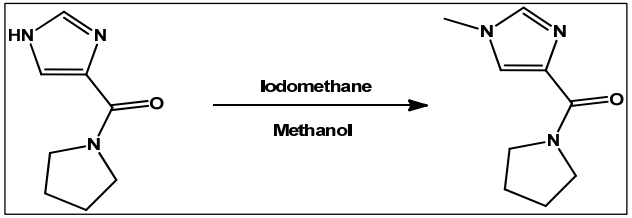


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
reactant	Ethyl 1H-imidazole-4-carboxylate (14a)	23785-21-9	140.14			**250**	mg			1.78393	mmol	**1**	X	
reactant	Pyrrolidine	123-75-1	71.12	0.852		1022.4	mg	**1.2**	mL	14.3757	mmol	8.058444		
wu solvent	Methanol	67-56-1	32.04	0.791		19775	mg	**25**	mL					
wu solvent	Dichloromethane	75-09-2	84.93	1.325		430625	mg	**325**	mL					
product	(1H-imidazol-5-yl)(pyrrolidin-1-yl)methanone (18a)		165.19			294.6875	mg			1.78393	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	(1H-imidazol-5-yl)(pyrrolidin-1-yl)methanone (18a)		165.19			**217**	mg		1.313639	mmol	73.63734

total reaction mass	451672.40	mg
total reagents / reactants / cat. mass	1272.40	mg
total workup reagents mass		mg
total solvents (excl. water)	450400.00	mg
total water		mg
total waste	451455.40	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	2081.4	2081.4
solvent intensity	2075.6	2075.6
Sheldon E-factor	2080.4	2080.4
GSK Reaction Mass Efficiency	0.171	
Andraos Reaction Mass Efficiency	0.000	0.000
atom economy	0.782	
1 / stoichiom. factor (excess reagents)	0.296	
material recovery parameter	0.003	0.003
yield	0.736	

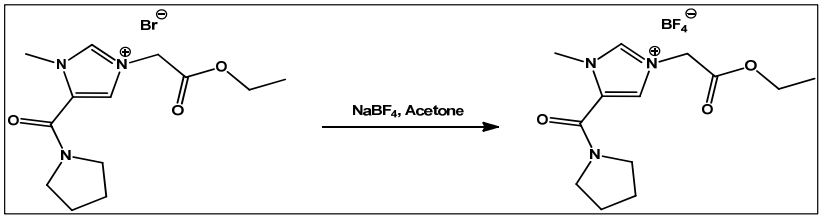


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
reactant	(1H-imidazol-5-yl)(pyrrolidin-1-yl)methanone (18a)		165.19			**150** mg		0.908045 mmol	**1**	X	
reactant	Iodomethane	74-88-4	141.94	2.28		383.04 mg	**168** µL	2.698605 mmol	2.971884		
solvent	Methanol	67-56-1	32.04	0.791		7830.9 mg	**9.9** mL				
wu solvent	Methanol	67-56-1	32.04	0.791		15820 mg	**20** mL				
wu solvent	Chloroform	67-66-3	119.38	1.492		566960 mg	**380** mL				
product	(1-methyl-1H-imidazol-5-yl)(pyrrolidin-1-yl)methanone (18b)		179.22			162.7399 mg		0.908045 mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	yield(%)
Output	(1-methyl-1H-imidazol-5-yl)(pyrrolidin-1-yl)methanone (18b)		179.22			**104** mg		0.580292 mmol	63.90567

total reaction mass	591143.94	mg
total reagents / reactants / cat. mass	533.04	mg
total workup reagents mass		mg
total solvents (excl. water)	590610.90	mg
total water		mg
total waste	591039.94	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	5684.1	5684.1
solvent intensity	5679.0	5679.0
Sheldon E-factor	5683.1	5683.1
GSK Reaction Mass Efficiency	0.195	
Andraos Reaction Mass Efficiency	0.000	0.000
atom economy	0.584	
1 / stoichiom. factor (excess reagents)	0.523	
material recovery parameter	0.001	0.001
yield	0.639	



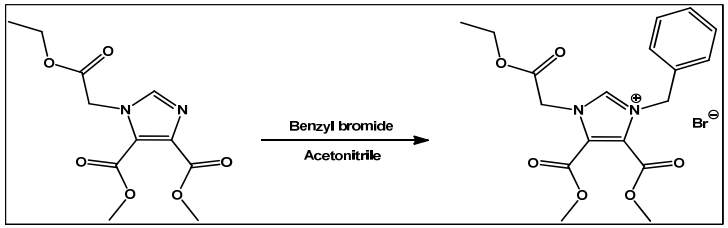
Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
reactant	3-(ethoxycarbonyl)-1-methyl-5-(pyrrolidine-1-carbonyl)-1H-imidazol-3-ium, bromide (18)		346.22			**100**	mg			0.288834	mmol	**1**	X	
reactant	Sodium tetrafluoroborate	13755-29-8	109.79			**70**	mg			0.637581	mmol	2.207432		
solvent	Acetone	67-64-1	58.08	0.791		7910	mg	**10**	mL					
wu solvent	Acetone	67-64-1	58.08	0.791		7910	mg	**10**	mL					
product	3-(ethoxycarbonyl)-1-methyl-5-(pyrrolidine-1-carbonyl)-1H-imidazol-3-ium, tetrafluoroborate (19)		353.12			101.993	mg			0.288834	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	3-(ethoxycarbonyl)-1-methyl-5-(pyrrolidine-1-carbonyl)-1H-imidazol-3-ium, tetrafluoroborate (19)		353.12			**100**	mg		0.28319	mmol	98.04599

total reaction mass	15990.00	mg
total reagents / reactants / cat. mass	170.00	mg
total workup reagents mass		mg
total solvents (excl. water)	15820.00	mg
total water		mg
total waste	15890.00	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	159.9	159.9
solvent intensity	158.2	158.2
Sheldon E-factor	158.9	158.9
GSK Reaction Mass Efficiency	0.588	
Andraos Reaction Mass Efficiency	0.006	0.006
atom economy	0.774	
1 / stoichiom. factor (excess reagents)	0.775	
material recovery parameter	0.011	0.011
yield	0.980	

3-benzyl-1-(2-ethoxy-2-oxoethyl)-4,5-bis(methoxycarbonyl)-1H-imidazol-3-ium bromide



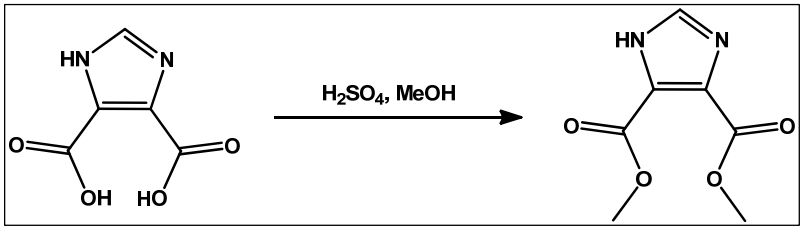
Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
reactant	Dimethyl 1-(2-ethoxy-2-oxoethyl)-1H-imidazole-4,5-dicarboxylate		270.24			**500**	mg			1.9	mmol	**1**	X	
reactant	Benzyl bromide	100-39-0	171.03	1.438		649.914	mg	0.451957	mL	3.8	mmol	**2**		
solvent	Acetonitrile	75-05-8	41.05	0.786		1572	mg	**2**	mL					
wu solvent	Diethyl ether	60-29-7	74.12	0.706		10590	mg	**15**	mL					
product	3-benzyl-1-(2-ethoxy-2-oxoethyl)-4,5-bis(methoxycarbonyl)-1H-imidazol-3-ium bromide		441.27			838.413	mg			1.9	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	3-benzyl-1-(2-ethoxy-2-oxoethyl)-4,5-bis(methoxycarbonyl)-1H-imidazol-3-ium bromide		441.27			**620**	mg		1.405035	mmol	73.94924

total reaction mass	13311.91	mg
total reagents / reactants / cat. mass	1149.91	mg
total workup reagents mass		mg
total solvents (excl. water)	12162.00	mg
total water		mg
total waste	12691.91	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	21.5	21.5
solvent intensity	19.6	19.6
Sheldon E-factor	20.5	20.5
GSK Reaction Mass Efficiency	0.539	
Andraos Reaction Mass Efficiency	0.047	0.047
atom economy	1.000	
1 / stoichiom. factor (excess reagents)	0.721	
material recovery parameter	0.087	0.087
yield	0.739	

Dimethyl 1*H* -imidazole-4,5-dicarboxylate



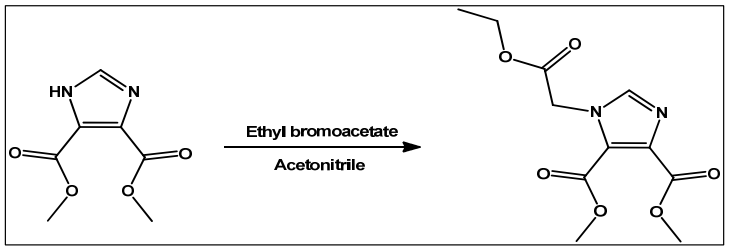
Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
reactant	4,5-Imidazoledicarboxylic acid	570-22-9	156.1			**500** mg		3.203075 mmol	**1**	X	
reactant	Sulfuric acid	7664-93-9	98.0778			628.3011 mg		6.40615 mmol	**2**		
solvent	Methanol	67-56-1	32.04	0.791		7910 mg	**10** mL				
wu solvent	Water		18				**20** mL				
wu solvent	Ethyl acetate	141-78-6	88.11	0.902		18040 mg	**20** mL				
product	Dimethyl 1H-imidazole-4,5-dicarboxylate	3304-70-9	184.15			589.8463 mg		3.203075 mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	yield(%)
Output	Dimethyl 1H-imidazole-4,5-dicarboxylate	3304-70-9	184.15			**456** mg		2.476242 mmol	77.30828

total reaction mass	27078.30	mg
total reagents / reactants / cat. mass	1128.30	mg
total workup reagents mass		mg
total solvents (excl. water)	25950.00	mg
total water		mg
total waste	26622.30	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	59.4	59.4
solvent intensity	56.9	56.9
Sheldon E-factor	58.4	58.4
GSK Reaction Mass Efficiency	0.404	
Andraos Reaction Mass Efficiency	0.017	0.017
atom economy	0.523	
1 / stoichiom. factor (excess reagents)	1.000	
material recovery parameter	0.042	0.042
yield	0.773	

Dimethyl 1-(2-ethoxy-2-oxoethyl)-1H-imidazole-4,5-dicarboxylate



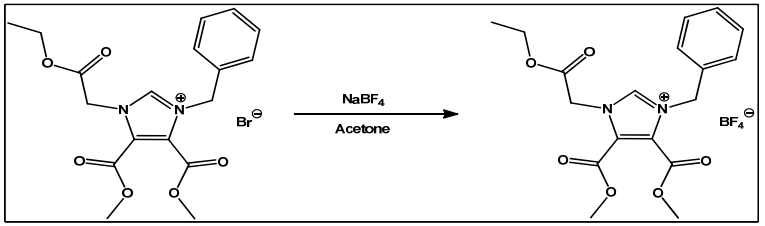
Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
reactant	Dimethyl 1H-imidazole-4,5-dicarboxylate	3304-70-9	184.15			**500** mg		2.715178 mmol	**1**	X	
reactant	Ethyl bromoacetate	105-36-2	167	1.506		906.8694 mg	0.602171 mL	5.430356 mmol	**2**		
reagent	Potassium carbonate	584-08-7	138.204			375.2484 mg		2.715178 mmol	**1**		
solvent	Acetonitrile	75-05-8	41.05	0.786		1572 mg	**2** mL				
wu solvent	Dichloromethane	75-09-2	84.93	1.325		13250 mg	**10** mL				
wu solvent	Water		18				**20** mL				
product	Dimethyl 1-(2-ethoxy-2-oxoethyl)-1H-imidazole-4,5-dicarboxylate		270.24			733.7497 mg		2.715178 mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	yield(%)
Output	Dimethyl 1-(2-ethoxy-2-oxoethyl)-1H-imidazole-4,5-dicarboxylate		270.24			**597** mg		2.209147 mmol	81.3629

total reaction mass	16604.12	mg
total reagents / reactants / cat. mass	1782.12	mg
total workup reagents mass		mg
total solvents (excl. water)	14822.00	mg
total water		mg
total waste	16007.12	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	27.8	27.8
solvent intensity	24.8	24.8
Sheldon E-factor	26.8	26.8
GSK Reaction Mass Efficiency	0.335	
Andraos Reaction Mass Efficiency	0.036	0.036
atom economy	0.552	
1 / stoichiom. factor (excess reagents)	0.746	
material recovery parameter	0.107	0.107
yield	0.814	

3-benzyl-1-(2-ethoxy-2-oxoethyl)-4,5-bis(methoxycarbonyl)-1H-imidazol-3-ium tetrafluoroborate



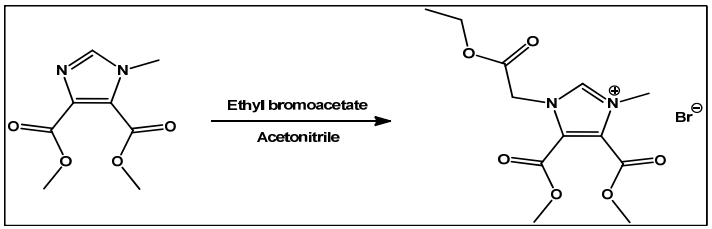
Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
reactant	3-benzyl-1-(2-ethoxy-2-oxoethyl)-4,5-bis(methoxycarbonyl)-1H-imidazol-3-ium bromide		441.27			**250** mg		0.566547 mmol	**1**	X	
reactant	Sodium tetrafluoroborate	13755-29-8	109.79			**74.8** mg		0.681301 mmol	1.20255		
solvent	Acetone	67-64-1	58.08	0.791		7910 mg	**10** mL				
wu solvent	Acetone	67-64-1	58.08	0.791		7910 mg	**10** mL				
product	3-benzyl-1-(2-ethoxy-2-oxoethyl)-4,5-bis(methoxycarbonyl)-1H-imidazol-3-ium tetrafluoroborate		448.17			253.9092 mg		0.566547 mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	yield(%)
Output	3-benzyl-1-(2-ethoxy-2-oxoethyl)-4,5-bis(methoxycarbonyl)-1H-imidazol-3-ium tetrafluoroborate		448.17			**249** mg		0.555593 mmol	98.06656

total reaction mass	16144.80	mg
total reagents / reactants / cat. mass	324.80	mg
total workup reagents mass		mg
total solvents (excl. water)	15820.00	mg
total water		mg
total waste	15895.80	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	64.8	64.8
solvent intensity	63.5	63.5
Sheldon E-factor	63.8	63.8
GSK Reaction Mass Efficiency	0.767	
Andraos Reaction Mass Efficiency	0.015	0.015
atom economy	0.813	
1 / stoichiom. factor (excess reagents)	0.961	
material recovery parameter	0.020	0.020
yield	0.981	

1-(2-ethoxy-2-oxoethyl)-4,5-bis(methoxycarbonyl)-3-methyl-1*H* -imidazol-3-ium, bromide



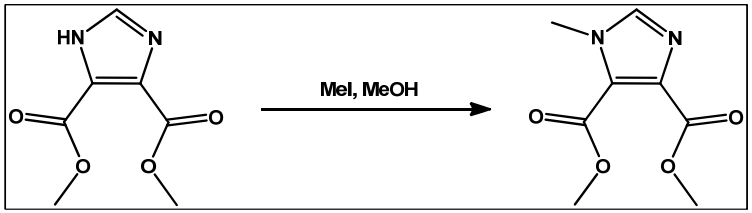
Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
reactant	1H-Imidazole-4,5-dicarboxylic acid, 1-methyl-, 4,5-dimethyl ester	42545-22-2	198.18			**250** mg		1.261479 mmol	**1**	X	
reactant	Ethyl bromoacetate	105-36-2	167	1.506		417.162 mg	**277** µL	2.497976 mmol	1.980196		
solvent	Acetonitrile	75-05-8	41.05	0.786		1572 mg	**2** mL				
wu solvent	Diethyl ether	60-29-7	74.12	0.706		14120 mg	**20** mL				
product	1-(2-ethoxy-2-oxoethyl)-4,5-bis(methoxycarbonyl)-3-methyl-1H-imidazol-3-ium, bromide		365.18			460.6671 mg		1.261479 mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	yield(%)
Output	1-(2-ethoxy-2-oxoethyl)-4,5-bis(methoxycarbonyl)-3-methyl-1H-imidazol-3-ium, bromide		365.18			**408** mg		1.117257 mmol	88.56722

total reaction mass	16359.16	mg
total reagents / reactants / cat. mass	667.16	mg
total workup reagents mass		mg
total solvents (excl. water)	15692.00	mg
total water		mg
total waste	15951.16	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	40.1	40.1
solvent intensity	38.5	38.5
Sheldon E-factor	39.1	39.1
GSK Reaction Mass Efficiency	0.612	
Andraos Reaction Mass Efficiency	0.025	0.025
atom economy	1.000	
1 / stoichiom. factor (excess reagents)	0.690	
material recovery parameter	0.041	0.041
yield	0.886	

1*H* -Imidazole-4,5-dicarboxylic acid, 1-methyl-, 4,5-dimethyl ester

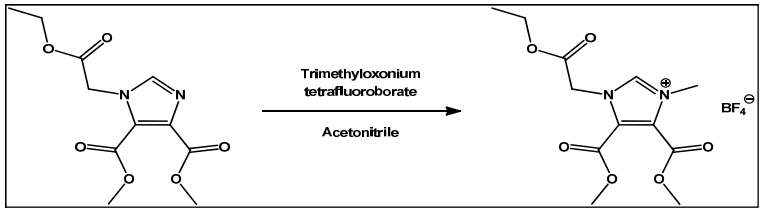


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
reactant	Dimethyl 1H-imidazole-4,5-dicarboxylate	3304-70-9	184.15			**300**	mg			1.629107	mmol	**1**	X	
reactant	Iodomethane	74-88-4	141.94	2.28		0.42582	g	0.186763	mL	**3**	mmol	1.8415		
solvent	Methanol	67-56-1	32.04	0.791		5.537	g	**7**	mL					
wu solvent	Dichloromethane	75-09-2	84.93	1.325		13.25	g	**10**	mL					
wu solvent	Water		18					**15**	mL					
product	1H-Imidazole-4,5-dicarboxylic acid, 1-methyl-, 4,5-dimethyl ester	42545-22-2	198.18			322.8564	mg			1.629107	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	1H-Imidazole-4,5-dicarboxylic acid, 1-methyl-, 4,5-dimethyl ester	42545-22-2	198.18			**273**	mg		1.377536	mmol	84.55773

total reaction mass	19512.82	mg
total reagents / reactants / cat. mass	725.82	mg
total workup reagents mass		mg
total solvents (excl. water)	18787.00	mg
total water		mg
total waste	19239.82	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	71.5	71.5
solvent intensity	68.8	68.8
Sheldon E-factor	70.5	70.5
GSK Reaction Mass Efficiency	0.376	
Andraos Reaction Mass Efficiency	0.014	0.014
atom economy	0.608	
1 / stoichiom. factor (excess reagents)	0.732	
material recovery parameter	0.037	0.037
yield	0.846	

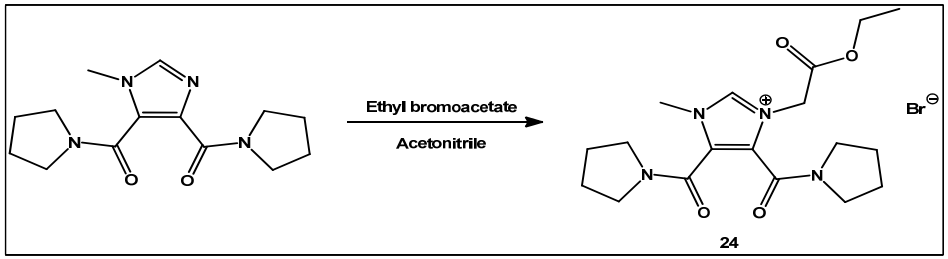


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
reactant	Dimethyl 1-(2-ethoxy-2-oxoethyl)-1H-imidazole-4,5-dicarboxylate (20b)		270.24			**250** mg		0.925104 mmol	**1**	X	
reactant	Trimethyloxonium tetrafluoroborate	420-37-1	147.91			**137** mg		0.926239 mmol	1.001227		
solvent	Acetonitrile	75-05-8	41.05	0.786		1572 mg	**2** mL				
product	1-(2-ethoxy-2-oxoethyl)-4,5-bis(methoxycarbonyl)-3-methyl-1H-imidazol-3-ium, tetrafluoroborate (23)		372.08			344.2126 mg		0.925104 mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	yield(%)
Output	1-(2-ethoxy-2-oxoethyl)-4,5-bis(methoxycarbonyl)-3-methyl-1H-imidazol-3-ium, tetrafluoroborate (23)		372.08			**318** mg		0.854655 mmol	92.38478

total reaction mass	1959.00	mg
total reagents / reactants / cat. mass	387.00	mg
total workup reagents mass		mg
total solvents (excl. water)	1572.00	mg
total water		mg
total waste	1641.00	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	6.2	6.2
solvent intensity	4.9	4.9
Sheldon E-factor	5.2	5.2
GSK Reaction Mass Efficiency	0.822	
Andraos Reaction Mass Efficiency	0.162	0.162
atom economy	0.890	
1 / stoichiom. factor (excess reagents)	1.000	
material recovery parameter	0.198	0.198
yield	0.924	

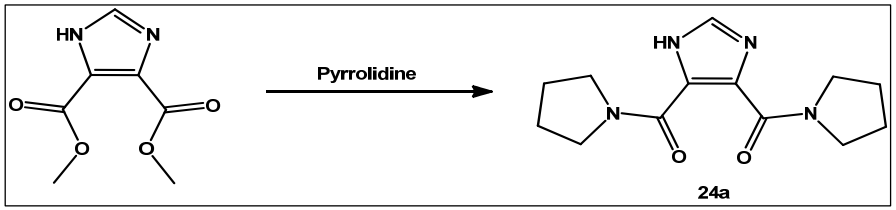


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
reactant	(1H-imidazole-4,5-diyl)bis(pyrrolidin-1-ylmethanone) (24b)		276.33			**200** mg		0.723772 mmol	**1**	X	
reactant	Ethyl bromoacetate	105-36-2	167	1.506		481.92 mg	**320** µL	2.885749 mmol	3.987094		
solvent	Acetonitrile	75-05-8	41.05	0.786		1572 mg	**2** mL				
wu solvent	Diethyl ether	60-29-7	74.12	0.706		17650 mg	**25** mL				
product	3-(2-methoxyacetyl)-1-methyl-4,5-bis[(pyrrolidin-1-yl)carbonyl]-1H-imidazol-3-ium bromide (24)		443.34			320.8772 mg		0.723772 mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	yield(%)
Output	3-(2-methoxyacetyl)-1-methyl-4,5-bis[(pyrrolidin-1-yl)carbonyl]-1H-imidazol-3-ium bromide (24)		443.34			**282** mg		0.636081 mmol	87.88408

total reaction mass	19903.92	mg
total reagents / reactants / cat. mass	681.92	mg
total workup reagents mass		mg
total solvents (excl. water)	19222.00	mg
total water		mg
total waste	19621.92	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	70.6	70.6
solvent intensity	68.2	68.2
Sheldon E-factor	69.6	69.6
GSK Reaction Mass Efficiency	0.414	
Andraos Reaction Mass Efficiency	0.014	0.014
atom economy	1.000	
1 / stoichiom. factor (excess reagents)	0.471	
material recovery parameter	0.034	0.034
yield	0.879	



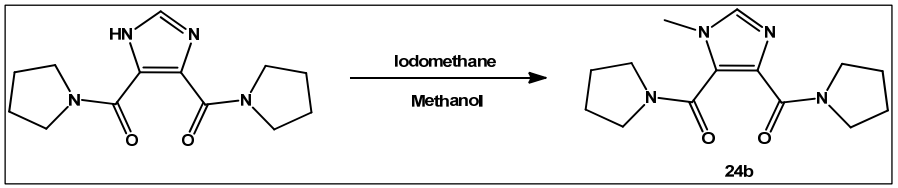
Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
reactant	Dimethyl 1H-imidazole-4,5-dicarboxylate (20a)	3304-70-9	184.15			**500** mg		2.715178 mmol	**1**	X	
reactant	Pyrrolidine	123-75-1	71.12	0.852		1022.4 mg	**1.2** mL	14.3757 mmol	5.294571		
wu solvent	Methanol	67-56-1	32.04	0.791		23730 mg	**30** mL				
wu solvent	Dichloromethane	75-09-2	84.93	1.325		490250 mg	**370** mL				
product	(1H-imidazole-4,5-diyl)bis(pyrrolidin-1-ylmethanone) (24a)		262.31			712.2183 mg		2.715178 mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	yield(%)
Output	(1H-imidazole-4,5-diyl)bis(pyrrolidin-1-ylmethanone) (24a)		262.31			**338** mg		1.288552 mmol	47.45736

total reaction mass	515502.40	mg
total reagents / reactants / cat. mass	1522.40	mg
total workup reagents mass		mg
total solvents (excl. water)	513980.00	mg
total water		mg
total waste	515164.40	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	1525.2	1525.2
solvent intensity	1520.7	1520.7
Sheldon E-factor	1524.2	1524.2
GSK Reaction Mass Efficiency	0.222	
Andraos Reaction Mass Efficiency	0.001	0.001
atom economy	0.804	
1 / stoichiom. factor (excess reagents)	0.582	
material recovery parameter	0.003	0.003
yield	0.475	

24b

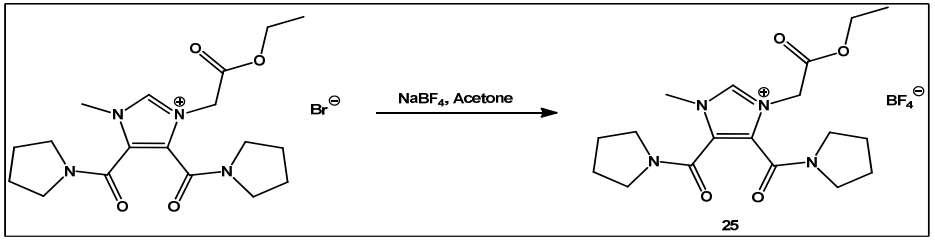


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
reactant	(1H-imidazole-4,5-diyl)bis(pyrrolidin-1-ylmethanone) (24a)		262.31			**250**	mg			0.953071	mmol	**1**	X	
reactant	Iodomethane	74-88-4	141.94	2.28		328.32	mg	**144**	µL	2.31309	mmol	2.426987		
solvent	Methanol	67-56-1	32.04	0.791		5.537	g	**7**	mL					
wu solvent	Dichloromethane	75-09-2	84.93	1.325		13.25	g	**10**	mL					
wu solvent	Water		18	1		15	g	**15**	mL					
product	Compound - (24b)		276.33			263.3621	mg			0.953071	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	Compound - (24b)		276.33			**220**	mg		0.79615	mmol	83.53519

total reaction mass	34365.32	mg
total reagents / reactants / cat. mass	578.32	mg
total workup reagents mass		mg
total solvents (excl. water)	18787.00	mg
total water	15000.00	mg
total waste	34145.32	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	88.0	156.2
solvent intensity	85.4	153.6
Sheldon E-factor	87.0	155.2
GSK Reaction Mass Efficiency	0.380	
Andraos Reaction Mass Efficiency	0.011	0.006
atom economy	0.684	
1 / stoichiom. factor (excess reagents)	0.666	
material recovery parameter	0.030	0.017
yield	0.835	



25

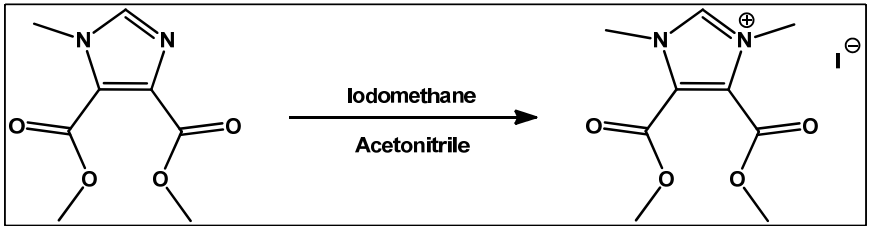
Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
reactant	3-(2-methoxyacetyl)-1-methyl-4,5-bis[(pyrrolidin-1-yl)carbonyl]-1H-imidazol-3-ium, bromide (24)		443.34			**250**	mg			0.563901	mmol	**1**	X	
reactant	Sodium tetrafluoroborate	13755-29-8	109.79			**74.8**	mg			0.681301	mmol	1.208191		
solvent	Acetone	67-64-1	58.08	0.791		7910	mg	**10**	mL					
wu solvent	Acetone	67-64-1	58.08	0.791		7910	mg	**10**	mL					
product	3-(2-methoxyacetyl)-1-methyl-4,5-bis[(pyrrolidin-1-yl)carbonyl]-1H-imidazol-3-ium, tetrafluoroborate (25)		450.24			253.8909	mg			0.563901	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	3-(2-methoxyacetyl)-1-methyl-4,5-bis[(pyrrolidin-1-yl)carbonyl]-1H-imidazol-3-ium, tetrafluoroborate (25)		450.24			**241**	mg		0.53527	mmol	94.92265

total reaction mass	16144.80	mg
total reagents / reactants / cat. mass	324.80	mg
total workup reagents mass		mg
total solvents (excl. water)	15820.00	mg
total water		mg
total waste	15903.80	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	67.0	67.0
solvent intensity	65.6	65.6
Sheldon E-factor	66.0	66.0
GSK Reaction Mass Efficiency	0.742	
Andraos Reaction Mass Efficiency	0.015	0.015
atom economy	0.814	
1 / stoichiom. factor (excess reagents)	0.960	
material recovery parameter	0.020	0.020
yield	0.949	

4,5-bis(methoxycarbonyl)-1,3-dimethyl-1H-imidazol-3-ium, iodide



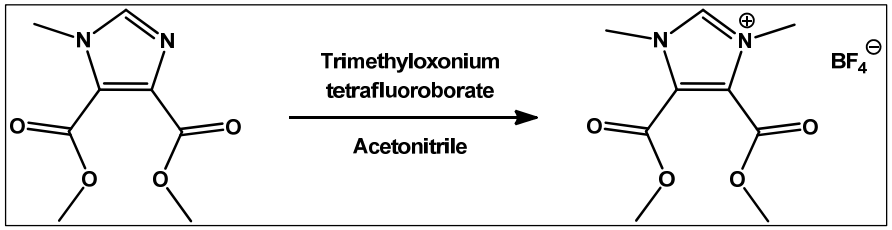
Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
reactant	1H-Imidazole-4,5-dicarboxylic acid, 1-methyl-, 4,5-dimethyl ester	42545-22-2	198.18			**250**	mg			1.261479	mmol	**1**	X	
reactant	Iodomethane	74-88-4	141.94	2.28		180.12	mg	**79**	µL	1.268987	mmol	1.005951		
solvent	Acetonitrile	75-05-8	41.05	0.786		1572	mg	**2**	mL					
product	4,5-bis(methoxycarbonyl)-1,3-dimethyl-1H-imidazol-3-ium, iodide		340.12			429.0544	mg			1.261479	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	4,5-bis(methoxycarbonyl)-1,3-dimethyl-1H-imidazol-3-ium, iodide		340.12			**368**	mg		1.081971	mmol	85.77001

total reaction mass	2002.12	mg
total reagents / reactants / cat. mass	430.12	mg
total workup reagents mass		**mg**
total solvents (excl. water)	1572.00	mg
total water		mg
total waste	1634.12	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	5.4	5.4
solvent intensity	4.3	4.3
Sheldon E-factor	4.4	4.4
GSK Reaction Mass Efficiency	0.856	
Andraos Reaction Mass Efficiency	0.184	0.184
atom economy	1.000	
1 / stoichiom. factor (excess reagents)	0.998	
material recovery parameter	0.215	0.215
yield	0.858	

4,5-bis(methoxycarbonyl)-1,3-dimethyl-1H-imidazol-3-ium, tetrafluoroborate

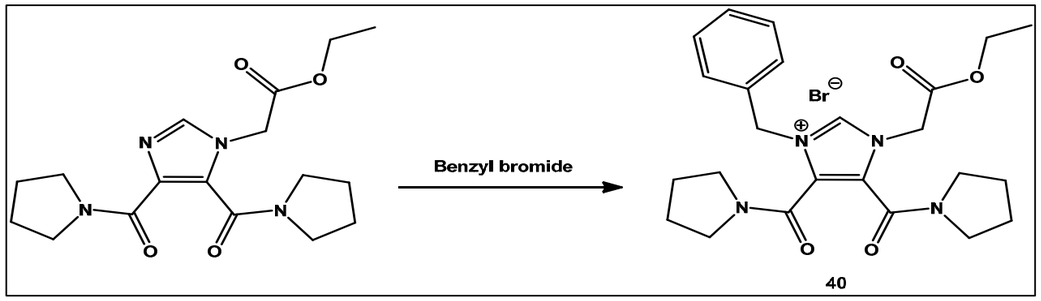


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
reactant	1H-Imidazole-4,5-dicarboxylic acid, 1-methyl-, 4,5-dimethyl ester	42545-22-2	198.18			**250** mg		1.261479 mmol	**1**	X	
reactant	Trimethyloxonium tetrafluoroborate	420-37-1	147.91			**240** mg		1.622608 mmol	1.286274		
solvent	Acetonitrile	75-05-8	41.05	0.786		1.572 g	**2** mL				
product	4,5-bis(methoxycarbonyl)-1,3-dimethyl-1H-imidazol-3-ium, tetrafluoroborate		300.02			378.4691 mg		1.261479 mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	yield(%)
Output	;(methoxycarbonyl)-1,3-dimethyl-1H-imidazol-3-ium, tetrafluoroborate		300.02			**344** mg		1.14659 mmol	90.8925

total reaction mass	2062.00	mg
total reagents / reactants / cat. mass	490.00	mg
total workup reagents mass		mg
total solvents (excl. water)	1572.00	mg
total water		mg
total waste	1718.00	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	6.0	6.0
solvent intensity	4.6	4.6
Sheldon E-factor	5.0	5.0
GSK Reaction Mass Efficiency	0.702	
Andraos Reaction Mass Efficiency	0.167	0.167
atom economy	0.867	
1 / stoichiom. factor (excess reagents)	0.891	
material recovery parameter	0.238	0.238
yield	0.909	

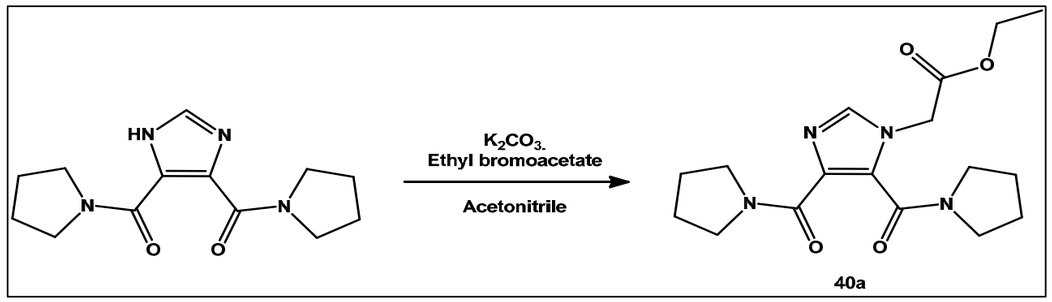


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
reactant	(40a)		348.39			**332.04** mg		953.0698 µmol	**1**	X	
reactant	Benzyl bromide	100-39-0	171.03	1.438		0.649976 g	**0.452** mL	3.800363 mmol	3.987496		
wu solvent	Diethyl ether	60-29-7	74.12	0.706		10.59 g	**15** mL				
product	1-Benzyl-3-(2-ethoxy-2-oxoethyl)-4,5-bis(pyrrolidine-1-carbonyl)-1H-imidazol-3-ium bromide (40)		519.43			495.0531 mg		953.0698 µmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	yield(%)
Output	1-Benzyl-3-(2-ethoxy-2-oxoethyl)-4,5-bis(pyrrolidine-1-carbonyl)-1H-imidazol-3-ium bromide (40)		519.43			**355** mg		683.4415 µmol	71.70948

total reaction mass	11572.02	mg
total reagents / reactants / cat. mass	982.02	mg
total workup reagents mass		mg
total solvents (excl. water)	10590.00	mg
total water		mg
total waste	11217.02	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	32.6	32.6
solvent intensity	29.8	29.8
Sheldon E-factor	31.6	31.6
GSK Reaction Mass Efficiency	0.362	
Andraos Reaction Mass Efficiency	0.031	0.031
atom economy	1.000	
1 / stoichiom. factor (excess reagents)	0.504	
material recovery parameter	0.085	0.085
yield	0.717	

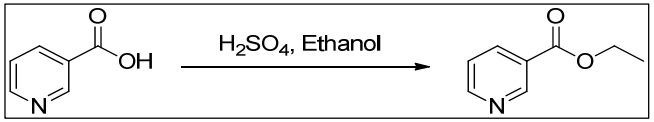


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
reactant	(1H-imidazole-4,5-diyl)bis(pyrrolidin-1-ylmethanone) (24a)		262.31			**250** mg		0.953071 mmol	**1**	X	
reagent	Potassium carbonate	584-08-7	138.204			**135** mg		0.976817 mmol	1.024915		
reactant	Ethyl bromoacetate	105-36-2	167	1.506		634.026 mg	**421** µL	3.796563 mmol	3.983506		
solvent	Acetonitrile	75-05-8	41.05	0.786		3930 mg	**5** mL				
wu solvent	Dichloromethane	75-09-2	84.93	1.325		6625 mg	**5** mL				
product	(40a)		348.39			332.0403 mg		0.953071 mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles		yield(%)
Output	(40a)		348.39			**332.04** mg		0.95307	mmol	99.9999

total reaction mass	11574.03	mg
total reagents / reactants / cat. mass	1019.03	mg
total workup reagents mass		mg
total solvents (excl. water)	10555.00	mg
total water		mg
total waste	11241.99	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	34.9	34.9
solvent intensity	31.8	31.8
Sheldon E-factor	33.9	33.9
GSK Reaction Mass Efficiency	0.326	
Andraos Reaction Mass Efficiency	0.029	0.029
atom economy	0.614	
1 / stoichiom. factor (excess reagents)	0.531	
material recovery parameter	0.088	0.088
yield	1.000	

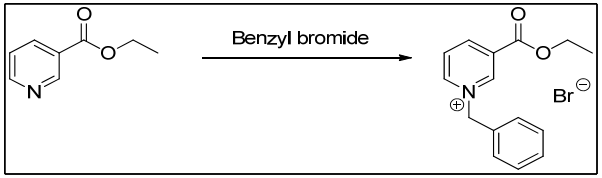


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
reactant	Nicotinic acid	59-67-6	123.11			**3.2**	g			25.99301	mmol	**1**	X	
reactant	Sulfuric acid	7664-93-9	98.0778			3.059205	g			31.19162	mmol	**1.2**		
reactant	Ethanol	64-17-5	46.07	0.816		40.8	g	**50**	mL	885.6089	mmol	34.07103		
reagent	Sodium bicarbonate	144-55-8	84.01			4.367346	g			51.98603	mmol	**2**		
wu solvent	Water		18	1		20	g	**20**	mL					
wu solvent	Dichloromethane	75-09-2	84.93	1.325		33.125	g	**25**	mL					
product	Ethyl nicotinate	614-18-6	151.16	1.102		3.929104	g	3.56543	mL	25.99301	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		yield(%)
Output	Ethyl nicotinate	614-18-6	151.16	1.102		**2.95**	g	2.676951	mL	19.51574	mmol	75.08073

total reaction mass	104.55	g
total reagents / reactants / cat. mass	51.43	g
total workup reagents mass		g
total solvents (excl. water)	33.13	g
total water	20.00	g
total waste	101.60	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	28.7	35.4
solvent intensity	11.2	18.0
Sheldon E-factor	27.7	34.4
GSK Reaction Mass Efficiency	0.057	
Andraos Reaction Mass Efficiency	0.035	0.028
atom economy	0.347	
1 / stoichiom. factor (excess reagents)	0.220	
material recovery parameter	0.608	0.492
yield	0.751	

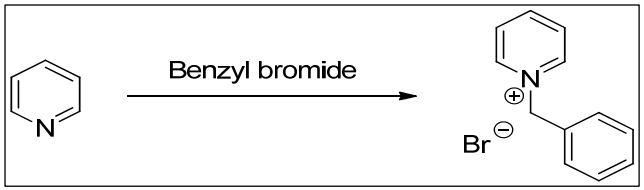


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
reactant	Ethyl nicotinate	614-18-6	151.16	1.102		**2.9**	g	2.631579	mL	19.18497	mmol	**1**	X	
reactant	Benzyl bromide	100-39-0	171.03	1.438		3.4512	g	**2.4**	mL	20.17892	mmol	1.051809		
solvent	Acetone	67-64-1	58.08	0.791		11.865	g	**15**	mL					
wu solvent	Ethyl acetate	141-78-6	88.11	0.902		20.295	g	**22.5**	mL					
wu solvent	Methanol	67-56-1	32.04	0.791		1.9775	g	**2.5**	mL					
wu solvent	Diethyl ether	60-29-7	74.12	0.706		7.06	g	**10**	mL					
product	Pyridinium, 3-(ethoxycarbonyl)-1-(phenylmethyl)-, bromide	72551-50-9	322.19			6.181205	g			19.18497	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	Pyridinium, 3-(ethoxycarbonyl)-1-(phenylmethyl)-, bromide	72551-50-9	322.19			**4.66**	g		14.46352	mmol	75.38983

total reaction mass	47.55	g
total reagents / reactants / cat. mass	6.35	g
total workup reagents mass		g
total solvents (excl. water)	41.20	g
total water		g
total waste	42.89	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	10.2	10.2
solvent intensity	8.8	8.8
Sheldon E-factor	9.2	9.2
GSK Reaction Mass Efficiency	0.734	
Andraos Reaction Mass Efficiency	0.098	0.098
atom economy	1.000	
1 / stoichiom. factor (excess reagents)	0.973	
material recovery parameter	0.134	0.134
yield	0.754	



Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
reactant	Pyridine	110-86-1	79.1	0.978		9.78 g	**10** mL	123.641 mmol	**1**	X	
reactant	Benzyl bromide	100-39-0	171.03	1.438		28.76 g	**20** mL	168.1576 mmol	1.360048		
solvent	Toluene	108-88-3	92.14	0.865		43.25 g	**50** mL				
wu solvent	Diethyl ether	60-29-7	74.12	0.706		21.18 g	**30** mL				
product	N-Benzylpyridinium bromide	2589-31-3	250.13			30.92631 g		123.641 mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	yield(%)
Output	N-Benzylpyridinium bromide	2589-31-3	250.13			**24.8** g		99.14844 mmol	80.19061

total reaction mass	102.97	g
total reagents / reactants / cat. mass	38.54	g
total workup reagents mass		g
total solvents (excl. water)	64.43	g
total water		g
total waste	78.17	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	4.2	4.2
solvent intensity	2.6	2.6
Sheldon E-factor	3.2	3.2
GSK Reaction Mass Efficiency	0.643	
Andraos Reaction Mass Efficiency	0.241	0.241
atom economy	1.000	
1 / stoichiom. factor (excess reagents)	0.802	
material recovery parameter	0.374	0.374
yield	0.802	

List of Publications

- **Highly recyclable, imidazolium derived ionic liquids of low antimicrobial and antifungal toxicity: A new strategy for acid catalysis**, L. Myles, R. Gore, N. Gathergood, S. J. Connon, *Green Chem*., 2010, **12**, 1157-1162.

- **A new generation of aprotic yet Brønsted acidic ionic liquids: low toxicity, high recyclability and greatly improved activity**, L. Myles, R. G. Gore, N. Gathergood, S. J. Connon, 2012, submitted.

- **A new generation of aprotic yet Brønsted acidic imidazolium ionic liquids: Effect of ester/amide groups in the C-2, C-4 and C-5 on antimicrobial toxicity and biodegradation,** R. G. Gore, L. Myles, M. Spulak, T. M. Garcia, S. J. Connon, N. Gathergood, 2012, submitted.

- **Book Chapter - 'Safer and Greener Catalysts - Design of high performance, biodegradable and low toxicity ionic liquids'**, (Book title: Ionic Liquids - New Aspects for the Future, InTech), in press.

- **Asymmetric Carbonyl-Ene Reaction of Trifluoropyruvate in "Low-toxic" Ionic Liquids,** R. G. Gore, T.-K.-T. Truong, M. Spulak, S. Connon, N. Gathergood, 2012, manuscript in preparation.