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GREENER SYNTHESES & SOLVENTS FOR FINE AND PHARMACEUTICAL CHEMICALS

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Abstract

In this PhD thesis new eco-friendly methodologies for the preparation of fine chemicals and Active Pharmaceutical Ingredients, with particular attention to the solvent use, were sought. A new green synthesis of task specific onium ionic liquids was achieved via the methylation of trialkylphosphines and amines using dimethyl carbonate as the methylating agent. Thus, a set of methoxycarbonylated onium salts were prepared. These products were further reacted with both water and protic acids to produce ionic liquids possessing different acid base properties.

The carbonate ionic liquids (CILs) obtained have been used as base catalysts for the condensation of aldehydes and ketones with nitroalkanes. In this study, basic ionic liquids catalysts have been compared to conventional organic base catalysts (for example DBU, PhTMG, NEt_3 and DMAP). In agreement with the main subject of this thesis, the reactions were conducted without the addition of solvent, avoiding the use of volatile and/or toxic solvents.

Not only did the CILs reveal themselves as efficient catalysts, also onium salts bearing other anions proved useful in catalysis. Nitrate exchanged phosphonium ionic liquids were able to promote electrophilic aromatic oxychlorination. In addition their liquid nature allowed to carry out the reaction in the phosphonium nitrate salt as the solvent, avoiding the usual chlorinated VOC. Our study also demonstrated the catalytic nature of the nitrate ionic liquid allowing to propose a mechanism in which the oxidant is atmospheric oxygen .

As an example of active pharmaceutical ingredient, the preparation of Tadalafil (commercially named Cialis™) through a more enviromental compatible route was studied. We focussed on the solvent issue. In collaboration with QUILL at the Queen's University of Belfast, the use of ionic liquids was considered in order to improve the overall mass index of the preparation. Dimethylcarbonate proved an excellent solvent for a particular synthetic step involved in the preparation, while an ionic liquid was successfully used to carry out two steps in a single batch in substitution of two volatile solvents.

In partnership with Galentis S.r.l. [a fine chemical manufacturer located in Marcon (VE)] we sought new synthetic methodologies involving reduced amounts of solvent (especially chlorinated ones) and/or more environmental acceptable solvents and reagents. In particular we investigated the preparations of the following compounds: i) chlorinated [2.2]-p-clyclophanes

(polymer intermediates) ii) trimethylorthoesters (used for steroids derivatisation) and iii) furaniminium bromide (intermediate in the Loperamide preparation).

Contents

List of abbreviations IX

1 Introduction 1

1.1 Green Chemistry 1

1.1.1 Sustainable development and Green Chemistry 1

1.1.2 Definition and Concepts of Green Chemistry 4

1.1.3 Green chemistry metrics 6

1.2 Critiques to green chemistry 8

1.3 Green chemistry in the fine chemicals and API industry sectors 10

1.4 Alternative solvents for Green Chemistry 11

1.5 Green chemistry tools used in this thesis 15

1.5.1 Organic carbonates 15

1.5.2 Ionic liquids 19

1.5.3 Green Solvents: relevant examples. 24

1.5.3.1 2-Methyltetrahydrofuran *24*

1.5.3.2 Cyclopentylmethylether *25*

1.5.3.3 Ethyl Lactate *25*

1.5.3.4 Dimethylcarbonate (DMC) *26*

1.6 Aim and summary of the Thesis 26

1.6.1 Ionic liquids synthesis and application to organic synthesis 27

1.6.1.1 Onium salts synthesis *27*

1.6.1.2 Carbonate ionic liquids as basic catalysts *27*

1.6.1.3 Electrophilic aromatic chlorination. *28*

1.6.2 Synthesis of fine chemicals and pharmaceutical active ingredients 28

1.6.3 Greener processes in collaboration with Galentis S.r.l. 29

1.6.3.1 Dichloro-[2.2]-p-cyclophanes *30*

1.6.3.2 Trimethylorthoesters *30*

1.6.3.3 Furanimium bromide *31*

1.7 References 32

2 Onium ionic liquids made with dimethylcarbonate: green solvents by a green synthesis 39

2.1 Introduction 39

2.2 Aim of the research 40

2.3 Results and discussion 41

2.3.1 Quaternarisation with DMC 41

2.3.2 Anion Metathesis...43

2.3.3 Characterisation by neat NMR 46

2.3.4 Properties of the synthesised Onium salts 47

2.3.4.1 Application as solvents...47

2.3.4.2 Catalytic properties of phosphonium salts 48

2.3.4.2.1 Basicity of methyl carbonate and bicarbonate -onium salts 48

2.3.4.2.2 Phosphonium salts catalysed alkylation of aniline by alkylene carbonate 49

2.4 Conclusions 50

2.5 Experimental section...52

2.6 References 60

3 Onium salts: applications as solvents/catalysts for organic reactions......63

3.1 Preamble 63

3.2 Basicity of carbonate ionic liquid. A case study: the Henry reaction...............64

3.2.1 Introduction 64

3.2.2 Aim of the research 65

3.2.3 Results and discussion..66

3.2.3.1 Evaluation of the catalytic activity of phosphonium carbonate salts by comparison with different organo bases. 66

3.2.3.2 The Henry reaction of different aldehydes with nitroethane.........................69

3.2.3.3 The Henry reaction of different ketones with nitroalkanes. 71

3.2.3.4 Mechanism proposal 75

3.2.4 Conclusions 76

3.2.5 Experimental section 77

3.2.5.1 General information..77

3.2.5.2 The addition of nitroethane to 3-phenilpropionaldehyde catalysed by different basic systems...77

3.2.5.3 Reaction of different aldehydes with nitroethane in the presence of CILs as catalysts...78

3.2.5.4 The addition of different nitroalkanes to cyclic ketones in the presence of CILs as catalyst *79*

3.2.5.5 Characterization data *81*

3.3 Phosphonium nitrate ionic liquid catalysed electrophilic aromatic oxychlorination. **83**

3.3.1 Introduction 83

3.3.2 Aim of the research 84

3.3.3 Results and discussion 85

3.3.3.1 Monochlorination of arenes *85*

3.3.3.2 Dichlorination of arenes *89*

3.3.3.3 Ionic liquid recycling *91*

3.3.3.4 Proposed nitrate catalysed electrophilic chlorination mechanism *91*

3.3.4 Conclusions 94

3.3.5 Experimental Section 95

3.3.5.1 General *95*

3.3.5.2 Ionic liquids *95*

3.3.5.3 Chlorination of arenes *95*

3.3.5.4 Chlorination of anisole (larger scale) *96*

3.3.5.5 Dichlorination of arenes (Method A) *96*

3.3.5.6 Dichlorination of anisole (Method B) *96*

3.3.5.7 Recycling Procedure *96*

3.3.5.8 Chloride assay *97*

3.3.5.9 Characterisation data *97*

3.4 Concluding remarks **99**

3.5 References **100**

4 Green alternative procedures for Tadalafil preparation **103**

4.1 Introduction **103**

4.2 State of the art **104**

4.2.1 Process details 104

4.2.2 Diastereoselectivity via CIAT process 105

4.3 Aim of the research **107**

4.4 Results **109**

4.4.1 Esterification of tryptophan promoted by DMC (step 1) 109

4.4.2 Pictet-Spengler reaction ionic liquid (Step 2) 111
4.4.3 The acyl-Pictet-Spengler reaction in ionic liquid 114
4.4.4 Pictet-Spengler reaction in dimethylcarbonate 114
4.4.5 Acetylation in ionic liquid (step 3) 115
4.4.6 Amination and cyclisation (step 4) 116
4.4.7 Alternative procedure (integrated) 116

4.5 Metrics for processes comparison 118

4.6 Conclusions 121

4.7 Experimental section 123

4.7.1 General 123
4.7.2 Esterification of tryptophan using DMC and H_2SO_4 123
4.7.3 Esterification of tryptophan using DMC and H_3PO_4 124
4.7.4 Esterification of tryptophan using MeOH and thionylchloride 124
4.7.5 Pictet-Spengler reaction in ionic liquids 124
4.7.6 Acyl-Pictet-Spengler reaction in ionic liquids 125
4.7.7 Pictet-Spengler reaction in DMC 125
4.7.8 Tadalafil syntheses 125
4.7.9 Ionic liquid recycling 126
4.7.10 Characterisation data 126

4.8 References 128

5 Greener processes in collaboration with Galentis S.r.l. 131

5.1 Introduction 131

5.2 Chlorination of [2.2]-paracyclophane in alternative solvents 133

5.2.1 Introduction: Chlorinated paracyclophanes in industry 133
5.2.2 Aim of the research 136
5.2.3 Results and discussion 137

5.2.3.1 [2.2]paracylophane chlorination in ionic liquids 137
5.2.3.2 [2.2]paracylophane chlorination in ionic liquids using a co-solvent 138
5.2.3.3 Reaction in ionic liquid using alkaline salts as additives 139
5.2.3.4 Chlorination under solvent free conditions 141
5.2.3.5 Chlorination in alternative Green Solvents 143

5.2.1 Conclusions 148
5.2.2 Experimental section 149

5.2.2.1 General informations *149*
5.2.2.2 Paracyclophane chlorination using nitrate ionic liquids *150*
5.2.2.3 Operations and apparatus for chlorine gas handling *150*
5.2.2.4 Chlorination of paracyclophane under solvent free conditions *152*
5.2.2.5 Chlorination of paracycloparacyclophane using alternative solvents *152*
5.2.2.6 Optimisation of conditions for chlorination of paracycloparacyclophane in DMC *152*
5.2.2.7 Characterisation data *153*
5.3 Trimethyl Orthoesters 155
5.3.1 Introduction 155
5.3.2 Aim of the research 158
5.3.3 Results and discussion 160
5.3.3.1 Orthoesters preparation in ionic liquids *161*
5.3.3.2 Orthoesters preparation using no added solvents *162*
5.3.3.2.1 First step 162
5.3.3.2.2 Second step: alcoholysis 164
5.3.3.3 Synthesis of trimethylorthobenzoate TMOB *165*
5.3.3.3.1 Anion metathesis 166
5.3.3.3.2 Alcoholysis of anion exchanged benzoimidate salts 167
5.3.4 Conclusions 169
5.3.5 Experimental section 172
5.3.5.1 General *172*
5.3.5.2 Pinner synthesis in ionic liquid *172*
5.3.5.2.1 First step 172
5.3.5.2.2 Second step (alcoholysis) 173
5.3.5.3 Reaction of benzonitrile with methanol - optimisation *173*
5.3.5.4 Pinner synthesis using no added solvent *173*
5.3.5.5 Benzoimidate anion exchange *174*
5.3.5.6 Pinner synthesis of trimethylorthobenzoate *174*
5.3.5.7 Characterisation data *175*
5.4 Furaniminium bromide 177
5.4.1 Introduction 177
5.4.2 Aim of the research 180
5.4.3 Results and discussion 181

5.4.3.1 Reaction with thionyl chloride in different alternative solvents 182

5.4.3.2 Amide formation using aqueous dimethylamine in different solvents........184

5.4.3.3 Amide formation using anhydrous amine in DMC....................................185

5.4.3.4 Amide formation through the imidoyl derivative 186

5.4.4 Conclusions 187

5.4.5 Experimental section 189

5.4.5.1 Acid chloride preparation in chloroform...189

5.4.5.2 Acid chloride preparation in toluene 189

5.4.5.3 Acid chloride preparation in dimethylcarbonate.......................................189

5.4.5.4 Furaniminium bromide preparation in dimethylcarbonate 189

5.4.5.5 Imidazole derivative ***44*** *synthesis and reaction with dimethylamine.........191*

5.4.5.6 Reaction of imidazole derivate ***44*** *with dimethylamine 191*

5.4.5.7 Characterisation data 191

5.5 References 192

6 Concluding remarks 197

6.1 Paper originated from this thesis...199

6.2 Acknowledgement 200

A1. Appendix...203

A2. Chapter 2 205

Onium ionic liquids made with dimethylcarbonate: green solvents by a green synthesis 205

A3. Chapter 3 239

Onium salts: applications as solvents/catalysts for organic reactions........239

A.3.1 Basicity of carbonate ionic liquid. A case study: the Henry reaction.........239

A4. Chapter 4 259

Green alternative procedures for Tadalafil preparation 259

A5. Chapter 5 265

Green synthetic strategies implementation in collaboration with Galentis S.r.l. 265

A.5.1 Chlorination of [2,2]-paracyclophane in alternative solvents 265
A.5.2 Trimethyl Orthoesters preparation 269
A.5.3 Furaniminium bromide preparation 273

List of abbreviations

AE	Atom economy
API	Active Pharmaceutical Ingredient
C_2mim	1Ethy-3-methyllimidazolium
C_4dmim	1-Butyl-2,3-dimethylimidazolium
C_4*i*Q	*N*-Butyl-*iso*-quinolinium
C_4mim	1-Butyl-3-methylimidazolium
CE	Carbon efficiency
cGMP	cyclic guanosine 3,5-monophosphate
CI	Cost index
CIAT	Crystallisation Induced Asymmetric Tranformation
CIL	Carbonate ionic liquid
CPME	Cyclopentylmethylether
DABCO	1,4-diazabicyclo[2.2.2]octane
DAlC	Dialkylcarbonate
DBU	1,8-Diazabicycloundec-7-ene
DCM	Dichloromethane
DEC	Diethylcarbonate
DMA	Dimethylamine
DMAP	Dimethylaminopyridine
DMC	Dimethylcarbonate
DMF	Dimethylformamide
DMS	Dimethylsulfate
DMSO	Dimethylsulfoxide
E	Environmental factor
EL	Ethyl Lactate
EMY	Effective mass yield
FDA	Food and Drug Administration
FID	Flame Ionisation Detector
GC	Gascromatography
GOST	Green Organic Syntheses Group
HMQC	Heteronuclear Multiple Quantum Coherence
IL	Ionic Liquid
INADEQUATE	Incredible Natural Abundance Double Quantum Transfer Experiment
LCA	Life Cycle Assessment
L-Phe	L-Phenylalanine
ME	Mass Efficiency
MeTHF	2-Methyltetrahydrofuran
MRP	Mass Recovery Parameter
MS	Mass Spectroscopy
$N_{6,6,6,1}$	Methyl-tri-*n*-hexylammonium

$N_{8,8,8,1}$	Methyl-tri-*n*-octylammonium
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Effect Spectroscopy
NTf_2	bistrifluoromethanesulphonylimide
OIL	Onium ionic liquid
$P_{4,4,4,1}$	Methyl-tri-*n*-butylphosphonium
$P_{6,6,6,1}$	Methyl-tri-*n*-hexylphosphonium
$P_{8,8,8,1}$	Methyl-tri-*n*-octylphosphonium
PDE	Phosphodiesterase
PhTMG	2-Phenyl-1,1,3,3-tetramethyl guanidine
$P_{i(4,4,4),1}$	Methyl-tri-*i*-butylphosphonium
PPA	3-Phenylpropionaldehyde
QUILL	Queen's University Ionic Liquid Laboratories
RME	Reaction mass efficiency
RT	Room Temperature
S^{-1}	Mass index
SF	Stoichiometric Factor
TBP	Tri-*n*-butylphosphine
TFA	Trifluoroacetate
TFFA	Trifluoroacetic acid
THA	Tri-*n*-hexylamine
THF	Tetrahydrofuran
THP	Tri-*n*-hexylphosphine
T*i*BP	Tri-*i*-butylphosphine
TMOB	Trimethylorthobenzoate
TMOP	Trimethylorthopropionate
TMOV	Trimethylorthovalerate
TMS	Tetramethylsilane
TOA	Tri-*n*-octylamine
TOP	Tri-*n*-octylphosphine
TsOH	*p*-Toluenesulfonic acid

1 Introduction

1.1 Green Chemistry

1.1.1 Sustainable development and Green Chemistry

According to the Cambridge dictionary[1] the word “sustainable” is defined as “able to continue over a period of time”. A second definition is also reported: “causing little or no damage to the environment and therefore able to continue for a long time”. The terms *sustainable* and *sustainability* have been used with this particular meaning from the 1980s. The idea of sustainability in the sense of human activity sustainability on planet earth dates back more than 40 years, to the new mandate adopted by IUCN, International Union for Conservation of Nature in 1969.[2] Over these decades the evolution of the definition of *sustainability* and more specifically of *sustainable development* evolved through a series of different approaches.[3] Sustainable development could be defined as *“meeting the needs of the present without compromising the ability of future generations to meet their own needs.”*[4] Essentially sustainable development is about common sense!

The reason why humanity is now facing with this problem is that it was finally recognised it is impossible to continue with this level of growing population and resources consumption.

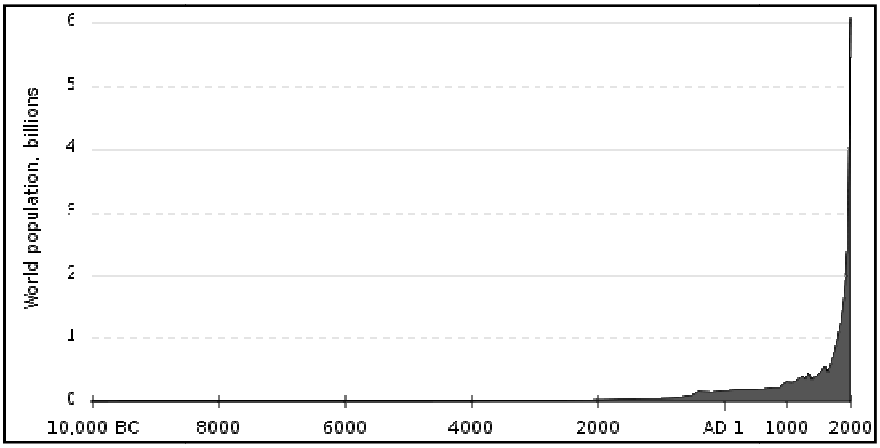


Figure 1.1 World human population (est.) 10,000 BC–2000 AD[5].

It was estimated that lifestyles and consumption patterns of people in the developed world, if replicated by everyone on earth, would require 3 planets to meet our needs.

Contrary to apparent popular belief we have only one!

The reduction of resource consumption and waste production through a return to a wholly agrarian, pre-industrial economy, even if it appears like a very appealing solution to someone, is not an option. In the UK, for instance, it has been estimated that a wholly agrarian, pre-industrial, economy could support only 15 M of the current 60 M population[6]. As Norbert Wiener, the father of cybernetics said over 50 years ago: 'we live by the grace of invention'.[7]

It is possible to formulate an equation[8] based on the Earth's capacity EC, the total population exploiting it P, the consumptive (essentially equating to economic) activity of the average person C, and an appropriate conversion factor between activity and environmental burden B.

$$E\,C = P \times C \times B$$

Since it is not simple to find other planets to exploit, we need to reduce the number of planets we need. To do so, it is possible to act on one of these entities:

1. The world population P
2. The average individual prosperity, wealth or economic activity C
3. The burden on the planet per unit of economic activity B

Since the points 1 and 2 are very difficult to control efficiently, we have to act on the third point. The only thing to do to equilibrate the growing population and expectation of people living in the emerging countries is to improve efficiency of economic activity, and this can be done in two ways:

a) Dematerialisation (use less resource per person)
b) Transmaterialisation (replacement of current raw materials including energy)

To achieve these goals, it will be critical to develop cleaner, less waste producing and more efficient technologies. Chemistry is one of the enabling tools.

It should be noted that the concern for environment of citizens and governments (often only for electoral purposes) is relatively recent. Only few decades ago there were little or no environmental regulations on chemical production, on their use and disposal, and it was not uncommon for chemical substances to be released directly to the air, water and land. Moreover, there was a deep lack of knowledge about the hazard of chemicals and their effects on the environment and human health. The concept of "dilution is the solution to pollution" was the guideline until the issue of the "environmental impact" of chemical substances come impetuously into the public debate after some well known disasters. It is from the early 1960s that the first negative, and sometimes tragic, consequences due to a misuse of chemicals emerged, causing public outcries that resulted in laws and regulations to control the manufacture, treatment or disposal of chemicals.[9]

A major consequence of all these misuses and accidents was that from 1960s environmental laws and regulations have proliferated at an exponential rate (figure 1.2).[10]

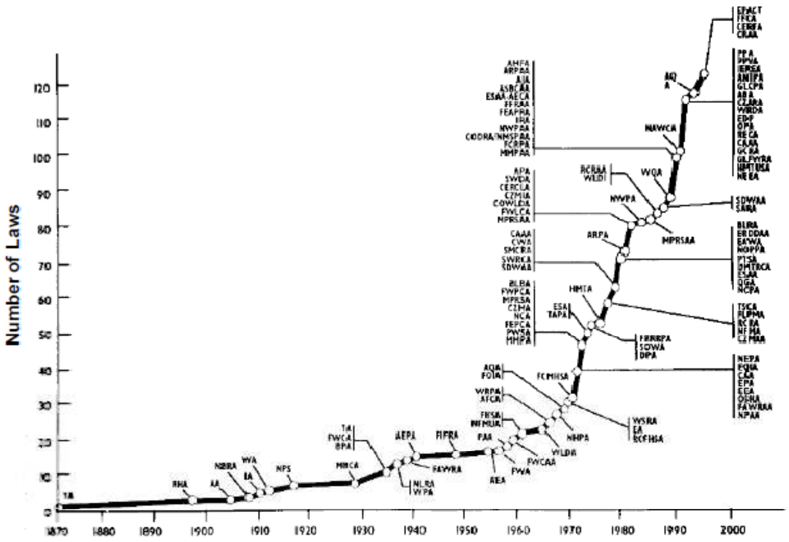


Figure 1.2 Proliferation of environmental laws and regulations (USA)

Many different ways were developed to reduce pollution, like the use of treatment technologies for remediation of compromised situations. This approach does not solve the problem at the source, but deals with the issue of transforming wastes into more innocuous forms in order to minimize the impacts of chemicals. A better approach is summarised in this sentence:

"Prevent is better than treat"

In this direction a new idea of designing human activity was developed and the term *"green"* was used to qualify everything that was characterized by an environmental protection orientation.

The application of fundamental engineering concepts for the improvement of manufacturing processes with the aim of reducing the impact on the environment is known as *Green engineering*. According to the definition promoted by the Environmental Protection Agency (EPA), green engineering is "the design, commercialization and use of processes and products that are feasible and economical while minimizing: generation of pollution at the source, and risk to human health and the environment".[11] The green engineer uses the tools of recycle, process intensity, and design optimization to maximize the efficiency of the process, and reduce its burdens on the environment.

Green engineering evaluates the manufacturing process as a system and seeks to optimize its design, and in the truest sense, incorporates the concepts of life-cycle analysis and environmental economics into an appropriate evaluation of the overall environmental impact.

For what concerns chemistry, the increased restrictions on the use of certain compounds also provided powerful incentives for industry (confronted by tremendous pressure, not only to reduce the release of toxic product to the environment, but also to reduce the use of hazardous chemicals) and chemists to find replacements, substitutes, or alternatives.[10] In particular, at the beginning of 1990s, chemists started facing the issue of the "environmental impact" trying to find a way not only to reduce pollution, but to prevent it already at the stage of synthetic pathway design. This new approach, that provides a fundamental methodology for changing the intrinsic nature of a chemical product or process to make it inherently of less risk to human health and the environment, was named later with the term "*green chemistry*".[12,13,14]

1.1.2 Definition and Concepts of Green Chemistry

Green chemistry has become an internationally recognized focus area of chemical science and it is defined by IUPAC as "*the invention, design and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances*".[9,10]

The definition includes the term "*hazardous*". Green chemistry is a hazard-based approach to risk reduction and pollution prevention by minimizing the intrinsic hazards of the substances, rather than focusing on those circumstances and conditions of their use that might increase their risk. This is a very important aspect, and to understand it there is the need to introduce the concept of risk. At its most basic level, risk can be described as the product of hazard times exposure:[10]

Risk = Hazard x Exposure

The traditional approaches to risk reduction focus on reducing exposure to hazardous substances. Regulations often require the best available control and treatment technologies, and the use of personal protective equipment in order to reduce risk by limiting exposure. But these approaches may fail because they rely on either equipment or human activity: equipment can rupture, air scrubbers can break down, etc. When failure occurs, risk is maximized because the resultant is an increased exposure to a constant hazard. The green chemistry approach, on the other hand, imposes to reduce risk by reducing hazard associated to chemical products and transformations. This different approach makes green chemistry virtually invulnerable to failure, since, even in the case of uncontrolled exposure the risk remains tolerable when using innocuous materials, *i.e.* the hazard is very low.

Moreover, the definition of green chemistry also illustrates another important point about the use of the term "*hazard*". This term is not restricted to physical hazards such as explosiveness, flammability and so on, but it includes also acute and chronic toxicity, carcinogenicity, and ecological toxicity. Furthermore, for the purposes of this definition, hazards must include global threats such as global warming, stratospheric ozone depletion, resource depletion and bioaccumulation, and persistent chemicals.

The twelve principles of green chemistry, as articulated by Anastas and Warner,[9] can guide chemists towards fulfilling their rôle in achieving sustainable development. These principles are listed below:

1. It is better to prevent waste rather than to treat or clean up waste after it is formed
2. Synthetic methods shoud be designed to maximise the incorporation of all materials used in the process into the final product
3. Wherever practicable, synthetic methodologies should be designed to use and generate substances that posses little or no toxicity to human health and the environment
4. Chemical products should be designed to preserve efficacy of function while reducing toxicity.
5. The use of auxiliary substances (e.g. solvents, separation agents) should be made unecessary wherever possible and innocuous when used.
6. Energy requirements should be recognised for their environmental and economic impacts and should be minimised.
7. A raw material or feedstock should be renewable rather than depleting, wherever technically and economically practicable.
8. Unnecessary derivatisation (blocking group, protection/deprotection, temporary modification of physical/chemical processes) should be avoided whenever possible
9. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents
10. Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products
11. Analytical methodologies need to be further developed to allow for real time, in-process monitoring and control prior to the formation of hazardous substances

12. Substances and the form of a substance used in a chemical process should be chosen so as to minimise the potential for chemical accidents, including releases, explosions and fire.

The 12 principles have become a widely accepted set of criteria for the rapid assessment of the "greenness" of a chemical route. Yet, they are not certainly exhaustive,[15] since they do not directly settle practical parameters that chemists can use to evaluate and compare the greenness of different processes. Also, they do not provide a quantitative measure of environmental performance.

To achieve improved chemical synthesis reducing or even eliminating toxic starting material, by-products and wastes, new alternative green chemistry tools are needed:

1. Alternative feedstocks/starting materials
2. Alternative reagents
3. Alternative solvents
4. Alternative products/target molecules
5. Alternative catalysts

1.1.3 Green chemistry metrics

Mathematical treatment of the environmental compatibility of a given reaction or process is an indispensable requirement for the definition of "green chemistry" as a proper scientifically based discipline. To assess "greenness" in a simple but quantitative approach, a set of parameters to measure efficiency of a given process and principally to rank such a process against others have been defined.[16]

Here are reported briefly the most used and helpful metrics for green processes engineering. All these parameters are named "*green chemistry metrics*". Some examples of the more widely used metrics are reported in Table 1.1.

The environmental factor (E) measures the greenness of a process considering the amount of waste that is generated for each kg of desired product: the main limit of this metric is the difficulty of define a boundary for what must be considered as waste.[17] The atom economy (AE), measures the degree of incorporation of reactants in the desired product but does not consider the yield or the nature of wastes.[18] The reaction mass efficiency (RME) and the carbon efficiency (CE) join together the concept of atom economy and yield, considering the mass or the carbon content respectively, but still the wastes are not considered.[19]

Table 1.1 Summary of the most used green chemistry metrics

Metric	Acronym	Formula
Environmental factor	**E**	$E = \frac{\text{total waste [kg]}}{\text{product [kg]}}$
Atom economy	**AE**	$AE = \frac{\text{m.w. product}}{\Sigma \text{ m.w. reagents}} \times 100$
Reaction mass efficiency	**RME**	$RME = \frac{\text{mass of product [kg]}}{\Sigma \text{ mass reagents [kg]}} \times 100$
Carbon efficiency	**CE**	$CE = \frac{\text{carbon mass in product [kg]}}{\Sigma \text{ carbon masses in reagents [kg]}} \times 100$
Mass index	$\mathbf{S^{-1}}$	$S^{-1} = \frac{\Sigma \text{ reagents + catalysts + solvents [kg]}}{\text{product [kg]}}$
Cost index	**CI**	CI = € / kg of product

The mass index (S^{-1}) is a metric that defines the overall mass flow in a chemical process, by taking into account the degree of incorporation of all the substances used in a process into the final desired product.[19] Finally, the cost index (CI) is a parameter that sets if a synthetic procedure is economically viable once all costs (upstream and downstream) are considered. It should be stressed here that in the design/evaluation of a process, the consideration of only one of these metrics does not give a complete information about the greenness of the procedure. Let’s consider for example AE: this is a good parameter for a preliminary evaluation of the greenness of a synthetic transformation, but it is not suitable as a standalone green chemistry metric, since it does not consider the yield and the wastes of a process. Other metrics often give a more realistic assessment of a reaction: for instance, RME examines the process in terms of yield and molar quantities involved. The mass index, S^{-1} considers the overall mass flow of the chemical process.

When a "greener process" is needed often conventional metrics are not enough Actually all the metrics previously described consider only masses of reactants, products, catalysts, solvents etc. On the other hand it would be a mistake to leave a discussion of metrics at the point of only considering mass implications. Clearly, wasted resources may have significant cost implications, but also hazardous processes could cause costs to rise up. Prevention may be a very expensive issue. As an example, given a process characterised by very high atom economy and a very low amount of by produced waste, the same process can use a very toxic reagent, or a very hazardous material (pyrophoric substances or extremely flammable gas); therefore it is not correct to say that this process is really "green". On the other hand we can consider the case of a company searching for a new process to avoid the use of a toxic reagent or solvent in the preparation of a chemical product. Sometimes to replace a solvent some modification to the synthetic procedure are required, so the new procedure involving an environmental friendly solvent could be characterised by a lower mass index or an higher E factor. If that is the case, it is not clear if the new synthetic route is really "greener".

Different approaches to take into account these issue were reported. For example *effective mass yield*, proposed by Hudlicky and co-workers[20], makes a distinction between benign and non-benign reagents, thus considering not only the mass of reactants, but also their nature.

$$\text{Effective mass yield} = \frac{\text{Mass of product x 100}}{\text{Mass of non benign reagent}}$$

Anyway no scale of "benigness" was introduced leaving the choice of what can be considered benign or not as a subjective matter. Koen Van Aken and co-workers developed a scale of safety and ecological friendliness they named *EcoScale*[21]. The EcoScale is obtained by assigning a value of 100 to an ideal reaction then subtracting penalty points for non-ideal conditions.

A complete LCA remains the best way to assess a new synthtic pathway or alternative material or procedure implementation. However simple, easy to calculate parameters like the described metrics, together with the 12 principles, can guide chemists to develop new, environmental friendly procedures or synthetic steps.

1.2 Critiques to green chemistry

Public awareness of environmental and social issues are in many cases now well developed and citizens tend to feel that the quality of the environment is important both to their own wellbeing and to the common good. For example a recent survey[22] on italian consumers, shows that more than 50 % of the people is oriented towards "green behaviours" (especially young generations). In other words: "*it's hip to be green!*"

The attention to environmental issues is now so high that almost everything is claimed to be "*green*". Companies understood this dynamics of consumer behaviour many years ago. The so called *green marketing* is the marketing of products that are presumed to be environmentally safe.[23] Companies launched a number of "green" products, bearing appealing green labels representing plants, trees and rivers (Figure 1.3).

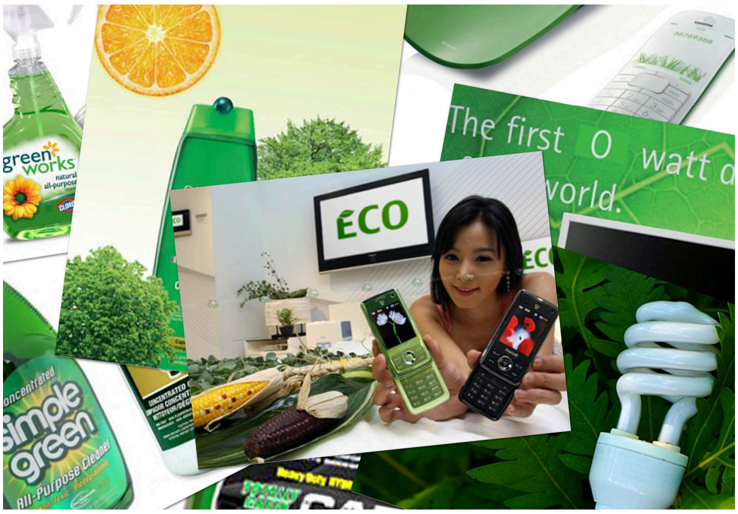


Figure 1.3 Green marketing takes advantage of the enthusiasm for sustainable development.

The term “*green*” is increasingly used and like all concepts that become a fashion it is likely to be inflated and progressively void of the original meaning. Obviously it is not sufficient to colour a product green to render it more environmental compatible. "*Greenwashing*" is a neologism indicating the unjustified claiming of environmental virtue by companies, industries, political entities or organizations to gain a positive image of their business (or products). This allows to divert attention from their responsibilities in negative environmental impacts. This tendency leads many to have suspicion toward all that is labelled as "green", because it seems more a marketing operation than a real improvement towards environmental compatibility.

In chemistry the problem is analogous. Some researches trot out green claims without sufficient thought. For example water (apparently a safe and environmentally friendly solvent) is not always so green: in reactions catalysed by small organic molecules, the final waste-stream of water contaminated with organics may be difficult and costly to clean up.[24] It is not enough to improve only one aspect to obtain a more environmental compatible process. For example, citing Walter Leitner, editor of Green Chemistry, "using a renewable feedstock may not make a reaction greener, if the new process turns out to be inefficient, hazardous, or hard to clean."

The term "green" is surely abused nowadays, a deeper thought on what is really environmental compatible is required. On the other hand a new process need not be absolutely green, but only relatively greener than its predecessor. Every single improvement, even in a single aspect of a synthesis could be a step forward towards sustainable development.

The key aim of Green Chemistry should be to attract more scientists to think about the improvement of the new technologies towards safer and more environmentally compatible chemistry, to the point that "Green Chemistry" as a separate field become unnecessary. In summary the objective of Green Chemistry should be the disappearance of the term green.

1.3 Green chemistry in the fine chemicals and API industry sectors

Scientists from various disciplines are involved in Green Chemistry in the pharmaceutical industry, and process chemists play a major role because process research can contribute to drastic improvements in the manufacture of active pharmaceutical ingredients (API)[25]. The processes of manufacturing structurally complex APIs require multiple steps and consequently generate large amounts of waste as can be seen in Table 1.2. Oil refining and bulk chemical production are nowadays the cleanest processes involving chemistry. It should be noted that volumes of these production are so huge that even if E-factors are below unity or less (especially in refining activities) the absolute amount of waste produced are far higher than that originated by fine chemicals and by the pharmaceutical industry. However oil refining and bulk chemical production use well established and deeply optimised technologies. Investments in these sectors were enormous during the last century and even before and the very low values of E-factor reported in Table 1.2 confirm that this effort in the field of research and development was fruitful.

Table 1.2 E-Factors across the chemical industry[17]

Industry Sector	Annual Production (t)	E-Factor	Waste Produced (t)
Oil Refining	10^6-10^8	Ca. 0.1	10^5-10^7
Bulk Chemicals	10^4-10^6	<1-5	10^4-5×10^6
Fine Chemicals	10^2-10^4	5-50	5×10^2-5×10^5
Pharmaceuticals	10-10^3	25-100	2.5×10^2-10^5

In the case of fine chemical and API production the scenario is completely different. An active ingredient often has such a high added value that its production is economically viable even if it causes the production of very high amount of waste and the consumption of raw materials. This was especially true before the sixties, when "dilution is the solution to pollution" approach was practiced.

The severe regulations imposed nowadays do not permit this to continue. The day by day growth of requirements[10] for industrial preparation in western countries drove companies to install plants in countries (China, India, etc.), where regulation were less stringent. Obviously this cannot be the solution for this problem for two reasons: *i*) we live on the same planet, therefore the problem is in the best case only delayed, *ii*) the consciousness of the inevitability of environmental preservation and human health protection policies is being formed also in emerging countries.

In current process chemistry, the term “industrially feasible” not only means “safe, scalable, convenient, and cost – effective” but also “environmentally friendly”.[26] The pharmaceutical industry has been accused in the past of being “ungreen”, but a reasoned observation will show that many of the ideas and much of the drive to push for changes in synthetic methodology, green chemistry, and engineering have come from certain groups and companies within the pharmaceutical industry.[27]

In 2007 GlaxoSmithKline (GSK) became the first company to set E factor goals.[28] In 2004 Pfizer started an influential program to reduce its use of chlorinated solvents with initial focus on dichloromethane due to its relatively high volume use in medicinal chemistry. The result was that the consumption of DCM was cut from 120 tonnes to 52. In 2008 the program was extended to include chloroform usage giving the result reported in Figure 1.4.

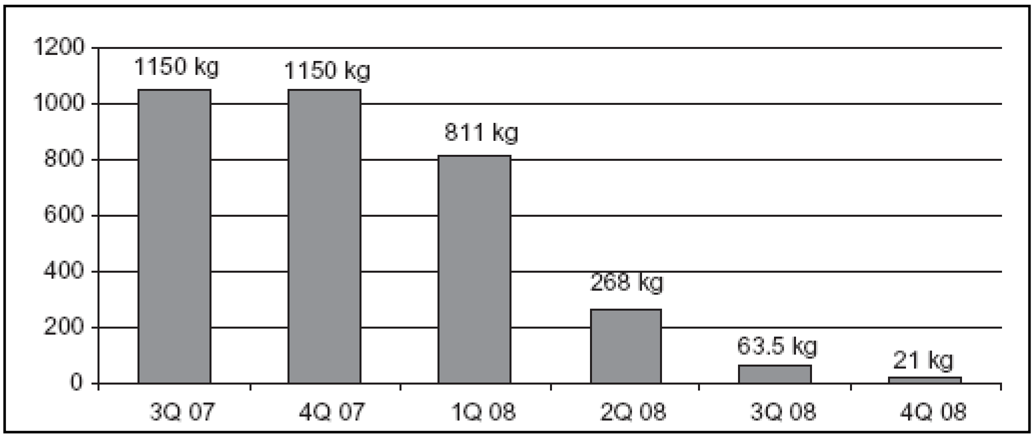


Figure 1.4. Chloroform use at Pfizer small molecule discovery sites.

The principles of Green Chemistry are currently most often applied to the redesign of API processes late in the development timeline or even post regulatory approval. Ideally, the principles of Green Chemistry should be incorporated into API manufacturing process design as early as possible. As the vast majority of APIs for patent-expired products are manufactured using processes developed without green chemical insights, the development of green processes for drugs manufactured by generic companies represents a great opportunity for innovation.[27]

1.4 **Alternative solvents for Green Chemistry**

The fifth principle of Green Chemistry regards the use of auxiliary substances, which can be defined as ones that aid in the manipulation of a chemical or chemicals. The most used auxiliary substances are by far solvents (Figure 1.5). This thesis work was particularly focussed on the solvent issue in the preparation of fine chemicals and APIs, therefore this paragraph is dedicated to this particular green chemistry tool.

Because of the wide range of hazards that can be exhibited by the large class of chemicals known as solvents, they have also tended to be some of the most highly regulated substances in the chemical industry.[29] The overall relevance of this issue can be better understood considering the quantities of solvents manipulated by the chemical industry. In recent years the worldwide consumption of organic solvents was be estimated around 20 million tons per year.[30]

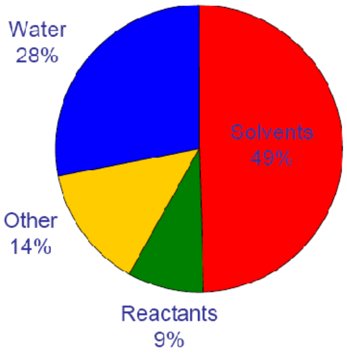
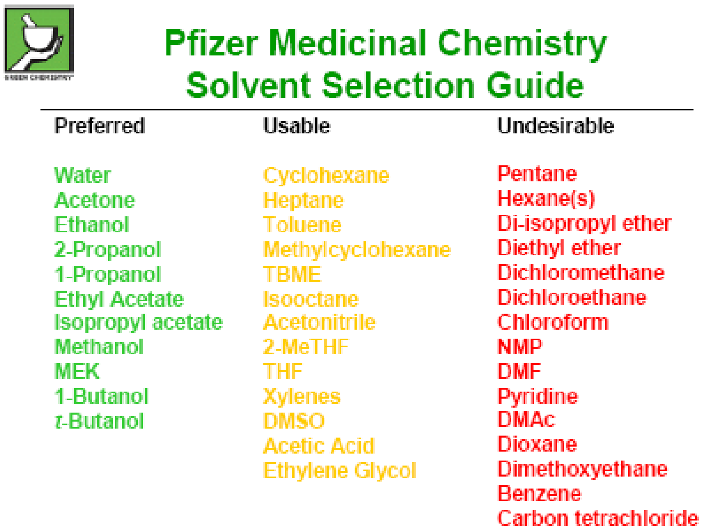


Figure 1.5. Contributions to the process mass intensity in the pharmaceutical industry.[31]

The development and selection of appropriate alternative solvents is becoming one of the crucial aspects to decrease environmental, health and safety impacts of industrial processes.

Researchers in academia and in industry are facing the issue of substitution of undesirable solvents, but also of the development of new solvent systems or even new compounds to be used as solvent.



Pfizer Medicinal Chemistry Solvent Selection Guide

Preferred	Usable	Undesirable
Water	Cyclohexane	Pentane
Acetone	Heptane	Hexane(s)
Ethanol	Toluene	Di-isopropyl ether
2-Propanol	Methylcyclohexane	Diethyl ether
1-Propanol	TBME	Dichloromethane
Ethyl Acetate	Isooctane	Dichloroethane
Isopropyl acetate	Acetonitrile	Chloroform
Methanol	2-MeTHF	NMP
MEK	THF	DMF
1-Butanol	Xylenes	Pyridine
t-Butanol	DMSO	DMAc
	Acetic Acid	Dioxane
	Ethylene Glycol	Dimethoxyethane
		Benzene
		Carbon tetrachloride

Figure 1.6. The Pfizer solvent selection guide.[31]

Some of the leading alternative green solvents include the following:[29]

Aqueous Solvents

Water is surely the safest and most environmentally compatible substance which can be used in chemical synthesis. While water is also one of the most widely used solvents certainly by nature and also by man, there has been a trend in the last century to develop industrial processes where water was not considered an adequate or in some cases, even a possible solvent. Recently the use of water as solvent in organic synthesis was reconsidered.[32] A number of new processes are now being developed employing aqueous based systems. Concerns about the greenness of water usage in chemical synthesis were considered, however carrying out organic reaction in water is desirable, when this does not cause the immission of contaminated aqueous waste or very energy demanding purification steps.

Supercritical or Dense Phase Fluids

An extremely important area of green solvent research and development is the area of supercritical or dense phase fluids. The use of dense CO_2 as solvent in new eco-friendly synthetic methodologies design is very attractive. CO_2 is not only an intrinsically eco-compatible and a non-flammable compound, but it is also very abundant in nature and it is a by-product in many industrial processes[33] as well. Moreover, CO_2 is relatively inexpensive[34] and, as a general rule, it can be quickly and completely separated from the reaction mixture through easy depressurization.[35] As a solvent, CO_2 is mostly employed in its supercritical state ($scCO_2$) that is rather low energy intensive as critical temperature and pressure are 31 °C and 74 bar respectively (figure 1.5).[36] By changing the conditions around the critical point, a unique set of properties are attained that can be used for solvent purposes. This way, an innocuous substance such as carbon dioxide, or even supercritical water, can be used as a solvent with reduced hazard in a wide range of applications ranging from reaction medium to cleaning solvent.

Ionic Liquids

This particular class of compound will be discussed in a dedicated paragraph (page 19, 1.5.2 Ionic liquids).

Solventless Systems

The complete avoidance of solvents provides one of the simplest solutions to the problem.[37] However not many reactions are amenable to solventless approach, particularly on large scale. In particular exothermic reactions can be dangerous on large scale, therefore before a solventless protocol can be implemented on industrial scale scrupulous studies in collaboration with chemical engineers are needed. Another drawback could be the efficient mixing of reagents and catalyst where needed, particularly when reagents or products are solid.

Finally solvents are still often required for extraction, separation and purification of products.

Reduced Hazard Organic Solvents

As can be argued looking at Figure 1.6 not all the organic solvents pose the same degree of hazard. Alternative new solvents but also solvents already used in different applications can be investigated in order to reduce the handling of toxic compounds but also to reduce physical hazard (explosivity, flammability etc.). It should be underlined that the substitution of a solvent is often a hard goal, since it requires the re-design of the preparation in many cases.

Fluorous Solvents

After the seminal work in fluorous solvents by Horvath,[38a] extensive investigations of the applications of these compounds have been performed.[38] Their unique solvent properties were considered useful in the development of environmental benign processes. However the environmental impact of their production and persistence and their high cost represent the main drawbacks related to their use.

1.5 Green chemistry tools used in this thesis

1.5.1 Organic carbonates

Conventional alkylation reactions reported in literature[39] are usually carried out using alkyl halides (RX, X = I, Br, Cl; R = alkyl) or dialkyl sulfates ($ROSO_3R$) as alkylating agents.

$$\mathrm{NuH + R_2SO_4 + MOH \longrightarrow NuR + MRSO_4 + H_2O}$$

$$\mathrm{NuH + RX + MOH \longrightarrow NuR + MX + H_2O}$$

Nu = generic nucleophile
R = alkyl
X = Cl, Br, I
M = alkaline metal

Scheme 1.1. Conventional alkylation procedures.

These reactions furnish very good yields of alkylated products, though, for several reasons, they exemplify the antithesis of green methods: *i*) the alkylating and carboxylating reactants are highly toxic and corrosive compounds; *ii*) the reactions require the use of stoichiometric amounts of bases, thereby producing stoichiometric amounts of salts as by-products which need to be disposed of; *iii*) most of these processes are exothermic reactions, and an accurate control of the reaction parameters is needed; *iv*) the use of organic solvents is generally required for both homogeneity and heat-control reasons. Alternative methods for the alkylation of nucleophilic substrates are therefore needed.[40] An alternative to these hazardous reactants is represented by the use of alkyl carbonates[41] (Figure 1.7).

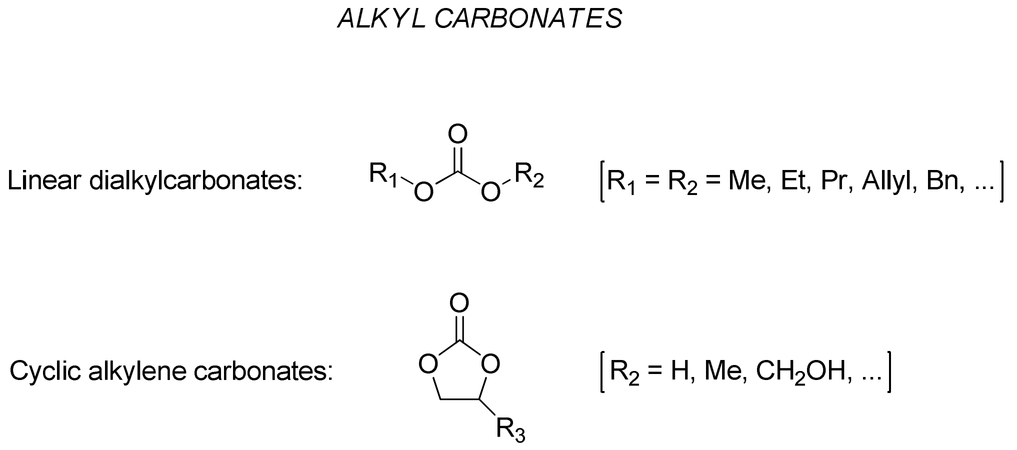


Figure 1.7. Examples of organic carbonates

These compounds are characterised by a very low toxicity when compared to the commonly used alkylating agents (methyl halides and dialkyl sulfates): DMC is classified only as a flammable liquid with non toxic properties (Table 1.3).[42]

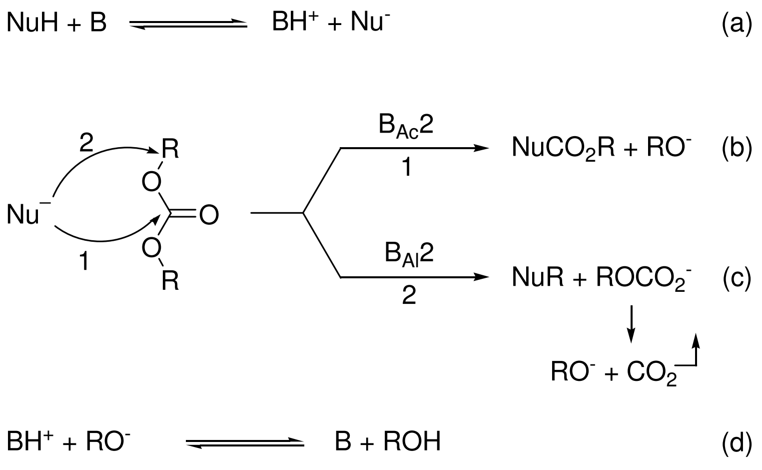
Table 1.3. Toxicological and ecotoxicological profile of DMC

property	**DMC**
oral acute toxicity (rats)	LD_{50} 13.8 g/Kg
acute toxicity per contact (cavy)	LD_{50}>2.5 g/Kg
acute toxicity per inhalation (rats)	LD_{50} 140 mg/L; (4 h)
mutagenic properties	none
irritating properties (rabbits, eyes, skin)	none
biodegradability (OECD 301 C)	> 90% (28 days)
acute toxicity (fish) (OECD 203)	NOEC[a] 1000 mg/L
acute toxicity on aerobial bacteria of wastewaters (OECD 209)	EC_{50}> 1000 mg/L

[a] NOEC = Concentration which does not produce any effect.

In the past fifteen years, the reactivity and the use of dialkyl carbonates, with emphasis on dimethyl carbonate ($MeOCO_2Me$), have been extensively investigated by our research group.[43]

Alkylation of a number of substrates can be carried out using dialkyl carbonates. The reaction pathways of a generic nucleophilic substrate (NuH) with DAlCs are reported in Scheme 1.2. At first, the base (B) catalyst promotes the formation of a nucleophilic anion (Nu^-) (eq. a).



Scheme 1.2 Double reactivity of dialkyl carbonates as alkylating (b) and carboxyalkylating (c) agents

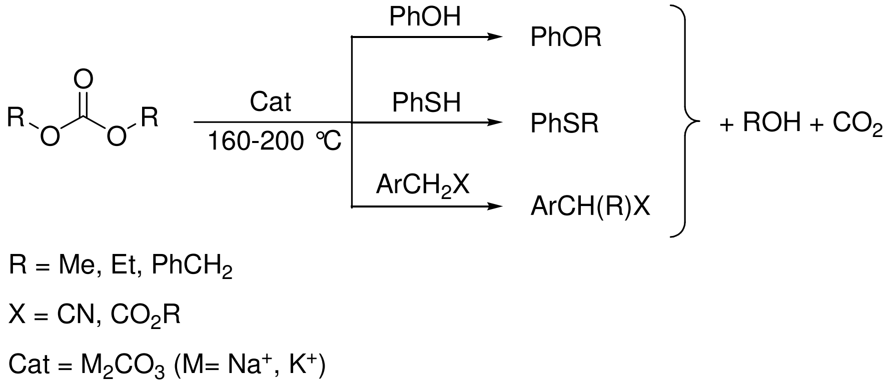
Due to the double electrophilic reactivity of DAlCs, two different reaction pathways may follow: *i*) a nucleophilic attack of Nu^- to the carbonyl group of the organic carbonate, producing the carboxyalkylated product and the corresponding alkoxide RO^- (path 1, $B_{Ac}2$ type mechanism, eq. b). Under such conditions DAlCs behave as a replacement for toxic phosgene in carboxylation reactions.

ii) A nucleophilic attack of Nu^- to the alkyl carbon of the carbonate with the formation of the alkylated product and of the alkyl carbonate anion $ROCO_2^-$ (path 2, $B_{Al}2$ type mechanism, eq. c). Under these reaction conditions the latter anion is unstable and easily undergoes decomposition to RO^- and CO_2. As such, DAlCs behave as safe replacements for alkyl halides or dialkyl sulphates in alkylation reactions. In both cases, the protonated moiety BH^+ can be neutralised by the reaction with an alcoholate anion, producing the corresponding alcohol ROH as by-product, and restoring the catalytic base B (eq. d). Remarkably, additional solvents are usually not required for both alkylation and carboxyalkylation processes.

Although a clear cut-off between these two pathways is not always possible, reaction conditions, more specifically the temperature and the nature of the catalyst, often allow to discriminate between the carboxyalkylation and the alkylation reactions.

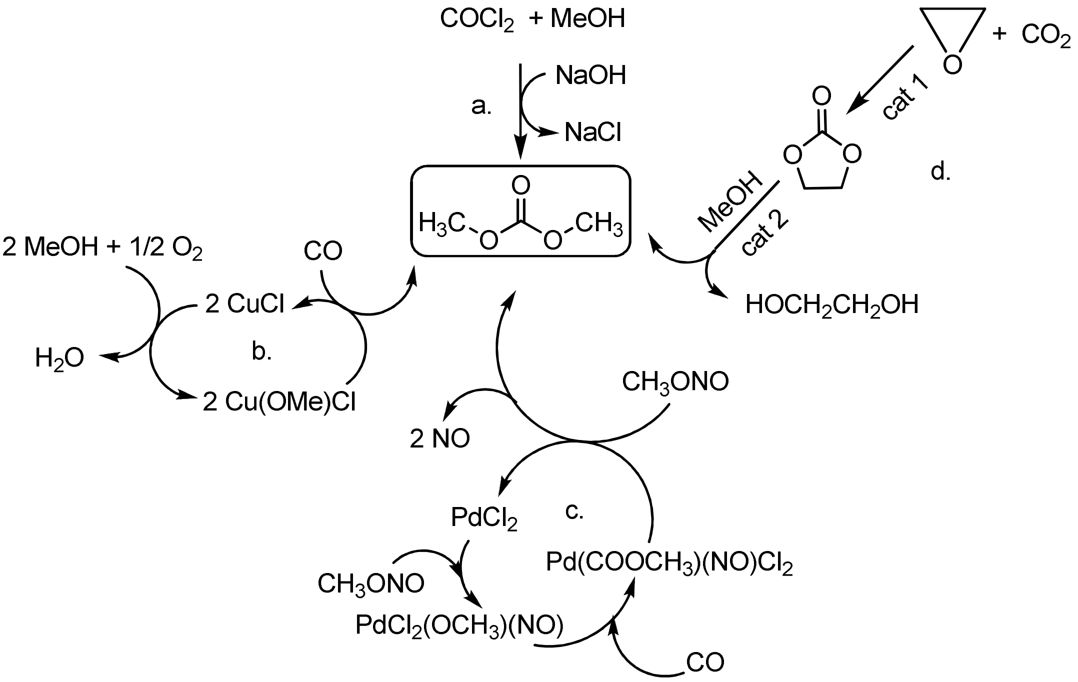
In the case of dimethyl carbonate, when an alkaline carbonate (M_2CO_3, M = Na, K) is used as a catalyst, it is generally observed that below or at the reflux temperature of DMC ($T \leq 90$ °C), a methoxycarbonylation reaction takes place almost exclusively. A $B_{Ac}2$ (bimolecular, base-catalyzed, acyl cleavage, nucleophilic substitution) mechanism operates: the nucleophile attacks the carbonyl carbon of DMC, giving the transesterification product. At higher temperatures (usually at $T \geq 120$ °C), DMC acts primarily as a methylating agent through a $B_{Al}2$ (bimolecular, base-catalyzed, alkyl cleavage, nucleophilic substitution) mechanism: the nucleophile attacks the methyl group of DMC, giving the methylation product.[43] Higher homologues of DMC, such as diethyl carbonate (DEC) and dibenzyl carbonate (DBnC) display an analogue reactivity. In the presence of alkaline carbonates as catalysts, at 160-200 °C the reaction of CH_2-active compounds (e.g. arylacetonitriles, arylacetoesters, sulphones bearing α-CH_2 groups, etc.), phenols and thiols with dialkyl carbonates gives the corresponding alkyl derivatives with a very high selectivity[43a,b] (Scheme 1.3).

Concerns about the greenness of DAlCs are related to their preparation (Scheme 1.4). Currently there still exist plant where DMC is produced from phosgene (eq. a).[44] This method is, of course, undesirable: not only does it use extremely toxic phosgene, but it also generates a stoichiometric amount of salt to be disposed of. Fortunately more environmentally compatible industrial syntheses were developed.



Scheme 1.3. Selective alkylation reactions with dialkyl carbonates.

The oxycarbonylation of methanol catalyzed by copper salts (eq. b), represents the first ever reported green and industrially viable alternative for the production of DMC.[45] This process was patented by Enichem in the early 80's and until a few years ago, an Italian plant in Ravenna produced up to 12000 t/y. Key advantages of this synthesis are the high safety improvement with respect to the phosgenation of MeOH, the high selectivity (and therefore, purity of the final product), and the sole formation of water as a by-product. Another interesting process is the carbonylation of methyl nitrite over a Pd-catalyst (eq. c), developed by UBE Industries in 1993.[46]

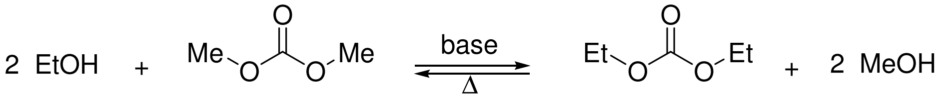


Scheme 1.4 Industrial synthesis of DMC

A two-stage process of insertion of CO_2 into ethylene oxide, followed by a transesterification reaction with MeOH (eq. D) was also developed.[47] This is the most recent breakthrough in the production of DMC, and it represents by far, the greenest and more promising solution stemming from cheap and safe carbon dioxide.

Other light DAlCs, for example diethyl carbonate (DEC), can be obtained by base-catalyzed transesterification of DMC with ethanol (Scheme 1.5).

Just like DMC, DEC possesses an interesting toxicological profile, being classified as an irritant, but non toxic compound.



Scheme 1.5 Transesterification of DMC with ethanol to give DEC

A number of reasons justify the use of dialkyl carbonates (DAlCs) for clean syntheses. It should be noted that: *i*) reactions with organic carbonates are always catalytic processes, producing no wastes except for alcohols which can be recycled to the synthesis of DAlCs, and CO_2 which does not involve disposal problems; *ii*) very often, light organic carbonates can be used not only as reactants, but also as reaction solvents. The use of a number of DAlCs, including dimethyl carbonate, diethyl carbonate, ethylene carbonate, propylene carbonate, butylene carbonate and glycerol carbonate, as solvents for organic reactions and for technical, electrochemical, and extractive applications has been recently reviewed by Börner et al.[48] The general conclusion of these Authors is that DAlCs posses solvency properties that should always be taken into consideration to replace conventional media in organic synthesis.

1.5.2 Ionic liquids

Ionic liquids (ILs) represent today one of the most fascinating areas of research towards alternative eco-friendly synthetic methodologies. Syntheses and applications of ionic liquids have shown an exponential growth only in the last 15 years (Figure 1.8).[49]

ILs have been known for a long time: the first observation of these compounds is historically dated 1914, when Paul Walden reported the physical properties of ethylammonium nitrate $[EtNH_3][NO_3]$.[50]

As their name suggests, ILs are materials composed entirely of cations and anions which, by definition, melt below or around 100 °C.[51] In the past, ionic liquids were considered to be rare, but now a large number of these compounds are known and are commercially available as either organic salts or mixtures consisting of at least one organic component.

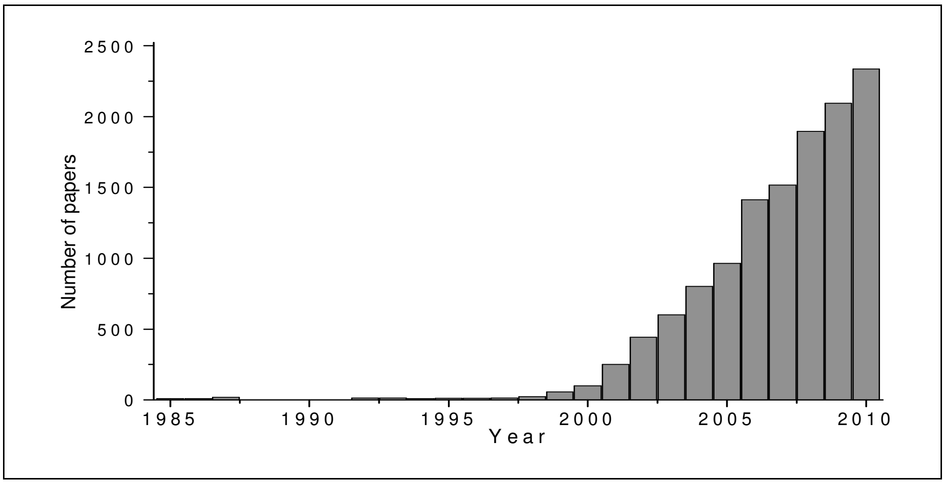


Figure 1.8. Publications with "ionic liquids" in the title as a function of time (Web of Science®).

Figure 1.9 reports the most common cations used to obtain ionic liquids. *N*,*N*-dialkylimidazolium, *N*-alkylpyridinium, alkylammonium and alkylphosphonium are the most conventional organic cations. The formation of these cations may be carried out either via protonation with a free acid, or by quaternization of an amine, phosphine or sulfide, most commonly using a haloalkane or dialkylsulfates.

Ionic liquids displaying different physical properties can be obtained modifying the anion by anion-exchange reactions. These reactions can be divided into two distinct categories: direct reaction of halide salts with Lewis acids, and the formation of ionic liquids via anion metathesis.

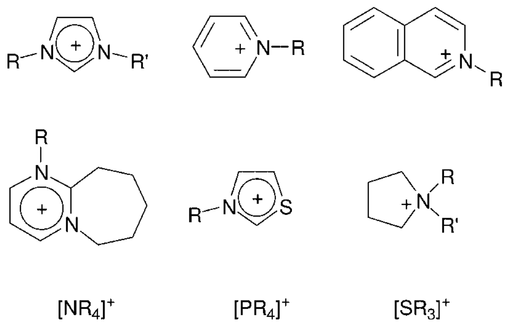
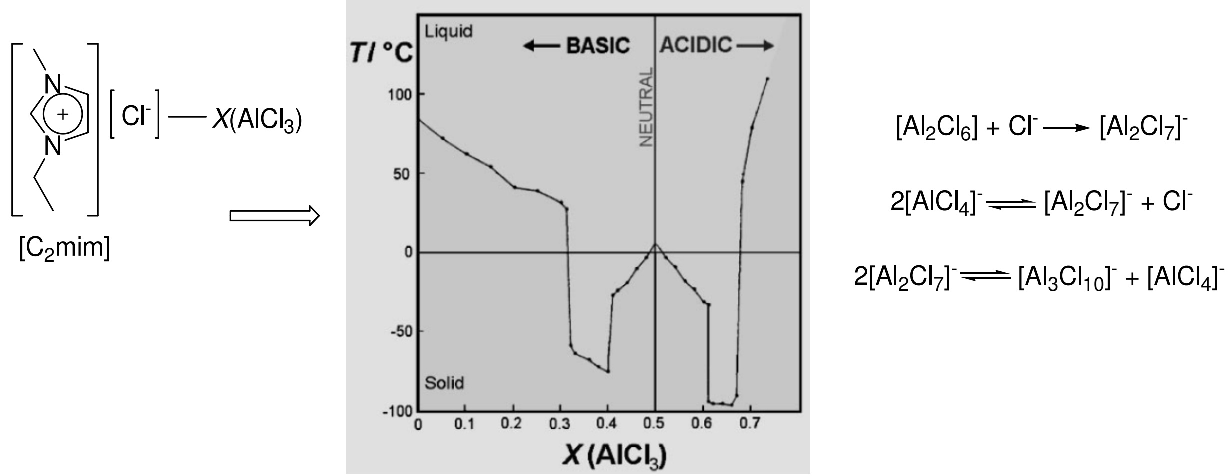


Figure 1.9. Examples of cations commonly used for the formation of ionic liquids.

The formation of ionic liquids by the reaction of halide salts with Lewis acids (most notably $AlCl_3$) dominated the early years of this area of chemistry. The great breakthrough came in 1951 with the report by Hurley and Weir on the formation of a salt that was liquid at room temperature based on the combination of 1-butylpyridinium with $AlCl_3$ in the relative molar proportions 1:2 (X = 0.66)[52]. In general terms, the reaction of a quaternary halide salt Q^+X^- with a Lewis acid MX_n results in the formation of more than one anion species, depending on the relative proportions of Q^+X^- and MXn. Such behavior can be illustrated for the reaction of [C2MIM]Cl with $AlCl_3$ by a series of equilibria (Figure 1.10).



$$[Al_2Cl_6] + Cl^- \longrightarrow [Al_2Cl_7]^-$$

$$2[AlCl_4]^- \rightleftharpoons [Al_2Cl_7]^- + Cl^-$$

$$2[Al_2Cl_7]^- \rightleftharpoons [Al_3Cl_{10}]^- + [AlCl_4]^-$$

Figure 1.10 The experimental phase diagram for the [C2mim]Cl-$AlCl_3$ system

Depending on the mole fraction of $AlCl_3$ [$X(AlCl_3)$], different anionic species such as Cl^-, $[Al_2Cl_7]^-$ and $[Al_3Cl_{10}]^-$ are present in the mixture (figure 1.9, right). This feature allows to manipulate the acid/base character of the ionic liquid by altering its composition: since Cl^- is a Lewis base while $[Al_2Cl_7]^-$ and $[Al_3Cl_{10}]^-$ are both Lewis acids, the binary ILs displays acid [$X(AlCl_3)>0.5$], basic [$X(AlCl_3)<0.5$], or neutral [$X(AlCl_3)=0.5$],[53] properties.[54] Thanks to this adjustable behaviour and to the good solubility for simples arenes, chloroaluminate ILs have been used simultaneously as solvents and catalysts for electrophilic aromatic substitutions reactions,[55] particularly for Friedel-Crafts acylation and alkylation reactions of aromatic compounds.[56]

Metathesis is the other route to exchange the anion to obtain different ionic liquids. Using a number of anion sources (Table 1.4). the halide anion is removed using different procedures to obtain a plethora of different ionic liquids. The first preparation of air- and water-stable ionic liquids based on 1,3-dialkylmethylimidazolium cations (sometimes referred to as "second generation" ionic liquids) was reported by Wilkes and Zaworotko in 1992.[57] This preparation involved a metathesis reaction between [C_2mim]I and a range of silver salts (Ag[NO_3], Ag[NO_2], Ag[BF_4], Ag[CH_3CO_2] and Ag_2[SO_4]) in methanol or aqueous methanol solution. The very low solubility of silver iodide in these solvents allowed its separation simply by filtration, and removal of the reaction solvent allowed isolation of the ionic liquids in high yield and purity. This method remains the most efficient for the synthesis of water-miscible ionic liquids, but is obviously limited by the relatively high cost of silver salts, not to mention the large quantities of solid by-product produced.

Table 1.4. Examples of ionic liquids prepared by anion metathesis. [58]

Salt	Anion source
[cation][PF_6]	HPF_6
[cation][BF_4]	HBF_4, NH_4BF_4, $NaBF_4$,
[cation][NTf_2]	Li[NTf_2]
[cation][CF_3SO_3]	$CF_3SO_3CH_3$,NH_4[CF_3SO_3]
[cation][CH_3CO_2]	Ag[CH_3CO_2
[cation][CF_3CO_2]	Ag[CF_3CO_2
[cation][$CF_3(CF_2)_3CO_2$]	K[$CF_3(CF_2)_3CO_2$]
[cation][NO_3]	$AgNO_3$, $NaNO_3$
[cation][$N(CN)_2$]	Ag[$N(CN)_2$]
[cation][$CB_{11}H_{12}$]	Ag[$CB_{11}H_{12}$]
[cation][$AuCl_4$]	$HAuCl_4$

The first report of a water-insoluble ionic liquid was two years later, with the preparation of [C_2mim][PF_6] from the reaction of [C_2mim]Cl and HPF_6 in aqueous solution.[59] The protocols reported in the above two papers have stood the test of time, although subsequent authors have suggested refinements of the synthesis.

The intriguing physical-chemical properties of ILs[60] account for their large interests in green chemistry. First of all, ILs have a negligible vapour pressure at near ambient conditions: many of them show no signs of distillation below the temperature of their thermal decomposition, and for a long time, it was almost universally believed that ionic liquids could not evaporate at all.[61] This feature allows to minimize the risks of atmospheric contamination and it remarkably reduces health and environmental concerns. Accordingly, ILs have been named "green solvents" and they can efficiently replace conventional volatile organic media in developing new synthetic methodologies, altough toxicity may be an issue and must be assessed.

Secondly, ILs display properties such as the dissolution power, polarity and hydro/lipophilicity, which are rather peculiar and different to those of conventional organic liquids. These features depend on the nature of the cation and the anion that compose the ionic liquid. In a first approximation, cations are responsible for the physical properties, whereas anions control chemical properties and reactivity.[58] For this reason, ILs have been named "designer solvents", as either the cation or the anion can be changed in order to tune their properties as solvents for chemical reactions. It is possible, at least in principle, to design ionic liquids able to optimize the relative solubilities of reactants and products, the reaction kinetics, the liquid range of the solvent, and even the intrinsic catalytic behaviour of the media and the air-stability of the system.[62]

A lot of studies have been conducted to determine correlations between the chemical structures of both cations and anions and the properties of ILs, in order to predict those properties already at the stage of ionic liquid design. Even if general quantitative methods are still not available, some general trends have been observed. The melting point of ionic liquids is affected by both the asymmetry and the size of cations,[63] as well as by the occurrence of hydrogen bonds between cations and anions.[64] Also, the ability of ions to act as hydrogen-bond donors and/or acceptors influences the polarity of ionic liquids, while the increase of the chain length of alkyl substituents on both cations and anions leads to a greater lipophilicity of these materials.

For these reasons, ILs can be good solvents for a wide range of both inorganic and organic compounds: unusual combinations of reagents/catalyst can be brought into the same phase by using ILs, or thanks to the immiscibility of ILs with polar or nonpolar solvents, innovative two-phase or multiphase systems can be originated to facilitate either the recovery of final reaction products or of the catalyst.

Ionic liquids have been investigated as solvents for a number of synthetic purposes: as substitutes for water in Diels-Alder reactions,[65] substitutes for organic solvents in alkylation reactions of indole and β-naphtol,[66] for the immobilization of homogeneous catalysts in biphasic reaction systems for hydrogenation reactions (even asymmetric),[67] for hydroformylation reactions,[67a,68] Heck reactions,[69] olefin dimerizations (butadiene,[70] propene,[71] butene[72] and ethene[73]) and polymerization processes.[74]

Today, ILs find also industrial applications in a number of processes, like cellulose dissolution, aluminum plating, hydrosilylation and so on, which have been recently reviewed by Seddon and Plechkova.[49] Among others, the BASIL™ process developed by BASF for the production of alkoxyphenilphospines as photoinitiator precursors (Figure 1.11), is probably the most successful example of an industrial process using an ionic liquid based-technology.[75]

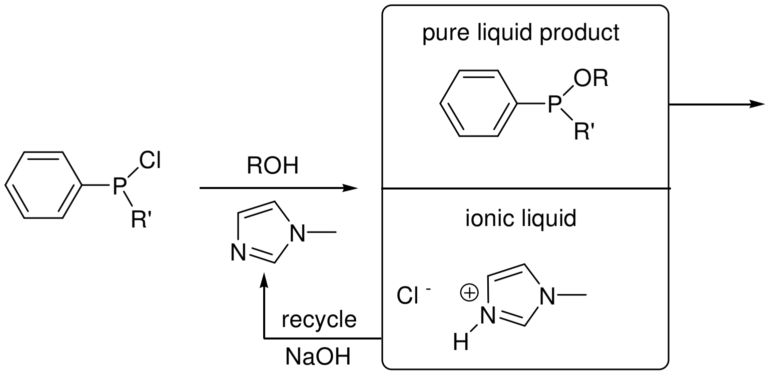


Figure 1.11 The BASIL^{TM} process.

Noteworthy are the studies by the Seddon's group at Queen's University of Belfast, on the synthesis and properties of ionic liquids. Prof. Seddon and prof. Swindall founded QUILL (Queen's University Ionic Liquid Laboratories), where dozens of researches from 1999 focus their work on ionic liquids application in variuos fields, from chemistry to aerospace.

Because of their low volatility they were often generically and acritically classified as green; a tag which aided a media-hyped backlash when some were found to be toxic. In reality, quoting prof. Seddon: "ionic liquids are just useful solvents which can be designed to be benign (even edible) if required". ILs are considered green solvents not only for their negligible vapour pressure, but more importantly because of the possibility to design them for a particular objective, allowing in some cases to perform new greener processes.

1.5.3 Green Solvents: relevant examples.

A number of solvents were recently proposed as alternatives for commonly used solvents for a series of organic reactions. These solvents, in most cases derived from renewable sources, are gaining interest by synthetic chemists because of their unconventional properties. Certain properties could allow to modify some chemical processes with the aim of reducing the number of steps, the work-up operations or to redesign synthetic procedures taking advantage of the new possibilities they offer.

1.5.3.1 2-Methyltetrahydrofuran

2-Methyltetrahydrofuran (MeTHF) is an aprotic ether solvent that, while being a strong Lewis base like THF, is only partially miscible with water[76]. MeTHF is increasingly being used in organometallic and biphasic chemical processes due to the interesting combination of properties it provides. An attractive feature of MeTHF is that it is derived from renewable resources, it can be obtained by the hydrogenation 2-furaldehyde. Furaldehyde is produced from agricultural waste like corncobs or bagasse[77].

1.5.3.2 Cyclopentylmethylether

Cyclopentyl methyl ether (CPME)[78] has become available in commercial quantities since November 2005 from Zeon Corporation[79] with approval by the Toxic Substances Control Act (TSCA) and the European List of Notified Chemical Substances (ELINCS). A high boiling point (106 °C) and characteristics such as low formation of peroxides, relative stability under acidic and basic conditions, formation of azeotropes with water coupled with a narrow explosion range render CPME an alternative to other ethereal solvents such as tetrahydrofuran (THF), 2-methyl tetrahydrofuran (2-MeTHF), dioxane (carcinogenic), and 1,2-dimethoxyethane (DME). Conventional drying is unnecessary for general organometallic reactions including Grignard reactions, enolate formation, Claisen condensation, general reductions, and Pd-based transformations.

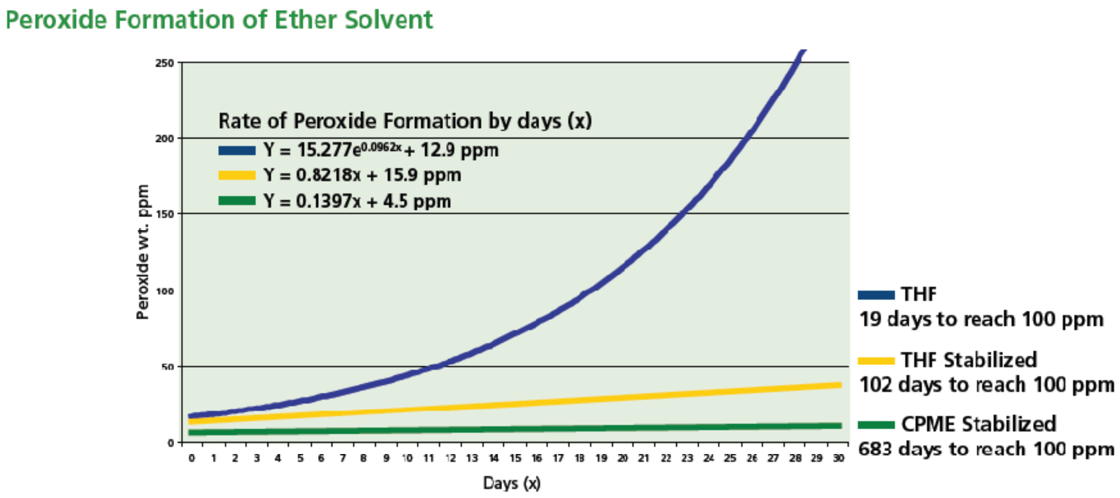


Figure 1.12. CPME is a safer solvent also because of the low rate of peroxide formation.[80]

1.5.3.3 Ethyl Lactate

Ethyl lactate[81] is considered a green, and economically viable, alternative to traditional solvents.[82] It has very favourable toxicological properties, it does not show any potential health risks, it is not teratogenic, and it readily undergoes metabolic hydrolysis because of estearase enzymatic activity to ethyl alcohol and lactic acid, this last compound being a natural metabolite in humans. Moreover, the low toxicity of EL may be inferred from its FDA (USA Food and Drug Administration) approved use in food products.

In addition it can be produced from renewable feedstocks at very low and competitive prices.[83] The production of EL from carbohydrate feedstocks is not a competition to food because low-cost agricultural waste may be considered as a source of carbohydrates. Although the open literature on uses of EL, pure or mixed, is not very extensive, reported results show that it may be applied successfully for different processes as its used as a cleaning solvent,17[84] for applications in the Pharmaceutical industriy[85] or for the paint industries. [86] The *caveat* being that it is an ester therefore reactive under the appropiate conditions.

1.5.3.4 Dimethylcarbonate (DMC)

Properties of DMC as a reactant were already discussed, nevertheless this liquid could act as an effective solvent for a number of reactions.[87] Its water immiscibility and its quite high polarity and solvation ability render this solvent a very attractive alternative to chlorinated hydrocarbons. In addition DMC could be obtained from renewable feedstock using methanol as starting material and by the very interesting processes developed by Enichem.[45]

The DMC reactivity was discussed in paragraph1.5.1, obviously this reactivity must be taken into account.

1.6 Aim and summary of the Thesis

This work has been carried out at the Dipartimento di Scienze Molecolari e Nanosistemi dell'Università Ca' Foscari, Venezia, in the *Green Organic Synthesis Team* (GOST). The group has a long-standing interest in the green chemistry area. In particular, among the research activities of GOST, an important field includes the setup of organic syntheses with environmentally benign reagents and solvents, mostly CO_2, safe chemicals such as dialkyl carbonates, and green catalysts including solid heterogeneous systems (zeolites) and homogeneous systems (ionic liquids).

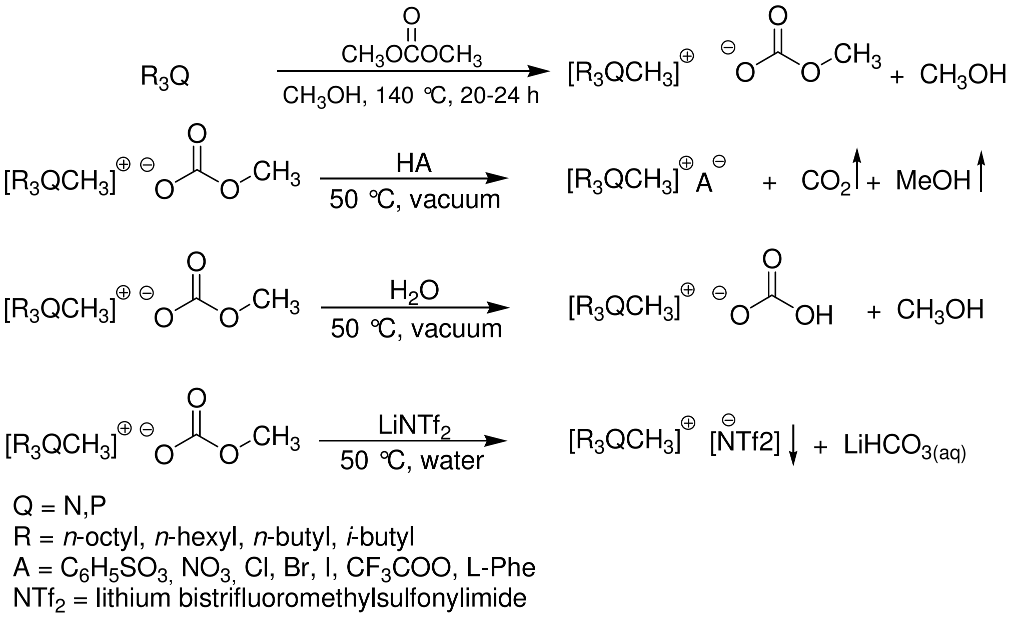
The general aim of this PhD work has been the development of new eco-friendly methodologies for the preparation of fine chemicals and Active Pharmaceutical Ingredients (API), with particular attention to the solvent use. The studies were performed using two different approaches. The first was essentially academic, with the aim of understanding the chemistry of certain processes in view of the principles of green chemistry. The second one was more applicative as a consequence of our collaboration with an industrial partner. By working with a company on the preparation of different fine chemicals, we had to consider also research and development aspects usually not encountered in the academic environment. This opportunity allowed to understand how important it is that these two environments, unfortunately very rarely connected (especially in Italy), come into contact. This cross-fertilisation led to collaboration that was profitable for both.

The work has been articulated in three main sections, a brief summary follows.

1.6.1 Ionic liquids synthesis and application to organic synthesis

1.6.1.1 Onium salts synthesis

Chapter 2. A new green synthesis of task specific onium ionic liquids (OILs) was achieved *via* the methylation of trialkylphosphines using dimethyl carbonate as the methylating agent. Thus, a set of methoxycarbonylated onium salts [R_3Q^+ $^-OCO_2CH_3$] (Q = N, P) were prepared (scheme 1.16, eq. a). These products were further reacted with both water and protic acids to produce ionic liquids possessing different acid base properties (Scheme 1.6, eqn. b and c).

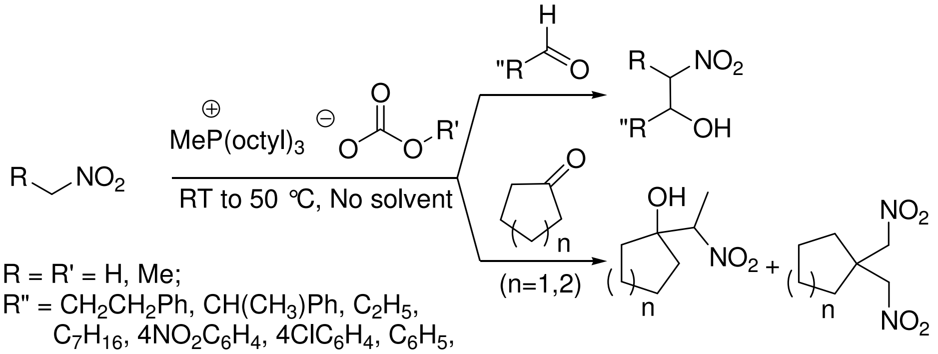


Scheme 1.6 Synthesis of task specific ILs: the quaternarization of trialkyl amines or phosphines (a), is followed by the metathetic anion exchange using a protic acid (b), by reaction with water (c) or by methatetic exchange in water to obtain an hydrophobic ionic liquid (d).

1.6.1.2 Carbonate ionic liquids as basic catalysts

Chapter 3, paragraph 3.1. Once prepared, carbonate ionic liquids CILs have been used as base catalysts for the condensation of aldehydes and ketones with nitroalkanes (Scheme 1.7).

In this study, basic ionic liquids catalysts have been compared to conventional organic base catalysts [for example, diazabicycloundecene (DBU), tetramethylphenylguanidine (PhTMG), triethylamine (NEt_3) and dimethylaminopyridine (DMAP)]. In agreement with the main subject of this thesis, the reactions were conducted without the addition of solvent, in in view of a preparation characterised by high Mass Efficiency and avoiding the use of volatile and/or toxic solvents.



Scheme 1.7 Henry reactions catalysed by CILs

1.6.1.3 Electrophilic aromatic chlorination.

Chapter 3, paragraph 3.2. Not only did the CILs reveal themselves as efficient catalysts, also onium salts bearing other anions proved useful in catalysis. Nitrate exchanged phosphonium ionic liquids were able to promote electrophilic aromatic oxychlorination. In addition their liquid nature allowed to carry out the reaction in the phosphonium nitrate salt as the solvent, avoiding the usual chlorinated VOC. Our study also demonstrated the catalytic nature of the nitrate ionic liquid allowing to propose a mechanism in which the oxidant is atmospheric oxygen .

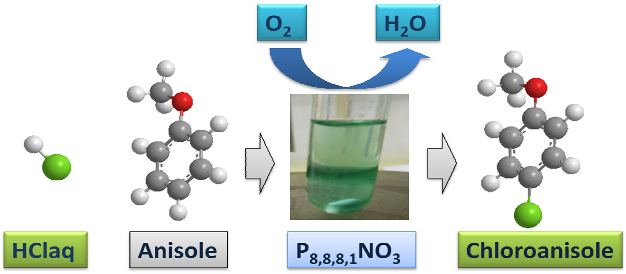


Figure 1.13. Nitrate phosphonium ionic liquid catalysed aromatic electrophilic oxychlorination. $P_{8,8,8,1}$ stands for trioctylmethylphosphonium.

1.6.2 Synthesis of fine chemicals and pharmaceutical active ingredients

Chapter 4. In agreement with the aim of this thesis besides the alternative green preparation of fine chemicals previously described, different procedures for the synthesis of active pharmaceutical ingredients (API) were sought. In particular we studied the preparation of the well know drug Tadalafil (commercially named Cialis™) through a more enviromental compatible route. Tadalafil is prepared from L-tryptophan through a series of steps in which different solvents and reagents are used. As it often happens in drug preparation the overall mass index of the preparation is quite low, causing a great amount of waste to be produced. We focussed on the solvents. In collaboration with QUILL at the Queen's University of Belfast, the use of ionic liquids was considered in order to improve the overall mass index of the preparation. (Figure 1.14) The experience of GOST in Venice on the use of dimethylcarbonate as reactant and solvent as well in combination with the great knowledge on ionic liquids application as solvents of the researchers working at QUILL, allowed to propose an alternative synthetic route in which both these green chemistry tools were involved. Dimethylcarbonate proved an excellent solvent for a particular synthetic step involved in the preparation, while an ionic liquid was successfully used to carry out two steps in a single batch in substitution of two volatile solvents.

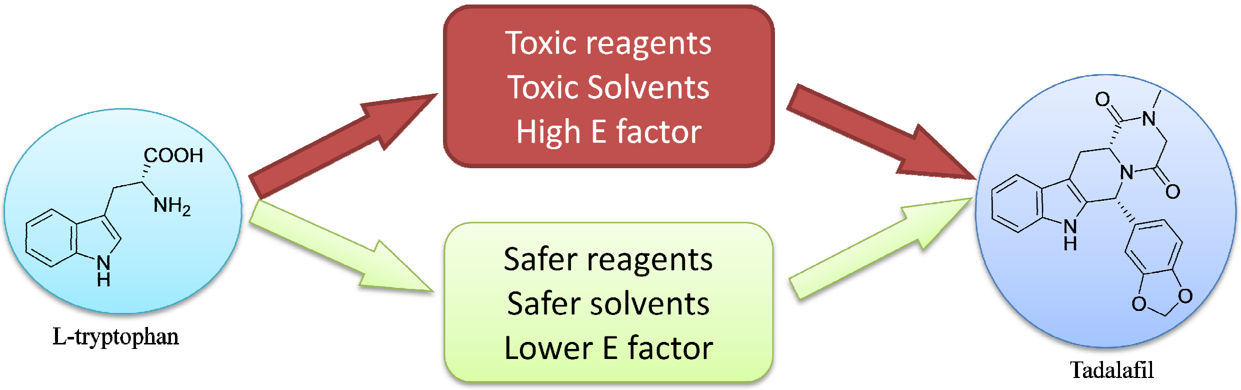


Figure 1.14. A greener synthetic route for Tadalafil preparation was sought.

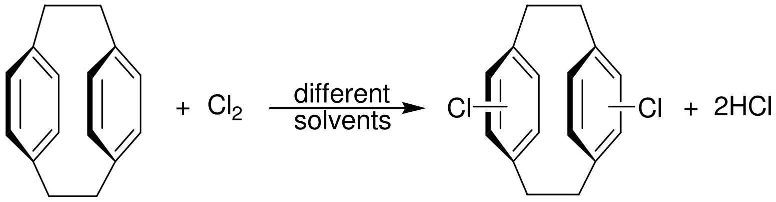
1.6.3 Greener processes in collaboration with Galentis S.r.l.

Chapter 5. The project of this PhD course was in partnership with Galentis S.r.l., a fine chemical manufacturer located in Marcon (VE). We sought for new synthetic methodologies involving reduced amounts of solvent (especially chlorinated ones[88]) and/or more environmental acceptable solvents and reagents. This collaboration allowed us to learn the industrial approach to the research and to deal with very interesting chemical preparations in the field of fine chemicals manufacture.

The company proposed some research topics, in particular we investigated the preparations of the following compounds.

1.6.3.1 Dichloro-[2.2]-p-cyclophanes

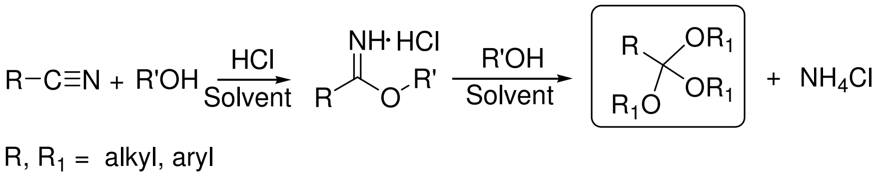
Chlorination of [2.2]-*p*-cyclophanes (Scheme 1.8). In particular our aim was to avoid the use of light chlorinated solvents such as dichloromethane and to find an alternative to the use of molecular chlorine gas.



Scheme 1.8. Chlorination of [2.2]-paracyclophane was studied using different solvents and procedures

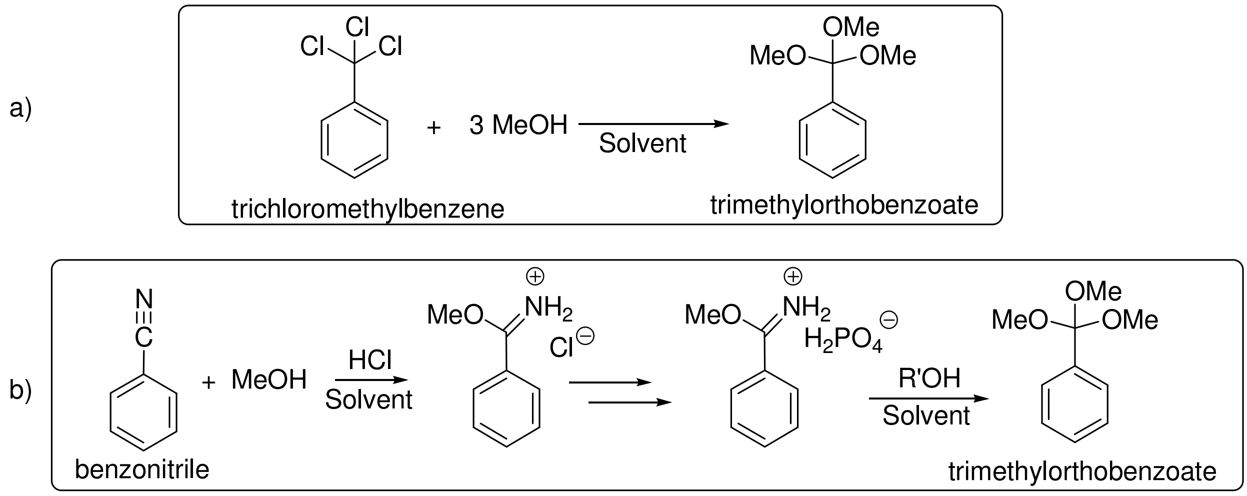
1.6.3.2 Trimethylorthoesters

Also in this case we sought for an alternative solvent to avoid the use of light chlorinated solvents for the preparation of these compounds, using the Pinner method[89] (Scheme 1.9). Synthesis of trimethylorthobenzoate through the Pinner method was studied.



Scheme 1.9. The Pinner method for the preparation of orthoesters

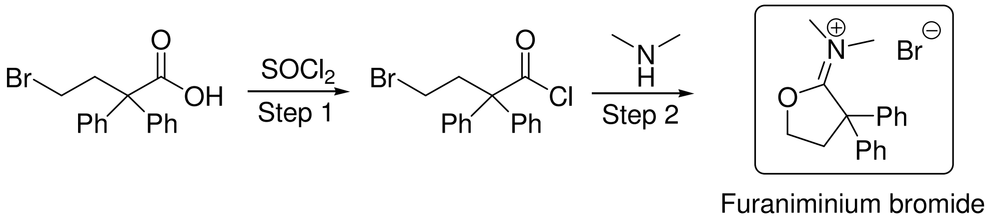
We developed a procedure for the preparation of this particular compound using this novel synthetic route This allowed to use benzonitrile (harmful) instead of trichloromethylbenzene (carcinogen) as starting material (Scheme 1.10).



Scheme 1.10. Routes for the preparation of trimethylorthobenzoate. The literature reported procedure (a) is compared with the synthetic procedure developed by us (b).

1.6.3.3 Furanimium bromide

The title compound is used as intermediate in the synthesis of loperamide.[90] Its preparation requires large amounts of chloroform in both the synthetic steps (Scheme 1.11).



Scheme 1.11 Preparation of furaniminium bromide consists of two steps.

The replacement of chloroform required to re-think the process. Very interesting results were obtained using dimethylcarbonate as the solvent and anhydrous dimethylamine instead of its aqueous solution.

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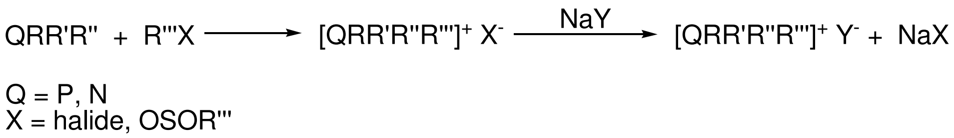
2 Onium ionic liquids made with dimethylcarbonate: green solvents by a green synthesis

2.1 Introduction

As already stated in chapter 1 (see paragraph 1.5.2), ionic liquids have elicited phenomenal interest among chemists. Their applications for clean catalysis and for the development of green and innovative processes in the chemical industry are well known.[1,2] However it is not correct to affirm that the use of ionic liquids is an eco-sustainable practice in any case. Ionic liquids are not "green" as such. However, as neoteric solvents,[3] they can be used as media in processes which can be assessed as "green".[4] The reason why often the use of ionic liquids is considered poorly environmental compatible mainly lies in the manufacturing process of these materials. The ionic liquid synthesis in fact, frequently involves two potentially environmentally adverse steps:[5] quaternarisation of a nitrogen or phosphorous atom, usually by alkylation with hazardous alkyl halides, followed by a halogen anion metathesis step that produces equimolar amounts of an inorganic salt (Scheme 2.1).[6,7]Atom economy[8] of this process is quite low, since both in the case of alkyl sulphates or alkyl halides part of the alkylating agent ends up in the co-formed inorganic salt. Furthermore the by-produced salts can be very difficult to separate, especially in the case of hydrophilic ionic liquids. Even if some optimisation of ionic liquid preparation were developed, for example by halide-free syntheses,[9,10] those procedures still use hazardous and highly toxic reagents such as methanesulfonyl chloride[11] or dialkylsulfates,[12] and generate unwanted by-products.



$$QRR'R'' + R'''X \longrightarrow [QRR'R''R''']^+ X^- \xrightarrow{NaY} [QRR'R''R''']^+ Y^- + NaX$$

Q = P, N
X = halide, OSOR'''

Scheme 2.1 Ionic liquid synthesis by quaternarisation followed by anion exchange

Quaternarisation of nitrogen (or phosphorous) generates the ionic onium (Q^+) species, and depending on the methylating agent used, this step ends up incorporating the counter-anion in the IL. Therefore the choice of an alkylating agent different from alkyl halides can circumvent inclusion of halogens in the ionic liquids, and it can also provide safer alternatives to the use of alkyl sulphates and halides.

Proionic (Production of Ionic Substances GmbH) for example has patented and commercialised a method for the quaternarisation of amines, phosphines, sulphides, and imidazoles, using dialkyl carbonates, that yields an alkyl carbonate or hydrogen carbonate anion.[13] This kind of ionic liquids are already commercialized as water-methanol solutions with the trademark CBILS© (Carbonate Based Ionic Liquid Synthesis).[14] However the patent is cryptic on the synthetic conditions, the characterization, the stability, and regarding their storage.

2.2 Aim of the research

The initial focus was on Aliquat336®, a largely available ammonium phase transfer catalyst which is however commercialised highly impure due to the presence of both C_{10} and C_8 alkyl chains, as well as of decanol and octanol. Pure trioctlymethylammonium chloride can be obtained by adapting a synthesis reported by Noyori *et al.* using dimethylsulfate (DMS),[15] followed by anion exchange to yield the chloride (see Scheme 2.1). However this synthesis suffered from a number of drawbacks, including long reaction times, use of toxic DMS, and the formation of a coloured ionic liquid.[16]

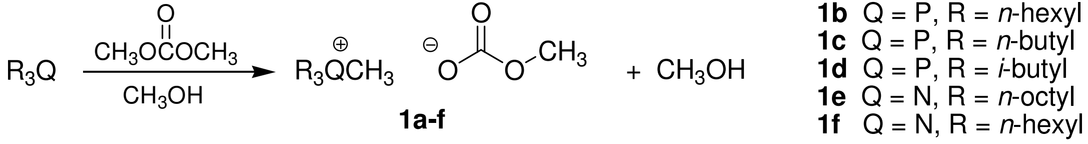
The research group in which I performed my studies has a long-standing interest in the use of dialkylcarbonates as green alkylating agents, particularly of DMC.[17,18] This knowledge was applied to the synthesis of task-specific and very pure ionic liquids via methylation of phosphines and amines. Our initial aim was therefore to develop an alternative synthetic procedure of these ionic liquids by using DMC as the green methyl source, and to prepare pure products in relatively large batches (20-40 grams).

The study[19] is divided into four sections that represent an integrated ionic liquid synthesis-application methodology : (a) the halide-free preparation of a series of pure methyl-onium (ammonium and phosphonium) ionic liquids through the use of DMC as quaternarisation agent; (b) a simple procedure for anion metathesis with Brønsted acids or water as new anion source, and no use of solvents; (c) the NMR characterisation of the ionic liquids in the neat phase; (d) the study of the properties of these onium salts.

2.3 Results and discussion

2.3.1 Quaternarisation with DMC

The synthesis of the ionic liquids involved the reaction of DMC with trialkylamine and trioalkylphosphine, to yield the corresponding methyl-oniummethylcarbonate salts (Scheme 2.2).

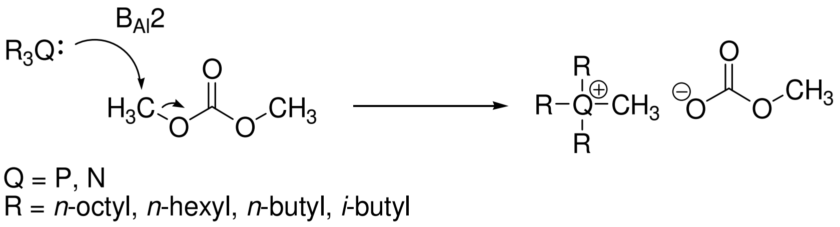


Scheme 2.2 Amine and phosphine quaternarisation with dimethylcarbonate

At first the less expensive and more easy to handle trioctylamine (TOA) with respect to trioctylphosphine (TOP) was selected as the reactant to determine the experimental conditions for the methylation with DMC. Taking into consideration the reactivity of DMC as a methylating agent,[20] different amine(and phosphine) to DMC mole ratios, different reaction temperatures were tested, with or without the use of added solvents. Attempts to carry out the reaction in the absence of added solvents, *i.e.* simply by heating a mixture of TOA and a 6-fold molar excess of DMC, proved impractical and yielded unidentified side products, probably due to the immiscibility of the reagents. However, by adding equal volumes of methanol and DMC, the reaction of TOA went to completion at 140 °C in 20 hours under N_2 atmosphere. Since the reaction temperature (>120 °C) was higher than the boiling point of DMC (90 °C), all quaternarisation reactions were run in a sealed steel autoclave. The starting mixture was biphasic in the presence MeOH as well, due to the high lipophilicity of trioctylamine, but it is likely that under the reaction conditions, a sufficient ratio of amine could come into contact with DMC driving the reaction forward. In addition, the build-up of the onium ionic liquid may have had a promoting effect on the methylation reaction, as demonstrated in a similar case.[21]

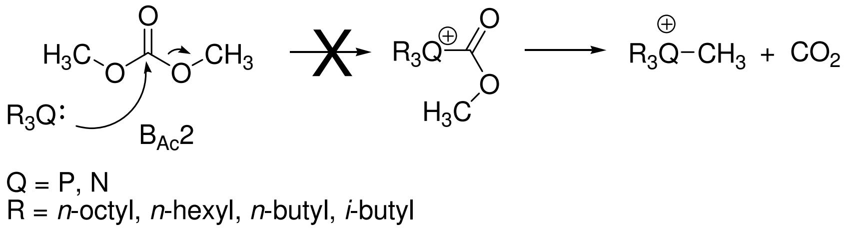
The resulting clear solution was simply stripped of methanol and DMC under vacuum (10^{-2} atm, 25 °C) to yield quantitatively the pure methylammonium methylcarbonate salt: $N_{8,8,8,1}[CH_3OCOO]$ **1e**. At this stage, NMR analysis showed the formation of pure ionic liquid that incorporated up to a mole of methanol. This could be removed only by prolonged heating and under high vacuum (10^{-3}atm, 40 °C), which however caused a slow darkening of the liquid. On the other hand, since the presence of methanol did not interfere with successive transformations, it was deemed inconsequential and thereon disregarded. The same procedure was then applied to obtain also trihexylmethylammonium methylcarbonate ($N_{6,6,6,1}[CH_3OCOO]$ **1f**) starting from trihexylamine. On the other hand, the procedure for the synthesis of the phosphine equivalent $P_{8,8,8,1}[CH_3OCOO]$ **1a** from TOP and DMC required complete oxygen elimination by degassing the reagent mixture. Careful freeze-pump-thaw cycles was found to be the only way to avoid the formation of phosphine oxide as an impurity. Once conditions were optimised for reaction of trioctylphosphine, different phosphines (tri-*n*-hexyl, tri-*n*-butyl, tri-*i*-butyl phosphine) were reacted with DMC to obtain the corresponding phosphonium salts (**1b-d**).

The reaction between the aliphatic nucleophilic amine or phosphine and DMC occurred probably through a direct nucleophilic attack of the amine or phosphine to the DMC methyl group by a $B_{Al}2$ mechanism (Scheme 2.3).[22]



Scheme 2.3 Amine methylation: $B_{Al}2$ mechanism.

Earlier studies on different substrates (amines, phenols, etc.) had indicated that, at high temperature (> 90 °C), the $B_{Ac}2$ nucleophilic attack to the carbonyl was disfavoured, and that the $B_{Al}2$ mechanism predominated, probably due to solvation effects dictated by the temperature.[23] For this reason the $B_{Ac}2$ mechanism to yield the carboxymethyltrialkyl-onium salt, followed by elimination of CO_2, was ruled out (Scheme 2.4).



Scheme 2.4 Amine and phosphine methylation: $B_{Ac}2$ mechanism

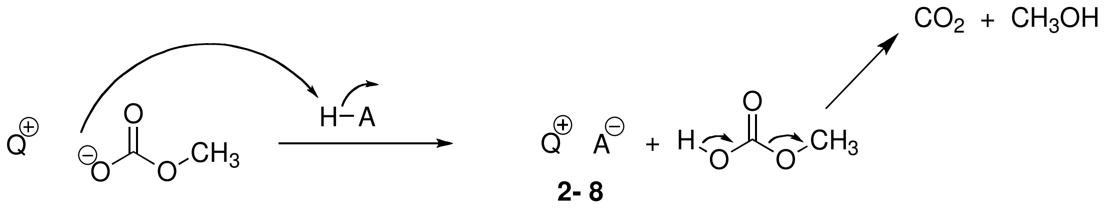
Highly hindered phosphines like tri-*i*-butylphosphine proved less reactive than the other phosphines tested, in fact the quaternarisation reaction required a higher reaction temperature (170 °C), anyway obtaining mixture of salt and unreacted phosphine requiring an additional purification step (see experimental section) that lowered the yield sensibly (87 %).

The prepared phosphonium and ammonium salts were clear, colourless to pale yellow liquids, stable in air and could be stored for prolonged periods of time. The phosphonium salts were perfectly colourless and proved to be more stable toward chemical and thermal degradation with respect to the ammonium analogue. The syntheses could be carried out on 20-30 g batches of reactant yielding quantitatively the desired pure product and the volatile by-products methanol and carbon dioxide.

The reactions reported in Scheme 2.2 afforded a quantitative yield, were 100% atom economic, they avoided the use of toxic and dangerous methyl halides and of DMS (Scheme 2.1), they were totally halogen free, and did not require work-up with additional solvents to isolate and purify the products. From an environmental standpoint they were therefore green reactions – albeit somewhat energy intensive.[24]

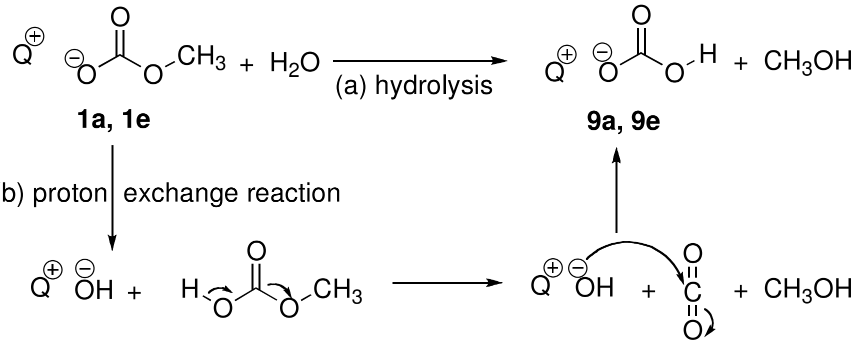
2.3.2 Anion Metathesis

The onium (Q^+) methylcarbonateionic liquids described above reacted readily with Brønsted acids (H-A, Scheme 2.5) to yield the anion (A^-) exchanged salt along with methylhydrogencarbonate (*i.e.* the half-ester of carbonic acid). The latter was unstable above -36 °C[25] and immediately decomposed to form methanol and CO_2, thus providing its built-in removal. This exchange procedure was tested for a number of acids, and it involved mixing the precursor ionic liquid with the acid under air, blandly heating (50 °C), and finally stripping methanol and CO_2 under vacuum to yield the pure products. It proved simple, rapid, clean, and free of any workup steps.



Scheme 2.5. Reaction products of oniummethylcarbonates with Brønsted acids.

While the reaction of the methylcarbonate ionic liquids **1** with Brønsted acids (Scheme 2.5) proceeded as expected to yield the anion (A^-) exchanged salts **2-8,** the outcome was different using water instead of HX. Water promoted transformation of the methylcarbonate anion into the hydrogencarbonate anion, to yield $P_{8,8,8,1}$[HOCOO] **9a** and $N_{8,8,8,1}$[HOCOO] **9e** (Scheme 2.6). Both the resulting onium hydrogencarbonate salts **9a** and **9e** were deliquescent white solids at room temperature. This reaction could take place either (a) by direct hydrolysis of the methylcarbonate anion with water acting as a nucleophile (top reaction Scheme 2.6), or (b) by an acid-base reaction with water acting as an acid in analogy to Scheme 2.5, followed by methylhydrogencarbonate decomposition,[25] and CO_2 sequestration by hydroxide (bottom, Scheme 2.6).



Scheme 2.6. Patways for transformation of methylcarbonate into hydrogen carbonate anion.

Although this mechanism has not been investigated and available data do not permit a choice between path (a) and (b) of Scheme 2.6, the methylcarbonate anion is probably more basic than it is electrophilic, thus favouring the bottom pathway.

The syntheses of $P_{8,8,8,1}[NTf_2]$ **10a** and $N_{8,8,8,1}[NTf_2]$ **10e** represented the only exceptions to the above anion-exchange procedures. By analogy with the Brønsted acid addition procedure, bis(trifluoromethanesulfonyl)amide ($[NTf_2]^-$) salts could be obtained by treatment of the methylcarbonateonium salt with bis(trifluoromethanesulfonyl)amine ($HNTf_2$), which is a very strong acid[26], but also a very expensive and difficult to handle material. On the contrary the lithium salt of the conjugated base is cheaper and appears like a stable white solid. Thanks to the lypophilic character of the NTf_2 anion, the desired ionic liquids could be precipitated out of an aqueous solution of $P_{8,8,8,1}[CH_3OCOO]$ and $N_{8,8,8,1}[CH_3OCOO]$ simply by addition of $LiNTf_2$.

The combination of the simple quaternarisation of phosphines and amines and the easy and free of additional solvents and work up step anion metathesis allowed us to prepare a number of different onium salts (Table 2.1).

Table 2.1 List of ammonium and phosphonium salts described in this study

Number	Q^+	A^-	mp (°C)	Anion precursor
1a	$P_{8,8,8,1}$	CH_3OCOO	< 0[a]	-
1b	$P_{6,6,6,1}$		< 0[a]	
1c	$P_{4,4,4,1}$		< 0[a]	
1d	$P_{i(4,4,4),1}$		< 0[a]	
1e	$N_{8,8,8,1}$		< 0[a]	
1f	$N_{6,6,6,1}$		< 0[a]	
2a	$P_{8,8,8,1}$	TosO	96-98	TosOH
2b	$P_{6,6,6,1}$		nd	
2c	$P_{4,4,4,1}$		56-59	
3a	$P_{8,8,8,1}$	NO_3	< 0[a]	HNO_3
3e	$N_{8,8,8,1}$		< 0[a]	
4a	$P_{8,8,8,1}$	Cl	~ 25[b]	HCl
4b	$P_{6,6,6,1}$		~ 5[b]	
4e	$N_{8,8,8,1}$		~ 25[b]	
5a	$P_{8,8,8,1}$	Br	~ 25[b]	HBr
5b	$P_{6,6,6,1}$		~ 25[b]	
5c	$P_{4,4,4,1}$		~ 25[b]	
5d	$P_{i(4,4,4),1}$		~ 25[b]	
6a	$P_{8,8,8,1}$	I	~ 5	HI
7a	$P_{8,8,8,1}$	CF_3COO	23-24	CF_3COOH
7e	$N_{8,8,8,1}$		nd	
8e	$N_{8,8,8,1}$	L-Phe	< 0[a]	L-phenylalanine
9a	$P_{8,8,8,1}$	HOCOO	~ 25[b]	H_2O
9e	$N_{8,8,8,1}$		~ 25[b]	
10a	$P_{8,8,8,1}$	NTf_2	< 0[a]	$LiNTf_2$
10e	$N_{8,8,8,1}$		< 0[a]	

[a] remained liquid below freezing; [b] deliquescent

2.3.3 Characterisation by neat NMR

If ionic liquids are intended as solvents, the most appropriate way to investigate their solvating ability for a given substrate is to avoid interferences by added solvents, which could falsify the measure. For example, the intermolecular solvent-solute interactions between a chiral ionic liquid and a chiral or pro-chiral substrate can be studied, with a view of understanding whether chiral interactions between solvent and solute take place.

This is why we developed a method for the acquisition of NMR spectra in the neat phase for the onium salts that were liquid at temperatures below 60 °C.

^{1}H- and ^{13}C{^{1}H}-NMR spectra of selected onium salts were therefore acquired neat, i.e. without mixing them with other (e.g. deuterated) solvents. The tubes were equipped with a sealed capillary, containing pure [D_6]DMSO and blocked in a coaxial position by means of a Teflon spacer, for locking and homogeneity purposes. In our hands, and contrary to what previously reported,[27] the amount of deuterated substance, in a capillary with an inner diameter of 1.0 mm was sufficient for an acceptable lock level and for easy homogeneity shimming.

All the spectra are described in the experimental part, and collected in the appendix.

The ^{1}H-NMR spectra were all quite similar to one another for the ammonium and phosphonium cations due to their structural identity. Instead, the ^{13}C{^{1}H}-NMR spectra provided a wealth of information relative to the carbon backbone, and on the purity of the compounds. In addition the ^{13}C spectra were collected under the regime of ^{1}H inverse gated decoupling, with the aim of minimizing NOE effects, hence, quantitative integration of the ^{13}C resonance peaks allowed to confirm cation to anion equimolarity. As an example, Figure 2.1 shows the ^{13}C{^{1}H}-NMR spectrum of $P_{8,8,8,1}[CH_3OCOO]$ **1a** with all the peak assignments, INADEQUATE and heteronuclear correlation experiments were used to assign each carbon atom along the aliphatic chains. It is possible to appreciate the^{13}C-^{31}P coupling in the case of carbons no. 1, 2, 3, and 9, while more distant from the phosphorus atom carbons appear as singlets. The carbonyl region is omitted for clarity.

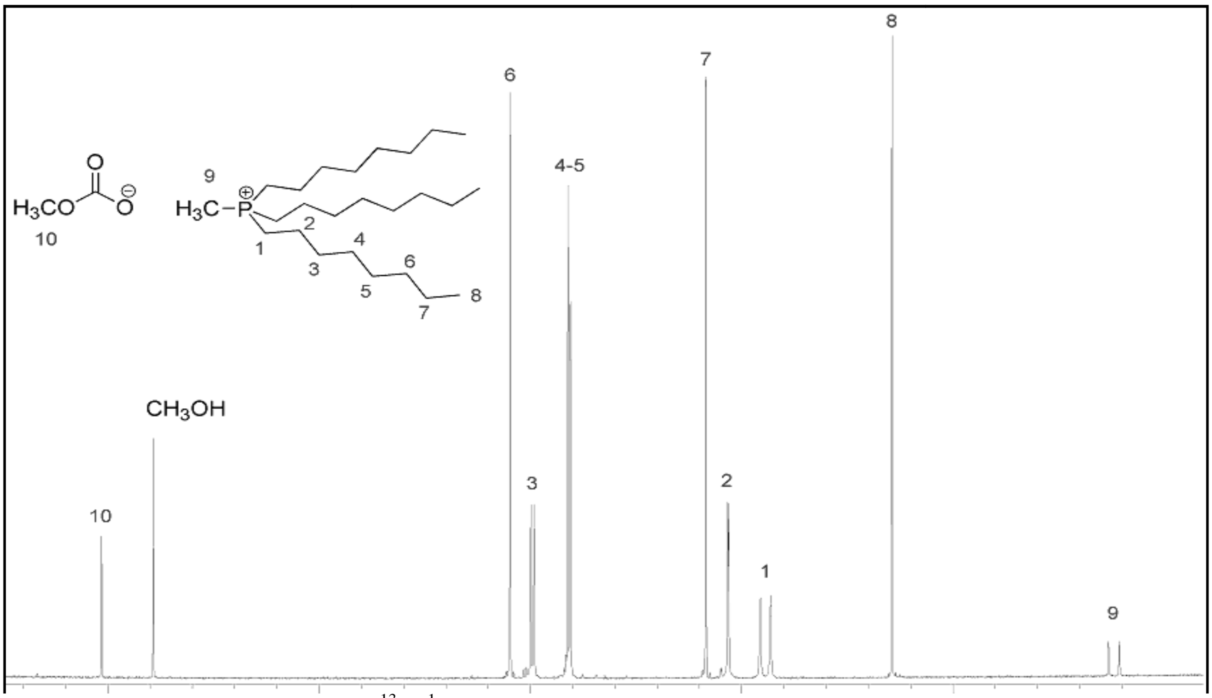


Figure 2.1. $^{13}C\{^1H\}$ NMR spectrum of neat $P_{8,8,8,1}[CH_3OCOO]$ **1a**

2.3.4 Properties of the synthesised Onium salts

2.3.4.1 Application as solvents

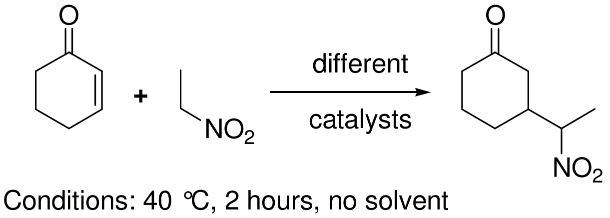
All the synthesised phosphonium and ammonium salt were liquid under 100 °C, so they can be correctly defined as ionic liquids.These compounds could be used in a number of chemical processes as solvents and in the preparation of multiphasic systems, which can be useful in a number of chemical processes. Phosphonium salts in particular are more likely to be used as solvents in chemical processes since they exhibited higher thermal and chemical stability with respect to ammonium based ionic liquids.

The most part of the prepared salts were water-soluble although salts composed by cation bearing long alkyl chains like trioctyl methyl phosphonium and ammonium and lipophilic anion such as bistrifluoromethansulfonylamide (NTf_2) were little if not at all soluble in water. The possibility of obtaining both hydrophilic and hydrophobic ionic liquids makes this synthetic method widely applicable for the preparation of “tailor-made” ionic liquids.

2.3.4.2 Catalytic properties of phosphonium salts

2.3.4.2.1 Basicity of methyl carbonate and bicarbonate -onium salts

Methylcarbonate and hydrogencarbonate onium salts were expected to be somewhat basic, but in fact exceeded our expectations and could be used as catalysts rather than as solvent-catalysts. The Michael reaction of nitroethane with cyclohexenone was chosen as a probe of their efficiency (Scheme 2.7).[28]



Scheme 2.7. Michael reaction of nitroethane with cyclohexenone

Trioctylmethylphosphoniummethylcarbonate **1a** and bicarbonate **8a** were unexpectedly active as strong bases, so much so that they needed not be used as functional solvents (i.e. in large quantities), but could be employed in truly catalytic amounts causing the reaction to proceed very rapidly (Only down to 0.004 molar equivalents did the reaction proceeded sufficiently slowly to allow GC monitoring).

Table 2.2. Michael reaction of nitroethane with cyclohexenone using different bases.[a]

	Catalyst	**pKa**	**Conv. (% GC)**	**Selectivity**[b]
1	$[P_{8,8,8,1}][OCOOCH_3]$ **1a**	-	87	100
2	$[P_{8,8,8,1}][OCOOH]$ **9a**	-	86	100
3	Phosphazene base P_1-*t*-Bu	27 [29,c]	82	100
4	DBU	24 [30,c]	77	92
5	DMAP	18 [30,c]	0	-
6	NaOH	15.7 [d]	7	100
7	DABCO	8.5 [31,c]	0	-
8	$NaHCO_3$	6.4 [d]	0	-

[a] Conditions: 40 °C, 2 hours, no solvent, catalyst:cyclohexenone molar ratio = 0.004 [b] Selectivity towards 15.
[c] pKa's of entries 3, 4, 5, 7 are in acetonitrile. [d] pKa's of entries 6, 8 are in aqueous solution.

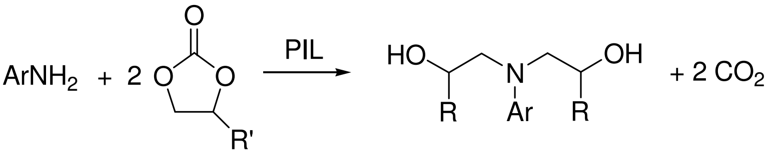
A series of experiments was therefore carried out with catalytic amounts of **1a** and **9a** on the model reaction (Scheme 2.7), and these were compared to results obtained using conventional basic catalysts able to generate carbonucleophiles, such as sterically hindered tertiary organic amines (DBU, DMAP, DABCO, phosphazene base P_1-*t*-Bu , sodium bicarbonate, and sodium hydroxide) obtaining the results reported in Table 2.2.

$P_{8,8,8,1}[CH_3OCOO]$ **1a** and $P_{8,8,8,1}[HOCOO]$ **9a** (entries 1 and 2, Table 2.2) proved more efficient than any of the other organic bases for the coupling of cyclohexenone and nitroethane.

The comparison of the catalytic activities of the trioctylmethylphosphonium bicarbonate **9a** (entry 2, Table 2.2) and of $NaHCO_3$ (entry 8, Table 2.2) was particularly striking, since **9a** behaved as a base approximately 2 orders of magnitude stronger (pKa> 25) than bicarbonate, suggesting that the basic properties of the [HOCOO] anion were tremendously enhanced when coupled to the onium cation. The reason for the high basicity of the methylcarbonate and bicarbonate anions is still under investigation, and may depend on the lypophilic environment surrounding the anions and on solvation effects.

2.3.4.2.2 Phosphonium salts catalysed alkylation of aniline by alkylene carbonate

Another interesting example of the possible applications of the synthesized salts we discovered was the use of phosphonium salts as catalysts for the alkylation of anilines by alkylene carbonates[32] in solvent free conditions.



PIL: 13 different ionic liquids based on phosponium salts
Ar = XC_6H_4-; X = *p*-OCH_3, *p*-CH_3, H, *p*-Cl
R= H, CH_3;

Scheme 2.8. Selective Bis-N-hydroxyalkylations of anilines by ethylene and propylene carbonates in the presence of phosphonium salts.

Kinetic measurements carried out using NMR through a recently developed procedure reported by the research group,[33] demonstrated that in presence of some of these phosphonium salt the formation of bis-*N*-(2-hydroxy)alkylanilines proceeds with higher rate. In particular the alkylation rate of aniline with ethylenecarbonate is doubled by the use of tosylate salts, while the reaction is up to eight-fold accelerated by the more efficient bromide exchanged phosphonium ionic liquids. This effect was explained by the interaction between the phosphonium cations and the carboxylic oxygen of the carbonate due to the weak Lewis acidity of phosponium cations,[34] and the great affinity between phosphorous and oxygen atoms.[35]

2.4 Conclusions

A green synthetic procedure of a class of ionic liquids starting from amines or phosphines and DMC was developed and fully described. The clear, colourless, halide free ionic-liquid precursors **1a-f** were isolated quantitatively and pure from the autoclave simply by removing the methanol and excess DMC under vacuum. They could then be simply anion-exchanged using acids or water (and no solvents) to yield a series of ionic liquids (Table 2.1) with different chemical and physical properties without any workup.

It should be here noted that the methylation of amines and phosphines with DMC has a few recent, scarcely described, precedents in the literature: the methylation of trimethylamine,[36] and the preparation of CBILS©.[14]Commercial CBILS© are sold as water-methanol solutions, for a reason that is not clear to us, but maybe due to the degradation of the methylcarbonate anion [CH_3OCOO] under their reaction conditions. Nonetheless, in our case, the ionic liquids were perfectly stable as such, and it was certainly preferable to isolate them in their pure liquid form. The synthesis of ammonium salts with DMC using 1-ethyl-3-methylimidazolium bromide as a catalyst/medium was also reported recently.[37] Here an imidazolium ionic liquid was used as promoter for the methylation with DMC, but the drawback was obtaining a mixture of ionic liquids that needed to be separated using additional solvents and lowering the product yield.[38]

As stated in the “aim of the research” paragraph our initial focus was obtaining pure trioctylmethylammonium chloride ($N_{8,8,8,1}Cl$) as alternative to Aliquat 336®. The quaternarisation made with DMC accompanied by the anion metathesis using hydrochloric acid, allows to obtain $N_{8,8,8,1}Cl$ in very high yield as a clear yellow liquid. On the other hand also the use of DMS for the preparation of the desired ionic liquid was reported.[16] In this case the product yield was equally very high, even if the obtained chloride salt appeared as a brown liquid. A comparison of the two preparations shows that DMC as methylating agent is not only highly preferable with respect to DMS and methyl halide because of its low toxicity,[39] but also in terms of mass flow. In Figure 2.2 common green chemistry metrics (see Chapter 1 for further details) for the discussed preparations are reported. For what concerns atom economy (AE) the improvement due to the use of DMC instead of DMS is an enhanchement from 78.3 % to 84.2 % (+ 7.5 %). Conversely the E-factor value relative to the DMC preparation was equal to 2.582, a 180 % increment with respect to the use of DMS. However this is not due to a lower greenness of our synthetic method. Taking into account the stoichiometric factor it is clear that in our case we can not consider DMC merely as a reactant, indeed it is also a solvent, so we considered the excess of this reactant as reaction medium. This solution is corroborated by the evidence that

DMC can be recovered (mixed with methanol) at the end of the reaction, allowing us to use this expedient for the processes parameter calculation (i. e. E-factor) in the case of solvent reclaiming.

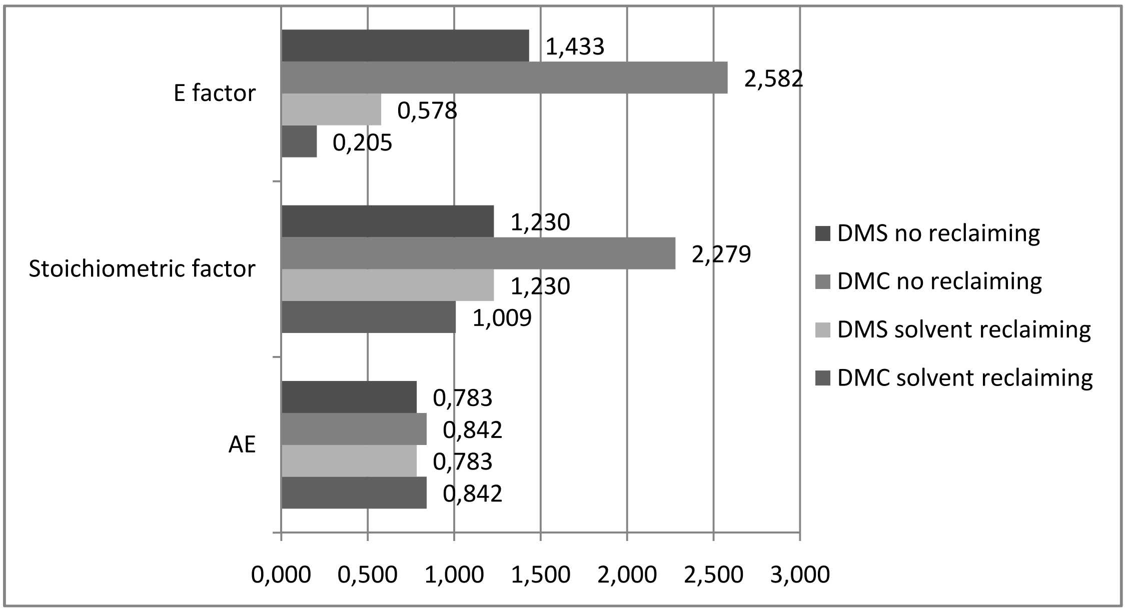


Figure 2.2. Green chemistry metrics comparison of different procedures for trioctylmethylammonium chloride.

A comparison between the two procedures was possible and a 64.5 % reduction of the mass of waste per mass of product was estimated. It is therefore possible to state that the use of DMS is undesirable since it is a very toxic material, it produces a strongly coloured ionic liquid and finally generates a more than double amount of waste than the use of DMC.

In conclusion the reaction conditions using DMC as methylating agent are more energy intensive (T=140 °C, sealed reactor) than those required for highly toxic dimethylsulfate (DMS) and methyl halides (CH_3X), however, the gain in greenness, largely compensated by including safety, handling and absence of waste products. For completeness, however, the general environmental issue associated with the preparation of most ionic liquids begins upstream with the starting nitrogen and phosphorous compounds that are often toxic. For example, tertiary phosphines are prepared from toxic and dangerous PH_3 and α-olefins.[40]

The bicarbonate-exchanged ionic liquids **8a** and **8e** showed very striking basicity, to the point of generating carbonucleophiles that could act as Michael donors, even when just in 0.4 mol % with respect to the substrate. Comparison with known strong hindered bases indicated that the bicarbonate and methyl carbonate anions bearing the described onium cations enhanced their basicity by approximately two orders of magnitude.

In addition phosphonium salts (bromides in particular) showed very interesting catalytic properties in the activation of alkylene carbonates for the alkylation of aromatic amines for the preparation of important target compounds.

This study by the research group is still in progress, with a view toward extending the applicability of the described basic catalysts to other reactions, as well as in search of methodologies to improve upon the greenness of these materials, for example, by immobilising them on solid supports.

The use of onium salts obtained by methylation with DMC and their anion exchanged derivatives as solvent/promoter or as catalyst for reaction under solvent free condition proved to produce very interesting results. Further uncovered applications of these ionic liquids will be discussed in the following chapter.

2.5 Experimental section

General. Reagents were ACS grade and used as received. DMC, methanol, TFAA, HNO_3, HCl, HBr, HI, p-toluenesulfonic acid and $LiNTf_2$, L-phenylalanine were from Sigma-Aldrich. Tri-*n*-octylphosphine (TOP), tri-*n*-butylphophine (T*n*BP), tri-*i*-butylphophine (T*i*BP) were from Strem Chemicals, tri-*n*-hexylphosphine (THP) was from TCI (trialkylphosphines should be used only if they appear as clear liquids: cloudiness or a white solid are indicative of the phosphine oxide). Tri-*n*-octylamine (TOA), tri-n-hexylamine (THA) were from Fluka. ^1H and ^{13}C NMR spectra of all ionic liquids were collected either neat at 60 °C on a Varian Unity 400 MHz spectrometer by locking the sample on DMSO-d_6 placed in a sealed capillary blocked in a coaxial position by means of a Teflon insert in the NMR tube. Chemical shifts were reported in δ values downfield from TMS. INADEQUATE experiments were used to assign all the ^{13}C-NMR signals in $P_{8,8,8,1}[CH_3OCOO]$ and $N_{8,8,8,1}[CH_3OCOO]$, HMBC experiments were used to assign the peak of residual MeOH in the same samples, and HMQC to assign all ^1H peaks based on the correlation with the ^{13}C signals. The ^{13}C satellites were used, where possible, as internal standards to calculate the amount of impurities.[41] Since however the ^1H NMR spectra were acquired in the neat phase, the vast majority of all the resonance bands was rather broad, making integration very tricky and subject to a large error. The absence of other signals indicates, conservatively, that the purity of the onium salts was greater than 95%.

Synthesis of methyltrialkyl-onium methylcarbonate salts **1a-f**: a sealed 200 mL steel autoclave fitted with a pressure gauge and a thermocouple for temperature control was charged with a trialkylphosphine (R_3P, 56 mmol; R= *i*-butyl, 15 mL, 12.2 g; R= *n*-butyl, 15.0 mL, 12.2 g; R= *n*-hexyl, 20.0 mL, 12.2 g; R= *n*-octyl, 25.0 mL, 20.8 g), or a trialkylamine (R_3N, 56 mmol; R= *n*-octyl, 24.5 mL 19.8 g; R= *n*-hexyl, 19.0 mL 15.1 g) dimethyl carbonate (30.0 mL, 32.1 g, 356 mmol) and methanol (30 mL). Three freeze–pump–thaw cycles werecarried out to ensure complete degassing of the mixture and air removal. The empty volume was then filled with nitrogen. The autoclave was heated for 24 h at the desired temperature (140 °C: R= *n*-octyl, *n*-hexyl, *n*-butyl; 170 °C: R=*i*-butyl) with magnetic stirring. Then, the reactor was cooled to rtand vented. Methanol and the residual DMC were removed from the mixture by rotary evaporation. A small amount (<1 equiv) of methanol could remain incorporated in the sample even after a prolonged high vacuum was applied. Isolated yields were: **1c** (17.4 g) 96%; **1b** (21.5 g) 94%; **1a** (27.5 g) 100%. These salts were fully characterized as such, by ^{1}H and ^{13}C NMR, and used without further purifications. **1d** (15.8 g, 87 %) was washed with *n*-hexane (3x15 mL) to remove some unreacted phosphine; then, it was characterized and used.

General anion exchange reaction procedure: a 50 mL round bottomed flask was charged with an equimolar mixture of methyltrialkylonium methylcarbonate (**1a-f**; 6 mmol, 1.75–2.76 g) and of a Brønsted acid (H–A: A =TsO, NO_3, Cl, Br, I, CF_3COO, L-Phe). $TsOH{\cdot}H_2O$ (1.14 g) and L-phenylalanine (1.21 g) were used as solids and methanol (5 mL) was added as a co-solvent. HNO_3 (0.39 mL), HCl (0.50 mL), HBr (0.68 mL) and HI (0.79 mL) were used in aqueous commercial solutions (69%, 37%, 48% and 57%, respectively), while pure TFAA (0.69 g) was added drop wise over 5 min The mixture was kept under magnetic stirring for 1 h at 40 °C. Then, water, methanol and unreacted acid were removed in vacuum obtaining the desired products **2-8(a-f)** in quantitative yields.

Synthesis of methyltrialkyl-onium hydrogencarbonate salts **9a-9e:** a 50 mL round bottomed flask was charged with a mixture obtained by adding 1 mL of water (1.0 g, 55.6 mmol) on 3.0 g of the selected methyltrialkyl-onium methylcarbonate (**1a**, 6.09 mmol; **1e**, 6.31 mmol) under air. Temperature was kept at 40 °C for 2 hours. Excess water and methanol were removed under reduced pressure to yield quantitatively $P_{8,8,8,1}$[HOCOO] **9a** (2.72 g) or $N_{8,8,8,1}$[HOCOO] **9e** (2.71 g) as viscous clear liquids. Both tend to solidify with cooling (mp ~ 25 °C) turning into a white hygroscopic solid.

Synthesis of methyltrialkyl-onium bis(trifluoromethane)sulfonimide salts **10a-e:** In a 250 mL round bottomed flask 8.12 mmol of the selected methyltrialkylonium methylcarbonate (**1a,** 4.0 g; **1e**, 3.86 g) were dissolved in 70 mL of water. An aqueous solution of $LiNTf_2$ (2.33 g, 8.13 mmol in 50 mL) was then added and the resulting mixture was stirred at 70 °C for 2 h. The resulting white precipitate was preferably extracted (but can be isolated by decanting as well) with CH_2Cl_2 to afford pure dry bis(trifluoromethane)sulfonimide salts **10a** (3.05 g, 4.87 mmol, 60%) and **10e** (2.95 g, 4.85 mmol, 60%) as clear colourless liquids.

Tri-*n*-octylmethylphosphonium methylcarbonate $[(C_8H_{17})_3PCH_3]^+[CH_3OCOO]^-$ ($[P_{8,8,8,1}][CH_3OCOO]$) 1a. (viscous clear colourless liquid) ^{1}H-NMR (neat, 60 °C, 400 MHz) δ (ppm relative to TMS, dmso-d_6): 3.15 (s, 3H, $C\underline{H}_3OCOO$), 2.33 (bt, 6H, P-$C\underline{H}_2$), 1.88 (d, 3H, J_{P-H} = 14 Hz, P-$C\underline{H}_3$), 1.42 (b, 6H), 1.27 (b, 6H), 1.11 (b, 24H), 0.70 (bt, 9H); $^{13}C\{^1H\}$ NMR (neat, 60 °C, 100 MHz) (δ/ppm relative to TMS, dmso-d_6, CH_2's assigned by 2D inadequate): 155.8 (1C, $\underline{C}$=O), 50.0 (1C, $\underline{C}H_3O$), 30.9 (3C, C_6), 29.9 (d, 3C, J_{P-C} = 15 Hz, C_3), 28.2 (3C, C_5), 28.0 (3C, C_4), 21.6 (3C, C_7), 20.7 (d, 3C, J_{P-C} = 4 Hz, C_2), 19.0 (d, 3C, J_{P-C} = 48 Hz, C_1), 12.8 (3C, C_8), 2.6 (d, 3C, J_{P-C} = 53 Hz, P-$\underline{C}H_3$). IR ν_{max} neat/cm^{-1} 2900, 2856, 1669.

Tri-*n*-hexylmethylphosphonium methylcarbonate $[(n\text{-}C_6H_{13})_3PCH_3]^+[OCH_3COO]^-$ ($[P_{6,6,6,1}][CH_3OCOO]$) 1b. (viscous pale yellow liquid): ^{1}H NMR ($CDCl_3$, 25°C, 400 MHz): δ (ppm) 3.44 (s, 3H; $C\underline{H}_3OCOO$), 2.22 (m, 6H; P-$C\underline{H}_2$), 1.92 (d, J_{P-H}=14, 3H, P-$C\underline{H}_3$), 1.42 (m, 12H), 1.24 (m, 12H), 0.82 (brt, 9H); ^{13}C NMR ($CDCl_3$, 25°C, 100 MHz): δ (ppm): 159.7 (1C; $\underline{C}$=O),), 51.5 (1C; $\underline{C}H_3O$), 30.4 (3C), 29.6 (d, J_{P-C} = 15Hz, 3C), 21.7 (3C), 20.9 (d, J_{P-C} = 4Hz, 3C), 19.3 (d, J_{P-C} = 49Hz, 3C, P-$\underline{C}H_2$), 13.3 (3C), 3.5 (d, J_{P-H} = 52Hz, 1C; P-$\underline{C}H_3$).

Tri-*n*-butylmethylphosphonium methylcarbonate $[(n\text{-}C_4H_9)_3PCH_3]^+[OCH_3COO]^-$ ($[P_{4,4,4,1}][CH_3OCOO]$) 1c. (viscous pale yellow liquid) ^{1}H NMR ($CDCl_3$, 25°C, 400 MHz): δ (ppm) 3.00 (s, 3H; $C\underline{H}_3OCOO$), 1.88 (m, 6H; P-$C\underline{H}_2$), 1.52 (d, 3H, J_{P-H} = 14 Hz; P-$C\underline{H}_3$), 1.06 (m, 12H), 0.50 (brt, 9H); ^{13}C NMR ($CDCl_3$, 25°C, 100 MHz): δ (ppm) 156.8 (1C; $\underline{C}$=O),), 50.7 (1C; $\underline{C}H_3O$), 22.5 (d, 3C, J_{P-H} =15 Hz), 22.3(d, 3C, J_{P-H} = 4 Hz), 18.6 (d, 3C, J_{P-H} = 49 Hz; P-$\underline{C}H_2$), 12.1 (3C), 2.8 (d, 1C, J_{P-H} = 53 Hz; P-$\underline{C}H_3$).

Tri-*i*-butylmethylphosphonium methylcarbonate $[(i\text{-}C_4H_9)_3PCH_3]^+[OCH_3COO]^-$ ($[P_{i(4,4,4),1}][CH_3OCOO]$) 1d: (viscous pale yellow liquid) ^{1}H NMR ($CDCl_3$, 25°C, 400 MHz): δ (ppm) 3.13 (s, 3H; $C\underline{H}_3OCOO$), 1.97 (dd, J_{P-H} = 13 Hz, J_{H-H} = 7 Hz, 6H; P-$C\underline{H}_2$), 1.73 (m, 3H; P-CH_2-$C\underline{H}(CH_3)_2$), 1.72 (d, J_{P-H} = 13Hz, 3H; P-$C\underline{H}_3$), 0.76 (d, 18H, J_{H-H} = 7Hz; P-CH_2-$CH(C\underline{H}_3)_2$); ^{13}C NMR ($CDCl_3$, 25°C, 100 MHz): δ (ppm) 157.8 (1C; $\underline{C}$=O), 51.2 (1C; $\underline{C}H_3O$), 29.5 (d, $J_{P\text{-}C}$ = 46 Hz, 3C; P-<u>C</u>H_2-CH(CH_3)$_2$), 23.7 (d, $J_{P\text{-}C}$ = 9 Hz, 6C; P-CH_2-CH(<u>C</u>H_3)$_2$), 22.9 (d, 3C, $J_{P\text{-}C}$ = 5 Hz; P-CH_2-<u>C</u>H(CH_3)$_2$), 6.2 (d, 1C, $J_{P\text{-}C}$ = 50 Hz,; P-<u>C</u>H_3).

Tri-*n*-octylmethylammonium methylcarbonate $[(C_8H_{17})_3NCH_3]^+[CH_3OCOO]^-$ ($[N_{8,8,8,1}][CH_3OCOO]$) 1e. (viscous clear yellow liquid) ^{1}H-NMR (neat, 60 °C, 400 MHz) (δ/ppm relative to TMS, dmso-d_6): 3.36 (6H, N-C<u>H</u>$_2$), 3.11 (6H, N-C<u>H</u>$_3$ and C<u>H</u>$_3$O), 1.54 (b, 6H), 1.08 (b, 30H), 0.67 (9H); $^{13}C\{^1H\}$ NMR (neat, 60 °C, 100 MHz): δ (ppm relative to TMS, dmso-d_6, CH_2's assigned by 2D inadequate) 155.5 (1C, <u>C</u>=O), 59.9 (3C, C_1), 50.0 (1C, <u>C</u>H_3O), 46.8 (1C, N-C<u>H</u>$_3$), 30.9 (3C, C_6), 28.2 (6C, C_5-C_4), 25.7 (3C, C_3), 21.6 (3C, C_7), 21.3 (3C, C_2), 12.8 (3C, C_8). IR ν_{max} neat/cm^{-1} 2900, 2857, 1669.

Tri-*n*-hexylmethylammonium methylcarbonate $[(C_6H_{13})_3NCH_3]^+[CH_3OCOO]^-$ ($[N_{6,6,6,1}][CH_3OCOO]$) 1f. ^{1}H-NMR (neat, 60 °C, 400 MHz) (δ/ppm relative to TMS, dmso-d_6): 3.32 (b, 6H, N-C<u>H</u>$_2$), 3.10 (3H, N-C<u>H</u>$_3$), 3.06 (3H, C<u>H</u>$_3$O),1.52 (b, 6H), 1.12 (b, 24H), 0.67; $^{13}C\{^1H\}$ NMR (neat, 60 °C, 100 MHz): δ (ppm relative to TMS, dmso-d_6) 155.6 (1C, C=O), 60.1 (3C, C_1), 50.0 (1C, <u>C</u>H_3O), 46.9 (1C, N-<u>C</u>H_3), 30.4 (3C, C_6), 25.3 (3C, C_3), 21.5 (3C, C_7), 21.3 (3C, C_2), 12.8 (3C, C_8). IR ν_{max} neat/cm^{-1} 3186, 2956, 2930, 2860, 1677, 1634.

Tri-*n*-octylmethylphosphonium tosylate $[(n\text{-}C_8H_{17})_3PCH_3]^+[CH_3C_6H_5SO_3]^-$ ($[P_{8,8,8,1}][OTs]$) 2a. (white solid): ^{1}H NMR ($CDCl_3$, 25°C, 400 MHz): δ (ppm) 7.70 (d, 2H, J = 8Hz), 7.06 (d, 2H J = 8Hz,), 2.28 (s, 3H; -C<u>H</u>$_3$), 2.18 (m, 6H; P-C<u>H</u>$_2$), 1.88 (d, 3H, $J_{P\text{-}H}$ = 14 Hz, P-C<u>H</u>$_3$), 1.35 (m, 12H), 1.20 (m, 24H), 0.83 (brt, 9H); ^{13}C NMR ($CDCl_3$, 25°C, 100 MHz): δ (ppm) 144.0 (1C), 138.7 (1C), 128.3 (2C), 125.8 (2C), 31.6 (3C), 30.5 (d, 3C, $J_{P\text{-}C}$ = 15 Hz,), 28.9 (3C), 28.8 (3C), 22.5 (3C), 21.6 (d, $J_{P\text{-}C}$ = 5 Hz, 3C), 21.1 (1C), 19.9 (d, 3C, $J_{P\text{-}C}$ = 48 Hz, P-<u>C</u>H_2), 13.9 (3C), 4.1 (d, 1C, $J_{P\text{-}H}$ = 52 Hz; P-<u>C</u>H_3).

Tri-*n*-hexylmethylphosphonium tosylate $[(n\text{-}C_6H_{13})_3PCH_3]^+[CH_3C_6H_5SO_3]^-$ ($[P_{6,6,6,1}][OTs]$) 2b. (viscous clear colourless liquid) ^{1}H NMR ($CDCl_3$, 25°C, 400 MHz): δ (ppm) 7.73 (d, J = 8 Hz, 2H), 7.09 (d, J = 8 Hz, 2H), 2.31 (s, 3H; -C<u>H</u>$_3$), 2.22 (m, 6H; P-C<u>H</u>$_2$), 1.93 (d, $J_{P\text{-}H}$ = 14 Hz, 3H, P-C<u>H</u>$_3$), 1.39 (m, 12H), 1.25 (m, 12H), 0.85 (brt, 9H); ^{13}C NMR ($CDCl_3$, 25°C, 100 MHz): δ (ppm) 144.5 (1C), 138.6 (1C), 128.3 (2C), 125.8 (2C), 31.0 (3C), 30.1 (d, 3C, $J_{P\text{-}C}$ = 15 Hz), 22.2 (3C), 21.4 (d, 3C, $J_{P\text{-}C}$ = 5 Hz), 21.1 (1C), 19.8 (d, $J_{P\text{-}C}$ = 49 Hz, 3C, P-<u>C</u>H_2), 13.8 (3C), 3.9 (d, 1C, $J_{P\text{-}H}$ = 52 Hz,).

Tri-*n*-butylmethylphosphonium tosylate $[(n\text{-}C_4H_9)_3PCH_3]^+[CH_3C_6H_5SO_3]^-$ ($[P_{4,4,4,1}][OTs]$) 2c. (viscous clear colourless liquid) ^{1}H NMR ($CDCl_3$, 25°C, 400 MHz) δ (ppm): 7.61 (d, 2H, J = 8 Hz), 7.00 (d, 2H, J = 8 Hz), 2.21 (s, 3H; -C<u>H</u>$_3$), 2.06 (m, 6H; P-C<u>H</u>$_2$), 1.72 (d, 3H, $J_{P\text{-}H}$ = 14 Hz; P-C<u>H</u>$_3$), 1.28 (m, 12H), 0.77 (brt, 9H); ^{13}C NMR ($CDCl_3$, 25°C, 100 MHz):

δ (ppm) 144.1 (1C), 138.9 (1C), 128.4 (2C), 125.8 (2C), 23.7 (d, 3C, $J_{P\text{-}H}$ = 16 Hz), 23.4 (d, $J_{P\text{-}H}$ = 5 Hz, 3C), 21.2 (1C), 19.6 (d, 3C $J_{P\text{-}H}$ = 49 Hz), 13.4 (3C), 4.0 (d, 1C, $J_{P\text{-}H}$ = 52 Hz).

Tri-*n*-octylmethylphosphonium nitrate $[(C_8H_{17})_3PCH_3]^+[NO_3]^-$ ($[P_{8,8,8,1}][NO_3]$) 3a. ^{1}H-NMR (neat, 60 °C, 400 MHz) δ (ppm relative to TMS, dmso-d_6): 2.25 (b, 6H; P-C$\underline{H}_2$), 1.79 (d, 3H, $J_{P\text{-}H}$ = 13 Hz; P-C$\underline{H}_3$), 1.43 (b, 6H), 1.26 (b, 6H), 1.11 (b, 24H), 0.70 (bt, 9H); ^{13}C{^{1}H} NMR (neat, 60 °C, 100 MHz) δ (ppm relative to TMS, dmso-d_6): 30.9 (3C, C_6), 29.8 (d, 3C, $J_{P\text{-}C}$ = 15 Hz, C_3), 28.1 (3C, C_5), 28.0 (3C, C_4), 21.7 (3C, C_7), 20.5 (3C, C_2), 19.0 (d, 3C, $J_{P\text{-}C}$ = 49 Hz, C_1), 13.0 (C3, C_8), 2.5 (d, 1C, $J_{P\text{-}C}$ = 51 Hz, P-$\underline{C}H_3$). IR ν_{max} neat/cm^{-1} 2930, 2856, 1467, 1340.

Tri-*n*-octylmethylammonium nitrate $[(C_8H_{17})_3NCH_3]^+[NO_3]^-$ ($[N_{8,8,8,1}][NO_3]$) 3e. ^{1}H-NMR (neat, 60 °C, 400 MHz) δ (ppm relative to TMS, dmso-d_6): 3.30 (b, 6H, N-C$\underline{H}_2$), 3.01 (3H, N-C$\underline{H}_3$), 1.58 (b, 6H), 1.17 (b, 6H), 1.11 (b, 24H), 0.71; ^{13}C{^{1}H} NMR (neat, 60 °C, 100 MHz) (δ/ppm relative to TMS, dmso-d_6): 60.4 (3C, C_1), 46.8 (1C, N-C$\underline{H}_3$), 30.9 (3C, C_6), 28.2 (6C, C_5-C_4), 25.6 (3C, C_3), 21.7 (3C, C_7), 21.2 (3C, C_2), 12.9 (3C, C_8). IR ν_{max} neat/cm^{-1} 2930, 2856, 1467, 1377.

Tri-*n*-octylmethylphosphonium chloride $[(C_8H_{17})_3PCH_3]^+Cl^-$ ($[P_{8,8,8,1}]Cl$) 4a. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.49 – 2.32 (m, 1H), 2.09 (d, 1H, J = 13.5 Hz), 1.59 – 1.38 (m, 2H), 1.35 – 1.13 (m, 4H), 0.84 (bt, 1H, J = 6.9 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 31.4 (3C, C_6), 30.4 (d, 3C, $J_{P\text{-}C}$ = 15 Hz, C_3), 28.6 (6C, C_4-C_5), 22.2 (3C, C_7), 21.5 (d, 3C, $J_{P\text{-}C}$ = 4 Hz, C_2), 20.2 (d, 3C, $J_{P\text{-}C}$ = 49 Hz, C_1), 13.66 (3C), 4.70 (d, 1C, $J_{P\text{-}C}$ = 52 Hz; P-$\underline{C}H_3$).

Tri-*n*-hexylmethylphosphonium chloride $[(n\text{-}C_6H_{13})_3PCH_3]^+Cl^-$ ($[P_{6,6,6,1}]Cl$) 4b. (white solid) ^{1}H NMR ($CDCl_3$, 25°C, 400 MHz): δ (ppm): 2.26 (m, 6H; P-C$\underline{H}_2$), 1.91 (d, 3H, $J_{P\text{-}H}$ = 13 Hz, P-C$\underline{H}_3$), 1.34 (m, 12H), 1.15 (m, 12H), 0.71 (brt, 9H); ^{13}C NMR ($CDCl_3$, 25°C, 100 MHz): δ (ppm): 30.6 (3C), 29.9 (d, 3C, $J_{P\text{-}C}$ = 15 Hz), 21.9 (3C), 21.3 (d, 3C, $J_{P\text{-}C}$ = 4 Hz), 20.3 (d, 3C, $J_{P\text{-}C}$ = 49 Hz), 13.5 (3C), 4.9 (d, 1C, $J_{P\text{-}C}$ = 53 Hz).

Tri-*n*-octylmethylammonium chloride $[(C_8H_{17})_3NCH_3]^+Cl^-$ ($[N_{8,8,8,1}]Cl$) 4e ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.48 – 3.35 (m, 1H), 3.31 (s, 1H), 1.65 (s, 1H), 1.29 (dd, 5H, J = 22.7, 14.9 Hz), 0.85 (t, 1H, J = 6.8 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 61.5 (3C, C_1), 48.9 (1C, N-$\underline{C}H_3$), 31.6 (3C, C_6), 29.07 (3C, C_5), 28.94 (3C, C_4), 26.30 (3C, C_3), 22.49 (3C, C_7), 22.40 (3C, C_2), 13.95 (3C, C_8).

Tri-*n*-octylmethylphosphonium bromide $[(n\text{-}C_8H_{17})_3PCH_3]^+Br^-$ ($[P_{8,8,8,1}]Br$) 5a. (white hygroscopic solid) ^{1}H NMR ($CDCl_3$, 25°C, 400 MHz): δ (ppm): 2.39 (m, 6H; P-C$\underline{H}_2$), 2.06 (d, 3H, $J_{P\text{-}H}$ = 13 Hz, P-C$\underline{H}_3$), 1.45 (m, 12H), 1.23 (m, 24H), 0.82 (brt, 9H); ^{13}C NMR ($CDCl_3$, 25°C, 100 MHz): δ (ppm): 31.4 (3C), 30.4 (d, $J_{P\text{-}C}$ =15Hz, 3C), 28.9 (3C),28.8 (3C), 22.5 (3C), 21.6 (d, 3C, $J_{P\text{-}C}$ = 5 Hz), 21.1 (1C), 19.9 (d, 3C, $J_{P\text{-}C}$ = 48 Hz), 13.9 (3C), 4.1 (d, 1C, $J_{P\text{-}C}$ = 52 Hz; P-$\underline{C}H_3$).

Tri-*n*-hexylmethylphosphonium bromide [(*n*-$C_6H_{13})_3PCH_3$][Br] ([$P_{6,6,6,1}$]Br) 5b. (viscous pale yellow liquid) ^{1}H NMR ($CDCl_3$, 25°C, 400 MHz): δ (ppm): 2.26 (m, 6H; P-C$\underline{H}_2$), 1.91 (d, 3H, $J_{P\text{-}H}$ = 13 Hz, P-C$\underline{H}_3$), 1.34 (m, 12H), 1.15 (m, 12H), 0.71 (brt, 9H); ^{13}C NMR ($CDCl_3$, 25°C, 100 MHz): δ (ppm): 30.6 (3C), 29.9 (d, 3C, $J_{P\text{-}C}$ = 15 Hz), 21.9 (3C), 21.3 (d, 3C, $J_{P\text{-}C}$ = 4 Hz), 20.3 (d, 3C, $J_{P\text{-}C}$ = 49 Hz), 13.5 (3C), 4.9 (d, 1C, $J_{P\text{-}C}$ = 53 Hz).

Tri-*n*-butylmethylphosphonium bromide [(*n*-$C_4H_9)_3PCH_3$][Br] ([$P_{4,4,4,1}$]Br) 5c. (viscous clear colourless liquid) ^{1}H NMR ($CDCl_3$, 25°C, 400 MHz): δ (ppm):1.99 (m, 6H; P-C*H_2*), 1.62 (d, J(P,H)=13, 3H, P-C*H_3*), 1.07 (m, 12H), 0.50 (brt, 9H); ^{13}C NMR ($CDCl_3$, 25°C, 100 MHz): δ (ppm): 22.6 (d, 3C, $J_{P\text{-}C}$ = 16 Hz), 22.5 (d, 3C, $J_{P\text{-}C}$ = 4 Hz),19.3 (d, 3C, $J_{P\text{-}C}$ = 49 Hz), 12.3 (3C), 4.1 (d, 1C, $J_{P\text{-}C}$ = 52 Hz).

Tri-*i*-butylmethylphosphonium bromide [(*i*-$C_4H_9)_3PCH_3$][Br] ([$P_{(4,4,4),1}$]Br) 5d. (white hygroscopic solid) ^{1}H NMR ($CDCl_3$, 25°C, 400 MHz): δ (ppm): 2.17 (dd, $J_{P\text{-}C}$ = 13 Hz, $J_{H\text{-}H}$ = 7 Hz, 6H; P-C$\underline{H}_2$), 1.88 (d, 3H, $J_{P\text{-}H}$ = 13 Hz; P-C$\underline{H}_3$), 1.87 (m, 3H; P-CH_2-C$\underline{H}$($CH_3)_2$), 0.84 (d, 18H, $J_{H\text{-}H}$ = 7 Hz,; P-CH_2-CH(C$\underline{H}_3)_2$); ^{13}C NMR ($CDCl_3$, 25°C, 100 MHz): δ (ppm): 29.9 (d, 3C, $J_{P\text{-}C}$ = 46 Hz), 23.9 (d, 6C, $J_{P\text{-}C}$ = 9 Hz,), 23.0 (d, 3C, $J_{P\text{-}C}$ = 5 Hz), 7.5 (d, 1C, $J_{P\text{-}C}$ = 50 Hz).

Tri-*n*-octylmethylphosphonium iodide [(*n*-$C_8H_{17})_3PCH_3$][I] ([$P_{8,8,8,1}$]I) 6a. (viscous yellow liquid) ^{1}H NMR ($CDCl_3$, 25°C, 400 MHz): δ (ppm): 2.41 (m, 6H; P-C$\underline{H}_2$), 2.09 (d, 3H, $J_{P\text{-}C}$ = 13 Hz, P-C$\underline{H}_3$), 1.49 (m, 12H), 1.26 (m, 24H), 0.84 (brt, 9H); ^{13}C NMR ($CDCl_3$, 25°C, 100 MHz): δ (ppm): 31.5 (3C), 30.4 (d, 3C, $J_{P\text{-}C}$ = 15 Hz), 28.7 (3C) ,28.8 (3C), 22.4 (3C), 21.6 (d, 3C, $J_{P\text{-}C}$ = 5 Hz), 20.7 (d, 3C, $J_{P\text{-}C}$ =48Hz; P-$\underline{C}H_2$), 13.8 (3C), 5.6 (d, 1C, $J_{P\text{-}C}$ = 52 Hz).

Tri-*n*-octylmethylphosphoniumtrifluoroacetate [(n-$C_8H_{17})_3PCH_3]^+[CF_3COO]^-$ ([$P_{8,8,8,1}$][TFA]) 7a. (viscous clear liquid) mp = 23-24 °C. ^{1}H-NMR (neat, 60 °C, 400 MHz) δ (ppm relative to TMS, dmso-d_6): 2.25 (b, 6H, P-C$\underline{H}_2$), 1.84 (d, 3H, $J_{P\text{-}H}$ = 14 Hz, P-C$\underline{H}_3$), 1.39 (b, 6H), 1.23 (b, 6H), 1.09 (b, 24H), 0.68 (bt, 9H); ^{13}C{^{1}H} NMR (neat, 60 °C, 100 MHz) δ (ppm relative to TMS, dmso-d_6): 158.9 (q, 1C, $J_{F\text{-}C}$ = 37 Hz, $\underline{C}$=O), 115.3 (q, 1C, $J_{F\text{-}C}$ = 290 Hz, $\underline{C}F_3$), 30.6 (3C, C_6), 29.4 (d, 3C, $J_{P\text{-}C}$ = 14 Hz, C_3), 27.8 (3C, C_5), 27.6 (3C, C_4), 21.4 (3C, C_7), 20.2 (d, 3C, $J_{P\text{-}C}$ = 5 Hz, C_2), 19.1 (d, 3C, $J_{P\text{-}C}$ = 48 Hz, C_1), 12.6 (C3, C_8), 2.4 (d, 3C, $J_{P\text{-}C}$ = 53 Hz, P-$\underline{C}H_3$). IR ν_{max} neat/cm^{-1} 2900, 1688, 1467, 1199, 1164, 1122.

Tri-*n*-octylmethylammoniumtrifluoroacetate [($C_8H_{17})_3NCH_3]^+[CF_3COO]^-$ ($N_{8,8,8,1}$[CF_3COO]) ([$N_{8,8,8,1}$][TFA]) 7e. ^{1}H-NMR (neat, 60 °C, 400 MHz) δ (ppm relative to TMS, dmso-d_6): 3.21 (b, 6H, N-C$\underline{H}_2$), 3.00 (3H, N-C$\underline{H}_3$), 1.51 (b, 6H), 1.14 (b, 6H), 1.09 (b, 24H), 0.68 (bt, 9H); $^{13}C\{^1H\}$ NMR (neat, 60 °C, 100 MHz) δ (ppm relative to TMS, dmso-d_6): 158.2 (q, 1C, $J_{F\text{-}C}$ = 31 Hz, $\underline{C}$=O), 116.9 (q, 1C, $J_{F\text{-}C}$ = 299 Hz, $\underline{C}F_3$), 60.2 (3C, C_1), 47.0 (1C, N-$C\underline{H}_3$), 30.7 (3C, C_6), 28.0 (3C, C_5), 27.9 (3C, C_4), 25.3 (3C, C_3), 21.5 (3C, C_7), 21.1 (3C, C_2), 12.7 (3C, C_8). IR ν_{max} neat/cm^{-1} 2900, 2858, 1688, 1378, 1199, 1170, 1125.

Tri-*n*-octylmethylammonium L-phenylalaninate $[(C_8H_{17})_3NCH_3]^+[L\text{-}Phe]^-$ ($[N_{8,8,8,1}][L\text{-}Phe]$) 8e. ^{1}H-NMR (neat, 60 °C, 400 MHz) δ (ppm relative to TMS, dmso-d_6): 6.96 (2H), 6.84 (2H), 6.73 (2H), 3.01 (b, 6H, N-$C\underline{H}_2$), 2.93 (3H, N-$C\underline{H}_3$), 2.27 (1H), 1.33 (b, 6H), 0.96 (b, 30H), 0.56; $^{13}C\{^1H\}$ NMR (neat, 60 °C, 100 MHz) δ (ppm relative to TMS, dmso-d_6): 175.6, 141.1, 128.5, 126.6, 124.0, 59.9 (3C, C_1), 57.4, 42.7, 47.4 (1C, N-$C\underline{H}_3$), 30.9 (3C, C_6), 28.2 (6C, C_5-C_4), 25.6 (3C, C_3), 21.6 (3C, C_7), 21.3 (3C, C_2), 12.9 (3C, C_8). IR ν_{max} neat/cm^{-1} 3411, 2927, 2857, 1599, 1380.

Tri-*n*-octylmethylphosphoniumhydrogencarbonate $[(C_8H_{17})_3PCH_3]^+[HOCOO]^-$ ($[P_{8,8,8,1}][HOCOO]$) 9a. ^{1}H-NMR (neat, 60 °C, 400 MHz) δ (ppm relative to TMS, dmso-d_6): 2.33 (b, 6H, P-$C\underline{H}_2$), 1.84 (bd, 3H, P-$C\underline{H}_3$), 1.33 (b, 6H), 1.23 (b, 6H), 1.05 (b, 24H), 0.64 (bt, 9H); $^{13}C\{^1H\}$ NMR (neat, 60 °C, 100 MHz) δ (ppm relative to TMS, dmso-d_6): 158.9 (1C, $\underline{C}$=O), 31.0 (3C, C_6), 29.8 (d, 3C, $J_{P\text{-}C}$ = 15 Hz, C_3), 28.2 (6C, C_5-C_4),21.6 (3C, C_7),20.9 (3C, C_2), 19.1 (d, 3C, $J_{P\text{-}C}$ = 49 Hz, C_1),12.9 (C3, C_8),2.9 (d, 3C, $J_{P\text{-}C}$ = 52 Hz, P-$\underline{C}H_3$). IR ν_{max} neat/cm^{-1} 2900, 2850, 1650, 1631.

Tri-*n*-octylmethylammoniumhydrogencarbonate $[(C_8H_{17})_3NCH_3]^+[HOCOO]^-$ ($[N_{8,8,8,1}][HOCOO]$) 9e. ^{1}H-NMR (neat, 60 °C, 400 MHz) δ (ppm relative to TMS, dmso-d_6): 5.14 (s, OH), 3.14 (b, 6H, N-$C\underline{H}_2$), 2.96 (b, 3H, N-$C\underline{H}_3$), 1.45 (b, 6H), 1.12 (b, 6H), 1.35 (b, 24H), 0.62 (bt, 9H); $^{13}C\{^1H\}$ NMR (neat, 60 °C, 100 MHz) δ (ppm relative to TMS, dmso-d_6): 160.3 (1C, $\underline{C}$=O), 59.9 (3C, C_1), 47.8 (1C, N-$C\underline{H}_3$), 30.9 (3C, C_6), 28.1 (6C, C_5-C_4), 25.3 (3C, C_3), 21.6 (3C, C_7), 21.1 (3C, C_2), 12.8 (3C, C_8). IR ν_{max} neat/cm^{-1} 3406, 2500, 2856, 1650, 1631.

Tri-*n*-octylmethylphosphoniumbis(trifluoromethane)sulfonimide $[(C_8H_{17})_3PCH_3]^+[NTf_2]^-$ ($[P_{8,8,8,1}][NTf_2]$) 10a. ^{1}H-NMR (neat, 60 °C, 400 MHz) δ (ppm relative to TMS, dmso-d_6): 1.96 (b, 6H, P-$C\underline{H}_2$), 1.55 (d, 3H, $J_{P\text{-}H}$ = 13 Hz, P-$C\underline{H}_3$), 1.34 (b, 6H), 1.24 (b, 6H), 1.09 (b, 24H), 0.68 (bt, 9H); $^{13}C\{^1H\}$ NMR (neat, 60 °C, 100 MHz) δ (ppm relative to TMS, dmso-d_6): 119.1 (q, 2C, $J_{F\text{-}C}$ = 321 Hz, $\underline{C}F_3$), 30.6 (3C, C_6), 29.3 (d, 3C, $J_{P\text{-}C}$ = 15 Hz, C_3), 27.8 (3C, C_5), 27.5 (3C, C_4), 21.4 (3C, C_7), 20.2 (d, 3C, $J_{P\text{-}C}$ = 5 Hz, C_2), 19.0 (d, 3C, $J_{P\text{-}C}$ = 48 Hz, C_1), 12.6 (C3, C_8), 2.3 (d, 3C, $J_{P\text{-}C}$ = 52 Hz, P-$\underline{C}H_3$). IR ν_{max} neat/cm^{-1} 2930, 2859, 1468, 1352.

Tri-*n*-octylmethylammoniumbis(trifluoromethane)sulfonimide $[(C_8H_{17})_3NCH_3]^+[NTf_2]^-$ ($[N_{8,8,8,1}][NTf_2]$) 10e. ^{1}H-NMR (neat, 60 °C, 400 MHz) δ (ppm relative to TMS, dmso-d_6):2.98 (b, 6H, N-C<u>H</u>$_2$), 2.73 (3H, N-C<u>H</u>$_3$), 1.45 (b, 6H), 1.12 (b, 6H), 1.07 (b, 24H), 0.67 (t, 9H, J = 7.2 Hz); ^{13}C{^{1}H} NMR (neat, 60 °C, 100 MHz) δ (ppm relative to TMS, dmso-d_6): 119.1 (q, 1C, J_{F-C} = 322 Hz, <u>C</u>F$_3$), 60.8 (3C, C_1), 46.9 (1C, N-C<u>H</u>$_3$), 30.5 (3C, C_6), 27.8 (6C, C_5-C_4), 25.0 (3C, C_3), 21.4 (3C, C_7), 21.0 (3C, C_2), 12.6 (3C, C_8) IR ν_{max} neat/cm^{-1} 2929, 2859, 1469, 1378, 1353.

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3 Onium salts: applications as solvents/catalysts for organic reactions

3.1 Preamble

In chapter 1 the primary importance of ionic liquids in synthesis and in various industrial applications were already underlined. In chapter 2 the synthesis and the most relevant properties of a series of onium salts obtained by a green synthesis were reported. As previously discussed most of these onium salts were liquid at temperatures below 100 °C, therefore they can be defined as ionic liquids.[1] In addition outstanding catalytic properties of the synthesised onium ionic liquids were discussed. The enhanced basicity of methylcarbonate and hydrogencarbonate demonstrated that these compounds were suitable as organo-catalysts for organic reactions.[2] To explain this behaviour the very high lipophilicity of a cation bearing long alkyl chains like trioctylmehylphosphonium was considered to act as "spacer" between the ion pair leaving the anion practically naked.[3] This could impart higher basic/nucleophilic character to anions causing these unexpected properties. Even non basic phosphonium salts demonstrated to act as catalysts in organic reactions,[4] probably due to the weak Lewis acidity of phosphorous atoms[5] and its high affinity for the oxygen atom.[6] Recently both nucleophilic and electrophilic characters of these ionic liquids were demonstrated to act simultaneously to explain their catalytic activity in the case of the self condensation of cyclohexenone through a Baylis-Hillman type reaction[7].

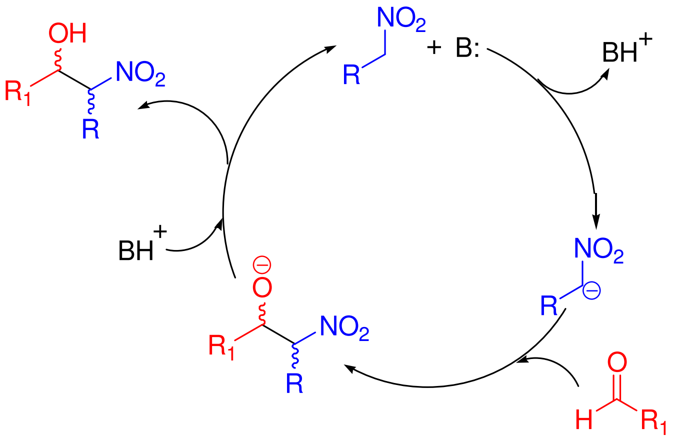
Catalysis by ionic liquids (ILs) is gaining a preeminent position.[8] Modern literature reports a number of transformations including esterifications, nitrations, aldol condensations, Friedel-Crafts substitutions, acetalysations, etc., where ILs as such or binary/ternary IL-based systems act as efficient catalysts.[9] For this reason a study of the applications of the onium salts described in chapter 2 as solvents and/or catalysts for organic reactions was performed. In particular reactions carried out in ionic liquids as catalysts/solvents or in neat conditions using little amount of ILs were object of this thesis work, in agreement with the aim of minimizing the usage of common and often low eco-sustainable solvents and in partnership with API company.

This chapter is divided into two separate sections in which two new applications of ionic liquids prepared using dimethylcarbonate as quaternarisation agent will be disclosed. The first one is related to the already assessed basicity of the carbonate ionic liquid (CILs), exploited in the catalysis of the nitroaldol condensation (the Henry reaction). The second one reports a completely new application of onium ionic liquids prepared by our green synthesis; where nitrate exchanged phosphonium ionic liquids catalyse the aromatic electrophilic oxychlorination when used without the need of commonly used (chlorinated) solvents.[10]

3.2 Basicity of carbonate ionic liquid. A case study: the Henry reaction.

3.2.1 Introduction

A peculiar field of catalysis by ionic liquids is represented by C-C bond forming reactions.[11] Among several examples, a remarkable one is the Henry reaction of nitroalkanes with carbonyl derivatives.[12] This reaction is base catalysed and proceeds through formation of the nitronate anion (by proton extraction from nitroalkane), this specie is able to attack a carbonyl group yielding the corresponding nitroaldol (Scheme 3.1). A large quantity of examples using both heterogeneous and homogeneous catalysts was reported including ionic bases such as alkali metal hydroxides, alkoxides, carbonates, and sources of fluoride anion (e.g. tetrabutylammonium fluoride, TBAF) or nonionic organic amine bases including tetramethylguanidine (TMG), diazabicycloundecane (DBU) and 1,5-Diazabicyclo(4.3.0)non-5-ene (DBN)[13].



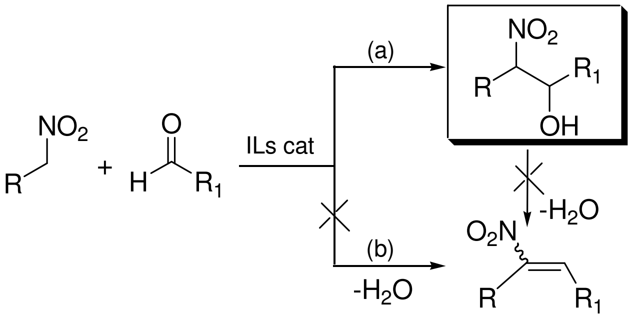
Scheme 3.1 Base catalysed Henry reaction. It is important to note that all the involved steps are reversible.

Due to a number of factors, including the reversibility of the reaction, as well as the tendency for easy epimerization of the nitro-substituted carbon atom, the Henry Reaction typically produces a mixture of enantiomers or diastereoisomers. However enantioselective nitroaldol condensation procedures were reported.[14]

From a "green" perspective, the Henry reaction is very appealing since it is very highly atom economic (AE = 100 %). With the aim of a truly green procedure, particular attention must be dedicated to the reaction medium. Solvent free conditions as well as excess of nitroalkane with no other solvent involved are frequently described in the literature.[15] Studies on the nitroaldol condensation in $scCO_2$ were also reported.[16]

One of the main drawbacks of the Henry reaction is the potential for side reactions throughout the course of the reaction. Aside from the reversibility of the reaction (Retro-Henry) which could prevent the reaction from proceeding, the β-nitro alcohol has the potential to undergo dehydration (Scheme 3.2, pathway b).

Different ILs including chloroaluminate systems, tetramethylguanidinium and quinolinium salts, (supported) basic 1,2 dimethylimidazoliumhydroxides and acetates, are also reported as catalysts for such a process. [17] In this case, ILs are not only catalysts, but they allow to modulate the selectivity (Scheme 3.2, pathway a).



Scheme 3.2 Use of ILs as catalyst as method for dehydration prevention.

The mechanisms of activation of nitroalkane and aldehydes, depend on the nature of organo-catalysts, nonetheless both acidic and basic ILs steer the Henry addition to the formation of nitroaldols, while the competitive dehydration to conjugated nitroalkenes is ruled out.

3.2.2 Aim of the research

In order to understand limits and potential of the observed interesting catalytic activity (basicity) of phosphonium methyl carbonate and bicarbonate, an unprecedented application of methylcarbonate and bicarbonate salts **1a** and **9a** is here below reported. A good extimation of the activity could be furnished by the pKa,[18] however, since the conjugated acid of the methylcarbonate anion is unstable[19] an extimation of the pKa is difficult to obtain.

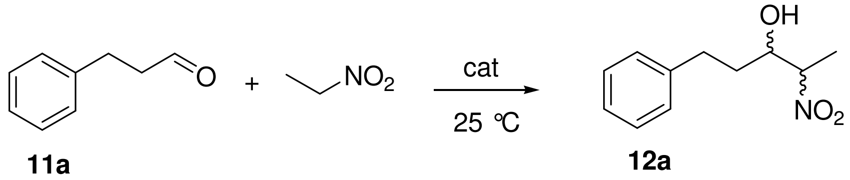
Once the behaviour of these ionic liquids as catalysts for the Henry reaction was understood, the second step was to focus on the application of this compounds as catalysts for the preparation of nitroaldols in solvent free conditions. The aim was to develop a "greener" reaction protocol through the reduction of the quantity of solvents and of nitroalkane excess. In addition, although the toxicity of **1a** and **9a** is unknown,[20] their eco-friendly synthesis imparts a green plus to the overall life cycle of the obtained products.[21]

Furthermore, since the carbonate ionic liquids exhibited excellent performance as catalysts for the Michael addition[2], comparable to the strongest organic superbases, their use could perhaps be extended to the condensation of nitroalkanes with ketones. This chemical process is known to be tricky due to the low electrophilicity of ketones with respect to aldehydes.

3.2.3 Results and discussion

3.2.3.1 Evaluation of the catalytic activity of phosphonium carbonate salts by comparison with different organo bases.

The addition of nitroethane to 3-phenylpropionaldehyde (PPA, **11a**) was chosen as the model reaction for initial experiments (Scheme 3.3).[22]



Scheme 3.3 Reaction of PPA with nitroethane.

Onium salts **1a** and **9a** were compared to four different conventional bases, shown in Table 3.1.

Table 3.1 Bases chosen as catalysts for reaction of nitroethane with PPA

Name	Abbreviation	pKa[a]
Trioctylmethylphosphoniummethylcarbonate	$[P_{8,8,8,1}][OCOOCH_3]$	?
Trioctylmethylphosphoniummethylcarbonate	$[P_{8,8,8,1}][OCOOH]$	?
1,8-Diazabicyclo [5.4.0]undec-7-ene	DBU	24.34
phenyltetramethyl guanidine	PhTMG	20.84
triethyl amine	NEt_3	18.82
dimethylamino pyridine	DMAP	17.95

[a] values in acetonitrile[23]

The rationale for the choice of these bases was to operate under homogeneous conditions (as with ILs) and to cover a relatively wide pKa range approximately from 24 to 18. DBU, Et_3N, and DMAP were commercially available, while PhTMG was prepared from 1,1,3,3-tetramethylurea and aniline, using a reported procedure.[24]

A set of experiments were carried out under the following conditions. At 25 °C, PPA (0.5 mmol) was dissolved in $CDCl_3$ (1 mL) in a NMR tube and set to react with a preformed solution of the selected catalyst (see above, 0.025 mmol, 0.05 molar equivalents with respect to PPA) in nitroethane (2.5 mmol, molar ratio nitroethane:PPA= 5). The ^{1}H NMR analysis of the reaction mixture showed that PPA and the corresponding aldol derivatives (mixture of syn and anti isomers) (**12a**) displayed distinctive diagnostic signals. In all cases, no other compounds, except for PPA and **12a** were observed. Moreover, the very low catalyst loading did not cause appreciable interferences. Each spectrum was the sum of 8 transients for phase quadrature and 4 seconds of delay time were applied to assure complete relaxation of protons between each pulse.

Using an automated procedure spectra were acquired at predetermined time intervals and integration of the cited diagnostic proton signals allowed to estimate at any time the relative concentration of PPA and the two nitroaldol derivatives **12a**.

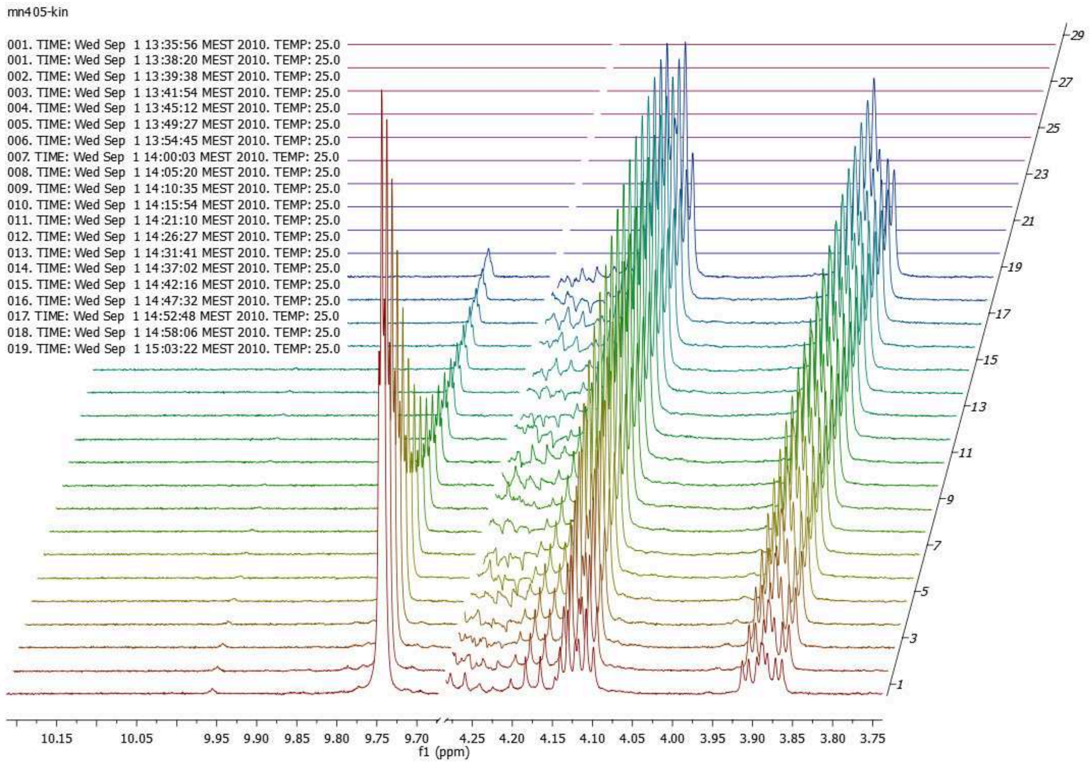


Figure 3.1 ^{1}H-NMR spectra of reaction mixture at different reaction times. Aldehydic proton and the C<u>H</u>OH signals of the two nitroaldol diastereoisomers are shown.

An excellent and simple NMR-monitoring of the reaction course with time was therefore possible. In Figure 3.1 overlaid spectra at different reaction times for the reaction of PPA and nitroethane catalysed by [$P_{8,8,8,1}$][$OCOOCH_3$] are reported.

Once data for all the catalysts were collected, the reaction profiles could be drawn for each base as reported in Figure 3.2, where the amount of nitroaldol products (**12a**) is plotted against time.

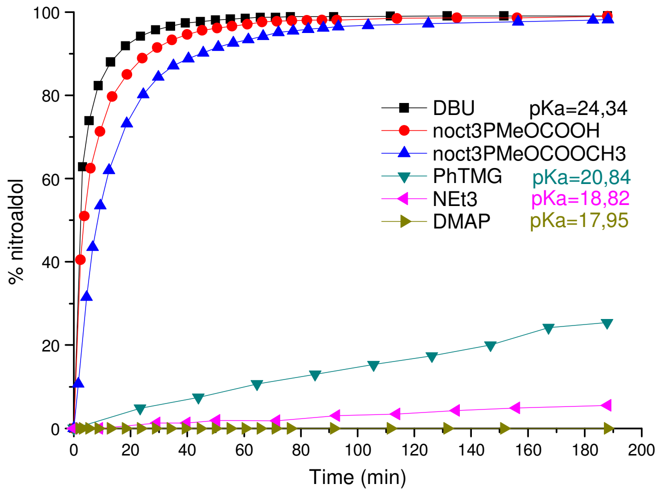


Figure 3.2 Reaction profiles using different bases. (pKa values in acetonitrile).

Deriving curves obtained plotting nitroaldol concentrations vs time is possible to calculate the initial rate for all the used catalysts. The results are reported in Table 3.2.

Table 3.2 Initial rates of Henry reaction of PPA and nitroethane using different catalysts

Catalyst	**pKa**	**Initial rate (mol $L^{-1}min^{-1}$)**
DBU	24.34	0.4193
[$P_{8,8,8,1}$][OCOOH], **9a**	?	0.3516
[$P_{8,8,8,1}$][$OCOOCH_3$],**1a**	?	0.2185
PhTMG	20.84	0.0042
NEt_3	18.82	0.0006
DMAP	17.95	-

Strength of the different catalysts emerged quite clearly from this comparison. CILs, especially the bicarbonate salt **9a**, allowed a reaction outcome comparable to that obtained with DBU: after 25 min, the conversion of PPA into aldol **12a**, was 80, 89, and 94% in the presence of **1a**, **9a**, and DBU, respectively (blue, red, and black profiles). By contrast, the reaction turned out to be extremely sluggish using both PhTMG and Et_3N. The corresponding conversions were 27 and 6%, respectively, after 180 min (teal and fuchsia profiles). Finally, even after 20 hours, no appreciable formation of nitroaldol **12a** was observed in the presence of DMAP (olive profile).

The overall trend suggested a very good parallel between the catalytic activity and the dissociation constants (pKa) of the catalysts. The higher the pKa, the stronger the base, the better its performance. In particular, the activity of **1a** and **9a** salts placed them in the range of organo-superbases (pKa≈24).

This is not perfectly coherent with what observed in the case of the Michael reaction, where carbonate ionic liquids exhibited higher activity than DBU.[2] A number of aspects, including solvation, strength of ion pairs, cation size, etc, offered an intriguing basis for discussion. Further investigation will be surely performed in the future in order to acquire a deeper comprehension of the physical basis for the behaviour of these ionic liquid, yet to be clarified.

3.2.3.2 The Henry reaction of different aldehydes with nitroethane

In search for a synthetic application of salts **1a** and **9a,** a further investigation on carbonate ionic liquids as catalysts for the Henry condensation of different aldehydes with nitroethane was performed.

We focussed on the reaction in solvent free conditions, avoiding the use of additional organic solvent, according to the scope of this thesis. At first experiments to determine the optimal catalyst:substrate ratio were carried out. The aim was to obtain acceptable yield of product in a reasonable reaction time using the lowest amount of catalyst and the smallest excess of nitroalkane.

In the case of the addition of nitroethane to 4-NO_2-benzaldehyde reaction proceeded to high conversions in few hours even using nitroalkane in only 20% excess. No additional solvents were necessary. Reduction of the amount of catalyst from 10 to 0,1 % molar ratio (with respect to aldehyde) was tested. Results are reported in Table 3.3.

A very low catalyst loading was sufficient: using only 1% of catalyst:substrate molar ratio, conversion was nearly quantitative in 2 hours. Further catalyst loading reduction causes the conversion to decrease drastically, maybe because of catalyst neutralization by the acid impurities often present in aldehyde samples[25].

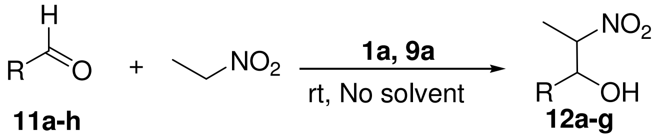
Table 3.3 Catalyst loading optimisation[a]

Entry	Catalyst (%)	T (° C)	Time (h)	Conv. (%)
1	10	25	2	97
2	5	25	2	94
3	1	25	2	95
4	0,5	25	2	73
5	0,1	25	4	5

[a] Conditions: Nitroethane:aldehyde molar ratio 1.2:1, no added solvent, 25 °C.

Optimization of the reaction of nitroethane with PPA and 4-nitrobenzaldehyde allowed to extend these results to different substrates. Four aliphatic and four aromatic aldehydes were reacted with nitroethane (Scheme 3.4) under the following conditions:

i) the CIL-to-substratemolar ratio was set to 0.01
ii) nitroethane was used in 1.2 molar excess with respect to aldehydes
iii) no additional solvents were used.



R = CH_2CH_2Ph, $CH(CH_3)Ph$, C_2H_5, C_7H_{16},
$4NO_2C_6H_4$, $4ClC_6H_4$, C_6H_5, $4NMe_2C_6H_4$

Scheme 3.4 Different aldehydes were reacted with nitroethane in solvent free conditions.

Results for catalyst **1a** are summarized in Table 3.4.

Experiments were carried out at 25 °C, starting from 1.5 mmol of aldehyde. Final reaction mixtures were quenched by adding a 1% HCl aqueous solution (1.0 mL). Aqueous phase was discharged and volatile materials (unreacted nitroethane and aldehyde) were removed by rotary evaporation, yielding the desired nitroaldol derivatives **12a-g** as mixtures of diastereoisomers. The very low catalyst loading allowed to obtain the product with acceptable purity, since the main impurity was the chloride salt $[P_{8,8,8,1}]Cl$ (< 1%).

The spent catalyst could be removed simply by filtration over silica gel (2.0 g). Table 3.4 shows the per cent of nitroaldol products as determined by NMR of the mixture before the work up stage as well as the isolated yield after the purification on silica.

Aliphatic aldehydes (**11a-d**) were readily converted into the corresponding aldol derivatives (**12a-d**) which were isolated as highly pure (>95%) products in excellent yields (88-

97%, entries 1-4). The behaviour of aromatic aldehydes was greatly affected by aryl substituents: i) compounds **11e-11f**, activated by EW groups, displayed a reactivity comparable to aliphatic substrates (entries 5-6). This was especially true for *p*-nitrobenzaldehyde (**11e**). ii) The conversion of benzaldehyde did not exceed 35% and it did not improve for prolonged reaction times (up to 24 h, entry 8), due to the onset of the equilibrium between benzaldehyde and its nitroaldol product.[22] iii) The electron donating dimethyl amino substituent completely deactivated aldehyde **11h** and not even traces of the aldol derivative were detected (entry 9).

Table 3.4 The reaction of different aldehydes with nitroethane in the presence of the catalyst **1a**.[a]

Entry	**RC(O)H, R**	**time (h)**	**Nitroaldolproduct, 12 (%, by NMR)**	**Y (%)[b]**
1	**11a**: CH_2CH_2Ph	2	96	88
2	**11b**: $CH(CH_3)Ph$	2	96	93
3	**11c**: C_2H_5	2	93	90
4	**11d**: $C_{10}H_{21}$	2	99	97
5	**11e**: $4\text{-}NO_2C_6H_4$	2	95	91
6	**11f**: $4\text{-}ClC_6H_4$	3	82	71
7	**11g**: C_6H_5	2	35	35
8		24	34	35
9	**11h**: $4\text{-}NMe_2C_6H_4$	20	0	-

[a]The molar ratio nitroethane:aldehyde and catalyst:aldehyde were of 1.2 and 0.01, respectively.

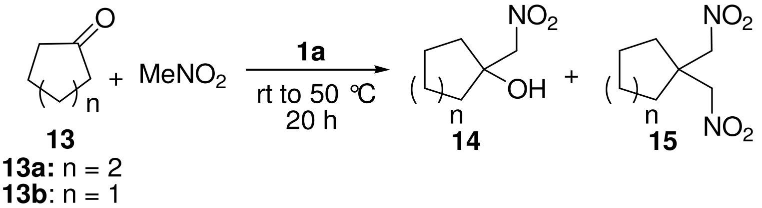
[b]Isolated yield of nitroaldols after purification through silica gel.

Reactions of substrates **11c** and **11d**, with nitroethane were carried out also on a larger scale starting from 30 mmol of aldehyde. After 2 hours, both products **12c** and **12d** were isolated in 92 and 97 % yields, respectively.

Finally, under the conditions of Table 3.4, hydrogen carbonate salt **9a** did not show appreciable differences from methylcarbonate **1a**. The reactions of aliphatic aldehydes catalysed by **9a**, were as fast as with **1a**, and no other practical advantages were observed during the isolation of aldol products.

3.2.3.3 The Henry reaction of different ketones with nitroalkanes.

Both electronic and steric effects make ketones less prone than aldehydes towards Henry additions. C_5-C_6 cyclic ketones however, may represent model substrates for such reactions.[26] These observations prompted us to explore the efficiency of our procedure for the reactions of cyclohexanone and cyclopentanone (**13a** and **13b**, respectively) with an activated nucleophile precursor such as nitromethane, in the presence of salts **1a** or **9a** as catalysts. Experiments were carried out at different temperatures (25 and 50 °C) for 20 hours. Under the conditions of Table 3.5, the Henry reactants (nitromethane and ketone) were mixed in a 1.2 molar ratio, with 10% molar equivs. of **1a** or **9a**. (Scheme 3.5).



Scheme 3.5. Addition of nitromethane on cyclic ketones.

The use of **1a** rather than **9a** as catalysts, did not appreciably affected the reaction outcome (compare entries 1-2, 3-4, 5-6, and 7-8). The increase of the temperature however, induced a dramatic change of the product distribution. At 25 °C, the reaction of cyclohexanone was faster than cyclopentanone, and it proceeded with a good selectivity (up to 97%) toward the aldol **14a** (entries 1-2). Cyclopentanone instead, yielded products **14b** and **15b** in 2:1 ratio, respectively (entries 3-4). At 50 °C, dinitroderivatives **15** became major products (entries 5-8).

Table 3.5 The Henry reaction of cyclic ketones with nitromethane catalysed by ILs **1a** and **9a**[a]

Entry	Ketone	Cat.	T (°C)	Conv. (%, by NMR)	Products (%, by NMR)		Aldol 14 (Y, %)[b]
					14	15	
1	**13a**	**1a**	25	63	61	2	58
2	**13a**	**9a**	25	68	57	11	
3	**13b**	**1a**	25	39	27	12	25
4	**13b**	**9a**	25	40	27	13	
5	**13a**	**1a**	50	53	24	29	
6	**13a**	**9a**	50	58	24	34	
7	**13b**	**1a**	50	54	4	50	
8	**13b**	**9a**	50	57	9	48	

[a]The molar ratio nitromethane:ketoneandcatalyst:ketonewere of 1.2 and 0.10, respectively. [b]Isolated yield of nitroaldol **14** after purification through silica gel

Particularly, the selectivity for **15b** increased up to 93% (entry 7). Conversion of both ketones levelled off at moderate values (25-58 %), because the formation of **15** extensively consumed nitromethane.

Another set of experiments was carried with the aim of obtaining the dinitro derivatives **15** selectively. It should be noted that in the reaction of ketones and nitroalkanes, Kisanga *et al.* observed the formation of compounds **15** only when a very strong and air sensitive base (proazaphosphatrane) was used in combination with more than 2 equivalents of anhydrous $MgSO_4$[27], anyway obtaining the derivatives **15** in only 20 % yield using a 30% molar equivalents of catalyst.

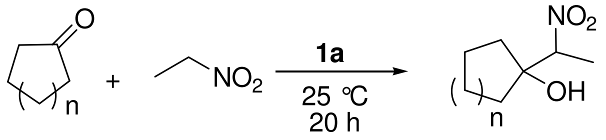
Catalyst **9a** did not improve the yield of product, while formation of unrecognized compounds was observed. This effect was higher at 50 °C using large excess of **9a** (> 20 % molar), causing the evaluation of conversion and selectivity to be unachievable by NMR. For this reason we decided to use only catalyst **1a** to carry out the experiments reported in Table 3.6. Using the methylcarbonate phosphonium salt it was possible to estimate by NMR the yield of both products **14** and **15** at the end of the reactions. The results proved that the reaction could proceed further if quantities of both nitromethane and catalyst **1a** were increased. At 50 °C products **15a-b** could be obtained with very high selectivity (91 and 98 % by NMR, respectively), allowing to isolate products in very good yields (81 and 91 % respectively).

Table 3.6 The Henry reaction of cyclic ketones with nitromethane catalysed by **1a**

Entry	**Ketone**	**1a:13**[a] **(mol:mol)**	**$MeNO_2$:13**[b] **(mol:mol)**	**T (°C)**	**Conv. (%, by NMR)**	**Products (%, by NMR)**		**Y (%)**[c]
						14	**15**	**15**
1	**13a**	0.1	1.2	50	53	24	29	
3		0.2	2.4	50	71	26	45	
4		0.2	5.0	50	74	22	52	
6		0.5	5.0	50	88	8	80	81
7	**13b**	0.1	1.2	50	54	4	50	
7		0.2	2.4	50	76	4	73	
9		0.2	5.0	50	74	3	71	
10		0.5	5.0	50	93	1	92	91

[a] The molar ratio nitromethane:ketone. [b] Thecatalyst:ketone molar ratio.[c] Isolated yield of nitroaldol **14** after purification through silica gel.

Finally reaction of cyclohexanone and cyclopentanone with nitroethane in place of nitromethane was studied with the aim of obtaining the corresponding nitroaldol. In this case, operating at 50 °C, formation of unrecognised products was a limitation for conversion and selectivity quantification, therefore conditions of Scheme 3.6 was chosen for this study.



13a: n = 2
13b: n = 1

16

Scheme 3.6 Nitroethane addition on ketones.

Using the same procedure described for the reaction of cyclic ketones with nitromethane, a set experiments varying catalyst **1a** loading and nitroethane excess was performed. Results are collected in Table 3.7. Conversions of both ketones were poorer than those observed with nitromethane. This result was expected since it is know that nitroethane reactivity is far lower than that of nitroethane[28]. Increasing the reaction temperature was detrimental, since formation of unrecognized products was observed. Experiments were therefore conducted only at room temperature.

Table 3.7 The Henry reaction of cyclic ketones with nitroethane catalysed by **1a**

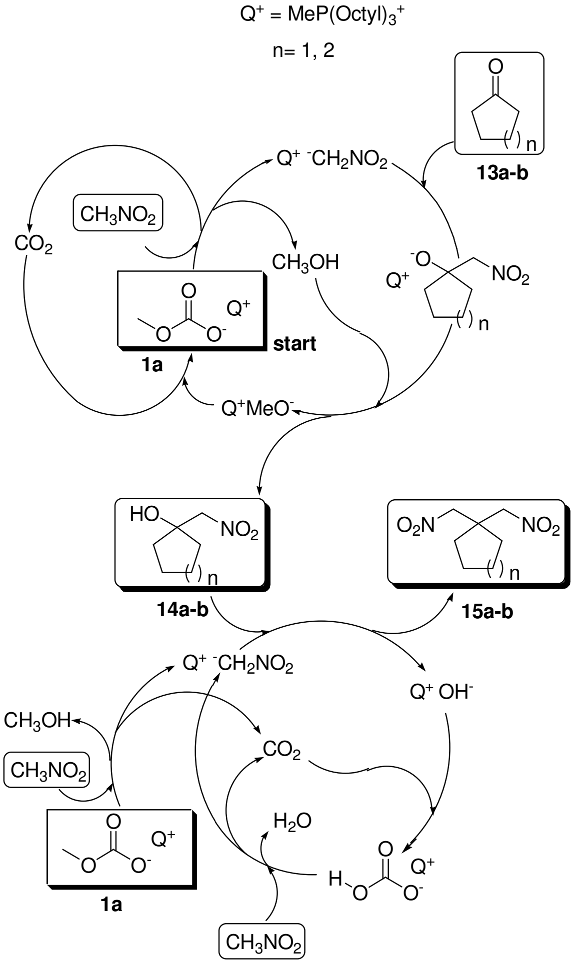
Entry	**Ketone**	**1a:5**[a] **(mol:mol)**	**EtNO$_2$:5**[b] **(mol:mol)**	**T (°C)**	**t (h)**	**Nitroaldol 16**	
						(%, by NMR)	Y (%)[c]
1	**13a**	0.1	1.2	25	20	23	
2		0.5	1.2	25	20	54	57
3		0.5	2.4	25	20	56	
4		0.5	5.0	25	20	52	
5		0.5	5.0	25	20	44[d]	
6		1.0	1.2	25	20	39	
7		1.0	5.0	25	20	57[e]	
8	**13b**	0.1	1.2	25	20	5	
9		0.5	5.0	25	20	20	17
10		1.0	1.2	25	20	20[d]	
11		1.0	5.0	25	20	25[e]	

[a]The molar ratio nitromethane:ketone. [b]The catalyst: ketone molar ratio. [c]Isolated yield of nitroaldol **16** after purification through silica gel. [d] 1 eq. of $MgSO_4$ was added. [e] Due to the high concentrations of the phosphonium salt evaluation of yield by NMR was rough, isolation of product yields very impure samples.

In contrast to what reported in the paper by Kisanga *et al.*,[27] in this case, addition of anhydrous $MgSO_4$ did not improve conversion to nitroaldol derivative, on the contrary the yield (by NMR) of nitroaldol derivatives **16** was somewhat lower in presence of the inorganic salt (entries 5 and 10 vs entries 4 and 9). In our case, probably, $MgSO_4$ interferes with the catalytic activity of CILs, lowering the conversion.

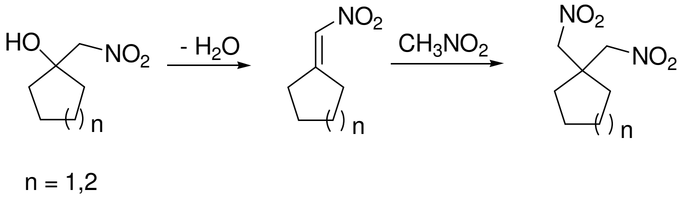
3.2.3.4 Mechanism proposal

During the work up stage, evolution of gas was observed after the addition of dilute HCl aqueous solution. This evidence was expected, since it is known that methylcarbonate and hydrogencarbonate anions decompose to CO_2 and methanol or water respectively in presence of Brönsted acids.[2] However, when mixtures were set to react at 50 °C, little or no evolution of gas was observed. These observations, along with the study on the mechanism proposed by Kisanga *et al.*, allowed us to propose a mechanism for the catalytic activity of carbonate ionic liquids in the nitroaldol condensation (Scheme 3.7).



Scheme 3.7 Proposed mechanism.

The reaction may either stop at this stage or, in the case of nitromethane, proceed further. The addition of a second nitromethyl group is achieved through elimination of a water molecule (Scheme 3.8).



Scheme 3.8 Route to dinitro derivatives formation according to Kisanga *et al.*[27]

As stated previously, water elimination is usually disfavoured using an ionic liquid as the catalyst for the Henry condensation. In our case no evidence of the formation of the nitroalkene derivative formation was collected (NMR spectra were free of signals attributable to vinyl protons). Nonetheless dinitro derivatives were obtained in high yield.

3.2.4 Conclusions

In summary, this study has demonstrated that bicarbonate and methylcarbonate phosphonium ionic liquids, act as powerful task specific (basic) organo catalysts for the Henry reaction of both aldehydes and ketones. The performance of these CILs do not appreciably differ from that of sterically hindered (non nucleophilic) strong bases such as DBU. Aldehydes, especially aliphatic ones, are readily and selectively transformed in the corresponding nitroaldols with excellent yields. CILs **1a** and **9a** allow a simplified Henry protocol thanks to: i) a modest excess of nitroalkanes; ii) very low catalyst loadings; iii) solventless conditions.

In the case of propionaldehyde **13c** and decylaldehyde **13d** a very interesting procedure for nitroaldol preparation was developed. The reaction was scaled up to 30 mmol (**12c**: 1.74g; **12d**: 4.68g) and the product separated by the dilute HCl solution used for catalyst inactivation simply by phase separation. Excess of nitroetane was removed at reduced pressure, obtaining the desired nitroaldols in almost quantitative yield (94 and 99% respectively). Using only 1% of catalyst, products obtained by this procedure were pure (> 95% by NMR), nevertheless spent catalyst could be removed by filtration on silica gel to give the pure products in excellent yield (**13c**: 3.67g, yield = 92 %; **13d**: 6.72g, yield = 97 %).

Ketones are remarkably less reactive than aldehydes. However, if a potent nucleophile precursor such as nitromethane is used, the Henry addition takes place along with a double nucleophile insertion producing dinitromethyl derivatives **15** selectively.

3.2.5 Experimental section

3.2.5.1 General information

Chemicals used were of reagent grade and used as received except liquid aldehydes, which were distilled just prior to use. 3-phenylpropionaldehyde (PPA, **11a**), 2-phenilpropionaldehyde (**11b**), propionaldehyde (**11c**), decanal (**11d**), benzaldehyde (**11g**) were from Aldrich, while 4-nitrobenzaldehyde (**11e**), 4-Cl-benzaldheyde (**11f**), 4-(dimethylamino)benzaldehyde (**11h**) cyclohexanone (**13a**) and cyclopentanone (**13b**) were from Fluka. Nitromethane and nitroethane were from Aldrich.

1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and dimethylamino pyridine (DMAP) were from Fluka, while triethyl amine were from Aldrich, Phenyl tetramethyl guanidine (PhTMG) was prepared from 1,1,3,3-tetramethylurea and aniline, using a reported procedure.[24]

Methoxycarbonate and bicarbonate phosphonium salts (CILs, **1a** and **9a**) were obtained according to our previously reported methodologies.[2]

^{1}H NMR and ^{13}C NMR spectra were collected in $CDCl_3$ solution at 25 °C on a Varian Unity at 400 and 100 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) downfield from TMS.

3.2.5.2 The addition of nitroethane to 3-phenilpropionaldehyde catalysed by different basic systems

All reactions were carried out following this procedure. A NMR tube was charged with PPA (0.5 mmol) in $CDCl_3$ (1 mL) and set to react with a preformed solution of the selected catalyst (see above, 0.025 mmol, 0.05 molar equivalents with respect to PPA) in nitroethane (2.5 mmol, molar ratio nitroethane:PPA= 5). The resulting reaction mixture was introduced in the NMR instrument and spectra recorded every 5 minutes (in the case of very fast reactions spectra were recorded with higher frequency in the first 10 minutes). ^{1}H NMR analyses of the reaction mixture showed that PPA produced the corresponding aldol derivative (**12a**) with no observable side products.

^{1}H NMR integration of distinctive diagnostic signals of **11a** and **12a** (see Figure 3.3) were used to estimate conversion at the selected time obtaining kinetic profiles of the reactions. No appreciable interferences by the catalyst signal were observed, due to its very low concentration.

3.2.5.3 Reaction of different aldehydes with nitroethane in the presence of CILs as catalysts

Reactions of Table 1 were carried out according to the following procedure. A 7 mL glass reactor shaped as a test tube, was charged with the aldehyde (**11**: 1.5 mmol; **11a**: 201 mg; **11b**: 201 mg; **11c**: 87 mg; **11d**: 243 mg; **11e**: 226 mg; **11f**: 210 mg; **11g**: 159 mg; **11h**: 223 mg) and a 11.5×10^{-2} M solution of methoxycarbonate phosphonium salt (**1a**) in nitroethane (0.13 mL). Under these conditions the molar ratio nitroethane:**11** and catalyst:**11** were 1.2 and 0.01, respectively.

The reactor was kept at room temperature (25 °C) and the mixture was kept under magnetic stirring throughout the reaction. After the desired time, usually 2 h (see Table 1 for details), the reaction mixture was quenched by adding a 1% HCl aqueous solution (1.0 mL). A sample of the organic phase was then analyzed by ^{1}H NMR, to give the amount of nitroaldol products (**12**) reported in Table 1. Diethylether (2 mL) was added to the reaction mixture, and the organic phase was separated by means of a separatory funnel.

The catalyst **1a** was removed by filtration on silica gel (2 g, eluent diethylether, 25 mL). The resulting solution was rotary evaporated (40 °C, 150 mbar) for ether and residual reactants removal. The products 4-nitro-1-phenylpentan-3-ol (**12a**: 276 mg, yield = 88%), 2-nitro-4-phenylpentan-3-ol (**12b**: 291 mg, yield = 93%), 2-nitropentan-3-ol (**12c**: 180 mg, yield = 90%), 2-nitrododecan-3-ol (**12d**: 336 mg, yield = 97%), 2-nitro-1-(4-nitrophenyl)propan-1-ol (**12e**: 308 mg, yield = 91%), 1-(4-chlorophenyl)-2-nitropropan-1-ol (**12f**: 229 mg, yield = 71%) and 2-nitro-1-phenylpropan-1-ol (**12g**: 95 mg, yield = 35%) were obtained as a mixture of diastereoisomers and characterized by ^{1}H and ^{13}C NMR.

The above described procedure was adapted for the following experiments [(i) and (ii)]:

*(i) reactions using bicarbonate phosphonium salt (**9a**) as the catalyst.* Being all the others conditions unaltered, catalyst **9a** was used in place of **1a**. The results, not reported here, did not showed appreciable differences between the two catalytic systems.

*(ii) reactions on larger scale carried out using substrates **11c** and **11d**.* A 25 ml glass flask was charged with the aldehyde (30 mmol; **11c**: 1.74 g; **11d**: 4.68 g), methoxycarbonate phosphonium salt (**1a**, 0.3 mmol, 148 mg) and nitroethane (2.7 g). Under these conditions the molar ratio nitroethane:**11** and catalyst:**11** were 1.2 and 0.01, respectively. The reactions were carried out at 25 °C for 2 h, then a 1% HCl aqueous solution was added (10 mL). The aqueous phase was discharged and the organic phase was found to be nitroaldol with high purity in almost quantitative yield (>90 %) with high purity (>95%). Products can be purified (removing catalyst) using the purification procedure described above (this time with 5g of silica gel, 200

mL of diethylether), nitroaldol products **12c** (3.67 g) and **12d** (6.72 g) were isolated in 92 and 97 % yields, respectively.

3.2.5.4 The addition of different nitroalkanes to cyclic ketones in the presence of CILs as catalyst

Reactions of Table 2 were carried out according to the following procedure. A 7 mL glass reactor shaped as a test tube, was charged with the ketone (**13**: 5.0 mmol; **13a**: 490 mg; **13b**: 420 mg), the phosphonium salt (**1**: 0.5 mmol; **1a**: 246 mg; **9a**: 223 mg) andnitromethane (6.0 mmol, 366 mg). Under these conditions the molar ratio nitromethane:**13** and catalyst:**13** were 1.2 and 0.1, respectively.

The reactor was heated at the desired temperature (25-50 °C, see Table 2 for details) and the mixture was kept under magnetic stirring throughout the reaction. After the appropriate time (20 h) the reaction mixture was quenched by adding a 1% HCl aqueous solution (3.0 mL). A sample of the organic phase was then analyzed by ^{1}H NMR, amounts of nitroaldol (**14**) and dinitromethyl (**15**) products (reported in Table 2) were calculated according to the following procedure.

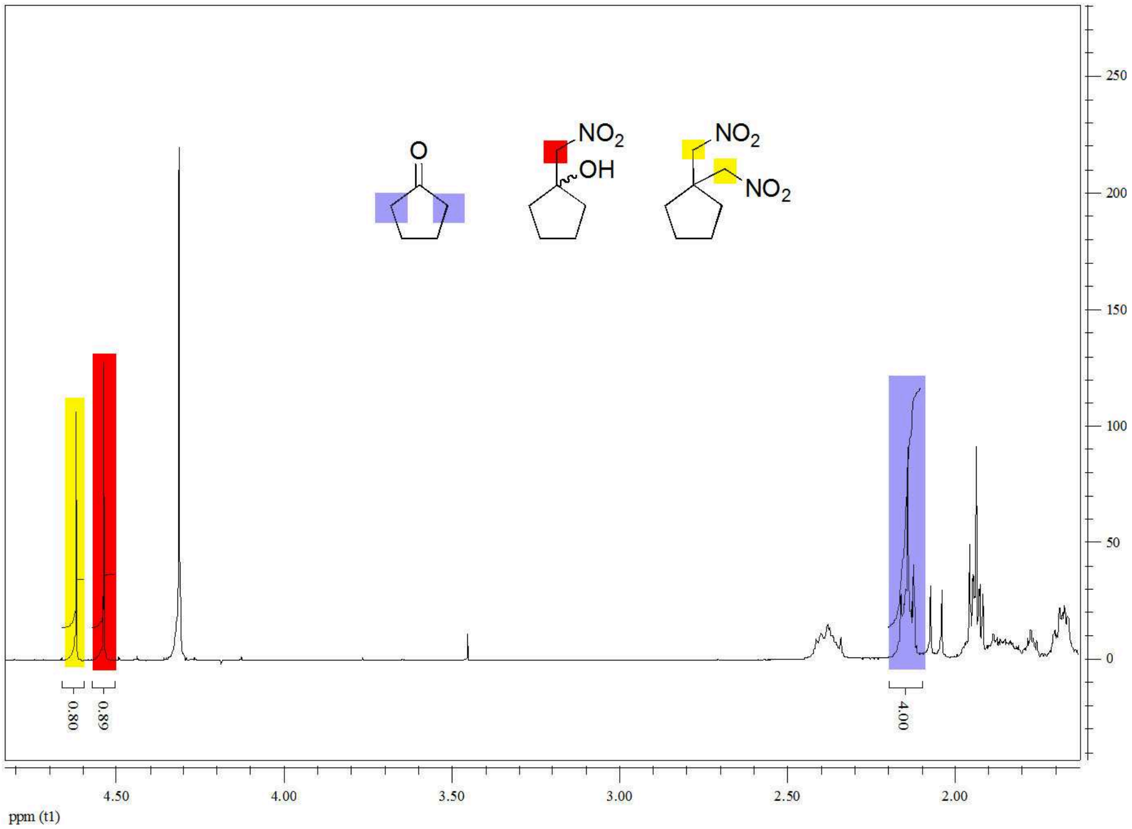


Figure 3.3^{1}H-NMR of the reaction mixture.Color shaped peaks and respective protons in structures identify reactant (lilac), nitroaldol (red) and dinitromethyl derivative (yellow).

Integration of the diagnostic signals of the reactant, nitroaldol and dinitromethyl derivatives[26b,27,29] (see Figure 3.3), was used to obtain components molar percentage constituting the mixture as follows:

% reactant = [(react)/4/SUM]*100
% nitroaldol = [(nitroald)/2/SUM]*100
% dinitromethyl derivative = [(dinitro)/4/SUM]*100

Where:
react = integration of the reactant signal shaped in lilac
nitroald = integration of the nitroaldol signal shaped in red
dinitro = integration of the dinitroaldol derivative signal shaped in yellow
SUM = [(react)/4 + (nitroald)/2 + (dinitro)/4]

At the end of reactions of entries 1 and 3 of Table 3.5, diethylether (3 mL) was added to the reaction mixtures, then the aqueous phase was discharged using a separator funnel. Products **14** were purified by FCC on silica gel eluting with ethylacetate in petroleum ether (30/70 vol/vol). The nitroalkanols **14** eluted first. Solvents was then removed in vacuum yielding pure 1-(nitromethyl)cyclohexanol (**14a**, 461 mg, yield = 58%) and 1-(nitromethyl)cyclopentanol (**14a**, 200 mg, yield = 25%) The structures were confirmed by ^{1}H NMR[29].

The above described procedure was adapted for the following experiments [(i) and (ii)]:

(i) Reaction with higher amount of nitromethane and catalyst. Being all the other parameters unaltered, nitromethane and catalyst **1a** were used with molar ratio nitromethane:**13b** of 2.4 and 5 and catalyst:**13b** of 0.2, 0.5 and 1.0 as reported in Table 3.6. Reactions were carried out at 50 °C for 20 h. The mixture of the nitroalkanol and the dinitro derivative was loaded onto a silica gel column using a small amount of ether. The isolation of the products **15** was then achieved by eluting with diethyl ether in petroleum ether. The ratio of ether was increased in 5% portions from 0% to 80% in 50 mL volumes, and 20 mL fractions were collected. The nitroalkanol **14** eluted first while the dinitro compounds **15** followed at about 50% diethyl ether in pentane. Solvents was then removed in vacuum yielding the dinitro adducts 1,1-bis(nitromethyl)cyclohexane (**15a**, 410 mg, yield = 81%) and 1,1-bis(nitromethyl)cyclopentane (**15b**, 426 mg, yield = 91%).

(ii) Reactions with nitroethane. Being all the other conditions unaltered, nitroethane was used in place of nitromethane, in the addition reaction to substrates **13a-b** using

nitromethane:**13b** and catalyst:**13b** molar ratio reported in Table 3.7. Reactions were carried out at 25 °C. At the end of the reactions, the corresponding nitroaldol derivatives 1-(1-nitroethyl)cyclohexanol (**16a**) and 1-(1-nitroethyl)cyclopentanol (**16b**) were the sole observed products. Products **16** were isolated by extraction with diethylether from the reaction mixtures and purified by column chromatography (as described for products **15**) yielding pure 1-(1-nitroethyl)cyclohexanol (**16a**, 248 mg, yield = 57 %) and 1-(1-nitroethyl)cyclopentanol (**16b**, 69 mg, yield = 17%).

3.2.5.5 Characterization data

The formation of nitroaldols **12a**-**g,** nitroaldols **14a-b** and **15a-b**, and dinitro derivatives **16a-b** was confirmed by the ^{1}H NMR spectra of reaction mixtures. Nitroaldols were isolated as mixtures of diastereoisomers. The spectroscopic data were in good agreement with those reported in the literature.

4-nitro-1-phenylpentan-3-ol 12a[30] ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.31 (t, 4H, J=7.5Hz), 7.19-7.24 (m, 6H, J=7.9Hz), 4.56 (p, 1H, J=7.0Hz), 4.51 (dq, 1H, J=3.0Hz, J=7.0Hz), 4.19 (td, 1H, J=3.3Hz, J=9.5Hz), 3.88-3.94 (m, 1H), 2.85-2.94 (m, 2H), 2.67-2.79 (m, 2H), 1.67-1.90 (m, 4H), 1.56 (d, 3H, J=6.9Hz), 1.54 (d, 3H, J=6.8Hz). ^{13}C-NMR ($CDCl_3$) δ 140.8, 140.7, 128.4, 128.3, 126.0, 87.6, 86.3, 72.0, 71.2, 34.5, 31.7, 31.2, 15.9, 12.3.

2-nitro-4-phenylpentan-3-ol 12b[31] ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.12-7.40 (m, 20H), 4.60-4.68 (m, 1H), 4.47-4.55 (m, 1H), 4.39-4.46 (m, 1H), 4.36 (dd, 1H, J=3.5Hz, J=7.7Hz), 4.22 (dq, 1H, J=2.3Hz, J=6.7Hz), 4.01-4.06 (m, 1H), 3.88 (t, 1H, J=6.0Hz),3.61-3.74 (m, 1H), 2.87-2.95 (m, 1H), 2.78-2.82 (m, 1H), 2.69-2.73 (m, 2H), 2.45 (bs, OH), 2.31 (bs, OH), 1.56-1.60 (m, 9H), 1.51 (d, 3H, J=6.9Hz), 1.43 (d, 3H, J=6.4Hz), 1.42 (d, 3H, J=6.9Hz), 1.37 (d, 3H, J=7.0Hz), 1.33 (d, 3H, J=7.1Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 142.68, 142.34, 141.66, 141.39, 129.10, 128.79, 128.25, 128.03, 127.86, 127.62, 127.39, 127.28, 127.19, 127.10, 87.69, 86.02, 84.98, 84.22, 77.22, 76.36, 76.22, 42.98, 42.11, 41.50, 40.71, 18.92, 17.97, 16.75, 16.26, 15.21, 14.51, 11.78, 11.26.

2-nitropentan-3-ol 12c[32] ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 4.46-4.57 (m, 2H), 4.06-4.11 (m, 1H), 3.80-3.86 (m, 1H), 1.55-1.66 (m, 1H), 1.53 (d, 3H, J=6.9Hz), 1.52 (d, 3H, J=6.8Hz), 1.38-1.50 (m, 3H), 1.01 (3, 1H, J=7.4Hz), 1.00 (t, 3H, J=7.4Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 87.4, 86.0, 74.0, 73.5, 26.1, 25.9, 16.0, 12.2, 10.0, 9.3.

2-nitrododecan-3-ol 12d[33]^{1}H-NMR ($CDCl_3$, 400 MHz) δ 4.47-4.57 (m, 2H), 4.15-4.20 (m, 1H), 3.86-3.94 (m, 1H), 2.30 (br s, 1H), 2.21 (br s, 1H), 1.55 (d, 3H, J=6.8Hz), 1.54 (d, 3H, J=6.8Hz), 1.24-1.53 (m, 32H), 0.87 (t, 6H, J=6.8Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 87.71, 86.35, 72.87, 72.12, 72.11, 72.09, 33.04, 32.92, 31.79, 29.42, 29.40, 29.32, 29.27, 29.19, 25.66, 25.07, 22.58, 16.07, 16.05, 13.98, 12.28, 12.25.

2-nitro-1-(4-nitrophenyl)propan-1-ol 12e[30] ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.22 (m, 4H), 7.59 (m, 4H), 5.55 (s, 1H), 5.18 (d, 1H, J=8.4Hz), 4.68-4.80 (m, 2H), 1.47 (d, 3H, J=6.8Hz), 1.37 (d, 3H, J=6.9Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 148.2, 147.8, 145.5, 145.2, 127.8, 126.9, 124.0, 123.8, 87.7, 86.7, 74.9, 72.8, 16.1, 11.8.

1-(4-chlorophenyl)-2-nitropropan-1-ol 12f[34] ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.32-7.36 (m, 4H), 7.26-7.30 (m, 4H), 5.32 (d, 1H, J=3.7Hz), 4.97 (d, 1H, J=9.0Hz), 4.60-4.74 (m, 1H), 1.45 (d, 1H, J=6.8Hz), 1.28 (d, 1H, J=6.8Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 137.0, 136.8, 134.8, 134.2, 129.0, 128.7, 128.2, 127.3, 88.1, 87.1, 75.3, 73.2, 16.1, 12.0.

2-nitro-1-phenylpropan-1-ol 12g[34] ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.36 (m, 1H), 5.37 (d, J=3.6Hz, 1H), 5.01 (d, 1H, J=9.1Hz), 4.76 (m, 1H), 4.69 (dq, J=3.7Hz, J=6.8Hz, 1H), 1.49 (d, J=6.8Hz, 1H), 1.30 (d, 1H, J=6.8Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 138.5, 138.3, 129.1, 128.9, 128.7, 128.5, 126.9, 125.9, 88.4, 87.4, 76.2, 73.9, 16.4, 12.1.

1-(nitromethyl)cyclohexanol 14a[27] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ4.43 (s, 2H), 2.52 (br s, 1H), 1.44–1.72 (m, 9 H), 1.26-1.36 (m, 1 H)^{13}C-NMR ($CDCl_3$, 100 MHz) δ84.8, 70.6, 34.9, 25.1, 21.4.

1-(nitromethyl)cyclopentanol 14b[27] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.53 (s, 2H), 2.80 (s, 1H), 1.99 – 1.76 (m, 4H), 1.76 – 1.60 (m, 4H).^{13}C-NMR ($CDCl_3$, 100 MHz) δ 83.76, 80.17, 38.25, 23.87.

1,1-bis(nitromethyl)cyclohexane 15a[27] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.69 (s, 4H), 1.65 – 1.45 (m, 10H). ^{13}C-NMR ($CDCl_3$, 100 MHz):δ 78.97, 38.44, 31.40, 25.03, 20.83.

1,1-bis(nitromethyl)cyclopentane 15b[27] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.61 (s, 4H), 1.81 – 1.72 (m, 4H), 1.72 – 1.63 (m, 4H).^{13}C-NMR ($CDCl_3$, 100 MHz): δ 79.1, 46.0, 34.4, 24.0.

1-(1-nitroethyl)cyclohexanol 16a[27] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.56 (q, J = 6.8 Hz, 1H), 2.41 (s, 1H), 1.57 (d, J = 6.8 Hz, 3H), 1.75 – 1.41 (m, 8H), 1.34 – 1.18 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 90.9, 71.6, 34.9, 33.1, 25.3, 21.4, 21.2, 13.5.

1-(1-nitroethyl)cyclopentanol 16b[27] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.56 (q, *J* = 6.8 Hz, 1H), 2.02 – 1.81 (m, 2H), 1.81 – 1.59 (m, 4H), 1.63 (d, *J* = 6.8 Hz, 3H), 1.59 – 1.45 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 90.2, 82.0, 38.9, 36.8, 23.9, 23.7, 15.1.

3.3 Phosphonium nitrate ionic liquid catalysed electrophilic aromatic oxychlorination.

3.3.1 Introduction

Chlorinated aromatic hydrocarbons are of substantial economic significance, and are important starting materials and additives in the production of high-quality insecticides, fungicides, herbicides, dyes, pharmaceuticals, disinfectants, rubbers, plastics, textiles, and electrical goods.[35]

Aromatic chlorination is usually achieved via electrophilic substitution. For example, the industrial syntheses of chlorobenzene and chlorotoluene are still largely based on the textbook liquid-phase chlorination process with gaseous chlorine in the presence of a Lewis acid catalyst[36] (*e.g.*$FeCl_3$). This system however has an intrinsically low atom economy[37] since only one of the two chlorine atoms is incorporated in the product, the other being wasted as chloride (HCl or salt) which requires appropriate disposal. In addition the Lewis acid is often not catalytic, and the procedure requires chlorinated solvents. Since the methods involving chlorine gas are extremely well established from a process and economic standpoint, they are still widely preferred industrially despite the hazards and toxicity associated with their use. In this context therefore, any method which reduces the amount of chlorine upstream and downstream, and that improves on the environmental performance of the process is desirable.

Thionyl chloride and *N*-chloro amides[38] as electrophilic chlorinating stoichiometric reagents are here mentioned for completeness, but are usually lab-scale setups and intrinsically inefficient from an atom economy standpoint.

Oxidative halogenation allows to use a more atom economical reagent for aromatic chlorination, *i.e.* the chloride (Cl^-) moiety. In this case all the chlorine ends up in the product, the downfall being that chloride needs to be oxidized to an electrophilic “Cl^+” species, hence the need for an additional oxidant such as aqua regia,[39] hypochlorous acid,[40] or hydrogen peroxide.[41]In these cases, atom efficiency can still be maintained provided the oxidant can be used in catalytic amounts (and successively reoxidized for example with air) (Scheme 3.9).

$$\mathrm{Ar{-}H + HCl + 0.5\,O_2 \xrightarrow{Cat} Ar{-}Cl + H_2O}$$

Scheme 3.9 Catalytic oxydative aromatic chlorination

A process of this kind was developed by Gulf for the oxychlorination of benzene in the liquid phase with aqueous hydrochloric acid, catalyticquantities of nitric acid, and air or oxygen.[42]

Recent studies reported that ionic liquids can be used simultaneously as solvent and promoter for oxidative halogenation of aromatic substrate. The papers by the groups of Earle[43] and Chiappe[44] claim that nitrate exchanged salts of imidazolium derivatives are not only able to act as solvent/promoter for electrophilic aromatic oxychlorination, but also they can be recycled. Hence authors argued that those ionic liquids are catalysts indeed, while the real oxidant is therefore atmospheric oxygen.

However information regarding the mechanism or the critical parameters that control rates, yields and selectivity were not examined in detail, considering the nitrate ionic liquid based chlorination system as a "black box".

3.3.2 Aim of the research

The driving force for the research here described was the collaboration with our industrial partner who asked to improve their aromatic chlorination process for the production of polymer intermediates (see chapter 6). The two main problem areas of the process were tackled: (i) the use of large quantities of dichloromethane (DCM) as solvent, and (ii) the use of Cl_2 as chlorinating agent. DCM is an effective but undesirable solvent, whose presence in consumer products is beginning to be regulated by the European Parliament[45] since it is a suspected human carcinogen. Cl_2 is dangerous and anti-atom economic – as stated earlier – because half of the Cl atoms end up as a waste.

Compared to the findings previously reported,[43,44] we sought a deeper understanding of the factors affecting selectivity, kinetics, and the reaction mechanism. Obtaining this knowledge could allow to improve the overall rate and conversion performance of the nitrate-promoted monochlorination step, and to achieve multiple stepwise chlorination of model substrates.

With this objective we studied the chlorination of aromatic substrates along the lines of the previously reported investigations. The peculiarity lies in the use of a phosphonium nitrate ionic liquid as oxidant, obtained by a green synthesis described in chapter 2.

3.3.3 Results and discussion

3.3.3.1 Monochlorination of arenes

Following the previous accounts on the use of nitrate ionic liquids as catalysts, the electrophilic chlorination of anisole as the model substrate was investigated using four different ionic liquids as nitrate sources. Along with the recently reported trioctylmethylammonium ($N_{8,8,8,1}$) and -phosphonium ($P_{8,8,8,1}$),[2] butylisoquinolinium (C_4isoQ) and butylmethylimidazolium (C_4mim) nitrate salts were also used (Figure 3.4).

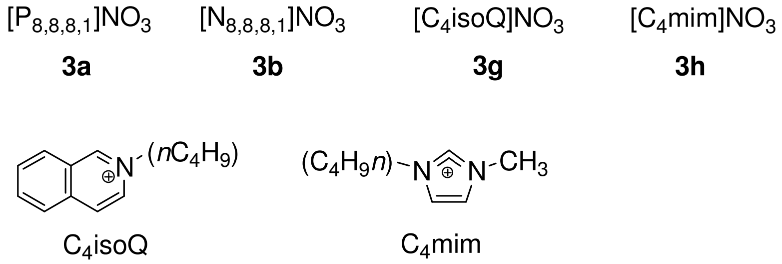
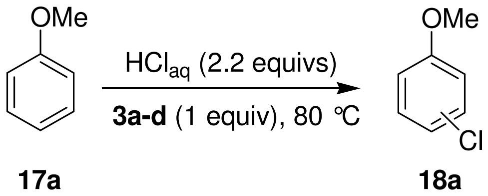


Figure 3.4 Cations employed for the nitrate ionic liquids

Chlorination of anisole was chosen as a probe for chlorination efficiency of the different ionic liquids. The reaction mixture was constituted by HCl_{aq}, anisole, and the IL, no other solvent being necessary Scheme 3.10.



Scheme 3.10 Chlorination of anisole using different ionic liquids

The resulting mixture was constituted of a single phase in the case of [C_4mim]NO_3 (**3c**) and [C_4isoQ]NO_3 (**3d**), while, when [$P_{8,8,8,1}$]NO_3, (**3a**) and [$N_{8,8,8,1}$]NO_3 (**3b**) were used, biphasic systems were obtained due to the very high lypophilicity of cations bearing long alkyl chains.

As reported in Figure 3.5, all four nitrate ionic liquids promoted the chlorination of anisole with more than 80% conversion at 80 °C using a molar ratio 2,2:1:1 of HCl:anisole:IL respectively, in 23 hours.

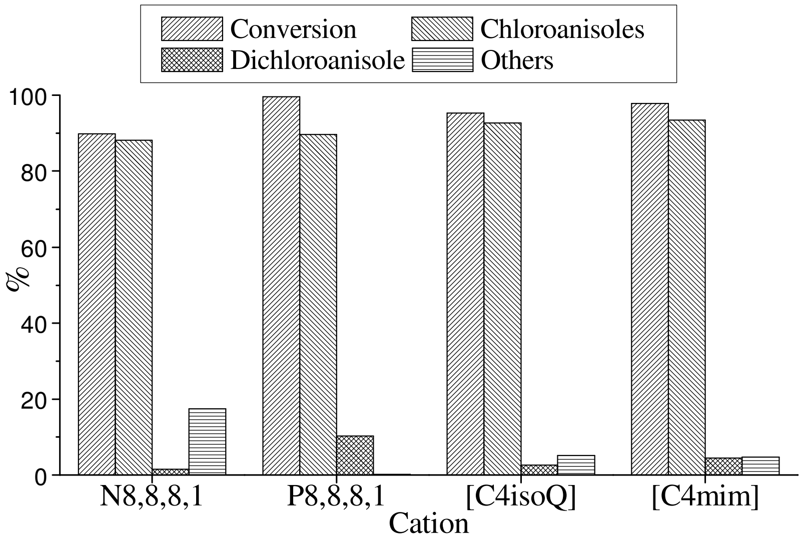
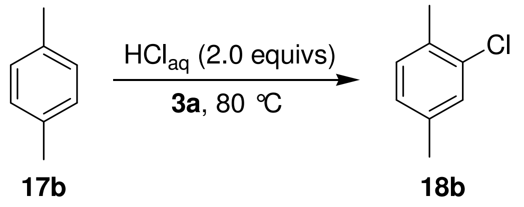


Figure 3.5 Chlorinating efficiency of four nitrate ionic liquids

Using $[N_{8,8,8,1}]NO_3$ as nitrate source the conversion reached 90% with high selectivity (99%), but significant amounts of chlorooctane, deriving from IL breakdown, were formed (17%). $[C_4isoQ]$ and $[C_4mim]$ nitrates behaved similarly to one another, and formed up to 5% of undesired products deriving from aromatic nitration. $[P_{8,8,8,1}]NO_3$ afforded the highest conversion (>99%) and chlorination selectivity (99% as sum of di- and monochloroanisoles), with the lowest amount of side-products. Remarkably the phosphonium ionic liquid afforded also the highest production of dichlorinated compound, indicating a higher activity than that observed in the case of other cations. For those reason $[P_{8,8,8,1}]NO_3$ **3a** was selected as solvent/promoter for this study and used thereafter.

In order to determine the optimal amount of nitrate ionic liquid, a different chlorination reaction was chosen. Operating with a less reactive reactant than anisole it is possible to observe significant changes in conversion and selectivity varying conditions. For this reason the electrophilic chlorination of *p*-xylene was conducted with varying substrate/**3a** molar ratios of 0.5 – 1.0 – 2.0 – 4.0, under the conditions of Scheme 3.11.



Scheme 3.11 Chlorination of p-xylene for substrate/$[P_{8,8,8,1}]NO_3$ (**3a**) molar ratio optimisation

Results are summarised in Figure 3.6.

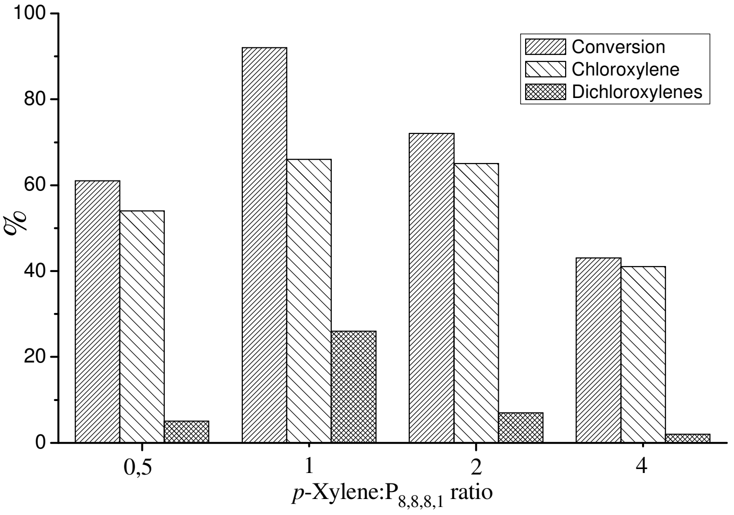
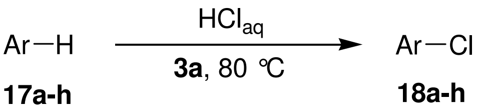


Figure 3.6 Electrophilic chlorination of *p*-xylene with varying amounts of $P_{8,8,8,1}NO_3$

After 24 hours it was apparent that the optimal ratio was 1.0. Significantly however, for xylene/**3a** molar ratios of 2.0 and 4.0, the reaction proceeded to 72% and 43% conversions respectively, indicative of catalysis by $[P_{8,8,8,1}]NO_3$. In fact, the total moles of chloride that were converted per mole of **3a** were greater than unity (1.8 and 2.0 respectively). Furthermore, dichloroxylenes were observed in all cases, up to 25% for the xylene/**3a** molar ratio of 1:1.

A number of aromatic model substrates was subjected to the electrophilic chlorination conditions using $[P_{8,8,8,1}]NO_3$: a mixture of aqueous HCl, the aryl reagent, and phosphonium nitrate was heated at 80 °C for the required time, and the products analysed by GC-MS.[46]



Ar-H = anisole (**a**), p-xylene (**b**), toluene(**c**), naphtalene (**d**), chlorobenzene (**e**), nitrobenzene(**f**), acetophenone (**g**), 4-OMe-acetophenone(**h**)

Scheme 3.12. Chlorination of aromatic substrates using HCl and **3a**.

Table 3.8 shows the results of the chlorination of different aromatics with HCl using **3a** as promoter. The molar ratio of aromatic substrate to ionic liquid was initially set to 1, based on the optimal amount of nitrate ionic liquid as determined above, as well as on the literature[43,44], although nitrate is in principle catalytic as seen before. The molar amount of substrate to HCl_{aq} was selected in the range between 1.0 and 2.4. One equivalent of HCl was sufficient for monochlorination of the activated substrates. In fact, anisole (**17a**), xylene (**17b**) and toluene (**17c**) yielded the monochloro adducts respectively in 85%, 78%, and 90% yields after 3 to 4 days at 80 °C (entries 1, 5, 8 of Table 3.8). By doubling the molar amount of HCl the same activated substrates reached high conversions to the monochloro adduct significantly faster (3 - 24 hours, entries 2, 6, 9 respectively). Under these conditions naphthalene (**17d**) was monochlorinated with good yields (75%) in 4 days as well (entry 4).

Deactivated aromatic substrates, such as chloro- (**17e**) and nitro-benzene (**17f**) yielded only traces of chlorinated product even in the presence of an excess of HCl (entries 11 and 12); while acetophenone (**17g**) and methoxyacetophenone (**17h**) underwent benzylic oxidation (entries 13 and 14) and yielded mixtures of the corresponding carboxylic acids, aldehydes and acyl chlorides. To verify consistency on a larger scale (~13 times), a reaction was run on 2.0 mL of anisole with the corresponding molar quantities of $[P_{8,8,8,1}]NO_3$ (**3a**) and HCl under the conditions of entry 2. Reaction was complete in three hours (90% yield by GC) and chloranisole **18a** was obtained as a pure product by vacuum distillation in 76% yield.

Table 3.8 Chlorination of arenes using a molar ratio substrate/$P_{8,8,8,1}NO_3$ = 1.[a]

Entry	Arene	Molar ratio Substrate/3a	HCl 37% (moleq)	t (h)	18[b] (%)	19[c] (%)
1	**17a**	1.0	1.0	60	85	-
2		1.0	2.2	3	97	-
5	**17b**	1.0	1.2	96	78	1
6		1.0	2.4	24	62	26
7		2.0	1.2	96	75	1
8	**17c**	1.0	1.2	96	90	-
9		1.0	2.4	20	85	-
10		2.1	1.1	96	94	-
3	**17d**	1.0	1.0	48	29	-
4		1.0	2.4	90	75	3
11	**17e**	1.0	4.3	24	7	-
12	**17f**	1.0	2.4	26	traces	-
13	**17g**	1.0	2.4	60	d	d
14	**17h**	1.0	2.4	60	d	d

[a] Conditions: T = 80 °C; [b] yield (by GC) on monochlorinated products; [c] yield (by GC) on dichlorinated products; [d] only benzylic oxidation products (Ar-COOH, Ar-CHO, ArCOCl) were observed.

Compared to other ILs, the $[P_{8,8,8,1}]NO_3$ (**3a**) ionic liquid proved to be the best in promoting the aromatic electrophilic chlorination reaction, in particular because the selectivity was higher than with all the other ionic liquids tested. In addition with $[P_{8,8,8,1}]NO_3$ the reaction rate was significantly higher than that observed by Earle[43] and Chiappe[44] using respectively $[bmim]NO_3$ and $[Hmim]NO_3$ as can be seen in Table 3.9. For example anisole chlorination was achieved in only 3 hours, using 2.2 HCl molar ratio (also on a preparative scale of 2 g), with near quantitative conversion and selectivity in our case (entry 1). Compared to 72 h (2.0 HCl molar ratio) or 48 hours (1.0 HCl molar ratio, but only 70% of product obtained) (entries 2 and 3). Furthermore **3a** promoted a particularly good selectivity: for example in the case of *p*-xylene no alkyl chlorination or oxidation was observed (entry 4). Chiappe[44] instead observed large amounts of α-chloro-*p*-xylene (1-(chloromethyl)-4-methylbenzene) and the oxidation product 4-methylbenzaldehyde (entry 5).

The comparison summarised in Table 3.9 indicated that the outcome of the chlorination reaction was strongly influenced by the structure of the cation of the ionic liquid.

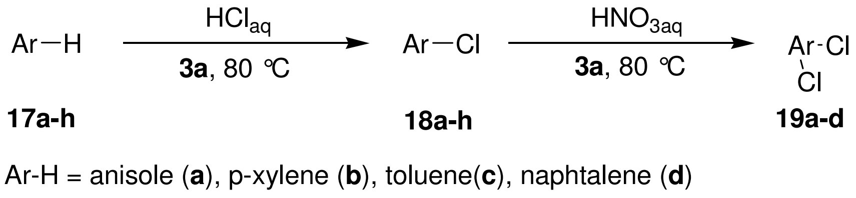
Table 3.9 Chlorination of arenes: comparison between $P_{8,8,8,1}NO_3$ (**3a**), $[bmim]NO_3$,[43] and $[Hmim]NO_3$.[44]

Run	**Arene**	**Ionic liquid**	**Molar ratio Substrate/ IL**	**HCl (moleq)**	**T (°C)**	**Cl_1[a] (%)**	**Other (%)**	**Time[b] (h)**
1	Anisole	$P_{8,8,8,1}NO_3$	1.0	2.2	80	97	-	3
2		$[bmim] NO_3$	1.25	2.0	100	99	-	72
3		$[Hmim]NO_3$	2.0	1.0	80	70	-	48
4	Xylene	$P_{8,8,8,1}NO_3$	1.0	1.2	80	78	-	96
5		$[Hmim]NO_3$	2.0	1.0	80	33	17	48
6	Naphthalene	$P_{8,8,8,1}NO_3$	1.0	2.4	80	75	-	90
7		$[Hmim]NO_3$	2.0	1.0	80	24	-	48

[a]monochlorinated yield (by GC); [b] time for monochlorination.

3.3.3.2 Dichlorination of arenes

By using two equivalents of HCl, the dichlorination of the activated arenes (**17a-d**) could also be accomplished. In this case however, the presence of additional nitrate anion was required: this was added dropwise halfway through the reaction (*i.e.* after complete monochlorination) in the form of nitric acid (Scheme 3.13).



Scheme 3.13 Dichlorination procedure by addition of HNO_3 through the reaction

In Table 3.10 results for dichlorination procedure of arenes are reported. Reaction times before (t1) and after (t2) the addition of aqueous nitric acid

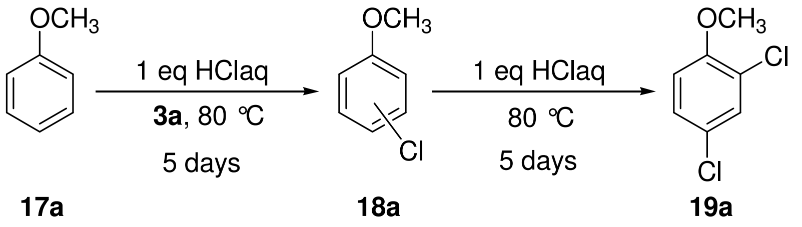
Anisole and *p*-xylene underwent dichlorination, thus obtaining in good to excellent yield products **19a** and **19b** after 60 and 72 hours respectively (entries 1 and 2). Naphthalene yielded up to 50% dichloro-naphthalene (**19d**) after 90 hours (entry 3); while toluene, proved quite reluctant to dichlorination, under these conditions yielding only 10 % of dichlorinated derivative **19c** (entry 4).

Table 3.10 Dichlorination of arenes.[a]

#	Arene	HCl 37% (moleq)	18[b] (%)	t_1[c] (h)	HNO_3[d] (moleq)	19[e] (%)	t_2[f] (h)
1	**11a**	2.2	97	3	1.0	92	60
2	**11b**	2.4	62	24	2.0	85[g]	72
4	**11c**	2.4	85	20	2.0	10	72
3	**11d**	2.4	78	90	1.0	53	90

[a] Conditions: T = 80 °C, molar ratio substrate/**3a** = 1;[b] yield (by GC) onmonochlorinated products; [c] time for complete monochlorination; [d] HNO_3 added once monochlorination was complete; [e] yield(by GC) of dichlorinated derivatives; [f] time for dichlorination; [g] isolated yield = 68%

Remarkably, the dichlorination of anisole could also be carried out stepwise without the intermediate addition of nitric acid. The first step was performed in the presence of one equivalent of HCl: monochlorination of anisole occurred in 5 days, then the addition of a second equivalent of HCl yielded **19a** (92%) after 5 more days (Scheme 3.14).



Scheme 3.14 The two-step dichlorination of anisole catalysed by $P_{8,8,8,1}NO_3$.

3.3.3.3 Ionic liquid recycling

When operating with an excess of hydrochloric acid, catalyst recycling was impossible. A dramatic decrease in activity was already observed after the first recycle when a HCl:anisole molar ratio of 2.2 was employed under the condition of entry 2 of Table 3.8. Once the ionic liquid was extracted and residual volatile materials were removed in vacuum, this was reused for a second run under the same condition. Even if anisole proved very reactive, the recycled catalyst did not promote any reaction and only unreacted anisole was recovered at the end of the reaction. This result was replicated twice and also p-xylene was tested as aromatic substrate.

We thought that excess of chloride anions could exchange nitrate anions of the active ionic liquid, which can move away from reaction mixture as gaseous NO_x. To prove our intuition spent ionic liquid chloride content was tested using the common method of titration with $AgNO_3$.[47] As expected chloride content of all the samples of spent catalyst was around 0.47 mmol Cl^- per 200 mg of ionic liquid, which is consistent with the formation of $[P_{8,8,8,1}]Cl$ (Molecular weight: 421,12).

$[P_{8,8,8,1}]NO_3$ **3a** recycling was demonstrated using anisole as substrate under the conditions of entry 1 of Table 1, using only one equivalent of HCl. Each recycle was conducted by extracting the organic products from the reaction mixture, removing residual water under vacuum, then adding fresh substrate and one equivalent of HCl_{aq} and heating at 80 °C for additional 120 h (Table 3.11). No decrease in activity was observed after four cycles.

Table 3.11 Catalyst recycling for anisole chlorination.[a]

Recycle	Conversion[b] (%)
1	95
2	92
3	93
4	94

[a]Conditions: T = 80 °C, molar ratio substrate/$P_{8,8,8,1}NO_3$ = 1;
[b]conversion (by GC).

3.3.3.4 Proposed nitrate catalysed electrophilic chlorination mechanism

Clear understanding of whether the electrophilic chlorination with **3a** and HCl was truly catalytic in nitrate was needed, in view of our aim to make this synthetic procedure useful on a preparative scale, and thus to address the issues on the chlorination process outlined in the beginning.

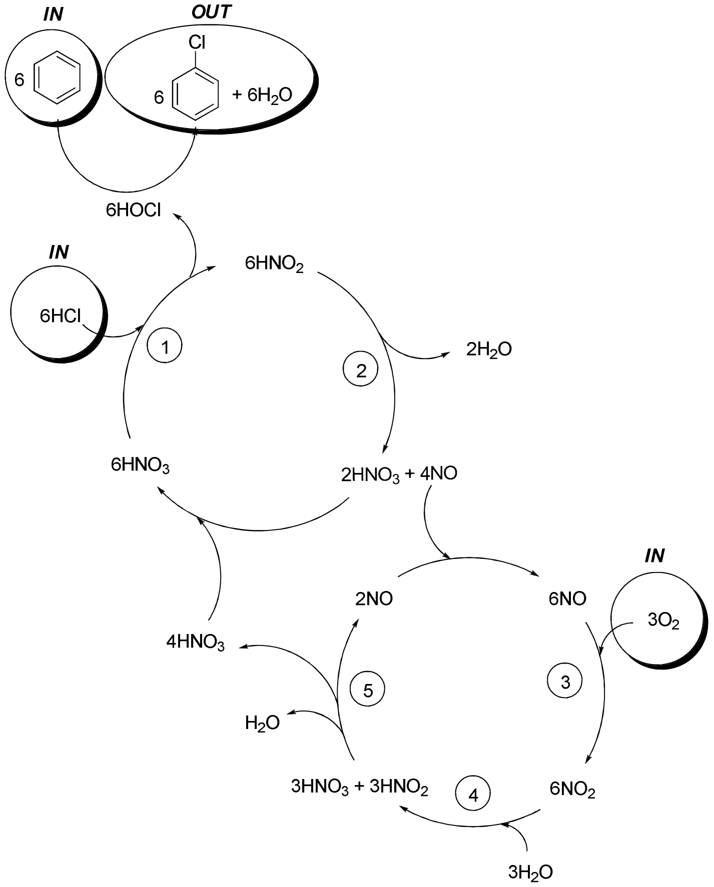
In previous accounts of similar reactions, slightly greater than equimolar amounts (1.25 eq[43] at best), or up to 2 equivalents[44] of nitrate ionic liquid as “catalyst” for the reaction were employed. Chiappe’s work[44] provided a first answer by demonstrating that by using 1.00 eq of HCl as chlorinating agent with respect to the aromatic, the ionic liquid was recovered unchanged and that it could be recycled repeatedly. It failed however to explain why two equivalents of [Hmim]NO_3 were needed, or to give evidence for the purported formation of chlorine gas as the chlorinating agent, and for nitrosyl chloride (NOCl) as the first intermediate towards nitrate regeneration. In fact, the nitrate ionic liquid was defined by them as a “stoichiometric catalyst”, or “promoter”.

Our experiments confirmed that the phosphonium ionic liquid could be recycled, in fact anisole could be monochlorinated for at least four times with the same $[P_{8,8,8,1}]NO_3$ (**3a**) It was however significant that recycling the system was possible only by using a stoichiometric amount of HCl and very long reaction times (120 hours). As noted before, with no excess of acid the reaction became longer even with a very active aromatic substrate like anisole (Scheme 3.14). Attempts to accelerate the reaction by operating with a large excess of HCl killed the catalyst. The spent catalyst was characterised by chloride titration, demonstrating it was mainly constituted by $[P_{8,8,8,1}]Cl$. At the end of each cycle the catalyst could be regenerated by adding concentrated aqueous nitric acid, thus exchanging the chloride anion with nitrate. Similarly, Earle's work[43] reported electrophilic chlorination using $[C_4mim]Cl$ together with nitric acid, indicating that a metathetic anion exchange took place *in situ*.

In summary, when an excess of hydrochloric acid was used the nitrate ionic liquid worked as a stoichiometric reagent and fast reactions occurred. At the other extreme, when HCl was used in equimolar amounts, the reaction was very slow, and the rate determining re-oxidation of the reduced nitrogen species by air permitted high conversion and catalyst reutilization. This was demonstrated by recycle experiments and by chlorinating both *p*-xylene and toluene using a 2:1 substrate:IL ratio. Under these conditions close to quantitative conversion was observed with very high selectivity (Table 3.8, entries 7 and 10), implying that the nitrate ionic liquid is in fact a catalyst.

The above evidence prompted us to reconsider the mechanism previously reported, and to propose a new hypothesis to account for the nitrate catalysed electrophilic aromatic chlorination (Scheme 3.15), that does not require formation of Cl_2 or NOCl. It involves oxidation of chloride by nitrate to yield nitrous acid (HNO_2) and hypochlorous acid (HOCl), the active chlorinating species (step 1), based on literature reports.[48]

Regeneration of nitric acid can then occur by disproportionation of nitrous acid (HNO_2) to nitric acid (HNO_3) and nitric oxide (NO) (step 2). Nitric oxide is then oxidised instantaneously by air to observable brown nitrogen dioxide (NO_2) (step 3), which in turn reacts with water to give nitric (HNO_3) and nitrous (HNO_2) acids (step 4). The latter disproportionates again to nitric acid and nitric oxide (step 5). The molar sum of all these redox and disproportionation reactions involving nitrogen-oxygen species shows that only one mole of nitrate is consumed and continuously regenerated for each mole of reactant, chloride, and arene. No benefits were observed by carrying out the reaction under pure oxygen.



Scheme 3.15 Proposed nitrate catalysed electrophilic chlorination mechanism with HCl.

The global reaction (eq 1) is therefore catalytic in nitrate, and uses oxygen as oxidant.

$$6\text{Ar-H} + 6HCl + 3O_2 \rightarrow 6\text{Ar-Cl} + 6H_2O \qquad \text{(eq 1)}$$

Dichlorination was more difficult, in fact addition of an excess of hydrochloric acid from the beginning did not yield quantitative amounts of dichlorinated products and further addition of HCl did not drive the reaction to completion but rather caused the catalyst to become inactive. The trick to achieve dichlorination was to add one equivalent of nitric acid half-way through the reaction (Table 3.10) to regenerate the $[P_{8,8,8,1}]NO_3$ catalyst.

Further evidence for the proposed catalytic mechanism, where the rate determining step is reoxidation to nitrate, was obtained by running the dichlorination in two steps (Scheme 2). In this case, only one equivalent of $[P_{8,8,8,1}]NO_3$ was used and no further addition of nitric acid was necessary, on condition that a long period was allowed for spontaneous regeneration of NO_3^-. In this example the atom economy was optimal as 100% of chlorine was incorporated in the product and the nitrate ionic liquid was effectively catalytic.

3.3.4 Conclusions

The work here described improves on the understanding of the electrophilic aromatic chlorination process with HCl, on its mechanism and on the factors that control rates, yields and selectivity. Catalysis by nitrate ionic liquids is established, as well as the fact that the kinetic bottleneck is represented by regeneration of the nitrate oxidant with atmospheric oxygen. Methods to overcome this drawback are indicated. By using $[P_{8,8,8,1}]NO_3$ **3a**, chloroanisoles (**17a**) were obtained more than twenty times faster compared to the previously reported procedure involving the use of $[C_4mim]NO_3$,[43] and at a lower reaction temperature (80 °C instead of 100 °C). Furthermore, quantitative (*i.e.* 100% selectivity) ring chlorination could be obtained for *p*-xylene using **3a**, in contrast with 66% selectivity (due to concurrent benzylic chlorination and oxidation) in the case of $[Hmim]NO_3$[44]. The knowledge here collected provides deeper comprehension of points emerged previously in the literature, and poses the basis for implementation of this synthetic methodology. In addition, the reported electrophilic aromatic chlorination reaction uses HCl_{aq} as chlorine source and is catalysed by **3a** in the absence of organic solvents, making it a greener alternative to processes which involve Cl_2 and organic (usually chlorinated) solvents: the products can be isolated by distillation, no solvent is required for purification, and 100% of chlorine is utilised. The reactive electrophilic species is an oxidized form of chlorine "Cl^+" – presumably HOCl – that is generated by the oxidation of chloride by nitrate, which in turn is regenerated by oxidation with air. With respect to traditional procedures, the present methodology improves on at least six of the 12 principles of green chemistry: better atom economy, use of catalysis, use of an alternative solvent[49]/catalyst (made by a green synthesis), reduced waste, use of safer reagents, safer synthetic procedures, lower potential for accidents. On route to truly green synthetic methodologies, it represents an improvement from implementing one or two of the principles (green-ish chemistry), to abiding by as many of the principles as possible (green-er chemistry).

3.3.5 Experimental Section

3.3.5.1 General

Reagents were ACS grade and used as received.

GC-MS analyses were performed with a HP-5890 gas-chromatograph equipped with a HP-5MS capillary column (30 m x 0.25 mm; coating thickness 0.25μm) and a HP-5970 quadrupole mass detector (EI, 70 eV).

Analytical conditions: injector and transfer line temperatures 260 and 280 °C respectively; oven temperature programmed from 50 °C (isothermal condition for three minutes) to 250 °C at 10°C min^{-1}; carrier gas helium at 1 ml/min^{-1}; split ratio 1:20. The ^{1}H NMR spectra were obtained in $CDCl_3$ with a 400 MHz instrument using TMS as the internal reference. All the chlorination reactions were carried in a flask equipped with a reflux condenser open to the air.

3.3.5.2 Ionic liquids

Phosphonium and ammonium ionic liquids were prepared according to a new method recently reported by us.[2] As reported in chapter 2 trioctylamine and trioctylphosphine were set to react with dimethyl carbonate to obtain methyltrioctylammonium methyltrioctylphosphonium methylcarbonate salts respectively. These compounds were anion-exchanged by reaction with nitric acid to yield the corresponding nitrate salts $[P_{8,8,8,1}]NO_3$ **3a** and $[N_{8,8,8,1}]NO_3$ **3b**.

1-*N*-butyl-3-methylimidazolium chloride ($[C_4mim]Cl$) was prepared by *N*-alkylation of methylimidazole with butyl chloride. 1-*n*-butyl-3-methylimidazolium nitrate ($[C_4mim]NO_3$, **3c**) was prepared by metathesis in methanol solution from the respective chloride salts with equimolar amount of $AgNO_3$**.**

N-butylisoquinolinium bromide was prepared by *N*-alkylation of isoquinoline with butyl chloride. *N*-alkylisoquinoliniumnitrate ($[C_4isoQ]NO3$, **3d**) was prepared by metathesis in methanol solution from the respective bromide salts with equimolar amount of $AgNO_3$**.**

3.3.5.3 Chlorination of arenes

The desired aromatic substrate (**17**: 1.4 mmol; **17a**: 151 mg; **17b**: 148 mg; **17c**: 129 mg; **17d**: 179 mg; **17e**: 158 mg; **17f**: 172 mg; **17g**: 168 mg; **17h**: 210 mg) was dissolved in $[P_{8,8,8,1}]NO_3$ (**3a** 1.4 mmol, 630 mg). To the resulting solution, aqueous HCl (37%, 1.0 to 4.3 equivalents, 0.14 - 0.60 mL, according to Table 3.8) was added and the resulting mixture was heated at 80 °C for the required time with stirring. At the end of reactions the mixtures, after cooling at room temperature, were extracted with hexane (4 x 2 mL). The combined extracts were analyzed by GC-MS. For a representative product (dichloroxylenes **18b**), the yield was confirmed by isolating and purifying the product via FCC. All structures were assigned either by comparison to authentic samples via GC-MS, or by ^{1}H NMR.

3.3.5.4 Chlorination of anisole (larger scale)

Aqueous HCl (37%, 40.5 mmol, 3.35 mL) was added to anisole (18.39 mmol, 2.00 mL) and $[P_{8,8,8,1}]NO_3$ (**3a**, 18.39 mmol, 8.24 g). The resulting mixture was heated at 80 °C for 3 h with stirring. (90% yield by GC analysis {2:1 para - ortho ratio}). The products were then recovered and purified by vacuum distillation to yield 2.003 g of chloroanisoles **18a** (76%).

3.3.5.5 Dichlorination of arenes (Method A)

To a mixture of the desired arene (**17**: 1.4 mmol; **17a**: 151 mg; **17b**: 148 mg; **17c**: 129 mg; **17d**) dissolved in an equimolar amount of $[P_{8,8,8,1}]NO_3$ (**3a**, 630 mg), aqueous HCl (37%) was added under the condition of Table 3.10 and the resulting mixture stirred at 80 °C for the required time to achieve the highest amount of monochlorinated product. Then aqueous HNO3 (69%, 1.4 mmol, 0.09 ml) was added and reaction was continued for the required time (see Table 3.10).

3.3.5.6 Dichlorination of anisole (Method B)

Aqueous HCl (37%, 1.4 mmol, 0.12 mL) was added to anisole (**17a**, 1.4 mmol, 0.15 mL) and of $[P_{8,8,8,1}]NO_3$ (**3a**, 1.4 mmol, 630 mg). The resulting mixture was heated at 80 °C for 5 days. Then additional acqueous HCl (37%, 1.4 mmol, 0.12 mL) was added. The mixture was allowed to react at the same temperature for 5 more days.

3.3.5.7 Recycling Procedure

In the first cycle, aqueous HCl (37%, 1.4 mmol, 0.12 mL) was added to anisole (**17a**, 1.4 mmol, 0.15 mL) and $[P_{8,8,8,1}]NO_3$ (**3a**, 1.4 mmol, 630 mg). The resulting mixture was heated at 80 °C for 120 h. After product extraction, traces of organic solvents and water were eliminated under reduced pressure. A fresh amount of substrate and HCl (1.4 mmol, 0.12 mL and 1.4 mmol, 0.15 mL, respectively) were then added to the residual mixture which was then heated again for the next cycle.

3.3.5.8 Chloride assay

A 50 µM aqueous solution of $AgNO_3$ was used to titrate a sample of spent ionic liquid (around 200 mg) dissolved in methanol (100 mL). 1 mL of a solution of $K_2Cr_2O_7$ (10% w/v) was used for each sample as indicator.

3.3.5.9 Characterisation data

Chloroanisoles 18a. (97% yield {75% para and 22% ortho isomers} by GC analysis). GC/MS (relative intensity, 70 eV) *m/z*: 144 ($[M+2]^+$, 34%), 142 ($[M]^+$, 100), 129 ($[M+2-OCH_3]^+$, 18), 127 ($[M-OCH_3]^+$, 61), 101 ($[M+2-CH_2=CH_2]^+$, 23), 99 ($[M-CH_2=CH_2]^+$, 71), 75 (22), 73 (23), 63 (23).

Dichloroanisole 19a (Method A). (92% yield {90% ortho-para, 2% ortho-ortho isomers and 3% trichloro anisole} by GC analysis). GC/MS (relative intensity, 70 eV) *m/z*: 180 ($[M+4]^+$, 11%), 178 ($[M+2]^+$, 64), 176 ($[M]^+$, 100), 165 ($[M+4-OCH_3]^+$, 10), 163 ($[M+2-OCH_3]^+$, 62), 161 ($[M-OCH_3]^+$, 100), 137 ($[M+4-OCH_3-CH_2=CH_2]^+$, 8), 135 ($(M+2-OCH_3-CH_2=CH_2]^+$, 56), 133 ($[M-OCH_3- CH_2=CH_2]^+$, 86), 75 (25), 73 (25), 63 (42), 62 (23).

Dichloroanisole 19a (Method B). (92% yield {91% ortho-para and 1% ortho-ortho isomers} by GC analysis).

Chloro-*p*-xylene 18b. (78% yield by GC analysis). GC/MS (relative intensity, 70 eV) *m/z*: 142 ($[M+2]^+$, 10%), 140 ($[M]^+$, 33), 125 ($[M-CH_3]^+$, 11), 105 ($[M-Cl]^+$, 100), 77 (22), 51 (19)

Dichloro-*p*-xylenes 19b. (85% yield {60% 2,5 and 40% 2,3 isomers} by GC analysis). GC/MS (relative intensity, 70 eV) *m/z*: 178 ($[M+4]^+$, 5%), 176 ($[M+2]^+$, 30), 174 ($[M]^+$, 47), 159 ($[M-CH_3]^+$, 4), 141 ($[M+2-Cl]^+$, 32), 139 ($[M-Cl]^+$, 100), 103 (37), 77 (22), 51 (32). 2,5 isomer ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (s, 2H), 2.30 (s, J = 20.0 Hz, 6H) . 2,3 isomer ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (s, 2H), 2.37 (s, 6H).

Chlorotoluene 18c. (90% yield {47% para and 43% ortho isomers} by GC analysis). GC/MS (relative intensity, 70 eV) *m/z*: 128 ($[M+2]^+$, 9%), 126 (M^+, 29), 91 ($[M-Cl]^+$, 100), 89 (19), 63 (16).

Dichlorotoluene 19c. (10% yield by GC analysis). GC/MS (relative intensity, 70 eV) *m/z*: 164 ($[M+4-CH_3]^+$, 4%), 162 ($[M+2-CH_3]^+$, 18), 160 ($[M-CH_3]^+$, 31), 127 ($[M+2-Cl]^+$, 33), 125 ($[M-Cl]^+$, 100), 89 (42), 63 (19).

1-Chloronaphtalene 18d. (78% yield by GC analysis). GC/MS (relative intensity, 70 eV) *m/z*: 164 ($[M+2]^+$, 31%), 162 ($[M]^+$, 100), 127 ($[M-Cl]^+$, 51), 126 (23), 63 (17).

Dichloronaphtalene 19d. (53% yield, conversion by GC analysis). GC/MS (relative intensity, 70 eV) *m/z*: 200 ($[M+4]^+$, 10%), 198 ($[M+2]^+$, 65), 196 ($[M]^+$, 100), 163 ($[M+2\text{-}Cl]^+$, 8), 161 ($[M\text{-}Cl]^+$, 36), 98 (16).

3.4 Concluding remarks

The onium salts synthesized with a new green methodology using dimethylcarbonate as alkylating agent furnished a very attractive preparation approach for a pletora of ionic liquid. It was possible to obtain ionic liquid with various chemical and physical characteristic, giving to these onium salt broad application.

Both hydrophilic and hydrophobic ionic liquids were obtained with a wide liquid range which render these compounds feasible as solvents for a number of chemical reactions.

However onium salt obtained with DMC was far more than inert liquids to be used as solvent. The carbonate ionic liquids (CILs) were the firsts to be obtained and exhibited surprising basic properties. The ability in promoting organic reaction catalysed by bases was as high as they could be used in very low amounts. This behaviour allowed us to carry out reaction adding only catalytic amount of CILs (down to 0.4 %) in solvent free conditions.

In this chapter the basicity of CILs was compared to the one of hindered organic amines commonly used as promoters in organic reactions catalysed by bases. It appeared that CILs were able to catalyse the addition of nitroalkanes to aldehydes efficiently as in the case of organo superbases.[50] In addition synthetic application of CILs as catalyst for nitroaldol preparation in solvent free condition was also emphasized as a very interesting green procedure.

Not only basic properties of CILs were found to be useful in catalysis, in fact also anion exchanged phosphonium salts like phosphonium tosylates **2** and bromides **5** showed very interesting ability in accelerating alkylation of anilines.[4]

Finally nitrate exchanged onium salts could be used as promoter for catalysts in the electrophilic aromatic oxyxhlorination.[10] In particular $[P_{8,8,8,1}]NO_3$ **3a** proved to be the best performing ionic liquid for this reaction and was used to understand deeper the process of oxychlorination mediated by ionic liquid with respect to what precedently reported.[43,44] This allowed us to state doubtless that nitrate ionic liquids act as catalyst while the oxydant is atmospheric oxygen indeed.

Further investigation will be surely possible, in particular the immobilisation of these salts for application as supported catalysis will be a very interesting topic. The possibility of removing catalyst from reaction mixture in a very simple way (by filtration for example) or the use of grafted CILs as basic catalyst in heterogeneous catalysis could be a very interesting field of study for future researches.

3.5 References

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4 Green alternative procedures for Tadalafil preparation

4.1 Introduction

In recent years PDE-5 inhibitors have become successful and highly profitable in the treatment of male erectile dysfunction (MED)[1]. These compounds can increase the level of the cyclic guanosine 3,5-monophosphate (cGMP), which is an important secondary messenger that controls many physiological processes. The level of intracellular cGMP is determined by the activities of the cyclase that synthesizes it and the type-V phosphodiesterase (PDE-5) that degrades it. Inhibition of PDE-5 increases the level of cGMP, and therefore can be used as a therapeutic strategy, not only for male erectile dysfunction but also for the treatment of cardiovascular diseases.[2] The most popular PDE-5 inhibitors are shown in Figure 4.1.

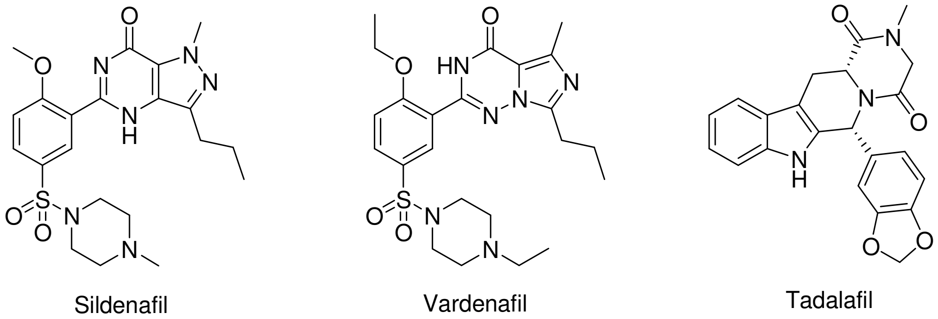


Figure 4.1. Structure of three PDE-5 inhibitors

Recently the syntheses of tadalafil (Cialis™, Icos/Lilly) have gathered much interest from synthetic and medicinal chemists,[3] because it is a cGMP specific PDE-5 inhibitor with an improved PDE5/PDE6 selectivity compared with sildenafil (Viagra™, Pfizer) and vardenafil (Levitra™, Bayer/GlaxoSmithKline). A better selectivity to the right enzyme can prevent a series of side effects related to inhibition of different PDE enzymes sited in different tissues. Furthermore tadalafil with respect to sildenafil and vardenafil, is claimed to cause a longer lasting effect[4], up to 36 hours (6 hours in the case of vardenafil, 4 hours for sildenafil).

The synthesis of a drug is a complex process as it usually consists of a high number of synthetic steps, each requiring a number of different reagents and solvents. Even more challenging is turning a drug preparation into an environmentally compatible process. Finally, even the assessment of the greenness of a synthetic procedure can prove very challenging due to the large number of operations that must be taken into account. The synthetic route for the preparation of Sildenafil is made up by 6 steps, similarly more than 5 steps are needed to obtain Vardenafil;[3c] preparation of tadalafil requires fewer steps (see below), so this particular PDE-5 inhibitors is a good candidate for a study and evaluetion of alternative green procedures for the preparation of a drug of primary interest.

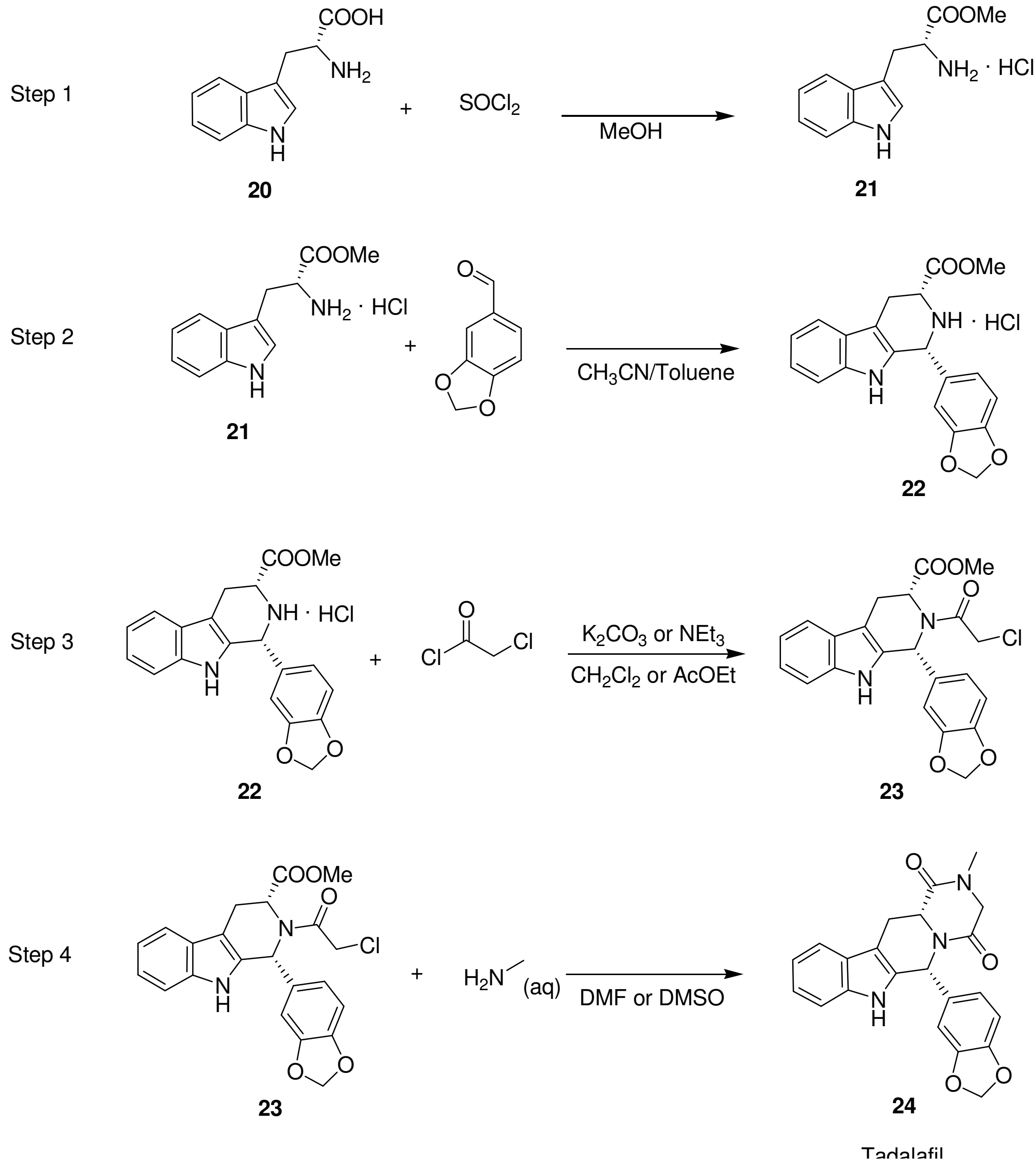
4.2 State of the art

4.2.1 Process details

The common approach to Tadalafil synthesis (see Scheme 4.1) is to start from D-tryptophan (the unnatural enantiomer). The first step is an esterification, usually with thionylcloride in methanol to obtain the methyl ester (**1**). This compound is then reacted with piperonal obtaining the derivative **2** via Pictet-Spengler reaction.[5] Intermediate **3** is obtained by reaction between **2** and chloroacetylchloride under basic conditions in an aprotic solvent. Finally reaction of **3** with methylamine (in a polar solvent) proceeds by nucleophilic displacement followed by cyclization to afford the target compound.

As shown in Scheme 4.1 the preparation requires four separate synthetic steps. This is not a high number of steps, especially for a drug preparation. However this preparation requires a number of solvents and reactants of common use, but surely not definable as "green". Thionyl chloride for example is a useful reactant for the activation of carboxylic acid functionality, although it is a very hazardous reactant. In addition it is poorly atom economic, since it reacts evolving hydrogen chloride and sulphur dioxide as gaseous by-products.

Solvent usage should also be considered. At least four different solvents are needed (MeOH, CH_3CN, toluene, dichloromethane or ethylacetate, dimethylformamide or dimethylsulphoxide) and all of these solvents are undesirable for their low environmental compatibility. Methylene chloride used in the third step (acetylation) was already successfully replaced using ethyl acetate in a recent paper.[6]



Scheme 4.1 Literature synthesis of Tadalafil

4.2.2 Diastereoselectivity via CIAT process

Product stereochemistry is of primary importance, since only the R, R stereoisomer (one of the four possible isomers) is biologically active. To obtain the product in enantiomerically pure form, not only is an enantio-pure starting material necessary, but a diastereoselective synthesis is also needed. In particular a second stereocenter is formed during the second step (Pictet-Spengler reaction), thus reaction between tryptophan methyl ester and piperonal yields two different diastereoisomers here named *cis* and *trans* for briefness.[7]

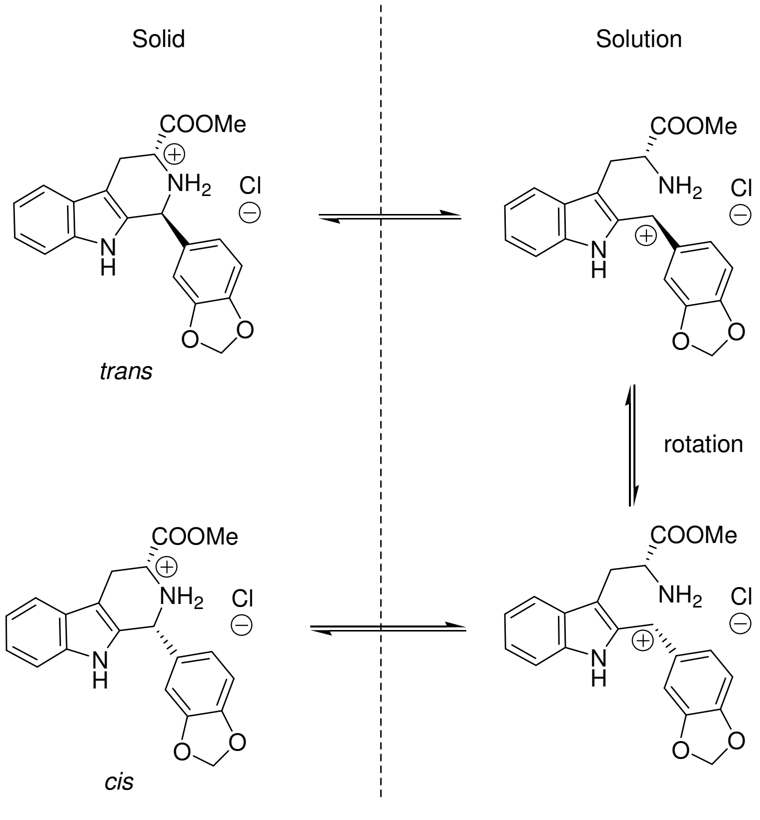
It is reported[8] that the diastereoselectivity of this reaction depends dramatically on solvent choice (Table 4.1).

Table 4.1 Influence of the solvent on yield and diastereoselectivity[a].

Entry	Solvent	Temp. (°C)	Time (h)	Yield (%)	Selectivity *cis:trans*
1	i-PrOH	83	8	92	97:3
2	MeOH	65	19	71	46:54
3	EtOH	78	20	75	88:12
4	CH_3NO_2	101	4	94	99:1
5	CH_3CN	81	8	91	99:1
6	DMSO	90	20	54	50:50
7	DMF	90	20	52	51:49

[a]Taken from ref 8.

Using acetonitrile or nitromethane as the solvent, in which both the product and the reagent are insoluble, very high diastereoselectivity is achieved and the desired *cis* compound can be obtained with excellent yield.



Scheme 4.2

On the contrary in polar solvents like methanol or DMSO where reagent and product are solubilised, little or no diastereoselectivity was observed. Choosing a solvent in which product is insoluble diastereoselectivity is claimed to increase because the *cis* diastereoisomer is less soluble than the *trans*.

Actually the diastereoisomers can convert through an acid catalysed mechanism (Scheme 4.2); this transformation evidently occurs in solution. Since *cis* compound is the less soluble, the equilibrium is driven towards this particular diastereoisomer, consequently it is possible to enrich the mixture in *cis* compound simply heating the mixture in the proper solvent.

Thus, to achieve very high selectivity, it is sufficient to wait for the appropriate time (4-10 hours) keeping the suspension at high temperature (80-100 °C). The process is crystallisation driven and it is known as CIAT process[9](Crystallisation Induced Asymmetric Transformation).

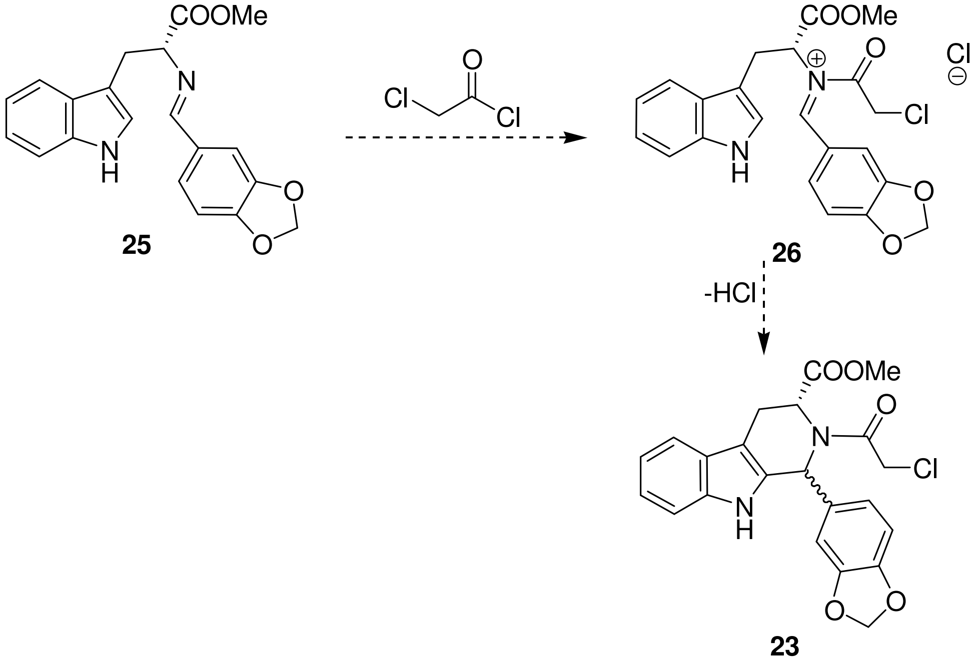
4.3 Aim of the research

Having to change conditions, solvents and intermediate isolation at every step render the synthesis of tadalafil very labour intensive and costly. The reduction of the number of steps, the use of eco-friendly solvents and/or ionic liquids as reaction media, in as many of the steps as possible, could represent interesting process improvements.

All the following are possible areas of improvement that will be discussed in the following paragraphs.

1) In the first step an alternative procedure for the esterification of the starting material (D-tryptophan), avoiding the use of very hazardous and poorly atom economical reagents like thionylchloride is highly desirable. A different activating agent should be found to remove the by-produced water from the esterification. This different agent should be safe, non toxic and provide a higher atom economy.
2) In the second step the reaction is highly atom economic (AE = 100%), but the use of acetonitrile or nitromethane represents a serious drawback. Both these solvents can be conceivably replaced by a "greener" solvent, such as an ionic liquid to reduce the release in the atmosphere or a non toxic solvent, possibly derived from renewable feedstocks.
3) It is also possible to rethink the reaction sequence. The so-called acyl Pictet-Spengler reaction is also reported (Scheme 4.3), in which the preformed Schiff base is activated by generation of the corresponding N-acyliminium ion[10]. In addition enantioselective acyl-Pictet-Spengler reactions are also reported[11] using a chiral catalyst it is possible to obtain asymmetric Pictet –Spengler adducts in good to excellent enantiomeric excess, starting from symmetric reactants. This approach could be very useful in the synthesis of Tadalafil, because if this strategy were suitable in our case, it would be possible to obtain compound **23** (Scheme 4.1)

directly from tryptophan methyl ester in one-pot. Preparation of Tadalafil employing the acyl-Pictet-Spengler reaction was reported in a recent paper[12]. Authors claim the reaction to yield compound **23** in moderate yield using dichloromethane as the solvent. The use of ionic liquid solvents could impart different stereoselectivity with respect to reactions in dichloromethane.



Scheme 4.3 Acyl-Pictet-Spengler reaction for intermediate 3 preparation

4) In the last step, DMSO or DMF used during the reaction with dimethylamine are surely to be avoided, in particular when mixed with water. For example we thought to use an ionic liquid as the solvent for this reaction. In this case the separation from water should be simple, because the negligible vapour pressure of ionic liquid allows to strip water leaving the dry ionic liquid solvent ready for reuse. Since alkylation of amine is reported to be accelerated in ionic liquids[13], this step should also be faster in this kind of solvent.

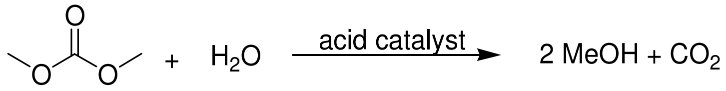
At the very beginning we focussed on finding a solvent where two or more reaction steps could be conducted without the need of intermediate isolation and purification. Successively we tried to revise every single step of this drug synthesis, to develop a "greener" alternative process.

4.4 **Results**

4.4.1 Esterification of tryptophan promoted by DMC (step 1)

Since both the first and the second steps require acidic catalysis, we initially tested systems in which the ionic liquid was contemporarily the solvent and the catalyst. However use of hydrophilic (such as [C_4mim][HSO_4] or [C_4mim][H_2PO_4]) or hydrophobic acidic ionic liquids (such as [$P_{6,6,6,14}$][HSO_4]) proved no reaction occurs using ionic liquids as solvent/catalyst.

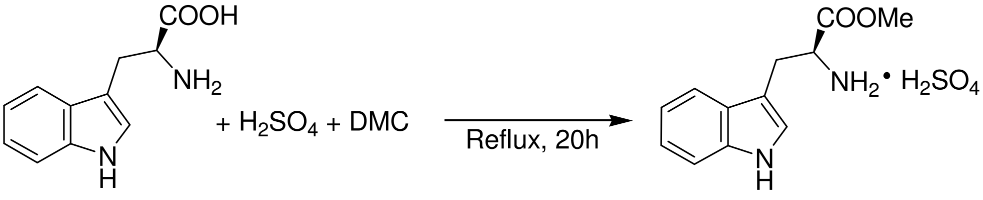
Ionic liquids are obviously not the only possible solution; a literature review revealed that is possible to obtain methyl esters of amino acids using dimethylcarbonate (DMC) and an equimolar amount of sulphuric acid. A recent patent[14] claims that DMC can act as a dhydrating agent (see Scheme 4.4) driving the esterification reaction to completion.



Scheme 4.4. DMC as a dehydrating agent.

Esterification of tryptophan was not included in that patent. In our case the reaction proceeded smoothly, yielding O-Me-tryptophan hydrogensulfate almost quantitatively (Scheme 4.5). To study this reaction we first used L-tryptophan (the natural enantiomer) just because it is cheaper and the chemical behaviour is obviously identical to D-tryptophan.

Once we optimised the processes with the non-correct enantiomer, we verified the applicability of the procedures with D-tryptophan.



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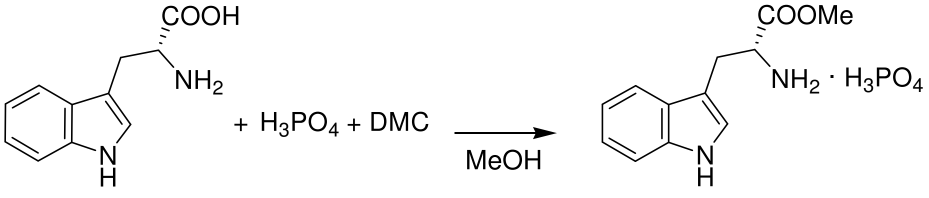
Scheme 4.5. Esterification of tryptophan using DMC as solvent/reactant.

At the end the reaction mixture consisted of two separate phases (Figure 4.2), the upper was dimethylcarbonate, the lower was mainly the product in which a certain amount of dimethylcarbonate was dissolved.

Figure 4.2. Reaction mixture after 20 hours.

Removing dimethylcarbonate (rotavap) results in the formation of an amber coloured solid. Unfortunately at the end of the esterification the product was not obtained in crystalline form, so it was impossible to use the crude methyl ester in the second step directly. To overcome this drawback a study on different procedures to obtain a crystalline methyl ester was carried out. In particular we tried to obtain a different salt bearing an alternative anion i.e. using phosphoric acid instead of sulphuric acid it is possible to obtain O-Me-tryptophan dihydrogenphosphate using the procedure in Scheme 4.6.



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Scheme 4.6. Esterification catalysed by phosphoric acid.

The addition of methanol was found to be indispensable since the phosphate salt is so insoluble that the reaction did not proceed using pure dimethylcarbonate as the solvent.Using a mixture of dimethylcarbonate and methanol in a 4:1 ratio the reaction was complete after 48 h at reflux temperature (≈ 80 °C). Isolation of O-Me-tryptophan dihydrogenphosphate salt by filtration afforded a white, microcrystalline solid.

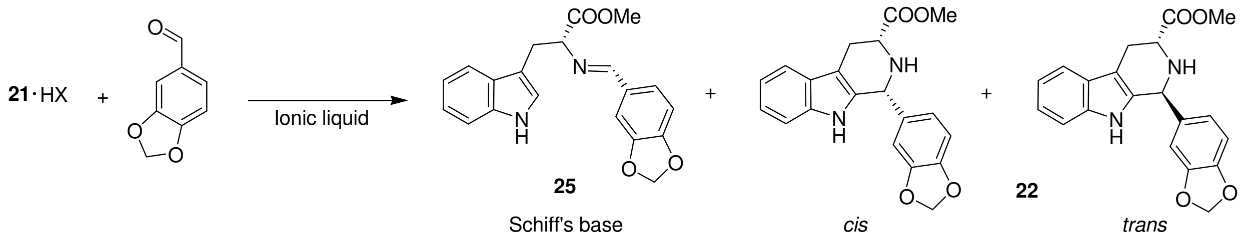
Treatment of D-tryptophan methyl ester salts with aqueous sodium bicarbonate yielded the free base D-tryptophan methyl ester, which could be extracted with the same dimethylcarbonateused as reaction medium. The solvent was removed at reduced pressure and the product isolated as a pale yellow solid. Then different D-tryptophan methyl ester salts bearing various anions (Cl^-, HSO_4^-, CH_3COO^-) were prepared simply adding the appropriate amount of acid to the free base D-tryptophan methyl ester and used as starting materials in the second step.

4.4.2 Pictet-Spengler reaction ionic liquid (Step 2)

Initially we tried to perform this reaction directly on the biphasic mixture obtained by the esterification reaction with sulfuric acid in DMC (Figure 4.3). Addition of piperonal directly in the reaction flask at the end of the esterification resulted disappointingly in the formation of a mixture of uncharacterisable degradation products. Equally, addition of piperonal to the suspension obtained at the end of reaction using phosphoric acid resulted in the formation of a dark oil composed by unreacted O-Me-tryptophan, and the Pictet-Spengler adduct (approximately 30 % by NMR). In addition the non-crystalline form of the product was detrimental in terms of diastereoselectivity (*cis:trans* ratio was 50:50 by NMR).

The crystalline dihydrogen phosphate salt was reacted with piperonal in DMC. Unfortunately reaction in DMC did not proceed even in presence of methanol. Addition of large quantity of methanol cause the reaction to proceed very slowly (50 % conversion after 72 h) but, disappointingly, little or no diastereoselectivity was observed (cis:trans = 55:45 by NMR).

Despite the number of attempts varying conditions such as temperature, dilution and excess of piperonal results was disappointing. Therefore we decided to change strategy, in particular we focussed on the reaction of those salts in an ionic liquid (Scheme 4.7).



HX = none, HCl, H_2SO_4, CF_3COOH
Ionic liquid = $[C_2mim]BF_4$, $[C_4dmim]NTf_2$, $[C_2mim][TFA]$, $[C_2Mim][HSO_4]$

Scheme 4.7 Pictet-Spengler reaction in ionic liquids between Tryptophan methyl ester and piperonal yield the Schiff base as an intermediate and the *cis* and *trans* adducts as products.

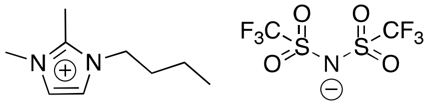
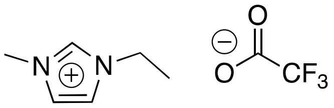
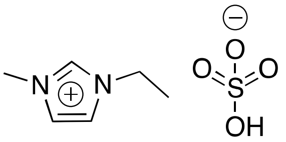
A literature review indicates that the Pictet-Spengler reaction is hardly ever reported in ionic liquids. One paper[15] reports that it is possible to carry out this reaction using $[C_2mim]BF_4$ as a solvent. However these conditions did not promote any diastereoselectivity. Remarkably, the use of $[C_2mim]BF_4$ as a solvent is claimed to cause the reaction to proceed even in absence of the acid catalyst, operating at relatively high temperature (100 °C).

Tetrafluoroborate ionic liquids are well known to decompose at high temperature releasing hydrogen fluoride[16]. That's why in these conditions tryptophan can be used as the neutral form and no acid catalyst was needed.To prove hydrogen fluoride was actually the catalyst we used a more stable ionic liquid, bearing the practically inert bistrifluoromethanesulfonamide (NTf_2^-) anion. As expected no Pictet-Spengler adducts were observed at 100 °C after 18 hours, the Schiff base was the sole product as usually happens in aprotic medium and in the presence of a dehydrating agent[17].

As previously discussed, the second step in the synthesis of Tadalafil generates a new chiral centre. To obtain only the *cis* adduct the equilibrium reported in Scheme 4.2 must be driven to the desired diastereoisomer by precipitation, as in the CIAT process. It is very difficult to find an ionic liquid in which the Pictet-Spengler adduct is insoluble, since it is obtained as a salt. Therefore an ionic liquid with a strong interaction with the adduct is needed, in order to strongly destabilise the trans adduct.

In search for the conditions that would lead to good yields of the desired diastereoisomer, we tried a number of ionic liquids (Table 4.2) as solvents.

Table 4.2 Ionic liquids used as solvents for Pictet-Spengler reaction

Ionic liquid	Chemical name	Structure
[C_4dmim][NTf_2]	1-butyl-2,3-dimethyl-imidazolium bis(trifluoromethylsulfonyl)amide	
[C_2mim][TFA]	1-ethyl-3-methyl-imidazolium trifluoroacetate	
[C_2mim][HSO_4]	1-ethyl-3-methyl-imidazolium hydrogensulfate	

A series of reaction were carried out varying tryptophan salt anion, acid catalyst, reaction temperature and times and the solvent.

At the end of the selected reaction time, mixtures were analysed using ^{1}H-NMR spectroscopy. For every reaction we took in consideration the conversion, the selectivity towards the Pictet-Spengler adduct and lastly the diastereoselctivity as *cis* to *trans* ratio. Results are summarised in Table 4.3.

The reaction was always very slow at room temperature, while at higher temperature (> 80° C), the formation of the desired product in moderate to good yields was achieved in reasonable reaction time (< 24 hours). However at high temperature no diastereoselection was observed (Table 4.3, line 3-6), while at 20 °C, even if the conversion was quite low, interestingly the *cis:trans* ratio was 80:20 (Table 4.3, line 3-6). Therefore we tried to find the conditions in which reaction proceeded smoothly at room temperature or lower to preserve diastereoselectivity. Hence we thought to use trifluoroacetic acid as a catalyst as reported in Table 4.3 line 10-18 (this organic acid is commonly used as a catalyst in this kind of reaction[18]). Unfortunately only mixtures of diastereoisomers and Schiff base were obtained. Selectivity toward the desired *cis* product was only 80 % in the best case, so no competition with the established procedure was possible.

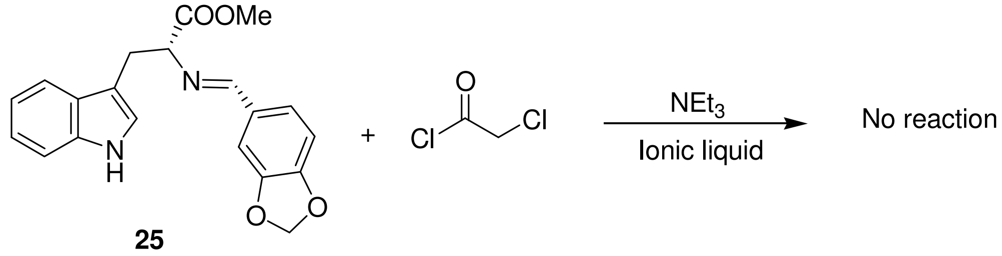
Table 4.3 The reaction of tryptophan methyl ester with piperonal in different ionic liquids[a]

#	**HX**	**Ionic liquid**	**Cat**	**T(°C)**	**Time (h)**	**Conv. (%NMR)**	**Schiff base (%NMR)**	**cis+trans (%NMR)**	**cis/trans (NMR)**
1	HCl	[C$_4$dmim][NTf$_2$]	none	20	22	<5	-	-	-
2				60	5	10	-	10	60/40
3				80	24	>80	-	>80	50/50
4				100	6	>80	-	>80	50/50
5		[C$_2$mim][HSO$_4$]	none	80	2	60	-	60	60/40
6				80	6	70	-	70	60/40
7		[C$_2$mim][TFA]	none	20	2	40	40	-	-
8	TFA	[C$_2$mim]TFA	none	20	5	15	13	2	80/20
9				20	23	21	13	5	80/20
10	None	[C$_4$dmim][NTf$_2$]	TFA^b	20	2	90	90	-	-
11			TFA^c	20	2	25	17	8	80/20
12				20	10	30	10	20	80/20
13				20	32	45	13	33	80/20
14				20	288	>80	-	>80	80/20
15			TFA^d	20	2	20	10	10	80/20
16				20	18	50	10	40	70/30
17				20	65	>80	-	>80	60/40
18				20	96	>80	-	>80	60/40

[a]All reaction were carried out using 1.25 g of ionic liquid as the solvent. The molar ratio tryptophan methyl ester: piperonal was 1.1. [b]TFA:tryptophan methyl ester molar ratio was 0.10. [c]TFA:tryptophan methyl ester molar ratio was 2.0. [d]TFA:tryptophan methyl ester molar ratio was 5:1

4.4.3 The acyl-Pictet-Spengler reaction in ionic liquid

With the aim to obtain compound **23** directly from tryptophan methyl ester in one-pot compound **25**, prepared according a reported procedure,[18] was reacted with chloroacetylchloride in different ionic liquids as the solvents. Reactions were carried in presence of triethylamine to neutralise the forming hydrochloric acid. Different conditions were tested varying reaction temperature, time and acylchloride excess. Notwithstanding our insistence the reactions did not proceed to the desired product (Scheme 4.8).



Ionic liquid: [C_4mim]BF_4, [C_4dmim]NTf_2, [C_2mim][CF_3COO]

Scheme 4.8 Acyl-Pictet-Spengler reaction in ionic liquids

No signals of the product were observed in the ^{1}H-NMR spectra of the mixture. We had to convince us that the ionic liquid medium is not suitable for this reaction. Probably side reactions are favoured because of the very high polarity of the solvent.

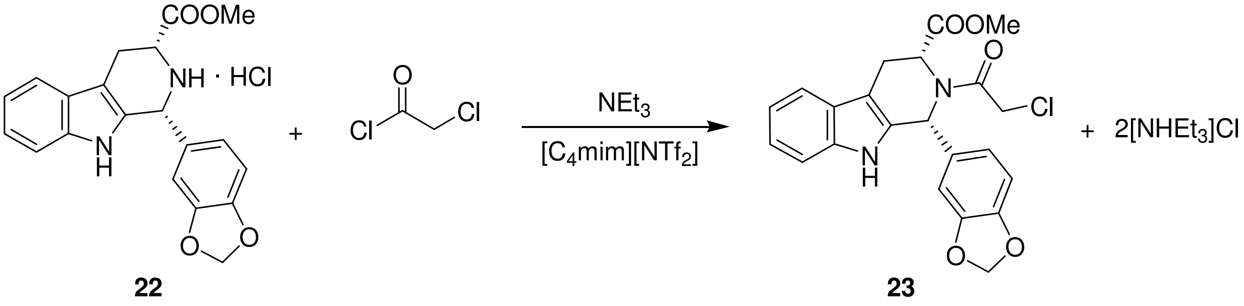
4.4.4 Pictet-Spengler reaction in dimethylcarbonate

Since the acyl-Pictet-Spengler route was unfruitful we reconsidered the so-called CIAT process. From a "green chemistry" standpoint we thought it should be an excellent goal to use the same solvent in more than one step. In particular we used successfully dimethylcarbonate (DMC) as solvent/catalyst in the esterification process, so we decided to verify the possibility of employing this eco-friendly solvent in the Pictet-Spengler reaction. The DMC characteristics seemed immediately to be very useful in this transformation. Its polarity is suitable since hydrochloride salts are surely not soluble in this solvent, in addition its boiling point is quite high (90 °C, higher than acetonitrile b. p., only 10 °C lower than nitromethane b. p.) permitting to work at temperatures comparable to the reported procedure in nitromethane. Moreover DMC is water immiscible as opposed to nitromethane and acetonitrile, allowing to use the solvent without any anhydrification procedure.

As we expected dimethylcarbonate proved to be an excellent solvent for the reaction of O-Methyl-tryptophan hydrochloride with piperonal. The desired compound was obtained in very good yield (95 %) and with excellent diastereoselectivity (98 %), proving that our intuition was good and dimethylcarbonate can be considered as a "green" alternative to common used solvent as nitromethane and acetonitrile.

4.4.5 Acetylation in ionic liquid (step 3)

Third step is merely an acetylation of the amine functionality with chloroacetylchloride after neutralisation of the hydrochloride **2**. This reaction was performed using [C_4dmim][NTf_2] as the solvent using triethylamine to obtain the free amine and neutralise hydrogen chloride (Scheme 4.9).



Scheme 4.9 Acetylation reaction in ionic liquid

The reaction proceeded with very high conversion and selectivity (chloroacetyl derivative **3** as the sole product in up to 95 %), showing no significant changes in reactivity due to the ionic liquid. On the other hand no particular advantages in using ionic liquids were observed at this stage in terms of easier work up or solvent handling, conversely isolation of product from ionic liquid was more difficult than in common solvent.

The reaction outcome was evaluated merely via NMR of the reaction mixture at the end of reaction time. The extraction of the product from the ionic liquid would require an additional solvent, this obviously is not acceptable since the aim of this work is the solvent usage reduction. Hence we decided to do not isolate the product from the reaction mixture. As we report in the following paragraph, fortunately this choice does not represent a drawback for the development of a process for the Tadalafil preparation.

4.4.6 Amination and cyclisation (step 4)

Since methylamine is usually sold as aqueous solution, we had to choose between two approaches:

1. Use a hydrophilic ionic liquid and carry the reaction in a single phase
2. Use a hydrophobic ionic liquid and carry the reaction in a biphasic system (Figure 4.3)

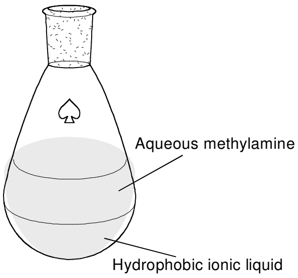
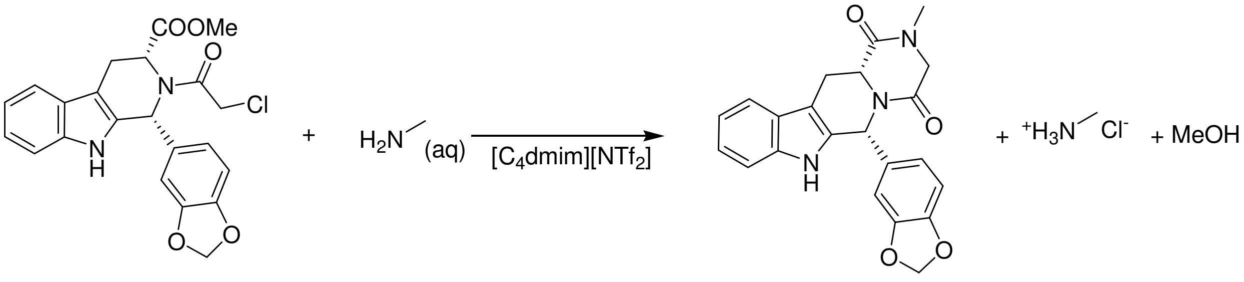


Figure 4.3 Schematic representation of a biphasic system for the amination step.

We decided to choose the second option, because in this way the ionic liquid phase would not be diluted by water altering dramatically the reaction medium, moreover, the water soluble ammonium chloride (by product) is easily removed from organic phase.

The reaction proceed with very high yield in Tadalafil (91%) when [C_4mim][NTf_2] was used as the solvent (Scheme 4.10), starting from compound **23** isolated using an alternative procedure[9].



23

24
Tadalafil

Scheme 4.10 Amination and cyclisation in [C4dimim][NTf2]

Tadalafil was obtained as a white solid, that could be simply filtered from the suspension at the end of the reaction and washed with methanol and water.

4.4.7 Alternative procedure (integrated)

As reported, a biphasic system can be used to remove any salt by-producted from the organic phase. The third step produces two moles of salt per mole of reagent, thus we considered to integrate both the third and the fourth steps in a single procedure in which two reactions are performed in the same flask using [C_4mim][NTf_2] as the solvent.

In the first stage of this integrated procedure hydrochloride **22** was put to react with chloacetylchloride in the presence of triethylamine, as described in the *Acetylation in ionic liquid* paragraph. At the end of the acetylation step acqueous methylamine was simply added to the reaction mixture (Figure 4.4) forming the previously described biphasic system.

At this stage product **23** is dissolved in the ionic liquid, and tadalafil precipitates out as a white solid.

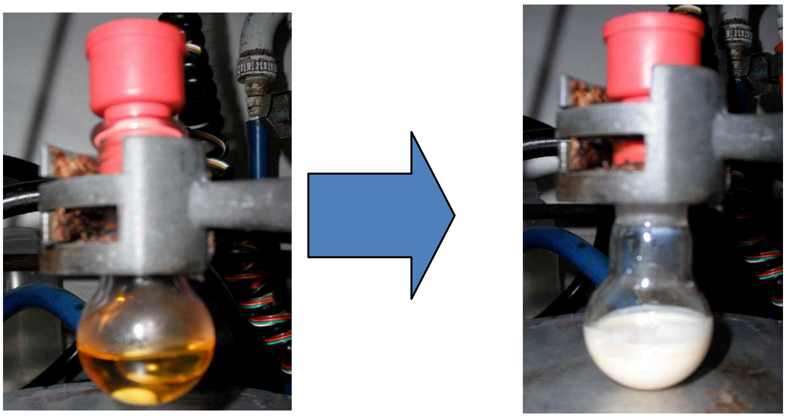


Figure 4.4 Reaction mixture apperarance at the beginning (left) and at the end (right) of the reaction time.

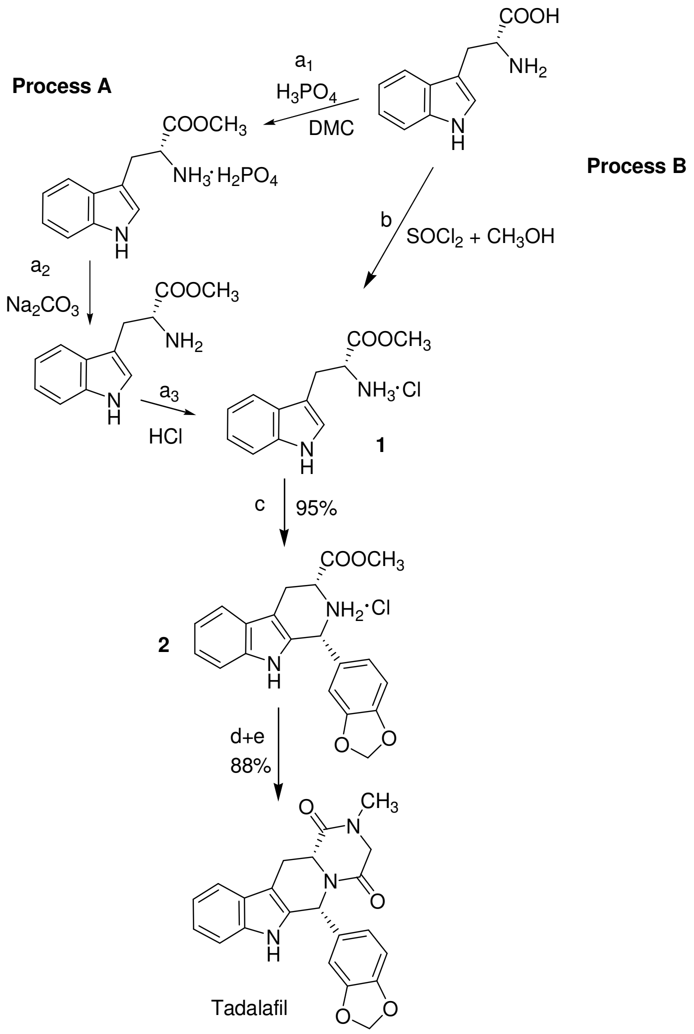
Remarkably reaction times during the last step are significantly lower using this procedure (5 hours) than in dimethylformamide (16-18 hours)[9]. Tadalafil **24** was obtained in very good yield (88% considering both steps) and with good optical purity (96%).^{1}H-NMR and^{13}C-NMR spectra confirmed the product identity, and revealed no traces of ionic liquid in the final product.

In order to verify the recyclability of the ionic liquid, the mother liquor, constituited by water, methanol, ionic liquid and salt by-product was concentrated at reduced pressure. Once volatile materials (methanol and partly water) were removed, ethyl acetate was added to the mixture. The organic phase was collected and consequently washed with 5 % hydrochloric acid, then with pure water. The ionic liquid phase was separated and dried by heating at 70 °C in vacuum. The ionic liquid recovery was higher than 89 %.

Recovered [C_4mim][NTf_2] was then used to carry out the integrated procedure. Using recycled ionic liquid Tadalafil was obtained in 85 % yield, confirming that ionic liquid can be recycled using a simple purification procedure, employing only dilute hydrochloric acid, water and ethylacetate.

4.5 Metrics for processes comparison

Two different processes in which all the information we reported are taken into account can be described (Scheme 4.11). In both processes the integrated procedure in ionic liquid represents a remarkable improvement in terms of raw material reduction and process simplification with respect to what reported in the literature.



Scheme 4.11. Reagent and conditions.Process A: (a1) DMC, reflux, 24h; (a2) Na2CO3aq; (a3) HCl in DMC, RT; Process B: (b) SOCl2/CH3OH, 40 °C, 4h. (c) DMC, reflux, 10 h; (d) Chloroacetilchloride, NEt3, [C4dmim][NTf2], 5 °C, 2 h; (e) CH3NH2aq, [C4dmim][NTf2], RT, 6 h.

In “process A” tryptophan esterification is achieved by using the dimethylcarbonate protocol in which phosphoric acid is employed. In this case the advantage represented by the avoidance of $SOCl_2$ is balanced by the disadvantage of requiring additional reactants. Aqueous Na_2CO_3, HCl and solvent for extraction are needed for the unavoidable anion exchange, causing a waste amount increment.

In “Process B”, **21** is obtained using $SOCl_2$ in methanol, anion exchange is not required as the desired product is obtained as the hydrochloride salt by removal of solvent and excess of reactant under vacuum.

A simple calculation of the Mass Indexes[19] allows to quickly compare the reported literature process with our two processes (A and B). As is clear in Figure 4.5 both our processes are characterised by better performance in terms of raw material usage with respect to the previously reported procedure. This is due to the employment of the integrated procedure in place of steps 3 and 4. By avoiding the chloroacetyl intermediate (compound **23** Scheme 4.1) and by the use of the same solvent ([C_4dmim][NTf_2]) for both the last two passages, it is possible to cut the mass index from 66.3 to 30.3, an outstanding 50% reduction. For what concerns comparison of processes A and B, the graphical representation of Mass indexes highlights what we already stated: the thionyl chloride route seems to be more acceptable than the hydrogensulfate salt and anion exchange route.

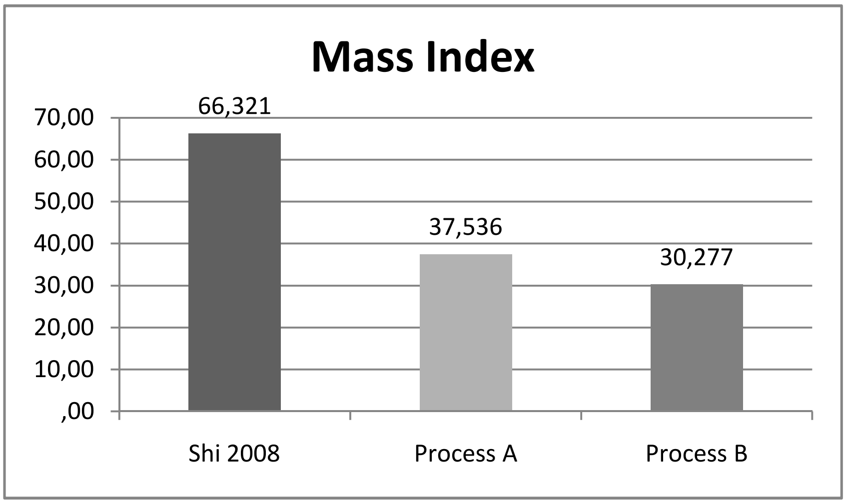


Figure 4.5. Mass Indexes relative to the discussed processes.

On the other hand the DMC route avoids the use of corrosive and toxic materials that is contrary to the principles of green chemistry.[20]

Atom economy[21] (AE), and mass efficiency[22] (ME) are summarised in Table 4.4 and Figure 4.6.

For the three processes the reaction mass efficiency (ME) is low (< 0.033), as expected based of the high mass indices (30.3 – 66.3). However, if the solvents were to be recovered and recycled, the ME value of process B would soar to a theoretical 0.196 (more than three times greater than the literature reported process). The generally low values of ME should not surprise since these processes involve at least three synthetic steps. Remarkably, the two final steps can be integrated and carried out in a single flask.

Table 4.4 Processes comparison using green chemistry metrics.

Parameter	Literature[23]	Process A	Process B
AE	0.542	0.531	0.542
Yield	0.818	0.769	0.811
ME	0.015	0.027	0.033
ME Solvent reclaiming[a]	0.058	0.084	0.196

[a] Calculated following the work by Andraos.

Outstandingly in the case of the solvent reclaiming scenario, MRP value relative to process B is equal to 0,755, which is very interesting, even if this is only theoretical. Values of RME and MRP are low indeed, nevertheless it is important to underline that these processes are made up by at least three synthetic steps. Remarkably, one of them is an integrated procedure in which two different reactions are carried out in a single flask.

Considering other metrics like atom economy (AE), reaction yield, and the stoichiometric factor (SF) it is possible to say the three processes performances are not so far from each other. Since the reactions composing the processes are basically equivalent, atom economy presents exactly the same value for literature process and process B (0,542). AE is slightly lower in the case of process A (0.531), since the anion exchange procedure lowers this parameter. Actually the lowering is only 2 %, therefore, it is possible to state that the use of phosphoric acid and DMC to obtain tryptophan methyl ester, does not affect AE dramatically, even if this requires anion metathesis.

Other metrics, such as atom economy (AE) and reaction yield indicate that the three processes perform similarly. Atom economy is identical for the published method and process B (0,542), and only slightly lower for process A (0.531) due to the anion exchange steps. This small 2% decrease indicates that the DMC route to obtain tryptophan methyl ester, does not affect AE significantly. In terms of reaction yield the literature process remains the best (81.8 %), followed by process B (81,1 %), while for process A this value is 6% lower (76.9 %).

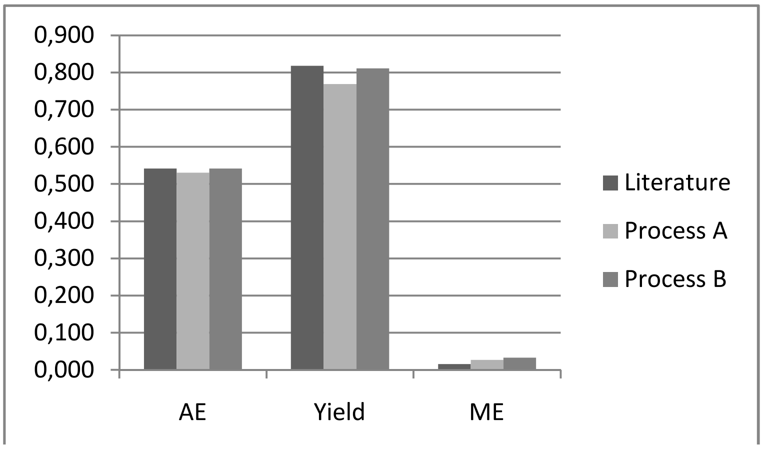


Figure 4.6 Processes comparison using common green chemistry metrics.

4.6 Conclusions

A study on the synthesis of Tadalafil in alternative solvents and using greener procedures was performed. Each step was tackled separately, then the knowledge we gathered was used to plan two new alternative processes for Tadalafil synthesis named process A and process B (Scheme 4.11).

During the study on the first step a procedure for the esterification of tryptophan using dimethylcarbonate (a non toxic solvent) avoiding the use of thionyl chloride (a highly corrosive and poorly atom economical reagent) was described. Remarkably we also demonstrated the methyl ester can be obtained using phosphoric acid rather than sulphuric acid. This result is very interesting since phosphoric acid is a very industrially attractive as an alternative to sulphuric acid, owing to its properties, in particular for its negligible corrosive potential of steel components. However the use of dimethylcarbonate in place of thionylchloride can be considered green only if not included in the total synthesis, since the hydrogensulphate or hydrogenphosphate product is not useful in the rest of the preparation of Tadalafil. The second step, in which the starting material is the methyl ester, requires the hydrochloride salt, in order to obtain the *cis* Pictet-Spengler adduct in pure form. So an anion exchange is necessary in the process, increasing raw material consumption and the overall atom economy is lower with respect to procedure involving the use of thionylchloride. In terms of mass index, process B seems to be an even better alternative to the literature reported process, rather than process A. However mass flow cannot be the only aspect to be considered, the use of a safer reactant should also represent an improvement to the chemistry of the process, even if the overall mass flow is higher.

Dimethylcarbonate proved to be a good alternative to traditional solvents (i. e. nitromethane or acetonitrile) in the diastereoselective Pictet-Spengler reaction. This solvent represents a noteworthy alternative not only for its low toxicity, but also for its properties, in particular the very low miscibility with water. To achieve the very high yield and diastereoselectivity reported in Table 4.1 a water miscible solvent like acetonitrile must be dried before using it as the solvent for the reaction, dimethylcarbonate can be used without any preliminary purification. Both the lower toxicity and the water immiscibility contribute to the "greenness" of the reported procedure, allowing to state that dimethylcarbonate is a green alternative solvent for the Pictet-Spengler reaction and that it is likely to be used also on an industrial scale.

In the acetylation step, the use of [C_4dmim][NTf_2] (an ionic liquid) as the solvent seemed to be detrimental at first, because product isolation from the ionic liquid was impossible without using an additional solvent. Fortunately this was not necessary employing the alternative integrated procedure; in this case the introduction of ionic liquid appeared to be very convenient in terms of reduction of number of steps and solvents usage. This was clearly demonstrated by the comparison of mass indexes relative to process A and literature process.

For what concerns the last step, reaction with methylamine proved to be accelerated by the ionic solvent, especially in the case of the integrated procedure. In this case reaction is three times faster than in dimethylsulphoxide/water mixture. When the last step is carried out in ionic liquid starting from the chloroacetylated derivative **23**, reaction time is similar to what reported in literature even using an ionic liquid as the solvent. The reason of this behaviour is the low solubility of **23** in [C_4dmim][NTf_2]. When the starting material is this compound the reaction mixture is actually a suspension from the beginning, causing the reaction to be quite slow. When the integrated procedure is carried out in its place, the mixture at the end of the reaction with chloroacetylchloride appears as a clear solution and reaction with methylamine proceeds very rapidly.

In summary processes A and B represent two interesting innovative methods for the preparation of Tadalafil in very high yield and using only [C_4mim][NTf_2] (an ionic liquid) and dimethylcarbonate as reaction media. Both the described process are characterised by better performances in terms of mass index. Process B in particular seems to be the best among the described three approaches. However, considering the avoidance of thionylchloride and the reduction of the amount of methanol used in process A, this sum of procedures can be taken into account when the safety of procedures counts more than raw material usage.

The use of an ionic liquid appears to represent an improvement in the described processes, nevertheless ionic liquids are very expensive materials. However we proved that the ionic liquid can be recycled, making the use of this particular and costly kind of solvent feasible for industrial application.

4.7 Experimental section

4.7.1 General

Reagents were ACS grade and used as received. ^1H and $^{13}C\{1H\}$ NMR spectra were recorded at 300 and 75 MHz respectively; chemical shifts were reported in δ values downfield from TMS.

All the tryptophan methyl esters salts were characterised after basic treatment to obtain the neutral methyl ester, properties and NMR data were in good agreement with those reported in the literature.[24] The Schiff base (R,E)-methyl 2-((benzo[d][1,3]dioxol-6-yl)methyleneamino)-3-(1H-indol-3-yl)propanoate **25**, reported in Scheme 4.8 as the reactant, was prepared according to a reported procedure[18].

All the ionic liquids used in this work ([C_4dmim][NTf_2], [C_2mim][NTf_2],[C_2mim][HSO_4], [C_2mim][TFA]), were furnished by QUILL centre (Queen's University Ionic Liquid Laboratories) and used as received.

4.7.2 Esterification of tryptophan using DMC and H_2SO_4

In a round bottomed flask D-Tryptophan (2.00 g, 9.79 mmol) was suspended in 7 mL of dimethylcarbonate. To the stirred suspension concentrated sulphuric acid (0.53 mL, 10.6 mmol) was slowly added and the resulting mixture was heated to reflux temperature (92 °C) for 18h. At the end of that time two liquid phases were observed. Both phases were slowly added to 20 mL of a 10% (w/w) solution of Na_2CO_3 with vigorous stirring. The organic phase was then separated and the aqueous phase extracted with 2 x 5 ml of dimethylcarbonate. Extracts were collected and dried over Na_2SO_4, the solvent was then removed at reduce pressure yielding compound **21** (2.00 g, 9.16 mmol 94%) as an oil that slowly crystallised into an off white solid.

4.7.3 Esterification of tryptophan using DMC and H_3PO_4

In a round bottomed flask L-Tryptophan (2.00 g, 9.79 mmol) was suspended in a mixture of 7 mL of dimethylcarbonate and 2 mL of methanol. To the stirred suspension phosphoric acid (1.04 g, 10.6 mmol) was added and the resulting mixture was heated to reflux temperature (ca 85 °C) for 24h. The resulting suspension was then filtered yielding compound **21·H_3PO_4** (2.88 g, 9.10 mmol 93%) as a white solid.

4.7.4 Esterification of tryptophan using MeOH and thionylchloride

Method A: The title compound was prepared according to a reported procedure[24], which was slightly modified. To a cooled (ice bath), stirred suspension of D-tryptophan (2.00 g 9.79 mmol) in 30 mL of MeOH, thionyl chloride (1.0 mL, 13.7 mmol) was slowly added. The resulting clear solution was then heated to 40 °C and kept at that themperature for 4 hours. Excess of thionyl chloride, HCl and SO_2 and the solvent were removed at reduced pressure. The resulting white solid (2.41 g, 9.46 mmol, 97%) was pure enough to use without further purification. Method B: To the mixture at the end of the reaction of tryptophane with dimethylcarbonate in presence of phosphoric acid (see previous paragraph), a 10% (w/w) solution of Na_2CO_3 (20 mL) was slowly added. The organic phase was then separated and the aqueous phase extracted with 2 x 5 ml of dimethylcarbonate. Extracts were collected, then a solution prepared bubbling gaseous HCl (365 mg, 10 mmol) in dimethylcarbonate (5 mL) was slowly added to the stirred solution. The resulting suspension was then filtered and the solid washed with DMC. The white solid was dried at 70 °C for 10 hours yielding compound **21·HCl** (2.29 g, 8.99 mmol, 92%).

4.7.5 Pictet-Spengler reaction in ionic liquids

In a 2 mL vial 1.00 mmol of the appropriate tryptophan methyl ester salt, 1.25 g of the selected ionic liquid and 165 mg (1.1 mmol) of piperonal were added (see **Table 4.3** for details). The resulting mixture was stirred at the reported temperature for the required time.

Reaction were monitored by ^{1}H-NMR spectra of the mixture in deuterated chloroform after neutralisation with aqueous Na_2CO_3. Conversion and selectivity towards Pictet-Spengler adducts (*cis* and *trans*) were evaluated by integration of the CH_2 signals of the piperonal residue of compounds ***22cis*, *22trans*** and **25** against the same signal of piperonal (see appendix).

Compounds ***22cis*, *22trans*** were separated by column chromatography.

4.7.6 Acyl-Pictet-Spengler reaction in ionic liquids

In a 2 mL vial compound **25** (350mg, 1.00 mmol), triethylamine (300 μL, 2.1 mmol), chloroacetylchloride (226 mg, 2.00 mmol) and 2.0 g of ionic liquid (see Scheme 4.8) were introduced. The resulting mixture was stirred at room temperature for up to 20 h.

Reactions were monitored by ^{1}H-NMR spectra of the mixture in deuterated chloroform.

4.7.7 Pictet-Spengler reaction in DMC

Solid **21·HCl** (2.00 g 9.16 mmol) was added into a solution of piperonal (1.650 g, 10.99 mmol) in 20 mL of DMC. The suspension was heated to reflux and kept at that temperature with stirring for 18 h. After the reaction was complete (monitored by TLC), the mixture was gradually cooled to room temperature. The pale yellow solid was filtered with a Buchner funnel, washed with small amounts of DMC and dried at 70 °C for 10 hours to yield **22·HCl** as a pale yellow solid (3.658 g, 10.44 mmol, 95%).

4.7.8 Tadalafil syntheses

Method A: To a suspension of **23**[25] (427 mg, 1.00 mmol) in 2.00 g of [C_4dmim][NTf_2], methylamine 40 % water solution (0.8 mL, 9.2 mmol) was added. The resulting mixture was stirred for 20 hours and then filtered washing with methanol to remove ionic liquid. The white solid was dried at 70° C for 6 hours (355 mg, 0.912 mmol, 91%). Method B: In a round bottomed flask sealed with a septum, compound **22·HCl** (194 mg, 0.500 mmol) was suspended in 1.5 g of [C_4dmim][NTf_2], triethylamine (109 mg, 1.08 mmol) was added and the resulting mixture was stirred for 1 hour until a clear solution was obtained. Then the mixture was cooled to 0 °C by means of an ice bath, and chloroacetylchloride (113 mg, 1.00 mmol) was slowly added through septum with a syringe. The mixture was kept at 0 °C for 1 hours and then allowed to warm to room temperature. After one additional hour methylamine 40 % water solution (0.40 mL, 4.6 mmol) was added. After 6 hours, using the procedure described in method A, compound 4 was isolated as a white solid (171 mg, 0.439 mmol, 88%).

4.7.9 Ionic liquid recycling

The mother liquor from the preparation of compound **24** and methanol used for washing were collected in a flask. Methanol was removed under reduced pressure (rotavap), yielding a mixture of [C_4dmim][NTf_2] and aqueous solution of by-produced salts during the integrated procedure for Tadalafil synthesis. Ethylacetate (5 mL) was added, and the resulting biphasic system was stirred for ten minutes, the organic phase was separated and the aqueous phase was washed with 2 x 3 mL of ethylacetate. Extracts were collected, dried over sodium sulphate and solvent removed at reduced pressure yielding crude [C_4dmim][NTf_2], which was purified from traces of water by heating at 70 °C under vacuum for 6 hours.

4.7.10 Characterisation data

O Me D-tryptophan ^{1}H-NMR (300 MHz $CDCl_3$)δ 8.26 (br s, 1H), 7.62 (d, J=7.8Hz, 1H), 7.35 (d, J=8.1Hz, 1H), 7.09-7.22 (m, 2H), 7.05 (d, J=2.2Hz, 1H), 3.84 (dd, J=4.8Hz, J=7.7Hz, 1H), 3.71 (s, 3H), 3.29 (dd , J=4.8Hz, J=14.4Hz, 1H), 3.06 (dd, J=7.7Hz, J=14.4Hz, 1H) ^{13}C-NMR ($CDCl_3$) 176.2, 136.7, 127.8, 123.4, 122.5, 119.9, 119.1, 111.6, 111.5, 55.4, 52.4, 31.2.

(1R,3R)-1-(3,4-methylenedioxyphenyl)-2,3,4,9-tetrahidro-9*H*-pyrido[3,4-*b*]indole-3-carboxylic methyl ester hydrochloride 22*cis*·HCl [α]D20=-81.1 (c 1.0, MeOH) ^{1}H-NMR (300 MHz, DMSO-d_6) δ10.83 (s, 1H), 10.59 (s, 1H), 10.13 (s, 1H),7.54 (d, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 1H), 7.15 – 6.95 (m, 4H), 6.10 (s, 2H), 5.86 (brs, 1H), 4.70-4.80 (m, 1H), 3.85 (s, 3H), 3.36 – 3.19 (m, 2H) ^{13}C-NMR (300 MHz, DMSO-d_6) δ 168.5, 148.4, 147.1, 136.7, 128.8, 125.4, 124.8, 122.0, 119.1, 118.1, 111.5, 110.2, 108.2, 106.2, 101.5, 57.5, 55.1, 53.0, 22.1.

(1R,3R)-1-(3,4-methylenedioxyphenyl)-2,3,4,9-tetrahidro-9*H*-pyrido[3,4-*b*]indole-3-carboxylic methyl ester 22 *cis*

^{1}H-NMR (300 MHz, $CDCl_3$), 7.52 (dd, J=7.7Hz, J=9.6Hz, 2H), 7.09-7.29 (m, 3H), 6.78-6.90 (m, 3H), 5.95 (s, 2H), 5.17 (s, 1H), 3.95 (dd, J=4.2Hz, J=11.1Hz, 1H), 3.82 (s, 3H), 3.21 (ddd, J=1.7Hz, J=4.1Hz, J=14.9Hz, 1H), 2.94-3.04 (m, 1H).^{13}C-NMR ($CDCl_3$) 173.0, 148.1, 147.7, 136.0, 134.6, 127.0, 121.9, 119.5, 118.1, 110.8, 108.7, 108.2, 101.1, 58.3, 56.8, 52.2, 25.6.

(1R,3R)-1-(3,4-Methylenedioxyphenyl)-2-chloroacetyl-2,3,4,9-tetrahydro-9H-pyrido[3,4-*b*]indole-3-carboxylic methylester 23 [8] $[\alpha]_D^{20}$=109.9 (c 1.0, $CHCl_3$) ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.88 (s, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.28 (d, *J* = 7.9 Hz, 1H), 7.0-7.14 (m, 2H), 6.81 (d, *J* = 8.1 Hz, 1H), 6.76 (s, 1H), 6.64 (s, 1H), 6.46 (d, *J* = 7.7 Hz, 1H), 5.98 (d, *J* = 5.9 Hz, 2H), 5.20 (d, *J* = 6.5 Hz, 1H), 4.84 (d, *J* = 13.9 Hz, 1H), 4.45 (d, *J* = 13.8 Hz, 1H), 3.47 (d, *J* = 16.0 Hz, 1H), 3.08 (dd, J = 16.0 Hz, 6.9 Hz, 1H), 3.04 (s, 3H). ^{13}C-NMR (DMSO-d_6) δ 170.3, 166.7, 146.8, 146.5, 136.3, 133.4, 129.8, 125.72, 122.3, 121.5, 118.6, 118.0, 111.1, 109.0, 107.5, 106.1, 100.9, 52.2, 51.7, 51.2, 43.1, 20.9.

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino-[2’,1’:6,1]pyrido[3,4-*b*]indole-1,4-dione 24 $[\alpha]_D^{20}$=68.2 (c 1.0, $CHCl_3$) ^{1}H-NMR (300 MHz, DMSO-d_6), 11.03 (s, 1H), 7.54 (d, 1H, J=7.6Hz), 7.30 (d, 1H, J=7.7Hz), 7.02 (td, J=6.9Hz, J=18.3Hz, 2H), 6.87 (s, 1H), 6.78 (s, 2H), 6.13 (s, 1H), 5.92 (s, 2H), 4.40 (dd, J=3.7Hz, J=11.1Hz, 1H), 4.18 (d, J=17.2Hz, 1H), 3.95 (d, J=17.2Hz, 1H), 3.52 (dd, J=4.3Hz, J=15.7Hz, 1H), 2.97 (m, dd, J=11.3Hz, J=15.5Hz, 1H), 2.93 (s, 1H). ^{13}C-NMR (DMSO-d_6) 166.7, 166.4, 146.9, 145.9, 136.8, 136.0, 133.8, 125.6, 121.1, 119.1, 118.7, 117.9, 111.1, 107.8, 106.8, 104.6, 100.7, 55.4, 55.1, 51.3, 32.7, 23.0

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5 Greener processes in collaboration with Galentis S.r.l.

5.1 Introduction

One of the scopes of the present PhD thesis was to study new green chemical transformations of interest for fine chemicals and API. As such the collaboration with Galentis is a valuable link to this field. Therefore in this chapter we address the use of innovative chemical technologies to overcome some of the common issues encountered in a company, such as the use of safer reagents, safer and more efficient solvents, new procedures for improved selectivity and/or efficiency optimisation. During my three years of PhD it was possible to perceive how the goals of Green Chemistry[1] are exactly the same of industry. Nowadays everyone is aware that to prevent is better than to treat and the 12 principles are felt by industry as primary needs. The use of safer solvents, reactants and procedures, the mass flow optimisation and the minimisation of energy consumption are perceived as of primary importance, also because achievement of these goals often leads to cost reduction. From our standpoint, this collaboration allowed to face issues not frequently addressed in the world of academia. Economic viability of a new procedure and the issues related to the implementation in industry of a chemical preparation developed in the university enriched our way of thinking about Green Chemistry as a real-world field of invention.

Galentis S.r.l. and its predecessors have been manufacturing pharmaceutical active ingredients and intermediates since 1985. They have, therefore, operated in the national and international markets of pharmaceutical fine chemicals for more than 25 years. Currently Galentis carries out, both for its own needs and, on behalf of third parties, unit operations such as chlorinations, brominations and, in particular, fluorinations. A segregated area for production of fluorosulfonic acid, perchloryl fluoride and fluorinating mixtures is also available. Other chemical reactions which are currently performed at the plant are: amination, phosphonation, sulphonation, chlorosulfonation, Hoffman rearrangment, nitration, Sandmeyer reaction, Ullmann reaction.

Galentis' strategy is to consolidate and expand its presence and image worldwide as a reliable supplier of products and manufacturing services with a high technological content. The company is owner of the patent, and sole producer in the world of the selective fluorination agent perchloryl fluoride, and is mainly involved in the manufacture of steroids and steroid intermediates particularly for fluorinated steroids and last generation steroidal bulk active ingredients.[2]

As a fine chemical producer, Galentis has to deal with the growing number of stringent regulations for environmental protection. This should not to be intended as a limitation to the market expansion of chemical companies, but, more conveniently, as an opportunity to develop new, optimised solutions for safe and environmentally compatible chemical productions with very high added value.

In collaboration with Galentis we sought new synthetic methodologies involving reduced amounts of solvent (especially chlorinated ones[3]) and/or more environmental acceptable solvents and reagents. Starting materials and auxiliaries derived from renewable feedstocks and/or safe, non toxic reagents, alternative solvents and catalysts were tools for the development of innovative solutions according to the principles of Green Chemistry.

In particular we investigated the preparations of the following compounds.

1. **Dichloro-[2.2]-*p*-clyclophanes**: these compounds are sold as mixture of different stereoisomers under the trade name Galxyl® C. This material is used as a precursor for polymer films preparation. The mechanical properties and the electric constants of these films render this material a very attractive product for coating in the field of protection, insulation and particle retention. Coatings made with Galxyl® C found applications in biomedical implants like in pace-makers or for circuit boards to be used in very severe environments like the arctic or the desert as well as outer space.[4]
2. **Orthoesters**: these compounds are commonly used as derivatisation agent for the synthesis of different steroidal anti-inflammatory active ingredients.
3. **Furanimium bromide**: this molecule is a key intermediate for the synthesis of the well known active ingredient named Loperamide[5], an opioid drug used against diarrhea resulting from gastroenteritis or inflammatory bowel disease.

Experimental tests were carried out in the laboratories of the "Dipartimento di Scienze Molecolari e Nanosistemi" at the "Università Ca' Foscari" in Venezia, but some scale-up tests and collateral activities were also conducted in the laboratories at the Galentis production site in Marcon (VE).

5.2 Chlorination of [2.2]-paracyclophane in alternative solvents

Galxyl® C is one of the most important productions of Galentis. Therefore development of new methodologies using alternative reagents and solvents for this production was crucial for the company. The main objective was to avoid the use of light chlorinated solvents in order to be able to produce this important chemical even in the future when the use of this kind of solvents will be phased out.

5.2.1 Introduction: Chlorinated paracyclophanes in industry

The emergence of cyclophane chemistry as a separate field of aromatic chemistry began with the classic studies carried out by Donald J. Cram in the early 1950s. [6] In 1951, Cram and Steinberg coined the term "paracyclophane". Cyclophanes have lead to a new field of research called host-guest chemistry or supramolecular chemistry. Donald J. Cram together with Charles J. Pedersen and Jean-Marie Lehn received the Nobel Prize for his pioneering work in the field of host-guest chemistry in 1987. Besides the work of Cram,[7] who laid the foundations of the chemistry, paracyclophanes attracted the interest of industrial companies for their ability to furnish polymers.[8] [2.2]Paracyclophanes (Figure 5.1) in particular are very attractive compounds for this particular application.[9]

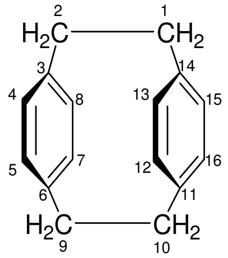

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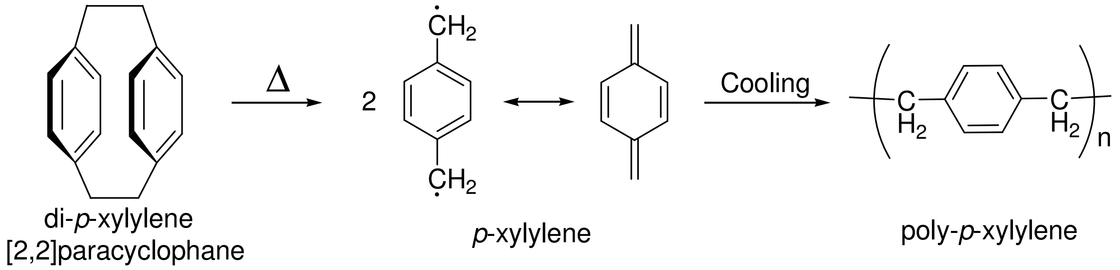
Figure 5.1 Molecular structure of unsubstituted [2.2]paracyclophane.

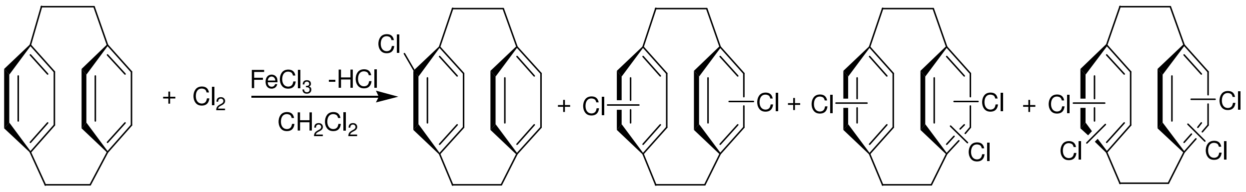
[2.2]Paracyclophane can be simply sublimed at reduced pressure and moderate temperature. By pyrolisis in the gas phase the *p*-xylylene monomer is obtained. The latter polymerises on a cold surface (Scheme 5.1) yielding films of very high uniform thickness on the surface of interest regardless of its geometrical complexity.



Scheme 5.1 Poly-p-xylylene from [2.2]paracyclophane.

Halogenation (mainly chlorination and bromination) of these compounds was one of the first reactions studied because the electrophilic aromatic substitution was used to acquire information on the nature of these compounds, in particular to define the entity of interaction (steric and electronic) between the two facing rings.[10]

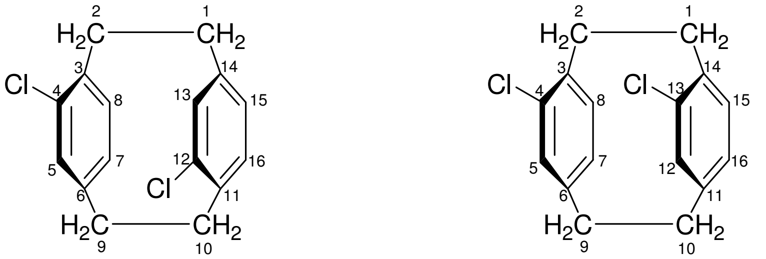
The literature reported procedure for the production of chlorinated [2.2]paracyclophanes[11] (Scheme 5.2) requires chlorine gas, ferric chloride in catalytic amounts and dichloromethane as solvent, operating at ambient temperature.



27 **28** **29** **30** **31**

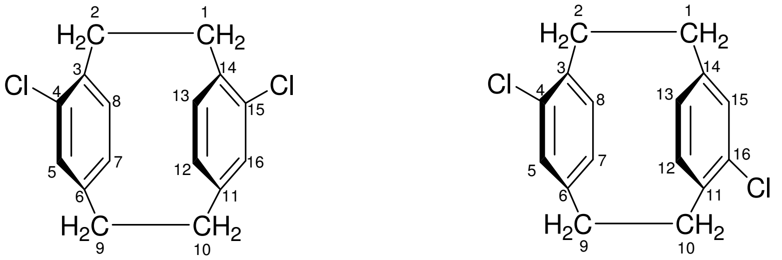
Scheme 5.2 Chlorination of paracyclophane using molecular chlorine

The chlorination process proceeds with the formation of the monochlorinated [2.2]paracylophane **28** first, while the second chlorine attacks the unsubstituted, more electron-rich ring. The amount of side-chain halogenation is minimal (< 1%). The reaction is very selective with respect to the number of chlorine introduced on each ring. It is therefore possible to obtain dichlorinated [2.2]paracyclophanes **29** with one halogen on each benzene ring in high purity. Further chlorine atoms can be added simply increasing the dosage of molecular chlorine, although the compounds of commercial interest are the dichlorinated [2.2]paracylophane **29** and the tetrachlorinated **31**. With the exception of compound **28**, all the chlorinated [2.2]paracylophanes are obtained as mixtures of isomers. For instance for what concerns compounds **29**, the described route could, in theory, yields four different isomers (Figure 5.2).



4,12 dichloro-[2,2]paracyclophane
Pseudo-*ortho* isomer

4,13 dichloro-[2,2]paracyclophane
Pseudo-*ipso* isomer



4,15 dichloro-[2,2]paracyclophane
Pseudo-*meta* isomer

4,16 dichloro-[2,2]paracyclophane
Pseudo-*para* isomer

Figure 5.2 Isomers of dichloro [2.2]paracyclophane.

However, under these conditions, the main products are two, more precisely the pseudo-*para* isomer (4,16 dichloro-[2.2]paracyclophane) and the pseudo-*ortho* isomer (4,12 dichloro-[2.2]paracyclophane).[12]

In the case of the industrial preparation of dichlorinated [2.2]paracyclophane as polymerisation precursor, the presence of different isomers does not make any difference since in any case only one chlorine atom is present on each ring, thus only one monomer is produced (Scheme 5.1). On the contrary in the case of tetrachlorinated compounds **31** a number of isomers is expected and the gaschomatographic analysis of the tetrachlorinated paracyclophane (produced by Galentis S.r.l.) showed the presence of four major isomers.

After chlorination, the crude material is neutralized, washed, bleached, filtered, concentrated, distilled, centrifuged, dried, and milled. Obviously the process as described is inherently efficient, but requires the use of a harmful and highly volatile solvent. In addition an extremely intensive workup in terms of materials used (primarily solvents), energy, and equipment for the separation of the reaction product is needed.

It should also be stressed that the use of molecular chlorine involves some drawbacks. Chlorine is generally very efficient, however, only half of the atoms of Cl_2 are used, because the other half originate hydrochloric acid (corrosive) as a by-product. In addition molecular chlorine is a gas at room temperature, as a result the transportation, storage and handling suffer of many complications because of the extreme reactivity and toxicity of this reagent.

5.2.2 Aim of the research

As previously stated, the development of a new synthetic procedure for production of chlorinated paracyclophanes avoiding the use of light chlorinated solvents is a significant objective for the company partner of this PhD project. Nonetheless a method that merely produces a chlorinated paracyclophane is not enough, as an economically viable, sustainable procedure is needed. In addition the product thus obtained should comply with the product specifications in terms of residual impurities, isomers distribution and other requirements. Therefore even if a method allows to achieve chlorination of the product using a very attractive, innovative process, it may be not suitable for the production on industrial scale. A series of possible solutions were therefore tested in constant collaboration with Galentis S.r.l. in order to identify an effective procedure.

The first step was to consider the current methods. The electrophilic chlorination typically employs one of the following reagents[13]:

- Molecular Chlorine
- Chlorine electrophile generated by oxidation of a chloride salt or of hydrochloric acid
- Other chlorine-containing electrophilic reagents

Given the difficulties entailed by the use of chlorine gas, methods that use a chloride salt (or HCl) in the presence of an oxidizing agent[14] or reagents such as N-chloro succinimide[15] are very attractive, although they often require the use of appropriate catalysts and/or large amounts of acids.

For what concerns the replacement of light chlorinated solvents, an interesting alternative could be represented by the use of ionic liquids.[16] As described in Chapter 3, two interesting papers[17,18] inspired us in the direction of oxychlorination reaction. We thus investigated the oxychlorination with HCl in the presence of a nitrate ionic liquid. Our study on aromatic electrophilic oxychlorination using phosphonium nitrate ionic liquids[19] demonstrated the catalytic nature of the nitrate anion and the rôle of atmospheric oxygen as the effective oxidant. The global reaction equation can therefore be written as follows.

$$\mathrm{Ar{-}H} + \mathrm{HCl_{(aq)}} + 0.5\,\mathrm{O_2} \xrightarrow{[\mathrm{IL}][\mathrm{NO_3}]} \mathrm{Ar{-}Cl} + \mathrm{H_2O}$$

Scheme 5.3 Reaction equation for phosphonium nitrate ionic liquids catalysed aromatic oxychlorination

The methodology employed $[P_{8,8,8,1}]NO_3$ as a solvent and catalyst for the chlorination and it gave excellent results with activated and less activated substrates such as anisole, toluene, *p*-xylene and naphthalene.

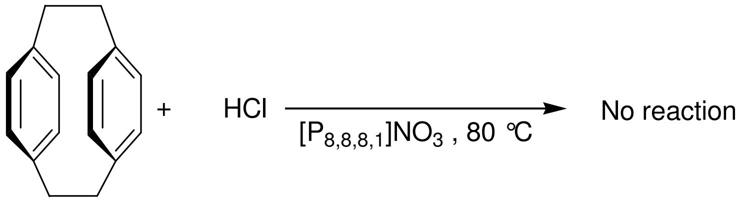
Another solution could be represented by maintaining the chemical process involving the use of molecular chlorine. In this case the innovation could merely lie in the replacement of the reaction medium. Besides the use of ionic liquids, the use of "green solvents" such as non toxic solvents or solvents derived from renewable feedstock with reduced environmental impact should also be considered.

5.2.3 Results and discussion

5.2.3.1 [2.2]paracylophane chlorination in ionic liquids

Starting from the knowledge acquired during the previously cited study on oxychlorination, we embarked on the application of that reaction protocol for the chlorination of [2.2]paracylophane using HCl as the source of chlorine atoms.

[2.2]Paracyclophane was set to react with HCl in the presence of $[P_{8,8,8,1}]NO_3$ as solvent/catalyst under the conditions reported in the second section of Chapter 2. In this case however the reactant did not dissolve in the ionic liquid and the resulting mixture appeared as a suspension. The reactions were monitored by sampling the mixtures at selected times. Samples were filtered through silica gel eluting with diethylether to remove the ionic liquid. The resulting dilute solutions in diethylether were analysed by GC/MS. Disappointingly no chlorination products were observed even after 120 hours using 2.4 equivs of HCl and 1.0 equivs of ionic liquid (Scheme 5.4).



Scheme 5.4 Chlorination of **27** using phosphonium nitrate as solvent/catalyst.

It seems questionable to attribute this lack of reactivity to steric and electronic factors, since it was possible to obtain not only chloroxylenes, but also dichloro-*p*-xylene using this chlorination procedure.[19] Therefore, we attributed this evidence to the very low solubility of the reagent in the ionic liquid.

It should be noted that also in common organic solvents **27** is poorly soluble. Therefore the search for an ionic liquid able to dissolve the investigated substrate revealed to be demanding. Various cations with higher possibility of π interaction were synthesised, then anion-exchanged to obtain the corresponding nitrate salts (Figure 5.3) and tested.

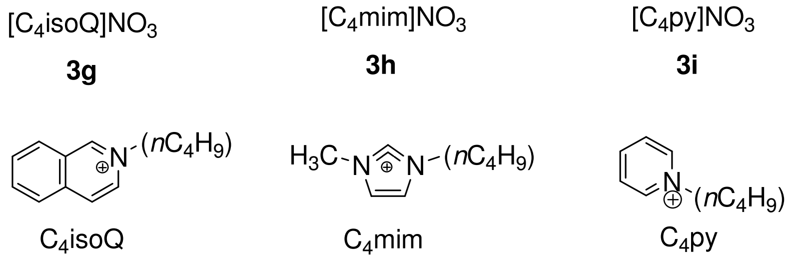
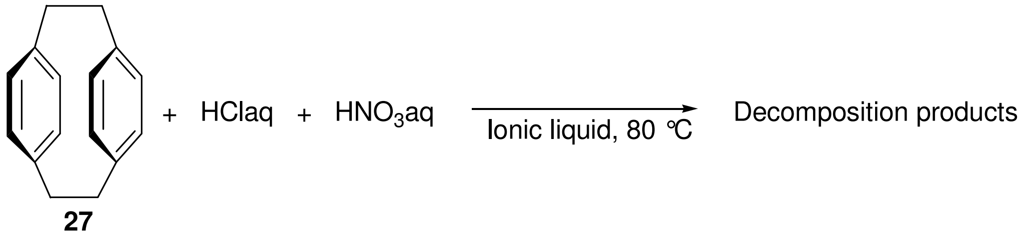


Figure 5.3 Ionic liquid used as solvent/catalyst for oxychlorination of **27**.

None of the tested cations was able to dissolve **27** under the reaction conditions (80 °C, substrate:ionic liquid molar ratio ranging from 1.0 to 2.0) and in fact little or no conversion (< 5%) was observed in all the tests performed. At this stage we tried also different ionic liquids bearing different anions, adding 1 equiv of nitric acid as the oxidant. We try to use the NTf_2 salts (**10a, 10g, 10i**) of the synthesised cations C_4isoQ, C_4mim, C_4py. The outcome was disappointing, since only unrecognised decomposition products were observed with no formation of the desired chlorinated paracyclophane. (Scheme 5.5).



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Ionic liquid = [$P_{8,8,8,1}$][NTf_2] **10a**, [C_4isoQ][NTf_2] **10g**, [C_4py][NTf_2] **10i**

Scheme 5.5 Different ionic liquids were tested as solvent for the oxychlorination of **27** in presence of HNO_3.

5.2.3.2 [2.2]paracylophane chlorination in ionic liquids using a co-solvent

Since the very low solubility of **27** seemed to inhibit the reaction, we decided to test the influence of a co-solvent. Different solvents were tested in order to find one which was able to solubilise **27,** at least partially, allowing the reaction to proceed. Obviously this expedient unavoidably varies the ambient with respect to the original procedure in pure ionic liquid.

It was observed that certain solvenst could dissolve at least 100 mg of **27** per 10 mL of solvent at 80 °C. These solvents were:

- Xylene
- Toluene
- Dichloromethane
- 1,4 Dioxane
- Tetrahydrofuran
- Diethyl carbonate (DEC)

Diethyl carbonate (DEC) was selected as co-solvent for this study, since it is the most enviromental acceptable because of its low toxicity and volatility.[20] The use of an organic solvent in conjunction with aqueous HCl allows to design two different system depending to the nature of the selected nitrate ionic liquid. The less hydrophilic $[P_{8,8,8,1}]NO_3$ distributed mainly in the organic phase, while, conversely, an ionic liquid with shorter alkyl chains, such as 1methyl-3butyl imidazolium nitrate ($[C_4mim]NO_3$), was found to distribute mainly in the aqueous phase (Figure 5.4).

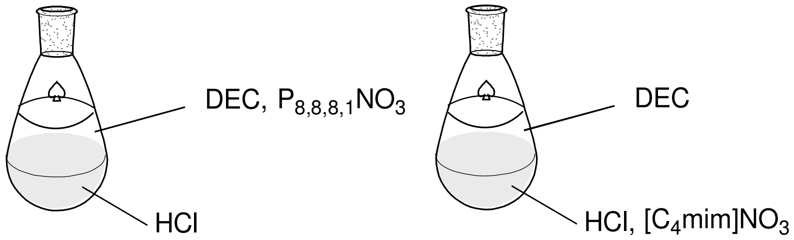


Figure 5.4 Ionic liquids distribution between aqueous and DEC phases

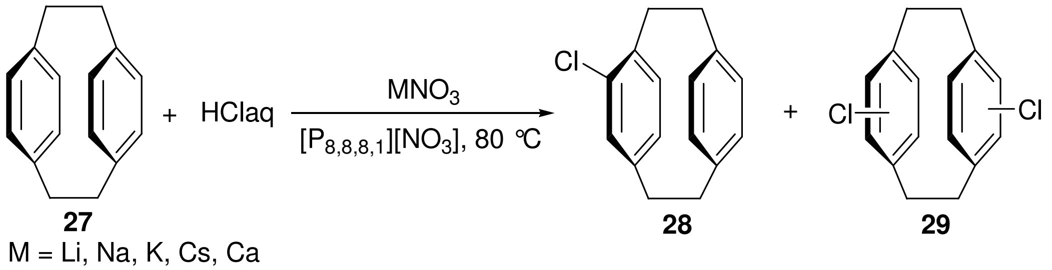
Having no idea of which system could be the most effective, we tested both. Unfortunately, no chlorination products were obtained in any case even after heating at 80 °C for 48 hours a mixture consisting in 10 mL of diethylcarbonate, 1 mmol of **27** and 1 mmol of the ionic liquid.

5.2.3.3 Reaction in ionic liquid using alkaline salts as additives

Searching for a way to bring **27** in solution we considered that the very low solubility of this compound was likely due to the π-π stacking interaction of the molecules of **27**. *Ab initio* calculations indicated that alkaly metals ions interact with [2.2]paracyclophane, in particular Li^+ exhibited the strongest interaction with the aromatic ring of 27 among the other cations tested.[21]

We have therefore begun a study on the effect of salts of alkali metals and alkaline earth metals in the reaction mixture. These, through interaction with the paracyclophane π system could break the π–π stacking and thus facilitate the solubilization of the reagent in the ionic liquid, increasing the conversion.

In a model reaction **27** was introduced into a reactor and $[P_{8,\,8,8,1}]$ NO_3, aqueous HCl and the selected amount of salt in question were added. The mixture was heated to 80 °C and stirred for 24 hours (Scheme 5.6).



Scheme 5.6 Reaction in ionic liquid using alkaline salts as additives

Results are collected in Table 5.1.

Table 5.1 Nitrate alkaline salts effect on the conversion[a]

Salt	27 mmol	3a mmol	$LiNO_3$ mmol	HCl mmol	Conv. (GC/MS)	28 %	29 %	Others[b] %
$LiNO_3$	0,5	1	1,5	4,8	84	32	34	18
$NaNO_3$	0,5	1	1,5	4,8	33	18	7	8
KNO_3	0,5	1	1,5	4,8	16	16	1	0
$CsNO_3$	0,5	1	1,5	4,8	9	9	0	0
$Ca(NO_3)_2{\cdot}4H_2O$	0,5	1	1,5	4,8	12	8	1	3
$Ca(NO_3)_2{\cdot}4H_2O$	0,5	0[c]	1,5	4,8	8[d]	6	0	2
none	0,5	1	1,5	4,8	2	-	-	2

[a] Data derived from GC/MS analysis of the reaction mixture after 24h at 80 °C; [b]unrecognised products; [c]$Ca(NO_3)_2{\cdot}4H_2O$ melts at 45 °C, therefore it can be used as a solvent at 80 °C; [d] The conversion extimation was probably affected by the formation of a white solid coproduct, which was not quantitated.

As expected an effect of salts on the conversion was observed. The effect is related to the size of the cation, in particular, the smaller the cation the higher the conversion, in agreement with what was expected from quantum mechanics.[21] Using calcium nitrate as the solvent/catalyst for the reaction, the formation of a white solid was also observed. This solid was insoluble in organic solvents and water, therefore it probably derived from the polymerization of the reagent, no further attempts to characterise it were made.

We then focused on $LiNO_3$ as the most promising salt for increasing the conversion while keeping acceptable selectivity towards chlorinated compounds **28** and **29**. Table 5.2 shows the results of some exploratory tests. Increasing the amount of $LiNO_3$ (entry 1-3) the conversion increased as expected, however working with only 10% excess of HCl (with respect to the stoichiometric) led to the formation of only small amounts of compound **29** while the major product was the monochlorinated **28**. Doubling the quantity of HCl, maintaining the amount of $LiNO_3$ equal to 3 equivs, allowed to increase conversion up to 84% (entry 4), but at the same time reducing the selectivity. Extensive formation of unrecognised product (18% of "others", probably derived from oxidation pathways) was observed. As observed in our precedent studies (see chapter 3), diluting the reaction mixture by adding higher amounts of ionic liquid, slowed down the reaction, allowing to achieve only 58% conversion after 24 h (entry 5).

Table 5.2 PCF chlorination in $P_{8,8,8,1}NO_3$ in presence of different amounts of $LiNO_3$.[a]

Entry	**27** mmol	**3a** mmol	**$LiNO_3$** mmol	**HCl** mmol	**Conv.** (GC/MS)	**28** %	**29** %	**Others** %
1	0.5	1	0.15	2.4	20	19	0	1
2	0.5	1	1.0	2.4	45	41	0	4
3	0.5	1	1.5	2.4	52	38	3	11
4	0.5	1	1.5	4.8	84	32	34	18
5	0.5	2.6	1.5	4.8	58	51	4	3

[a]Data derived from GC/MS analysis of the reaction mixture after 24h at 80 °C.

Anyhow, under the condition of entry 5 an interesting selectivity toward the monochlorinated compound **28** (90 %) was observed. However, the selectivity towards the desired product **29**, was in any case very low and it should be noted that the amount of lithium salt required to achieve discrete conversions was quite large. It might be interesting to conduct a thorough study of the reaction parameters in a systematic way, in the hope of optimizing them and direct the reaction towards the product of interest. On the other hand this protocol seemed not to be useful for our partner Galentis because of the expensive use of ionic liquid, large amounts of lithium salt and relatively low conversion and selectivity.

5.2.3.4 Chlorination under solvent free conditions

As stated above, **27** has proven extremely poorly soluble in common solvents, including dichloromethane, which, nevertheless, is the solvent currently used in the industrial process. This suggested that when the chlorinating agent was chlorine gas, a suspension of the reagent was sufficient for the reaction to proceed. At first, some attempts were made to conduct the reaction in ionic liquid, using it as a solvent, but unfortunately, with all the ionic liquids tested, this resulted only in the degradation of the organic salt.

To overcome this drawback a different approach was used. Considering that the best solvent is no solvent at all,[22] we tried to verify if it was possible to conduct the chlorination reaction of **27** in solvent free conditions. A study of the chlorination in the absence of solvent was therefore carried out by placing the reagent in contact with the solid catalyst (2 mol%) and finely grinding the resulting solid using techniques such as "ball milling".[23] The experimental set up consisted in a flask equipped with a mechanical stirrer and filled with a certain amount of glass beads. The details of the configuration of the apparatus are given in the experimental section.

The reactant **27** was added to the flask with a catalytic amount of anhydrous ferric chloride. The mixture of reactant and catalyst was ground for 15 minutes to ensure fine milling, before the addition of chlorine. As soon as the Cl_2 gas was introduced into the reactor the colour of the solid turned from white to light brown (Figure 5.5).

Figure 5.5 Chlorination of **27** using the "ball milling" tecnique.

After a time ranging from 10 to 20 minutes the formation of a sticky tenacious material was observed, this prevented further mixing.

The reaction took place, furthermore the GC/MS analysis of the material thus obtained revealed the formation of polychlorinated paracyclophanes (tetrachloro [2.2]paracylophane **31**, pentachloro [2.2]paracylophane **32** and hexachloro [2.2]paracylophane **33** as mixtures of isomers).[24] Results are reported in Table 5.3. A critical parameter was the duration of the exposure to chlorine gas. Besides the amount of gas and the stirring, another important parameter was the milling method. The lack of reproducibility was initially attributed to the impossibility of stirring the mixture beyond a certain point. As disperdant, in addition to glass balls, also teflon shavings (20 g) were added with the aim of preventing caking due to the formation of the sticky phase. Using this expedient the mixture proved to be pliable also after the first 20 minutes allowing to achieve quantitative conversion (entry 7). However, using this method the selectivity was very low in all cases, also the use of teflon shavings, after a more detailed investigation, proved to be insufficient to make the process reproducible. It should be stressed that mixtures of chlorinated products obtained by this procedure consisted of complex mixtures of isomers of little or no commercial value. Therefore, considering the problems of reproducibility, most likely due to poor temperature control, it seemed necessary to use a dispersing liquid for the reaction, to avoid "hot spots" that made the reaction absolutely unpredictable.

Table 5.3 PCF chlorination in solvent free conditions[a]

#	PCF (g)	Dispersant	Temp	Time[b] (min)	Conv %	31 %	32 %	33 %
1	1.00	Glass balls	RT	120[c]	0	-	-	-
2	0.52	Glass balls	RT	30	15	11	1.6	-
3	1.00	Glass balls	RT	45	65	36	21	4
4	1.00	Glass balls	RT	60	45	26	11	1.5
5	1.00	Glass balls	RT	150	85	45	33	3.5
6	0.21	Glass balls	RT	120	20	15	3	-
7	1.00	Glass balls Teflon (20 g)	RT	60	99	25	47	27
8	1.00	Glass balls Teflon (20 g)	0°C	60	24	13	4.5	-

[a] 250 mL flask was used for all the experiments; the mechanical stirring was kept at 60 rpm; chlorine was introduced at 1 mmol/min. [b] Total time of chlorine addition. [c] No ferric chloride was added.

5.2.3.5 Chlorination in alternative Green Solvents

Among all the possible liquids, only the less toxic and ones derived possibly from renewable resources were considered. Table 5.4 shows the main properties of some solvents derived from renewable resources compared to those of dichloromethane.[25]

Nine different solvents were tested for the chlorination of **27**, using a substrate:solvent ratio equal to 10 (mass/mass). In a closed reactor schematised in Figure 5.6 the reagent was suspended in the selected solvent in the presence of a catalytic amount of anhydrous $FeCl_3$ (1 mol%). The resulting mixture was treated with a stream of chlorine for the required time necessary to introduce two equivs of the gaseous reactant, in order to obtain the desired dichlorinated product **29**. At the end of each reaction, 1 mL of the reaction mixture was diluted in 10 mL of diethyl ether and analysed by GC/FID. Since the reaction is known to be extremely rapid no other work-up operations to remove unreacted chlorine were necessary. This prevented any possiblity of compromising the composition of the mixture.

Table 5.4 Main properties of some solvents from renewables compared to dichloromethane[a]

Solvent	From renewables	Dielectric constant	Boiling point (°C)	Flashing point (°C)	Water solubility (g/100g)	Price (€/L)
Dichloromethane	No	9.1	40	-	1.3	20
Dimethylcarbonate	Yes	3.09	90	22	13.9	34
(-)Ethyl L-lactate	Yes	N.A.	154	46	N.A.	30
Cyclopentyl methyl ether	No	4.76	106	-1	1.1	65
2-Methyltetrahydrofuran	Yes	6.97	78-80	-12	4.4	120
Acetone	Yes	20.7	56	-20	∞	23
1,3 Dioxolan	Yes	7.34	76	-6	∞	42
*iso*Butanol	Yes	17.9	108	29	9.5	20

[a] From Sigma Aldrich catalog and MDSDs.

Knowing that exactly 2 equivs of molecular chlorine were added, the percentage of chlorine incorporated in products **28, 29, 30** was calculated considering the amount and nature of the products detected by GC analysis (see experimental section for further details).

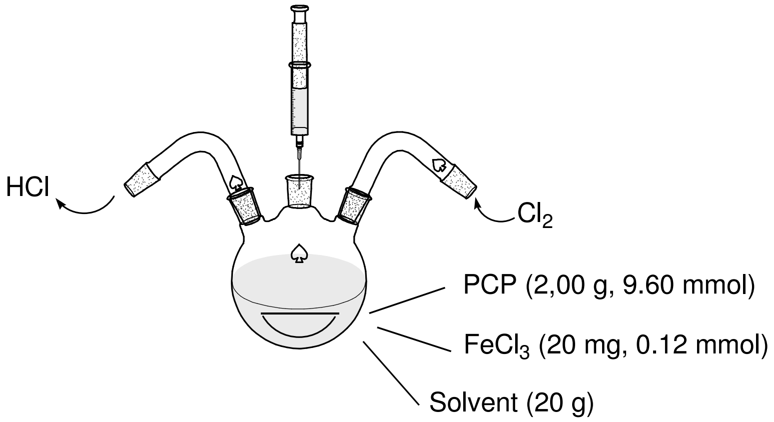


Figure 5.6 Experimental setup for **27** chlorination using alternative solvents

In addition, the degradation of the solvent was also considered taking into account the peak areas of the tested solvent and any by-products (determined via GC / FID). The results are shown in Figure 5.7. Looking at the figure it clearly appeared that the higher the decomposition of the product the lower is the conversion of the reactant and the yield of chlorinated paracyclophanes. This is obvious, since the degradation of the solvent took place by reaction with chlorine, which was thus unavailable for reaction with the aromatic substrate.

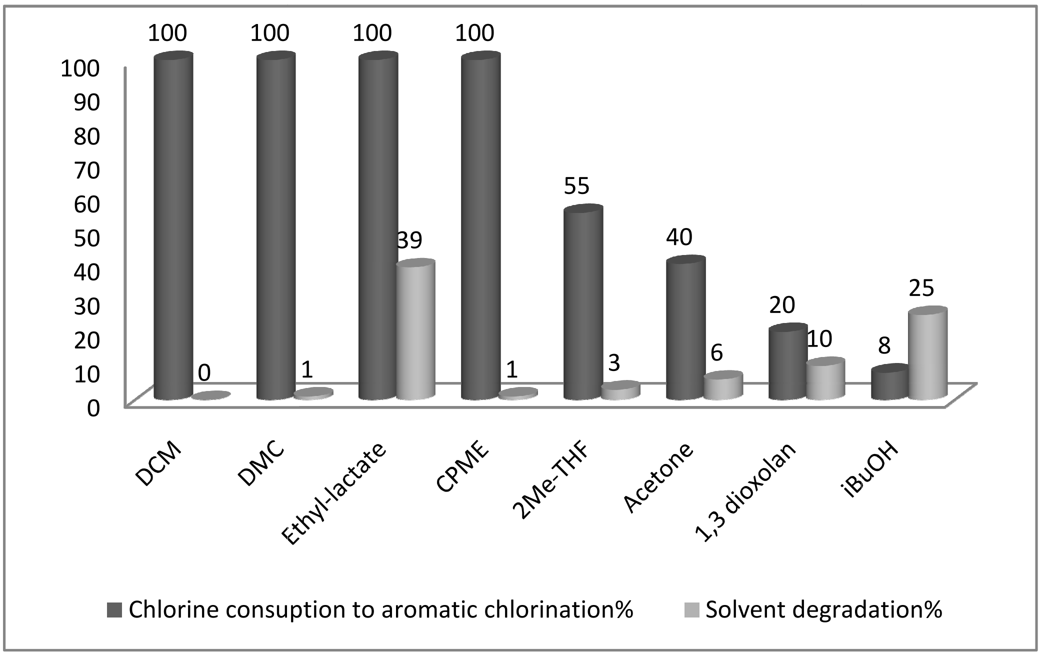


Figure 5.7 Chlorination of **27** in different alternative solvents, the selectivity toward chlorination of the reactant and decomposizion of the product were considered.

Conversely when ethyl lactate was used, very high conversion was achieved, but, at the same time, extensive decomposition of the solvent was observed. In this case the solvent did not react with chlorine, since all the introduced chlorine was consumed by chlorination of **27**. This behaviour was likely due to the action of hydrochloric acid which is generated as the aromatic chlorination byproduct (Scheme 5.2).

In summary looking at Figure 5.7 CPME and DMC proved to be good candidates for DCM replacement for the chlorination process. DMC in particular showed a very interesting behaviour. In all the tests performed the starting mixture appeared as a suspension since as already stressed the reactant was very insoluble. Fortunately the presence of one or more chlorine substituent on the aromatic rings favoured the solubilisation, causing the mixture to become a clear solution as the chlorination proceeded. At the end of the reaction in DMC, after allowing the mixture to stand for several minutes (from 10 minutes to half an hour approximatively), the formation of a microcrystalline white solid was observed.

GC/MS analysis revealed that this material was composed by only one isomer of dichloro derivative **29** paracyclophane with very high purity (95%), even if in rather low yield (30%).

A thorough examination of the NMR spectra allowed to determine that the isomer was 4,16-dichloro-[2.2]paracyclophane. Considering that the through-bond coupling constants between aromatic protons follow the general rule: J_{ortho}>J_{meta}>J_{para}, NMR signals could be assigned to protons a,b,c (see Figure 5.8) on the basis of the observed $J_{H\text{-}H}$.

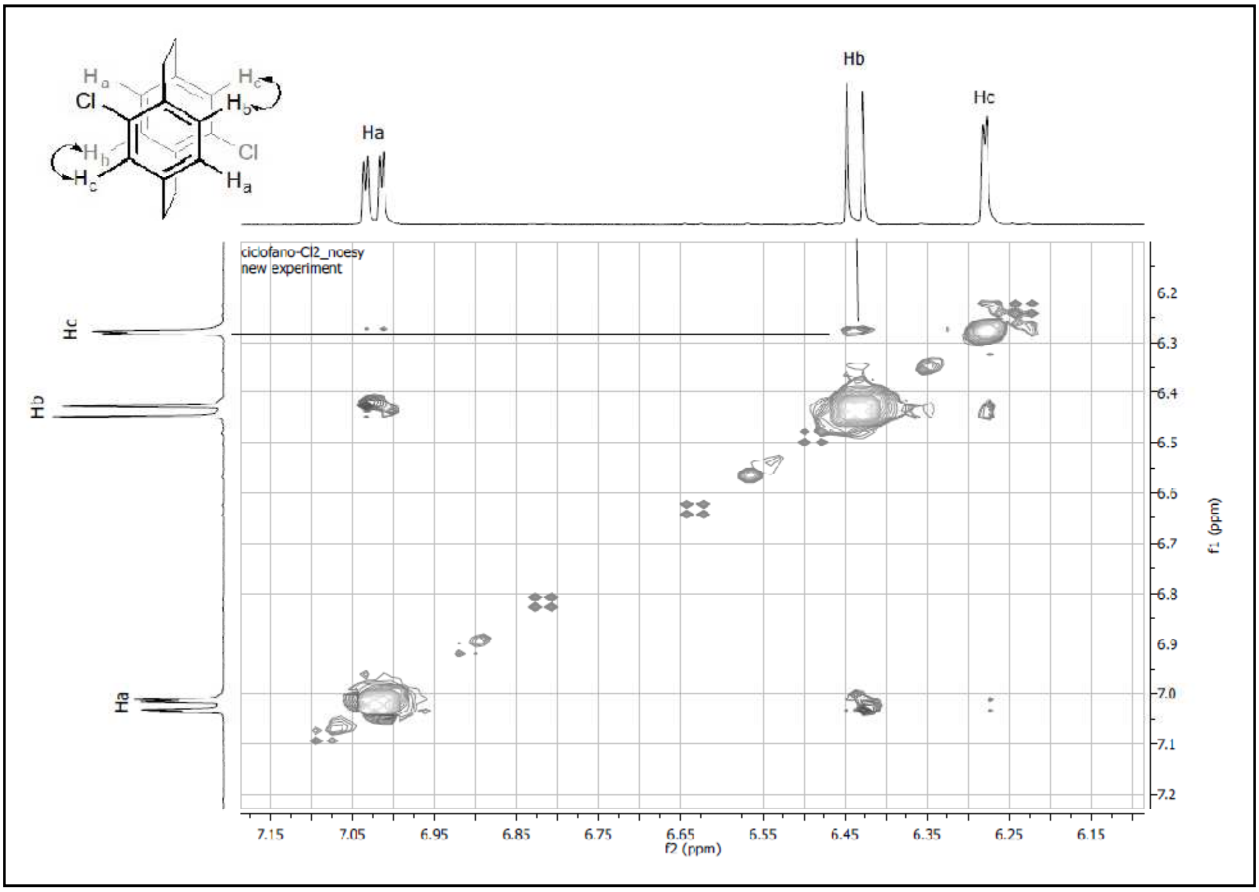


Figure 5.8 ^{1}H-NMR NOESY of the white solid obtained from the chlorination of **27** in DMC

^{1}H-NMR NOESY (Figure 5.8) showed a through-space coupling between protons H_b and H_c, necessarily attached to different aromatic rings. These evidence confirmed the assigned structure. The ability of DMC to furnish directly the aforesaid isomer resulted very interesting, allowing to isolate this compound, by crystallization, directly at the end of the reaction.

As stated in the *Aim of the research* paragraph, the selectivity towards the product **29** is a crucial issue when an alternative solvent/dispersant is seek for the production in industry. Figure 5.9 shows the selectivity of the reaction carried out using the four solvents which gave the best results in terms of conversion (cf. Figure 5.7). Selectivity values below 100% are mainly due to the concomitant formation of the monochloro and trichloro derivatives (**28** and **30** respectively). A little percentage of undesired products are represented by dichloro species (by GC/MS) different from the species which compose the mixture of isomers obtained in DCM, probably derived from the radical halogenation of the ethylenic bridge of the paracyclophane structure.

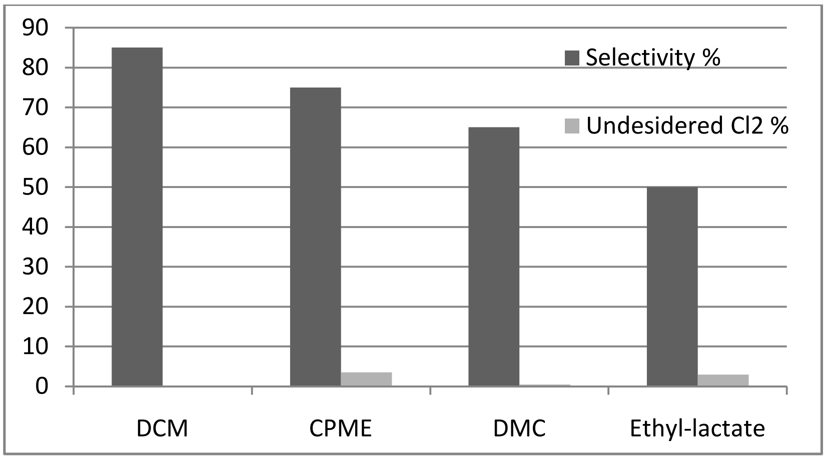


Figure 5.9 Selectivity toward the dichloro derivatives **29**.

Also in this case ethyl-lactate behaved in a different way with respect to the other solvents. Using this solvent, other unrecognised products were detected by GC/MS in approximatively 10% yield. In addition the extensive degradation of the solvent convinced us that ethyl-lactate was not suitable for this reaction.

On the other hand the positive result obtained using the DMC prompted us to select this solvent as an alternative to DCM. To improve the selectivity toward the desired product we conducted a study on reaction parameters optimisation. The key parameters to control the selectivity were found to be the flow of chlorine and the dilution of the mixture.

Using the previously described reaction set-up (Figure 5.6), a set of experiments were carried out varying the gas flow into the flask and the substrate to solvent ratio (Table 5.5).

Table 5.5 Optimisation of parameter influencing selectivity of chlorination in DMC[a]

Entry	Chlorine flow mmol/min	DMC/27 w/w	% by GC/MS			Cl_2 equivs
			28	**29**	**30**	
1	0.743	10	11	64	25	2.14
2	0.257	10	14	73	13	1.99
3	0.201	12.5	6	78	16	2.1
4	0.175	12.5	10	85	5	1.95

[a]Experimental conditions: 2.00 g of [2.2]paracyclophane **27** in 20 to 25 g of DMC.

Lowering the rate of addition of gaseous chlorine to 0.175 mmol/min (0.18 equivs per minute) as reported in line 4, it was possible improve the selectivity up to 85% (10% and 5% of monochloro trichloride respectively).

5.2.1 Conclusions

A series of different methodologies for [2.2]paracyclophane electrophilic aromatic chlorination were tested, focussing on the economic viability and industrial applicability of the procedure, as well as on the effectiveness of the core reaction. The integration of our tested chlorination processes in the industrial operation adopted by Galentis S.r.l. (here not described) was also considered as a guide-line for our research planning.

The oxychlorination of aromatic substrates catalysed by nitrate ionic liquid recently described by us[19] was tested using compound **27** as the substrate. Notwithstanding our insistence the reaction did not proceed even using strog excess of hydrochloric acid. This lack of reactivity was probably related to the inability of the ionic liquid to dissolve the reactant. None of the ionic liquids tested was able to improve the conversion of the reaction through solubilisation of **27**, even when also the anion was varied to improve the dissolution power. Harsh conditions revealed that the reactant is prone to oxidation and decomposition, maybe because of the ring strain on the ethylene bridge (in addition the nature of the benzylic CH_2 group enhance the reactivity of the molecule toward oxydation and radical side reactions).

The use of a co-solvent to enhance conversion unfortunately gave disappointing results. On the other hand a very interesting effect of the presence of alkaline metal salts on the conversion was observed. The addition of nitrate salt of alkaline metals, lithium in particular, cause the reaction to proceed toward the formation of chlorinated products **28** and **29**. This evidence is in agreement with our explanation for the low reactivity of the substrate, since a partial solubilisation of the reactant, achieved by interaction of small size cations and π system of **27**, allowed to achieve values of conversion up to 84%. Unfortunately this method demonstrated of low industrial applicability, in view of the fact that large amounts of $LiNO_3$ were need to achieve moderate conversion in quite long reaction time (24 hours). In addition very low selectivity was observed toward the desired dichloro derivative **29**.

Unexpectedly the substrate proved to be prone to chlorination by chlorine gas catalysed by $FeCl_3$ even in absence of any added solvent. The milling of solid **27** to obtain a fine powder was sufficient to achieve chlorination of the substrate in the presence of catalytic amount of anhydrous $FeCl_3$. However no dichloro derivatives **29** were detected at the end of reaction as only mixture of tetra to hexachlorinated were isolated. Lack of reproducibility of the procedure was observed as well, causing this method to be disregarded as a proposable alternative to the established industrial process.

The mere substitution of solvent, in the standard procedure was also tested. The use of different alternative solvents with respect to the commonly utilized light chlorinated hydrocarbons was tested. Besides the conversion and selectivity of the substrate, the chemical resistance to the aggressive environment to which solvents are exposed during the reaction was verified. The solvents chosen for the investigation were the less expensive and easier to remove, among them we considered the more acceptable in terms of environmental compatibility.

The well known solvent obtained from renewable resources ethyl lactate,[26] resisted to the action of molecular chlorine in presence of ferric chloride (all the introduced chlorine reacted with **27**), but it was sensible to HCl by-produced by the reaction. This behaviour rendered this solvent unuseful for this application and was therefore discarded. Remarkably DMC proved to be very resistant to degradation by chlorine and HCl, remaining unaltered at the end of the reaction. In addition the use of dimethylcarbonate allowed to isolate selectively the 4,16 dichloro-[2.2]paracylophane in 95% purity. Even if in rather low yield the high purity of the obtained product was a very interesting result, that could be useful for applications where only this isomer may be required.

Optimisation of reaction conditions allowed to improve conversion and selectivity. This result was encouraging and DMC could be a very interesting alternative to DCM for chlorination of aromatics. Galentis technical staff is currently verifying the viability of the implementation of chlorination in DMC in its production process.

5.2.2 Experimental section

5.2.2.1 General informations

Chemicals used were of reagent grade and used as received. [2.2]paracylophane and dichloro [2.2]paracylophane were from Galentis S.r.l. Anhydrous ferric chloride ($FeCl_3$), dichloromethane, dimethylcarbonate, (-)ethyl L-lactate, cyclopentyl methyl ether, 2-Methyltetrahydrofuran, acetone, 1,3 dioxolane and isobutyl alcohol were from Aldrich.

GC-MS analyses were performed with a HP-5890 gas-chromatograph equipped with a HP-5 MS capillary column (30 m x 0.25 mm; coating thickness 0.25μm) and a HP-5970 quadrupole mass detector (EI, 70 eV). Analytical conditions: injector and transfer line temperatures 260 and 280 °C respectively; oven temperature programmed from 100 °C (isothermal condition for three minutes) to 280 °C at 10°C min^{-1}; carrier gas helium at 1 ml/min^{-1}; split ratio 1:20.

^{1}H NMR and ^{13}C NMR spectra were collected in $CDCl_3$ solution at 25 °C on a Varian Unity at 400 and 100 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) downfield from TMS.

5.2.2.2 Paracyclophane chlorination using nitrate ionic liquids

[2.2]paracylophane **27** (104 mg, 0.50 mmol) was suspended in the selected ionic liquid (**3** 1.0 mmol, **3a** 448 mg, **3g** 248 mg, **3h** 201mg, **3i** 198 mg). Successively aqueous HCl (37%, 1.0 to 4.8 equivalents, 0.07 - 0.20 mL) was added and the resulting mixture was heated at 80 °C for up to 120 hours. Reaction mixture were collected at selected time, filtered through silica gel (100 mg) and eluted with diethylether. The resulting solutions were analyzed by GC-MS and the products recognised by mass spectra and by comparison with authentic sample where available.

5.2.2.3 Operations and apparatus for chlorine gas handling

Chlorine in commerce is a liquefied gas under pressure (6.8 bar at 20 °C)[27]. It is a clear, amber-colored liquid. The gas has a greenish-yellow color and a strong, pungent odor. It is an irritant to the skin and respiratory system. Chlorine needs careful handling because it is a highly toxic and reactive substance. Chlorine does not burn. However, chlorine is a strong oxidizing agent and poses a serious fire and explosion risk because it promotes combustion, like oxygen. Containers or cylinders may rupture violently due to over-pressurization, if exposed to fire or excessive heat for a sufficient period of time. Chlorine gas is heavier than air and will collect and persist in pits, hollows, depressions, and other confined or low-lying areas.

In the moisture-free state at ordinary temperatures, it is relatively non-corrosive. In the presence of moisture, however, it is highly corrosive.[28] Working with dry chlorine and avoiding the contact of moisture it is possible to use stainless steel pipes and valves without any relevant problem. Any pipe conveying chlorine from a cylinder or drum at a pressure greater than 0.5 bar gauge will form part of a ‘pressure system’. Its design and installation must therefore satisfy the requirements of the Pressure Systems and Transportable Gas Containers (PSTGC) Regulations 1989.[29] The pipework between the supply container and the point of use needs to be robust and as short as is practicable.

Figure 5.10 illustrates the apparatus used to carry out reactions that required the handling of chlorine gas.

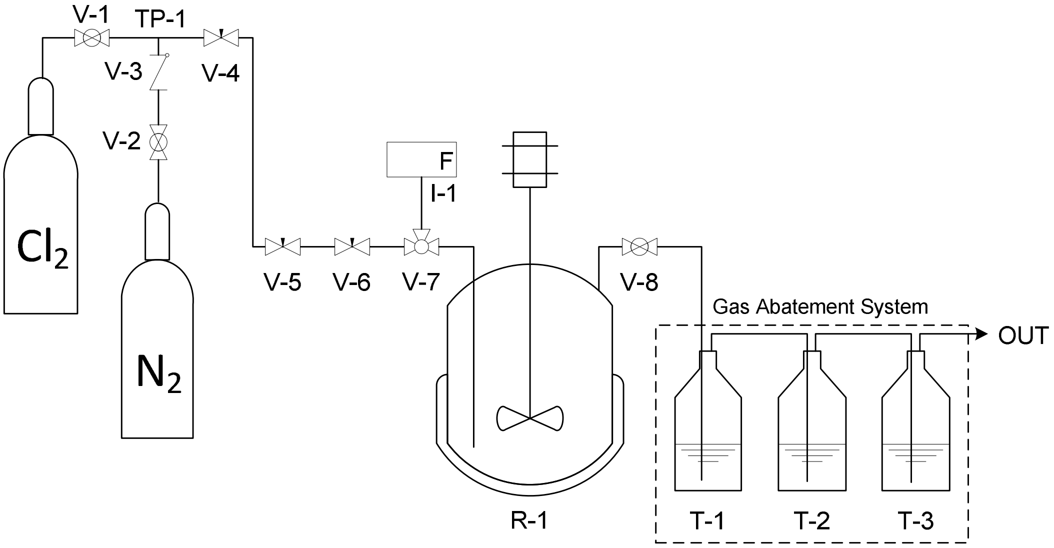


Figure 5.10 Schematic diagram of the apparatus used for chlorine handling

All the apparatus was located under a fume hood to prevent accidents due to leakage of chlorine or by-produced HCl. The chlorine cylinder outlet was connected by means of a 1/8" 316L stainless steel pipe to a ball valve (V-1) to turn the chlorine feed on/off. A supplementary nitrogen gas line (kept at 6.5 bar by means of a pressure reducing valve not representend in Figure 5.10), equipped with an on/off ball valve (V2) and a check valve (V-3) was connected to the main pipeline via a tee-piece (TP1). The gas pressure was roughly reduced by means of a needle valve (V-4). For fine flow regulation two micrometric needle valves (V-5 and V-6) were used upstream of a three-way ball valve (V-7). Valve V-7 was used to alternatively convey the gas stream to a flowmeter (I-1) or to the reaction flask (R-1). The reactor was a 250 mL three-neck round bottomed flask equipped with a mechanical stirrer. The pipe was connected to the flask using a silicon septum. The reaction flask outlet was connected through V-8 valve to the gas abatement system. The first trap (T-1) was filled with silicon oil to avoid the backwash from the HCl abatment solution (30% aqueous NaOH) contained in the second trap (T2). The chlorine abatment trap (T-3) was filled with a 10% sodium thiosulfate (NaS_2O_3) aqueous solution.

In a tipical procedure, keeping all the valves closed, the reaction flask was filled with the reaction mixture, it was then closed to external atmosphere and flushed with nitrogen by opening the valves V-2, V-4 V-5, V-6, V-7 (only in the direction of the flask) and V-8. After 20 minutes, the valve V-8 was closed and the gas stream conveyed to the fluxmeter I-1 using the three-way valve V-7. Acting on valves V-5 and V-6 the flow of nitrogen was regulated to the desired value. The corresponding flow of chlorine, given the same valves configuration, could be calculated by the following relation:[30]

$$flux\ Cl_2\ (mmol\ min^{-1}) = flux\ N_2(mL\ min^{-1}) * 2.616 * 10^{-3}$$

Once the desired flow was set, the stream was again conveyed through R-1 acting on valve V-7. Valve V-2 was closed and simultaneously valve V-1 was opened allowing chlorine gas to flow towards the reactor flask R-1.

The desired amount of chorine, calculated on the basis of the chlorine flow and the time of addition, was added. When the addition was finished, valve V-1 was closed and simultaneously valve V-2 was opened to flush the apparatus with nitrogen. This configuration was kept for at least 20 minutes to remove any remaining trace of unreacted chlorine.

5.2.2.4 Chlorination of paracyclophane under solvent free conditions

Using the apparatus described in Figure 5.10, [2.2]paracylophane **27** (0.50 g to 1.00 g, 2.40 - 4.81 mmol), a catalytic amount of anhydrous $FeCl_3$ (5 to 10 mg, 31 - 62 μmol) and the selected dispersant (see Table 5.3) were introduced in the reactor.

The mixture was stirred for 30 minutes to finely mill **27** and to disperd homogeneously the catalyst (anhydrous ferric chloride).

Valves were set in order obtain a chlorine addition rate of 1 mmol/min. After the required time (see Table 5.3) the chlorine flow was stopped and the apparatus flushed with nitrogen for 30 minutes with stirring. A sample of the resulting material (≈ 10 mg) was dissolved in $CHCl_2$ (5 mL). The resulting solution was washed with sodium thiosulfate 10% aqueous solution (5 mL) to remove any trace of residual chlorine. The organic layer was then analysed by GC/MS.

5.2.2.5 Chlorination of paracycloparacyclophane using alternative solvents

Referring to Figure 5.10, [2.2]paracylophane **27** (2.00 g, 9.60) was charged in the reactor and suspended in 20 g of the selected solvent (see Figure 5.7).

Chlorine valve was set in order obtain a chlorine addition rate of 0.25 mmol/min. After the required time the chlorine flow was stopped and the apparatus flushed with nitrogen for 30 minutes with stirring. A sample of the resulting material (≈ 10 mg) was dissolved in $CHCl_2$ (5 mL). The resulting solution was washed with sodium tiosulfate 10% aqueous solution (5 mL) to remove any trace of residual chlorine. The organic layer was then analysed by GC/MS.

5.2.2.6 Optimisation of conditions for chlorination of paracycloparacyclophane in DMC

Using the procedure reported in the previously paragraph the reaction was conducted varying the rate of chlorine addition and increasing the amount of dimethylcarbonate as reported in Table 5.5.

5.2.2.7 Characterisation data

[2.2]paracylophane 27 GC/MS (relative intensity, 70 eV) *m/z*: 208 ($[M]^+$, 21%), 104 ($[CH_2C_6H_4CH_2]^+$, 100) 78 (14) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 (s, 4H), 3.09 (s, 4H).

4-Chloro [2.2]paracylophane 28 GC/MS (relative intensity, 70 eV) *m/z*: 244 ($[M+2]^+$, 4%), 242 ($[M]^+$, 11), 140 ($[M+2\text{-}CH_2C_6H_4CH_2]^+$, 4), 138 ($[M\text{-}CH_2C_6H_4CH_2]^+$, 11), 104 ($[M\text{-}CH_2C_6H_4CH_2]^+$, 100), 78 (9).

Dichloro [2.2]paracylophanes 29 Mixture of isomers GC/MS (relative intensity, 70 eV) *m/z*: 278 ($[M+2]^+$, 6%), 276 ($[M]^+$, 10), 140 ($[M+2\text{-}CH_2C_6H_4CH_2]^+$, 31), 138 ($[M\text{-}CH_2C_6H_4CH_2]^+$, 100), 103 ($[M\text{-}CH_2C_6H_3CH_2\text{-}Cl]^+$, 20), 77 (14).

4,16 Dichloro [2.2]paracylophane ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (dd, *J* = 7.8, 1.8 Hz, 2H), 6.44 (d, *J* = 7.8 Hz, 2H), 6.28 (d, *J* = 1.8 Hz, 2H), 3.51 (ddd, *J* = 13.1, 10.3, 2.5 Hz, 2H), 3.13 (ddd, *J* = 13.1, 10.3, 5.3 Hz, 2H), 2.96 (ddd, *J* = 13.1, 10.8, 2.5 Hz, 2H), 2.77 (ddd, *J* = 13.4, 10.7, 5.3 Hz, 2H).

Trichloro [2.2]paracylophanes 30 Mixture of isomers GC/MS (relative intensity, 70 eV) *m/z*: 314 ($[M+4]^+$, 4%), 312 ($[M+2]^+$, 12), 310 ($[M]^+$, 12), 174 ($[M+2\text{-}CH_2C_6H_3ClCH_2]^+$, 7), 172 (($[M\text{-}CH_2C_6H_3ClCH_2]^+$, 12) 140 ($[M+2\text{-}CH_2C_6H_2Cl_2CH_2]^+$, 31), 138 ($[M\text{-} CH_2C_6H_2Cl_2CH_2]^+$, 100), 103 ($[M\text{-}CH_2C_6H_2Cl_2CH_2\text{-}Cl]^+$, 16), 77 (9).

Tetrachloro [2.2]paracylophanes 31 Mixture of isomers GC/MS (relative intensity, 70 eV) *m/z*: 350 ($[M+6]^+$, 1%), 348 ($[M+4]^+$, 4%), 346 ($[M+2]^+$, 9%), 344 ($[M]^+$, 7%), 176 ($[M+4\text{-}CH_2C_6H_3Cl_2CH_2]^+$, 11), 174 ($[M+2\text{-}CH_2C_6H_2Cl_2CH_2]^+$, 64), 172 ($[M\text{-}CH_2C_6H_2Cl_2CH_2]^+$, 100), 139 ($[M+2\text{-}CH_2C_6H_2Cl_2CH_2\text{-}Cl]^+$, 4), 137 ($[M\text{-}CH_2C_6H_2Cl_2CH_2\text{-}Cl]^+$, 13), 102 ($[M\text{-}CH_2C_6H_2Cl_2CH_2\text{-}Cl\text{-}Cl]^+$, 25), 75 (12).

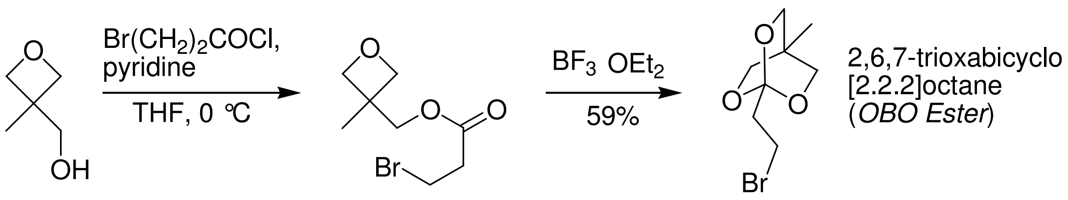
Pentachloro [2.2]paracylophanes 32 Mixture of isomers GC/MS (relative intensity, 70 eV) *m/z*: 384 ($[M+6]^+$, 1%), 382 ($[M+4]^+$, 4), 380 ($[M+2]^+$, 6), 378 ($[M]^+$, 5), 212 ($[M+6\text{-}CH_2C_6H_2Cl_2CH_2]^+$, 1), 210 ($[M+4\text{-}CH_2C_6H_2Cl_2CH_2]^+$, 7), 208 ($[M+2\text{-}CH_2C_6H_2Cl_2CH_2]^+$, 22), 206 ($[M\text{-}CH_2C_6H_2Cl_2CH_2]^+$, 22), 176 ($[M+4\text{-}CH_2(C_6HCl_3)CH_2]^+$, 11), 174 ($[M+2\text{-}CH_2(C_6HCl_3)CH_2]^+$, 64), 172 ($[M\text{-}CH_2(C_6HCl_3)CH_2]^+$, 100), 139 ($[M+2\text{-}CH_2(C_6HCl_3)CH_2\text{-}Cl]^+$, 3), 138 ($[M+2-CH_2(C_6HCl_3)CH_2-HCl]^+$, 5), 137 ($[M-CH_2(C_6HCl_3)CH_2-Cl]^+$, 10), 136 ($[M-CH_2(C_6HCl_3)CH_2-HCl]^+$, 12), 102 ($[M-CH_2C_6HCl_3CH_2-Cl-Cl]^+$, 18), 101 (15), 75 (10)

Hexachloro [2.2]paracylophanes 33 Mixture of isomers GC/MS (relative intensity, 70 eV) *m/z*: 420 ($[M+8]^+$, 1%), 418 ($[M+6]^+$, 3), 416 ($[M+4]^+$, 8), 414 ($[M+2]^+$, 9), 412 ($[M]^+$, 5), 223 ($[M+4-H-CH_2(C_6HCl_3]^+$, 31), 221 ($[M+2-H-CH_2(C_6HCl_3]^+$, 98), 219 ($[M-H-CH_2(C_6HCl_3)]^+$, 100), 210 ($[M+4-CH_2C_6HCl_3CH_2]^+$, 6), 208 ($[M+2-CH_2C_6HCl_3CH_2]^+$, 18), 206 ($[M-CH_2C_6HCl_3CH_2]^+$, 18), 197 (12), 195 (38), 193 (38), 151 (12), 149 (35), 123 (12), 63 (10).

5.3 **Trimethyl Orthoesters**

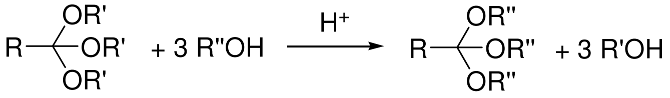
5.3.1 Introduction

Orthoesters are an important class of organic compounds. Their characteristic functional group consists of three alkoxy groups attached to the same carbon. Since orthoesters are among the few carboxylic acid protective groups that demonstrate a high level of stability toward strong nucleophiles and bases, most current applications are limited to protecting group chemistry.[31] Corey's OBO-ester protocol,[32] e.g. the BF_3 etherate mediated preparation of the 2,6,7-trioxabicylo[2.2.2]octane ring system from oxethanyl esters (Scheme 5.7), greatly facilitated the synthesis of orthoesters of functionalized carboxylates stimulating their use as protective groups.



Scheme 5.7 Corey's OBO-ester protocol for ester group protection

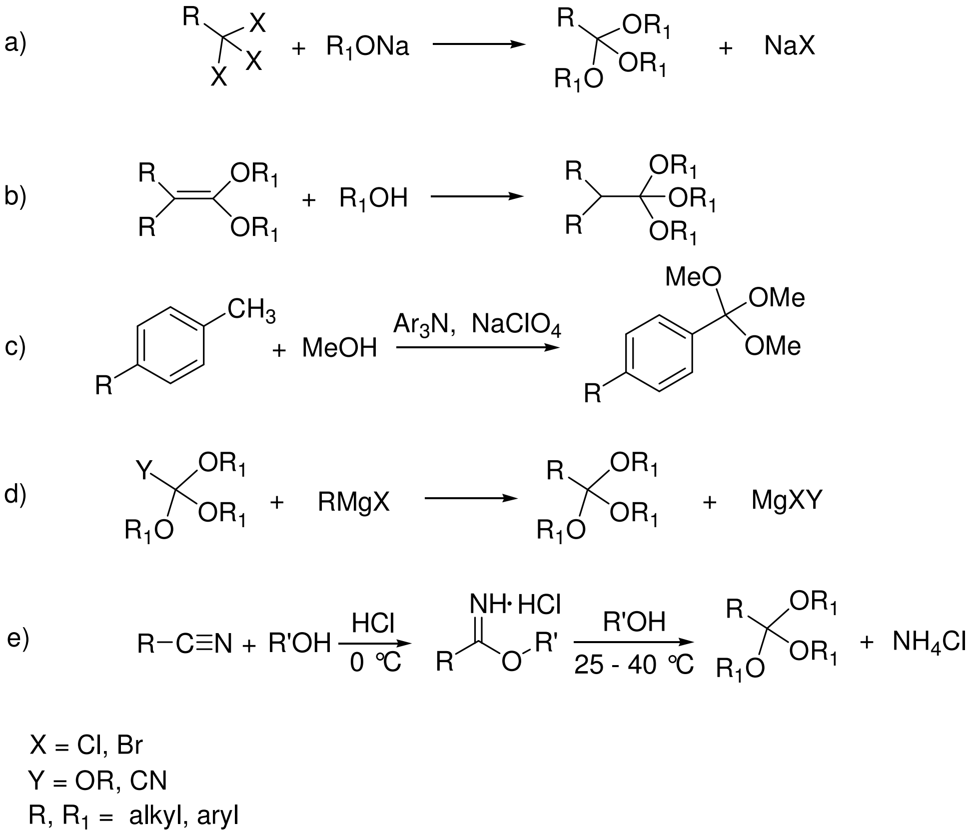
Just like acetals, orthoesters undergo transetherification,[33] allowing to prepare complex organic molecules bearing this functional group starting from simpler homologs (Scheme 5.8).



$$R{-}C(OR')_3 + 3\,R''OH \xrightarrow{H^+} R{-}C(OR'')_3 + 3\,R'OH$$

Scheme 5.8 Transetherification of orthoesters, a route for the synthesis of a variety of derivatives

Some general methods for the preparation of orthoesters[34] are reported in Scheme 5.9. A literature review revealed that the most relevant examples of the reported method for the preparation of orthoesters (Scheme 5.9) are: a) reaction of trihalogenated derivatives with alkoxides; b) addition of alcohols to ketene acetals; c) electrochemical oxidation of aldehyde acetals or toluene derivatives; d) reaction of Grignard reactants with orthocarbonates or trialkoxyacetonitriles; e) the reaction of nitriles with alcohols under acidic conditions and, successively, the alcoholysis of the resultant imido ester (Pinner synthesis).[35]



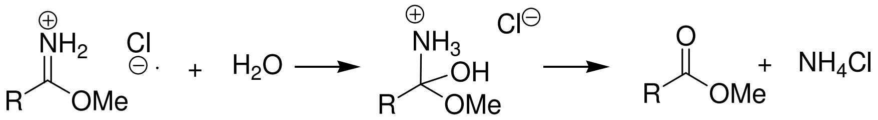
Scheme 5.9 Common routes for the preparation of orthoesters.

Of the methods reported in Scheme 5.9 we focused on the last protocol, the Pinner method later modified by Hill and Rabinovitz[36] and by Sah.[37] The reasons for this choice were: *i*) the consideration that this procedure requires a non toxic starting material (nitriles are generally classified as harmful, irritant), and light chlorinated solvents (e.g. dichloromethane) that it should be possible to replaced without any significant drawback; *ii*) the fact that this procedure is relatively simple and is easily applied on industrial scale; *iii*) the experience gained by Galentis on this process, where orthoesters (trimethylorthopropionate and trimethylorthovalerate in particular) are produced using the Pinner method.

The first step of the Pinner synthesis consists in the reaction of a nitrile with an alcohol (in our case methanol) in the presence of gaseous hydrogen chloride under anhydrous conditions to give the imidate chloridrate salt. The reaction is normally carried out at 0-10 °C in a solvent such as dichloromethane, chloroform, nitrobenzene, dioxane, benzene or ether.[38] All these solvents can conceivably be replaced with a more acceptable solvent since some of them are toxic (some of them are also suspected carcinogens),[3] volatile and/or extremely flammable.

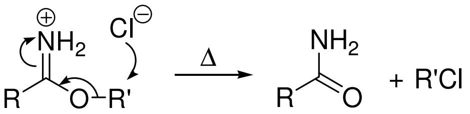
The second step is the alcoholysis of the imidate chlorhydrate salt. Pinner prepared simple and mixed orthoesters by the interaction of alkylformimidate salts with excess alcohol at room temperature. Later this result was extended to other imidate salts obtaining a series of orthoesters, however reaction times were very long, varying from several days to six weeks. Reaction times could be cut to a few hours using boiling ether or another low boiling organic solvent (*e. g.* dichloromethane).

Even if this protocol appears to be very simple some drawbacks are due to the relative low stability of the imidate intermediates, due to degradation pathways. By far the most serious of these is the hydrolysis to the ester (Scheme 5.10) in the presence of traces of water. In the case of the lower aliphatic members, which tend to be hygroscopic, the hydrolysis reaction is fast and complete.[35]



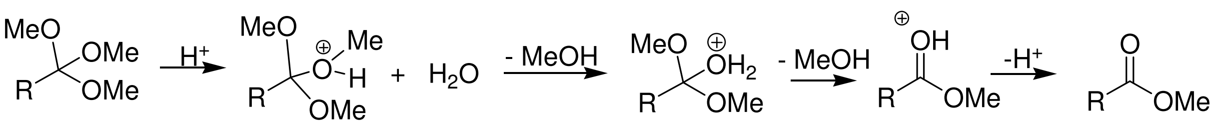
Scheme 5.10 Hydrolysis of imidate salt.

In addition imidate hydrohalides decompose when heated into the corresponding amides and alkyl halides.[35,39] (Scheme 5.11).



Scheme 5.11

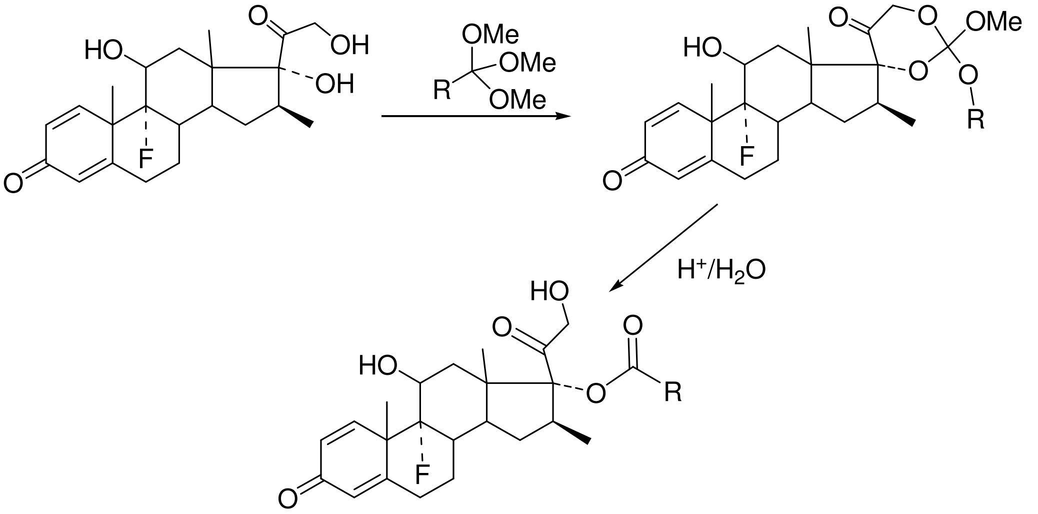
Conversely imidate bases are only slowly attacked by water. They can be obtained by treatment of the corresponding hydrohalides with bases such as sodium or potassium carbonate or aqueous hydroxide solution. Imidates in the form of free bases are stable liquids in the case of aliphatic members, while aromatic imidates tend to revert to the parent nitrile on heating.[38] Furthermore the desired products (orthoesters) are very sensible to the action of water under acidic conditions, as in the case of the Pinner synthesis. Hydrolysis of orthoesters takes place rapidly with the formation of the ester and 2 equivs of the corresponding alcohol (Scheme 5.12).



Scheme 5.12

Fortunately, orthoesters are very stable in the presence of water under basic conditions, to the point that they can be handled in contact of a basic aqueous phase.

Beside the applications of orthoesters as protective groups, these compounds exhibit a very interesting chemical beaviour when reacted with steroidal derivatives.[40] In fact, orthoesters are extremely useful reactants for the esterification of the hydroxyl group in the 17 position (Scheme 5.13). It is possible to achieve the selective esterification of the hydroxyl group thanks to the particular structure and reactivity of the orthoesters as indicated in Scheme 5.13. The reaction proceeds through a cyclic intermediate which, once hydrolyzed, furnishes selectively the desired compound.



Scheme 5.13 Selective esterification of hydroxyl group in 17 position of steroidal derivatives using trimethylorthoster.

This particular application of orthoesters (trimethylorthoesters in particular) represents the reason why Galentis was interested in the synthesis of these compounds. Keeping in mind the main business of Galentis, *i. e.* the production of steroidal derivatives, the market of derivatisation agents for steroidal active ingredients represents a strategical business. Galentis was particularly interested in the synthesis of trimethylorthoesters using an innovative procedure, in order to avoid the use of light chlorinated solvents and/or any toxic or scarcely safe to use material.

5.3.2 Aim of the research

We considered the improvement of the Pinner synthesis in terms of reaction mass efficiency,[41] in particular with the aim of lowering the amount of solvents used in the preparation of orthoesters. In addition we sought to develop new innovative protocols to avoid the use of toxic solvents and reactants in both the steps of Scheme 5.9 e.

To simplify the procedures we sought for an integrate procedure to carry out both steps in a single reactor, or even in one step. With the aim to avoid the amide formation side-reaction we tried to use alternative acids instead of gaseous HCl, where the chloride anion nucleophilicity is the cause of the competing reaction, for example non volatile acids like H_2SO_4 and H_3PO_4 or supported acids like the H form of ion exchange resins.

Besides these explorative tests the investigation focused on: i) the reaction of nitriles with methanol in the presence of hydrochloric acid involving reduced amount of solvents and/or using alternative solvents; ii) the one pot synthesis, carrying out both the first and the second step in the same reactor; iii) the alcoholysis reaction of the imido esters in alternative solvents.

An additional objective was tackled. The corticosteroids benzoyl derivatives are used as active ingredients in many anti-inflammatory preparations, e.g. topical corticosteroids such as beclomethasone benzoate. However the corresponding orthoester useful for their preparation (*i.e.* trimethylorthobenzoate) cannot be prepared from benzonitrile.[42] Contrarily to the case of aliphatic orthoesters which can be obtained from the corresponding nitriles, the production of trimethylorthobenzoate for the preparation of the cited active ingredients requires to use trichloromethylbenzene as starting material (cf. Scheme 5.9, eq. a). The latter is an undesirable reactant (Table 5.6) since it is a known carcinogen.

Table 5.6 Benzonitrile and trichloromethylbenzene comparison in terms of safety.[a]

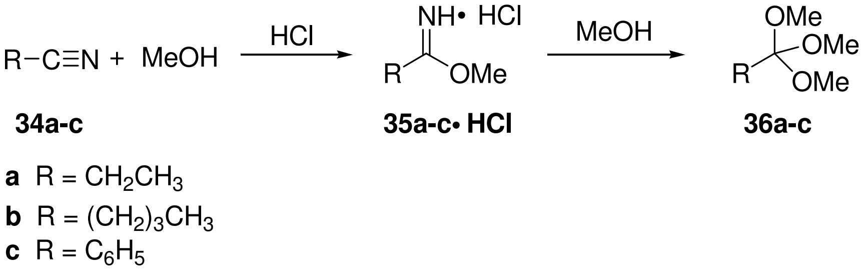
	Benzonitrile	**Trichloromethylbenzene**
H phrases	H302 Harmful if swallowed. H312 Harmful in contact with skin.	H302 Harmful if swallowed. H315 Causes skin irritation. H318 Causes serious eye damage. H331 Toxic if inhaled. H335 May cause respiratory irritation. H350 May cause cancer.

[a] From Sigma-Aldrich products MSDS.

The development of a process for the preparation of trimethylorthobenzoate starting from benzonitrile was also a target of this research, in order to move from a carcinogenic compound to a merely harmful starting material.

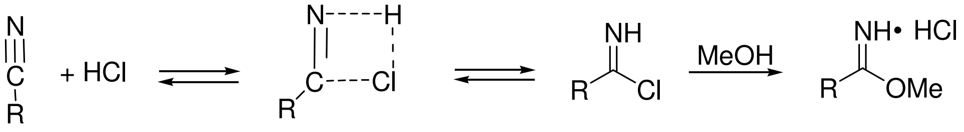
5.3.3 Results and discussion

The study was conducted on three starting materials: *i.e.* propionitrile **34a**, valeronitrile **34b** and benzonitrile **34c**, with a view to prepare the corresponding trimethylorthosters trimethylorthopropionate **36a**, trimethylorthovalerate **36b** and trimethylorthobenzoate **36c** (Scheme 5.14).



Scheme 5.14 Pinner synthesis of orthoesters. The preparation proceed through the formation of imidate **35** with the exception of the benzoyl derivative **35c** which does not yield the corresponding orthoester **36c**.

Some explorative tests were initially conducted using proprionitrile as the model substrate. Sulfuric and phosphoric acid did not promote the reaction of proprionitrile with methanol. Probably only a halogenhydric acid is able to activate the nitrile group, thanks to the nucleophilicity of the conjugate base. The formation of nitrile adducts with hydrochloric acid at low temperatures was extensively reported in the literature.[43] The reaction of nitrile with methanol likely proceeds through an imido chloride intermediate of the type reported in Scheme 5.15 wich rapidly undergoes methanolysis to yield the imidate **35**.



Scheme 5.15

Attempts to carry out the two steps of Scheme 5.14 in one pot by using from 4 to 10 equivs of methanol adding different amounts of gaseous HCl (from 1 to 3 equivs) were made.

Notwithstanding our insistence we were not able to develop an integrated procedure for the preparation of orthoesters from nitriles in a single step. The higher temperature required for the alcoholysis inhibited the imidate formation, probably lowering the solubility of HCl in the reaction mixture, reverting the equilibrium towards reactants (nitrile and hydrochloric acid, see Scheme 5.15). Keeping unaltered the procedure we therefore decided to study the reaction using alternative solvents, leaving unaltered the other conditions.

5.3.3.1 Orthoesters preparation in ionic liquids

Given our recent experience in the synthesis and the use of ionic liquids as solvents for organic reactions,[19,44] we tried to develop a procedure involving the use of these particular solvents for the preparation of orthoesters. The ionic liquid had to withstand the extremely acidic conditions of the first step and did not have to interfere with the species present in the reaction mixture. We therefore thought that an anhydrous chloride ionic liquid could be useful for this scope.

Since the first step required tempeartures between 0 and 10 °C and our recently prepared trioctylmethylphosphonium chloride **4a** was solid at room temperature, we chose for this application the homolog bearing shorter alkyl chains, *i. e.* the tri-n-hexyl-methylphosphonium chloride **4b** which allowed to obtain liquid reaction mixtures even at 5 °C.

The substrate selected for this study was propionitrile. The latter was mixed with the desired amounts of methanol and ionic liquid **4b**. The resulting mixture was saturated with gaseous HCl at 5 °C and allowed to stand at that temperature for 24 hours at 4 °C. The mixture was analysed by neutralising a sample and then removing the ionic liquid by filtration on silica gel (see experimental section for further details). Results thus obtained are reported in Table 5.7.

Table 5.7 Use of **4b** as solvent for imido ester preparation.[a]

Entry	34a:4b (mol:mol)	MeOH:substrate (mol:mol)	35a·HCl % by GC
1	6	1.14	98
2	6	2.28	76
3	3	1.14	91
4	3	2.28	72

As it clearly appears the reaction proceeded smoothly to the desired product in good to excellent yields with very high selectivity (no other by-products were detected by GC/MS). The dilution of the system, by an increased amount of ionic liquid, inhibited formation of imidate **35**, even if very modestly (entry 1 vs. entry 3). The methanol:substrate ratio affected the reaction outcome more importantly (entry 1 vs. entry 2) showing the optimal ratio was around 1:1.

To the reaction mixture obtained under the conditions of entry 1 of Table 5.7, 2.4 equivs of methanol (20% excess) were added. After 24 hours the formation of a white solid was observed. The GC /MS analysis of the mixture revealed the formation of the desired product trimethylorthopropionate **36a** and of the corresponding normal ester methylpropionate **37a** in 1:3 ratio. The conversion was quantitative and a 30% yield of orthoester was estimated by GC.

However distillation of the product from the reaction mixture proved very difficult. The desired product could be isolated in only 15% yield.

We tried also to recover the product **36a** by extraction using a solvent non miscible with the ionic liquid, *i. e. n*-heptane, though the use of such a solvent compromised the greeness of the procedure. The use of *n*-heptane improved the yield to 30%, but required a large amount of solvent with respect to the reactant **34a** (6:1 vol:vol). In addition the by-produced ammonium chloride (see Scheme 5.14) remained in the ionic liquid, preventing the ionic liquid recycle.

This result showed that trihexylmethylphosphonium chloride can be used as the solvent for the synthesis of trimethylorthopropionate, however the product proved very hard to isolate from the reaction mixture and the ionic liquid could not be recycled. All these drawbacks convinced us to move to a more conventional solvent system, simpler to implement in our partner's industrial plants.

5.3.3.2 Orthoesters preparation using no added solvents

5.3.3.2.1 First step

Since both nitriles and methanol are liquid at room temperature we next used a solvent-free[22] protocol for the synthesis of the orthoester. The reaction of nitriles with methanol in the presence of hydrochloric acid is known to occur using an excess methanol.[45]

To comprehend the key factors, we studied the reaction of nitrile **34c** in the presence of different amounts of HCl and MeOH. To consider the contribution of the HCl concentration, the MeOH:nitrile ratio, the HCl:nitrile ratio and the HCl:MeOH ratio, the total volume was kept constant (50 mL) by addition of a co-solvent (toluene). Benzonitrile was chosen as the reactant because imidate **35c·HCl** proved very poorly soluble in MeOH, thus the product could be simply isolated by filtration. In addition, keeping in mind that we were interested in the synthesis of TMOB, we needed a large amount of substrate for the alcoholysis study. Results are summarised in Table 5.8. It appeared clearly that the yield of the imidate **35c·HCl** was slightly if at all influenced by the addition of a co-solvent. Surprisingly the concentration of HCl resulting after the addition of the gaseous reactant did not affect the formation of **35c·HCl** (Figure 5.11, left), showing no relation between the yield of product and the HCl:nitrile ratio. Another unexpected result was the unaltered yield of **35c·HCl** in the presence of different amounts of MeOH. Varying the MeOH:**34c** ratio from 1.1 to 3.8, leaving almost unaltered the HCl:nitrile and the HCl:methanol ratios, no effect on the imidate **35c·HCl** formation was observed (entries 1, 3, 5).

Table 5.8 Reaction of nitrile with methanol in presence of different amount of HCl and methanol[a]

Entry	Co-solvent	MeOH:34c	HCl:34c	HCl:MeOH	HCl Mol/L	35c·HCl yield
1	Toluene	1.1	1.24	0.54	4.83	56
2	Toluene	1.1	1.23	1.08	4.87	92
3	Toluene	2.2	1.21	0.55	4.70	55
4	-	3.8	1.16	0.30	4.50	38
5	-	3.8	1.62	0.42	6.29	49
6	-	3.8	3.00	0.79	11.65	86
7	-	3.8	3.57	0.94	13.86	91

[a] The addition of HCl(g) was conducted at 5 °C under inert atmosphere. The resulting mixture was kept at 5 °C for 24 hours and the imidate filtered and weighted for yield quantification. [b] The amount of toluene was chosen to assure a initial volume of the mixture equal to 50 mL.

Conversely it was possible to observe that the yield of imidate **35c·HCl** was deeply influenced by the HCl:MeOH ratio. Actually the relation between this two entities was almost linear (Figure 5.11, right).

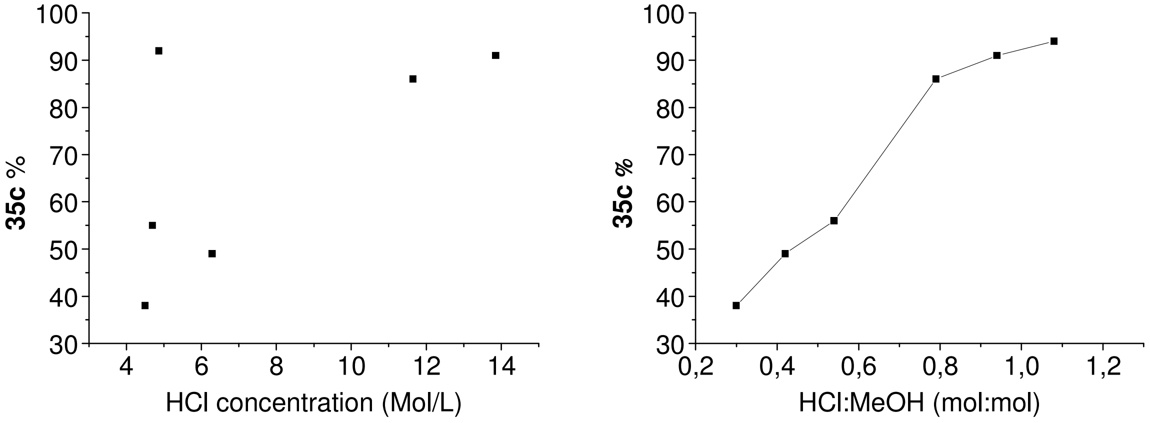


Figure 5.11 The influence on the imidate **35c·HCl** formation of the HCl concentration (left) and of the HCl:MeOH ratio (right)

Considering that the HCl:MeOH molar ratio proved to be the key factor for the preparation of the imidate intermediate, we developed a procedure for this reaction. Using excess methanol as the solvent required an excess of hydrochloric acid as well. The minimum amount of methanol to carry out the reaction with acceptable yield was found to be 3 equivs with respect to nitrile. The corresponding gaseous acid was added at 5 °C and the reaction mixture kept at that temperature for 24 hours. After the required time all the volatile materials were removed under vacuum at temperature lower than 10 °C leaving the imidate hydrochloride as a white solid. In Table 5.9 results for the three investigated nitriles are reported.

Table 5.9 Isolated yield of imidate hydrochloride using the solvent free procedure[a]

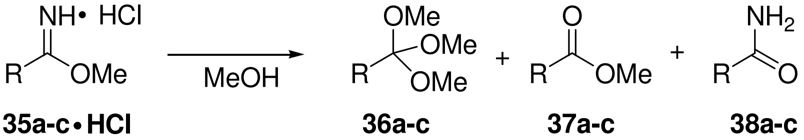
Entry	Nitrile	Product	Isolated yield %
1	CH_3CH_2CN **34a**	**35a·HCl**	91
2	$CH_3(CH_2)_3CN$ **34b**	**35b·HCl**	92
3	C_6H_5CN **34c**	**35c·HCl**	94

[a] Reaction conditions: 3:1 MeOH:nitrile molar ratio, 1:1 HCl:MeOH molar ratio, 24 hours at 5 °C.

Even if a strong excess of HCl was required, this procedure presented two main advantages. The productivity was very high since a very little reactor was required and no addition solvents are required avoiding all the safety issues related to the use of toxic and/or flammable and/or environmental unacceptable light organic solvents.

5.3.3.2.2 Second step: alcoholysis

For what concerns the second step of the Pinner method, the alcoholysis of the imidate hydrochloride could be carried out by simply adding an excess methanol (4.5 equivs) to the white solid **35·HCl**. In the case of the alkyl derivatives **35a·HCl** and **35b·HCl** the resulting mixtures appeared as clear solutions, while the imidate derived from benzonitrile (product **35c·HCl**) produced a suspension. After 48 hours at 25 °C, in the case of reactant **35a·HCl** and **35b·HCl**, the formation of a white precipitate was observed. The mixtures were analysed by GC/MS after removal of the ammonium chloride by treatment with aqueous K_2CO_3 and extraction with diethylether. The reaction proceeded with the formation of the desired orthoester **36**, along with the methyl ester **37** and the amide **38** as side products (Scheme 5.16).



Scheme 5.16 Products from alcoholysis of the imidate salt.

The composition of the mixture thus determined is described in Table 5.10.

As expected, in the case of the alkyl derivatives **35a·HCl** and **35b·HCl**, reaction proceeded to the desired products with no formation of amide derivatives **38a-b**. However an extensive hydrolysis of the orthoesters **36a-b** to the methyl esters **37a-b** was observed, probably due to a not rigorously anhydrous reaction environment. On the other hand, as previously discussed, the reaction of **35c·HCl** with methanol was extremely sluggish, with an extensive formation of amide **38c** as side product[42] was observed.

Table 5.10 Imidate alcoholysis using methanol as the solvent.[a]

Entry	Imidate	Time (h)	% by GC/MS			
			Conversion	**Orthoester 36**	**Ester 37**	**Amide 38**
1	**35a·HCl**	48	98	46	45	1
2	**35b·HCl**	48	97	50	47	-
3	**35c·HCl**	48	48	6	19	23
4		240	98	27	28	43

[a] Details of reaction conditions are given in the experimental section.

The observed yield of products **36a** and **36b** were comparable to that obtained usually via the Pinner method. However attempts to isolate the alyphatic orthoesters by distillation directly from the reaction mixture without using an extraction solvent proved inapplicable.

In analogy to what observed in the case of the reaction carried out in trihexylphosphonium chloride **4a,** a solvent (e.g. diethylether) was needed to isolate the product. This invalidated all our efforts to develop a process in which no additional solvent was needed.

However the informations we obtained were surely of interest for our industrial partner and, more remarkably, were extremely useful to propose a process for the preparation of trimethylorthobenzoate discussed below.

5.3.3.3 Synthesis of trimethylorthobenzoate TMOB

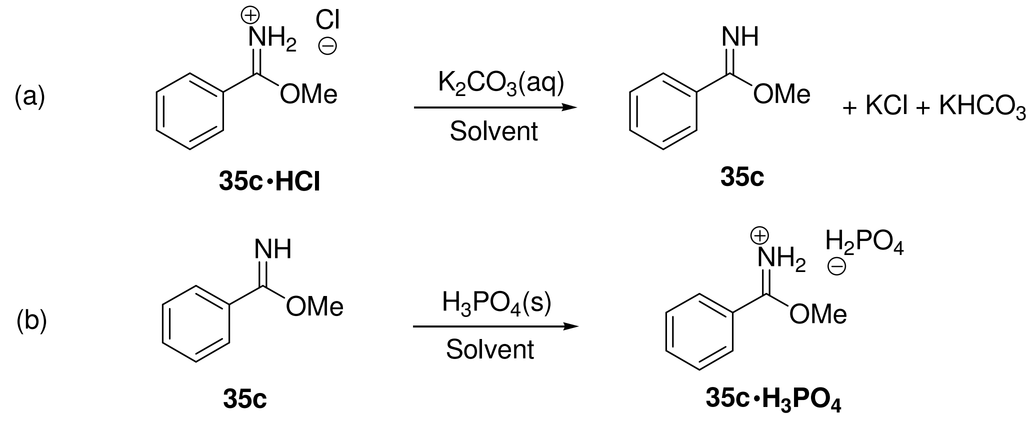
As previously discussed, the alcoholysis of the benzoimidomethylester **35c·HCl** did not proceed to yield the desired orthoester **36c** selectivitively. With respect to the alcoholysis of alkyl derivativatives **35a·HCl** and **35b·HCl** three main differences could be underlined: *i)* compound **35c** proved very poorly soluble in methanol and even less soluble when an apolar solvent was used as a co-solvent; *ii)* the reaction time was far longer; *iii)* the amide **38c** was the main product. Attempts to accelerate the alcoholysis by increasing the temperature favoured even more the formation of the side product **38c**. Probably the lack of reactivity and the favoured formation of **38c** are not related only to the scarce solubility of the reactant **35c·HCl**, as can be argued by considering data in Table 5.10. After 48 hours the amount of formed amide **38c** was more than 20% (by GC/MS), while in the case of the alcoholysis of **35a·HCl** only traces of amide **38a** were detected. In addition increasing the temperature to 50 °C accelerated the reaction (after 10 hours conversion was 82%) but also favoured the formation of **38c** (52%). Most likely the nature of the aromatic substituent is responsible of this extremely different reactivity. Both electronic and steric factors could contribute to the slow attack of methanol to the imidate carbon, as a phenyl group could sterically hinder attack, but also stabilise the positive charge on the imidate carbon. In addition the formation of benzamide **38c** could also be favoured by its thermodynamically stability, considering also its low solubility.

As discussed above, the degradation of imidates toward amides proceed by the nucleophilic attack of the chloride ion on the carbon attached to the oxygen atom (Scheme 5.11).

We therefore thought that a different (*e.g.* less nucleophilic) anion could prevent this side reaction. Phosphate was chosen as the model anion since phosphoric acid is an easy to implement protonating agent due to its low volatility, and also thanks to its relatively low corrosivity. Unfortunately phosphoric acid, precisely because of the very low nucleophilicity of its conjugated base (cf. Scheme 5.15), was not able to promote the reaction of benzonitrile and methanol to give the corresponding phosphate imidate salt **35c·**$\mathbf{H_3PO_4}$.

5.3.3.3.1 Anion metathesis

A solution was to obtain the imidate chlorohydrate first, then to exchange the chloride anion to obtain the imidate phosphate salt **35c·**$\mathbf{H_3PO_4}$ (Scheme 5.17). The imidate in neutral form **35c** was obtained by treatment of the corresponding hydrochloride **35c·HCl** with an aqueous base such as potassium or sodium carbonate and extracted using an organic solvent immiscible with water (such as dichloromethane, diethylether, toluene, xylenes, ethylacetate, dimethylcarbonate) (Scheme 5.17 a). This procedure allowed to obtain a clear solution of **35c**. Adding anhydrous H_3PO_4 (pKa = 2.12[46]), diluted in the minimum amount of methanol, the desired imidate dihydrogenphosphate **35c·**$\mathbf{H_3PO_4}$ precipitated as a white microcrystalline solid (Scheme 5.17 b) in almost quantitative yield (98 %). Only the first dissociation of phosphoric acid took place, since titration of a solution of imidate in neutral form by H_3PO_4 proved that the protonation of 1 mole of imidate required 1 mole of acid.



Scheme 5.17 Anion metathesis procedure.

This result was then extended to different acids such as CH_3COOH, H_2SO_4, HOTs. Acetic acid (pKa = 4.76 [47]) proved not strong enough to protonate the imidate. Conversely the stronger sulphuric, *p*-toluenesulfonic acid (pKa values equal to -3[48] and -2.8[49] respectively) allowed to obtain the respective salts. The sulphate salt **35c•H$_2$SO$_4$** separated from the organic solution as a liquid. The solvent was decanted leaving the impure product which was then used thereafter without any purification procedure. Conversely *p*-toluenesulfonate salt **35c·HOTs** appeared as a white solid (93%) and was isolated by filtration.

5.3.3.3.2 Alcoholysis of anion exchanged benzoimidate salts

The alcoholysis of salt **35c•H$_3$PO$_4$** was carried out by adding excess methanol (20:1 molar ratio) at room temperature. One of the main drawbacks of the alcoholysis of **35c**, besides the formation of the side product **38c**, was the extremely long reaction time. Using salt **35c•H$_3$PO$_4$** the reaction time proved even longer. After 24 hours the conversion was only20 %, but remarkably very low amide formation (2%) was observed. This result was encouraging since it confirmed our assumption: using a scarcely nucleophilic anion like the dihydrogenphosphate, the formation of benzamide was inhibited, although the conversion was still very low.

Using hydrochloride **35c•HCl** it was impossible to improve the conversion and the yield of TMOB **36c** by heating the reaction mixture since an higher alcoholysis temperature caused a more severe reactant degradation.

Having inhibited the main side reaction it was now possible to carry out the reaction at higher temperature. The alcoholysis of the imidate salts **35c•H3PO4**, **35c•H$_2$SO$_4$** and **35c•HOTs** was therefore studied by putting to react the selected salt with excess methanol at 65 °C. After 4 hours the reaction mixtures were analysed by GC/MS (using the previously reported procedure to neutralise the mixture) obtaining the results reported in Table 5.11.

Table 5.11 Alcoholysis of anion exchanged imidates in methanol at 65 °C.[a]

Entry	**$[PhC(NH_2)OCH_3]A$,**	**% by GC/MS[b]**			
	A	**Conversion**	**Orthoester 36**	**Ester 37**	**Amide 38**
1	$[H_2PO_4]^-$	80	62	22	3
2	$[HSO_4]^-$	100	-	88	-
3	$[p\text{-}CH_3C_6H_5SO_3]^-$	90	-	49	41

[a] Methanol:substrate molar ratio 20:1; [b] mixture composition after 4 hours.

Rewardingly the alcoholysis of the salt **35c•H_3PO_4** proceeded to the desired orthoester with very little formation of the side product **38c**. The only by-product was the methyl ester **37c** derived from alcoholysis of TMOB. The hydrogensulphate imidate **35c•H_3PO_4** reacted with methanol yielding mainly the methyl ester **37c.** No detectable amounts of either **36c** or **38c** were detected. Also in this case the anion was not nucleophilic enough to promote the formation of benzamide, however the technical hitches due to the nature of **35c•H_2SO_4** convinced us to discard the use of this salt as a viable strategy for the preparation of TMOB **36c**. For what concerns salt **35c•HOTs** an extensive degradation toward **38c** was observed. Remarkably the degradation by-product methyl-p-toluenesulfonate (16%) was detected by GC/MS, thus confirming the degradation mechanism here previously described (Scheme 5.11).

Considering the very interesting result obtained using the salt **35c•H_3PO_4** we focussed on this material for the synthesis of TMOB. The alcoholysis of **35c•H_3PO_4** was studied in details. Carrying out the alcoholysis at the reflux temperature of the mixture (~65 °C) the reaction was monitored at selected times. The reaction profile reported in Figure 5.12 allowed us to determine that the optimal reaction time was 6 hours.

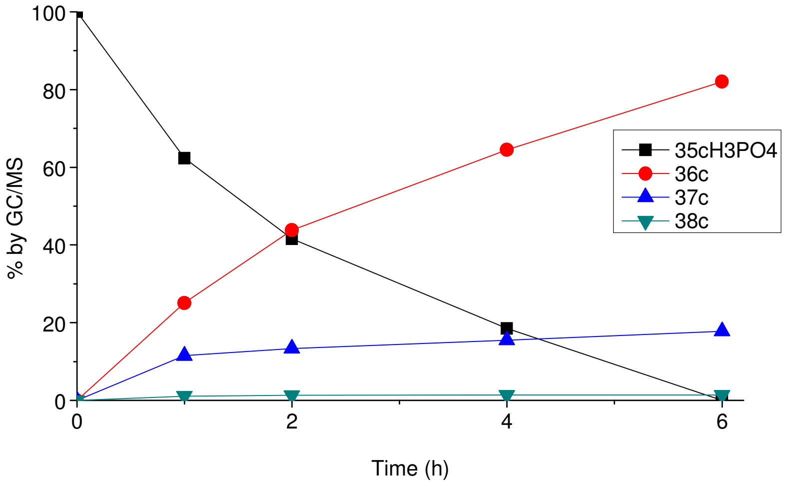


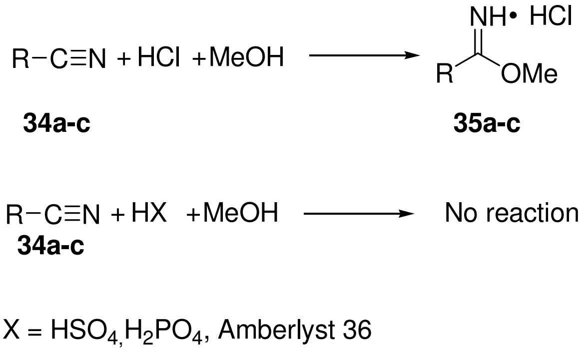
Figure 5.12 Reaction profile of the alcoholysis of **39c**.

The main side product was in this case methylbenzoate **37c**, which however could be maintained under 20% (by GC/MS) drying carefully the glassware and using anhydrous reactant. It was therefore possible to observe a very high selectivity (around 80 %) toward the desired product **36c**, while the amount of benzamide **38c** was kept under 5%.

5.3.4 Conclusions

Different methodologies for the synthesis of alkyl and aryl orthoesters were tested, taking into account not only the effectiveness of the core reaction but also the economic viability and industrial applicability of the procedures.

With the aim of avoiding the use of volatile hydrochloric acid different acids were tested. Non volatile and less corrosive acids such as sulphuric, phosphoric, and supported acids (like dry Amberlyst 36) were not able to promote the formation of imidoesters by addition of methanol to the nitrile function (Scheme 5.18).



Scheme 5.18

This evidence confirmed what is suggested in a literature review on this reaction: *i.e.* that the rôle of hydrochloric acid was not only to protonate the nitrile **34**, but also to carry a nuclophilic addition of halogen atom to produce an intermediate of the type of Scheme 5.15 in equilibrium with the parent nitrile and HCl. This intermediate reacts rapidly with methanol yielding the intermediate **35**.

The comprehension of the key factors influencing this synthetic procedure, prompted us to consider the implementation of different solvents and solution keeping unaltered the key steps of the Pinner method. We therefore sought for an innovative procedure in terms of solvent usage. The use of ionic liquid **4b** allowed to carry out the first step with no particular drawbacks yielding the desired intermediate **35a** in excellent yield once the conditions were optimised, even if it was not isolated. The alcoholysis step proceeded with the formation of the orthoester **36a**, but unfortunately the yield was quite low. The main by-product was the normal ester **37a**, likely derived by hydrolysis of **36a**, indicating that the ionic liquid was not dry enough. Preparation of anhydrous **4b** was not simple due to the hygroscopic nature of this compound. In addition the isolation of the target compound proved difficult, so the use of ionic liquid for the preparation of orthoester was no longer studied.

To eliminate any undesired addition of water in the reaction mixture by the use of not perfectly dried solvent we decided to try to avoid solvent usage altogether. The study of the reaction of benzonitrile with methanol using the latter as the solvent allowed to understand what are the key parameter influencing the yield. Surprisingly the formation of **35c•HCl** was found to be strongly influenced by the HCl: methanol ratio. Hence if methanol is used in excess to drive the reaction to completion, similarly HCl need to be added in strong excess. This is contrast with the concept of mass flow optimisation, since it revealed necessary to increase the amount of hydrochloric acid. However this device allows to avoid the use of light chlorinated solvent commonly used in industry. Consideration of economic viability and issues related to the resulting waste treating by Galentis prompted us to study the implementation of this procedure. The procedure was extended to alkyl substrates **34a** and **34b** with very good results. The second step was conducted at the same manner avoiding the use of any added solvent with good yield of trimethylorthoesters **36a-b** while the aromatic derivatives **36c** was not obtained with acceptable yield as expected considering the literature information.

As underlined in the introduction the obtaining of trimethylorthobenzoate (TMOB) using benzonitrile as the starting material was an extremely interesting objective. We found that the extensive degradation of the imidate **35c** was due to the nucleophilic nature of the chloride anion. The nucleophilic attack of this anion on the methyl group of the imidate led to the formation of benzamide. In the case of the aromatic derivative **35c**, this side reaction was particularly significant, to the point that Pinner method was inapplicable for the preparation of TMOB **36c**. Unfortunately as previously discussed, the same nucleophilicity of the chloride anion allows the formation of the chloro-imido adduct of Scheme 5.15 and therefore this anion is required to obtain the intermediate **35c•HCl**. Hence the only solution to avoid the side reaction to take place was to remove the chloride anion in favour of another. The best anion among the ones tested was the dihydrogenphosphate. The anion metathesis proved simple and effective and more remarkably the alcoholysis of the resulting anion-exchanged **35c•H_3PO_4** proceeded to the target product with very good yield and selectivity. In accordance with green chemistry principles the use of a new process using safer reactant represent an important innovation. The very toxic trichloromethylbenzene could be replaced by the merely harmful (just like a household detergent) benzonitrile. However an additional step (the anion metathesis) is required, thus increasing the amount of waste and lowering the atom economy of the overall process. Nevertheless the gain in "greenness" due to the use of a non toxic starting material offset the mass flow increase to the point that Galentis is very interested in the implementation of this procedure. A scale up test of this preparation was carried at the Galentis laboratories in Marcon (VE). The test was conducted on a 1.165 moles scale (120 g of benzonitrile) simulating the industrial operations (under the supervision of Dr. Luca Zambelli). The various step of the preparation of TMOB were conducted (Figure 5.13) using xylenes as the solvent. Details are here not given.

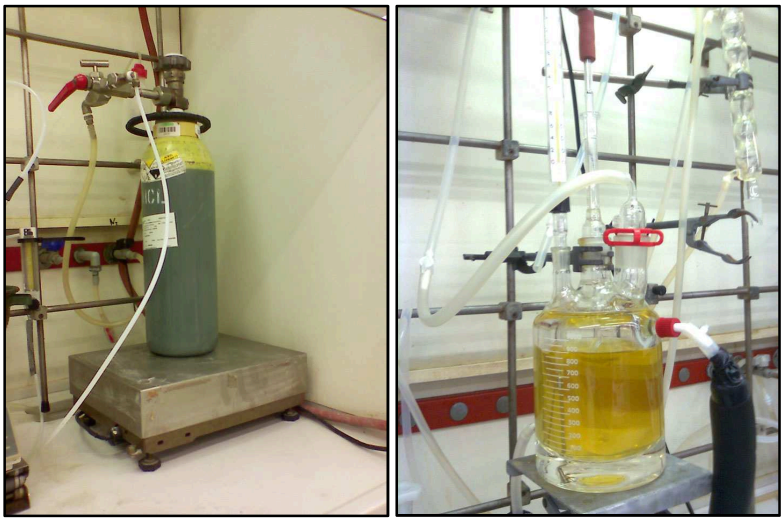


Figure 5.13 Pictures took during the scale up tests in Galentis. Hydrogen chloride cylinder (left) and a coated 1 L reactor (right) are shown.

A patent application was presented on June 23, 2011 by Galentis and the industrial process in the plant in Marcon (VE) is going to be defined.

5.3.5 Experimental section

5.3.5.1 General

Chemicals used were of reagent grade and used as received. Proprionitrile, valeronitrile, and benzonitrile were from Aldrich. Ammonium chloride, phosphoric, acetic, trifluoroacetic, p-toluenesulfonic acid were from Aldrich. Gaseous hydrogen chloride in cylinder was from SIAD. Orthoesters (trimethylorthopropionate and trimethylorthovalerate), where furnished Galentis S.r.l. Trihexylmethylphosphonium chloride **3b** was synthesised using the procedure reported in chapter 2.[44]

GC-MS analyses were performed with a HP-5890 gas-chromatograph equipped with a HP-5 MS capillary column (30 m x 0.25 mm; coating thickness 0.25μm) and a HP-5970 quadrupole mass detector (EI, 70 eV). Analytical conditions: injector and transfer line temperatures 260 and 280 °C respectively; oven temperature programmed from 50 °C (isothermal condition for three minutes) to 250 °C at 10°C min^{-1}; carrier gas helium at 1 ml/min^{-1}; split ratio 1:20.

All structures were assigned by comparison to authentic samples via GC-MS.

5.3.5.2 Pinner synthesis in ionic liquid

5.3.5.2.1 First step

In a 25 mL round bottomed flask equipped as in Figure 5.14 (flask A) propionitrile **34a** (1.54 g, 28 mmol), methanol (1.03 - 2.06 g, 32 - 64 mmol) and $[P_{6,6,6,1}]Cl$ **4b** (1.57 - 3.14 g, 4.66 - 9.32 mmol) under conditions of Table 5.7.

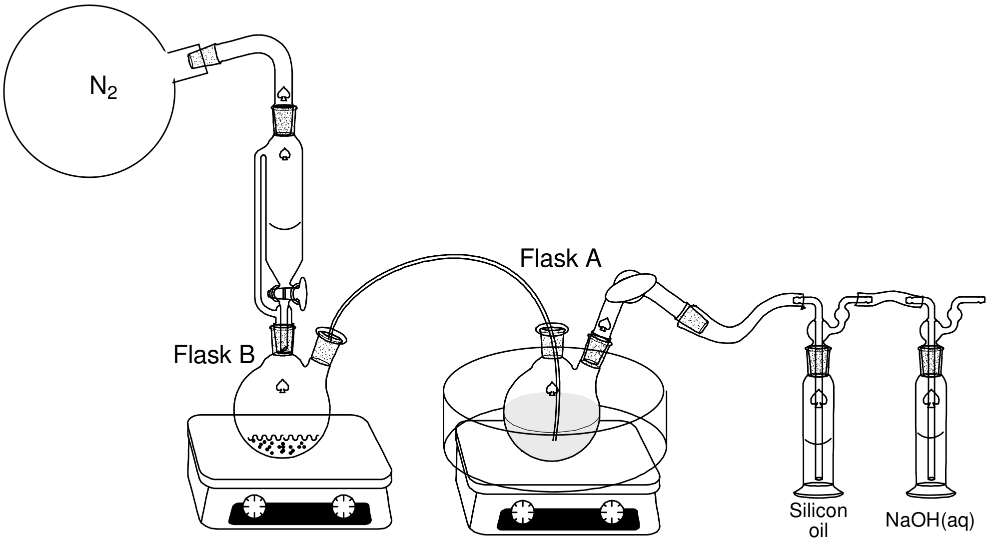


Figure 5.14 Experimental set up for reaction using HCl generated by addition of sulfuric acid on ammonium chloride.

The resulting mixture was cooled to 5 °C by means of an ice bath. Ammonium chloride (15.0 g, 280 mmol) was introduced in a second 100 mL flask (flask B) equipped with a dropping funnel charged with 15 mL (0.28 mol) of sulfuric acid. Once the mixture was cooled H_2SO_4 was slowly added to the mixture and the evolved HCl was conveyed in the flask A and bubbled in the reaction mixture. The addition of HCl took 2 hours, during which the temperature was kept under 10 °C. The mixture was then kept at 4 °C for 24 hours. At the end of the reaction a sample was collected, treated with a 10% K_2CO_3 aqueous solution (2 mL) and extracted with 2 mL of diethylether. The organic phase was filtered through silica gel (100 mg) which was then washed with additionl 2 mL of diethylether. The ethereal solution was then analysed by GC/MS.

5.3.5.2.2 Second step (alcoholysis)

From the reaction mixture described in the previous paragraph, excess methanol and HCl were removed in vacuum at room temperature, then fresh methanol (2.14 g, 67 mmol) was added. The resulting mixture was kept at room temperature for 24 hours with stirring. At the end of reaction time the resulting suspension was sampled and analysed using the previously described procedure. Trimethylorthopropionate **36a** was distilled under reduced pressure (500 mbar @ 92-98) in 15 % yield.

5.3.5.3 Reaction of benzonitrile with methanol - optimisation

Referring to the apparatus reported in Figure 5.14, benzonitrile **34c** (20 g, 194 mmol) and methanol (6.88 - 13.76 - 23.76 g, 215 - 429 - 742 mmol, see Table 5.8) were introduced in flask A (a 100 mL round bottomed flask). Toluene was added to reach a total volume equal to 50 mL (from 0 to 21 mL) and the resulting mixture was cooled to 5 °C by means of an ice bath. Gaseous hydrogen chloride (obtained dropping H_2SO_4 on 50 g of NH_4Cl in flask B) was bubbled in the cooled mixture. The addition was monitored by weighting the flask every 30 minutes. After the required amount of HCl was added (8.19 - 25.25 g) the reaction mixture was kept at 5 °C for 24 hours. The formed methylbenzoimidate hydrochloride **35c** was filtered and washed with 2 x 10 mL diethylether.

5.3.5.4 Pinner synthesis using no added solvent

Using the apparatus in Figure 5.14 the appropriate nitrile (28 mmol, **34a**: 1.54 g, **34a**: 2.33 g, **34c**: 2.89 g) and methanol (2.69 g, 84 mmol) were added in flask A. The mixture was cooled to 5 °C by means of an ice bath and at that temperature gaseous HCl (obtained by dropping H_2SO_4 on 15 g of NH_4Cl in flask B) was bubbled until the required amount (3.06 g, 84 mmol, measured by weighting the flask) was introduced. The mixture was then kept at 4 °C for 24 hour after which excess methanol and HCl were removed in vacuum.

The alcoholysis step was carried out by adding methanol (4.04 g, 126 mmol) on the solid imidate hydrochloride **35a-c** and stirring the resulting mixture for 24 hours at room temperature.

To the resulting white suspension diethylether (10 mL) was added with vigorous stirring. The solid fraction was then allowed to settle down and the upper clear solution was transferred, by means of a needle, in a flask containing a solution obtained by dissolving 3.00 g of Na_2CO_3 in 60 mL of water. The remaining solid was then washed with 2 x 2 mL of diethylether and the resulting solutions were added on the aqueous Na_2CO_3. The aqueous phase was discharged and extracted with 2 x 2 mL of diethylether. The ethereal extracts were collected, dried on Na_2SO_4 and the solvent was removed by rotary evaporation. The pale yellow liquid thus obtained was purified by distillation yielding trimethylorthopropionate (**36a**, 1.43 g, 38%) or trimethylorthovalerate (**36c**, 1.91 g, 42%). Trimethylorthobenjzoate **36c** was not isolated using this procedure.

5.3.5.5 Benzoimidate anion exchange

In a 50 mL flask O-methyl benzoimidate hydrochloride **35c** (1.60 g, 8.36 mmol) and diethyl ether (15 mL) were introduced. The resulting suspension was cooled to 5 °C and, under vigorous stirring, a solution obtained by dissolving K_2CO_3 (2.0 g, 14.5 mmol) in water (15 mL). The mixture was stirred until all the solid **35c** was dissolved, then the organic phase was separated and the aqueous phase extracted with 2 x 2 mL of diethylether. The organic extracts were collected, dried over Na_2SO_4 and introduced in a 50 mL flask. The ethereal solution was cooled to 5 °C and an equimolar amount of the selected acid (8.36 mmol, phosphoric acid: 819 mg, sulfuric acid: 820 mg, p-toluenesulfonic acid: 1.44 g) dissolved in 5 mL of methanol was added by means of a dropping funnel keeping the mixture vigorously stirred. The salts **39c** and **41c** precipitated out as white solids and were filtered (**39c**: 7.85 mmol, 93.9 %; **41c**: 2.28 g, 7.42 mmol, 88.7%), while the hydrogensulfate salt **35c•H_3PO_4** separated as an oil, the diethylether was removed at reduced pressure leaving a brown oil which was then used without purification.

5.3.5.6 Pinner synthesis of trimethylorthobenzoate

First step. Using an equipment as described in Figure 5.14 benzonitrile (20 mL, 194 mmol) and methanol (30 mL, 741 mmol) were introduced in a 250 mL flask (flask A) and the resulting mixture was cooled to 5 °C. Once the temperature was stabilised HCl (obtained by dropping 50 mL of H_2SO_4 on 53 g of NH_4Cl in flask B) was bubbled in the mixture with stirring. Sulfuric acid was added as slow as the whole addition took 4 hours. At the end of the addition the flask was kept at 4 °C for 24 hours. At the end of the reaction excess methanol and HCl were removed in vacuum and O-methyl benzoimidate hydrochloride **35c** (32.8 g, 191 mmol, 98.5%) was obtained as a white solid.

Anion exchange. In a 500 mL flask O-methyl benzoimidate hydrochloride **35c** (16.0 g, 83.56 mmol) and diethyl ether (160 mL) were introduced. The resulting suspension was cooled to 5 °C and, under vigorous stirring, a solution obtained by dissolving Na_2CO_3 (50 g, 472 mmol) in water (200 mL). The mixture was stirred until all the solid **35c** was dissolved, then the organic phase was separated and the aqueous phase extracted with 2 x 20 mL of diethylether. The organic extracts were collected, dried over Na_2SO_4 and introduced in a 500 mL flask. The ethereal solution was cooled to 5 °C and anhydrous H_3PO_4 (8.19 g, 83.57 mmol) dissolved in the minimum amount of methanol (15 mL) was added keeping the mixture vigorously stirred. The addition of the phosphoric acid took 20 minutes during which a white, microcrystalline solid precipitated. After the addition was complete, the resulting suspension was stirred for addition 15 minutes. The white solid was then filtered yielding 17.96 g (77.03 mmol, 92.2 %) of O-methyl benzoimidate dihydrogenphosphate **39c**.

Alcoholysis. O-methyl benzoimidate hydrochloride **39c** (17.21 g, 73.82 mmol) and methanol (47.5 g, 1.484 mol) were introduced in a two neck flask equipped with a reflux condenser and a septum for sampling. The resulting suspension was heated to the reflux temperature (65 °C) with stirring. After 6 hours the mixture was cooled to room temperature and the excess methanol removed at reduced pressure. To the resulting white suspension diethylether was added with vigorous stirring. The solid fraction was then allowed to settle down and the upper clear solution was transferred, by means of a needle, in a flask containing a solution obtained by dissolving 3.00 g of Na_2CO_3 in 60 mL of water. The solid was then washed with 2 x 10 mL of diethylether and the resulting solutions were added on the aqueous Na_2CO_3. The aqueous phase was discharged and extracted with 2 x 10 mL of diethylether. The ethereal extracts were collected, dried on Na_2SO_4 and the solvent was removed by rotary evaporation. The pale yellow liquid thus obtained was purified by distillation at reduced pressure (80 °C @5 torr) yielding 7.012 g (38.48 mmol, 52 %) of TMOB **36c**.

5.3.5.7 Characterisation data

Methylpropioimidate 35a GC/MS (relative intensity, 70 eV) *m/z*: 87 ($[M^+]$, 41%), 86 (47), 58 (70), 57 ($[M\text{-}CH_3\text{-}NH]^+$, 41), 56 ($[M\text{-}OCH_3]^+$, 100), 54 (14), 44 (20).

Methylvaleroimidate 35b GC/MS (relative intensity, 70 eV) *m/z*: 101 ([M-CH_2], 98%), 59 (11), 55 ([C_4H_7]$^+$, 100), 41 16), 39 (11).

Methylbenzoimidate 35c GC/MS (relative intensity, 70 eV) *m/z*: 135 ([M]$^+$, 10%), 134 ([M-H]$^+$, 35), 140 ([M-CH_3]$^+$, 31), 105 ([C_6H_5CO]$^+$, 19), 104 ([C_6H_5CNH]$^+$, 100), 103 (23), 91 (10), 77 (49), 76 (16), 51 (34,) 50 (18).

Trimethylorthopropionate 36a GC/MS (relative intensity, 70 eV) *m/z*: 105 ([M-OCH_3]$^+$, 56%), 103 ([M-OCH_3]$^+$, 100), 59 (16), 57 ([CH_3CH_2CO]$^+$, 48), 45 (7).

Trimethylorthovalerate 36b GC/MS (relative intensity, 70 eV) *m/z*: 131 ([M-OCH_3]$^+$, 87%), 105 (100), 101 ([M-2OCH_3]$^+$, 36), 85 ([$CH_3(CH_2)_3CO$]$^+$, 9), 61 (13), 59 (35), 57 (69).

Trimethylorthobenzoate 36c GC/MS (relative intensity, 70 eV) *m/z*: 151 ([M-OCH_3]$^+$, 100%), 105 ([C_6H_5CO]$^+$, 64), 91 ([M-?]$^+$, 18), 77 ([M-?]$^+$, 42), 59 ([M-?]$^+$, 12), 51 ([M-?]$^+$, 20).

Methylpropionate 37a GC/MS (relative intensity, 70 eV) *m/z*: 88 ([M]$^+$, 20%), 59 (27), 57 (86), 29 (100), 28 ([M-?]$^+$, 19), 27 (42). Database Wiley: Ref 3808, *match quality 94%.*

Methylvalerate 37b GC/MS (relative intensity, 70 eV) *m/z*: 101 ([M-?]$^+$, 1%), 87 ([M-?]$^+$, 29), 85 ([M-?]$^+$, 31), 74 ([M-?]$^+$, 100), 59 ([M-?]$^+$, 26), 57 (42), 55 (22), 43 (56), 42 (14), 41 (47), 39 (21). Database Wiley: Ref 12990, *match quality 95%.*

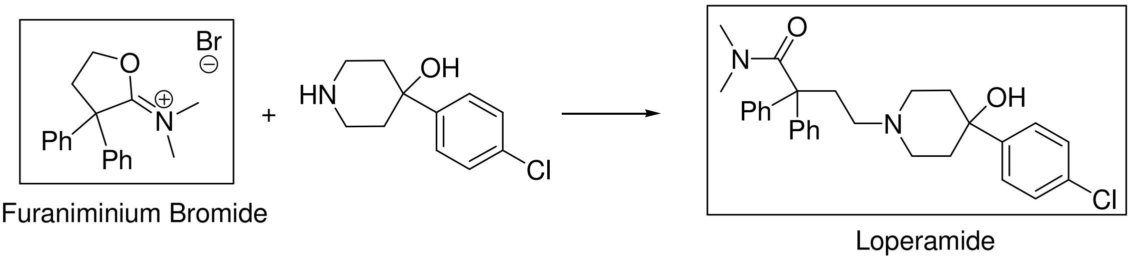
Methylbenzoate 37c GC/MS (relative intensity, 70 eV) *m/z*: 136 ([M]$^+$, 32%), 105 ([C_6H_5CO]$^+$, 100), 77 ([C_6H_5]$^+$, 73). Database Wiley: Ref 24271, *match quality 97%.*

Benzamide 38c GC/MS (relative intensity, 70 eV) *m/z*: 121 ([M]$^+$, 32%), 105 ([C_6H_5CO]$^+$, 100), 77 ([C_6H_5]$^+$, 98). Database Wiley: Ref 15171, *match quality 91%.*

5.4 Furaniminium bromide

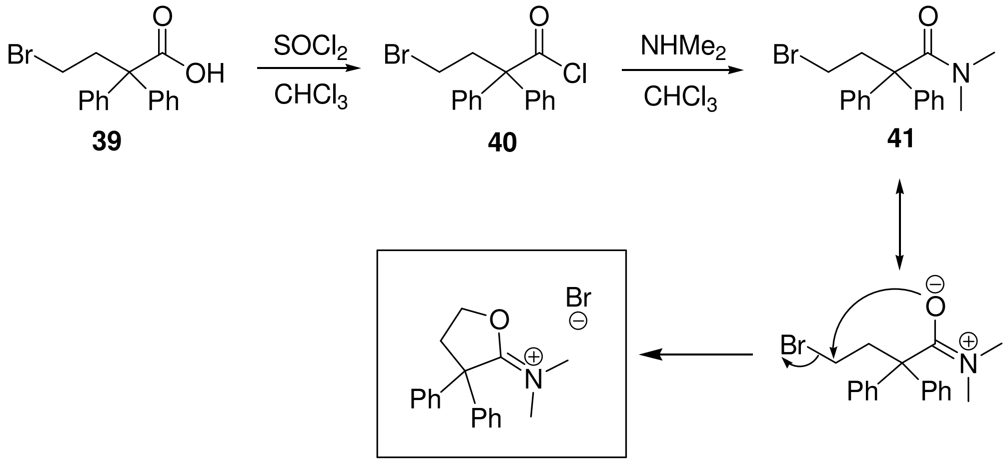
5.4.1 Introduction

Furaniminium bromide (dimethyl-(tetrahydro-3,3-diphenyl-2-furylidene)-ammonium bromide) is an intermediate for the synthesis of Loperamide (Scheme 5.19), a synthetic piperidine derivative[50] developed at Janssen Pharmaceutica.[51] This pharmaceutical active ingredient is an opioid drug used against diarrhea resulting from gastroenteritis or inflammatory bowel disease. In most countries it is available generically and under brand names such as Lopex, Imodium, Dimor, Fortasec and Pepto Diarrhea Control.



Scheme 5.19 Loperamide synthesis

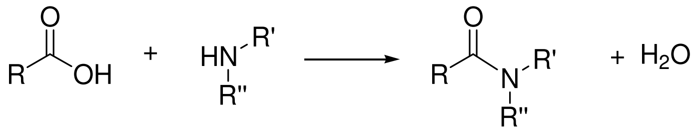
The two key intermediates for the preparation of Loperamide are the piperidine derivative and furanimium bromide. The preparation of furaniminium bromide **42** is schematized in Scheme 5.20. Starting from 4-bromo-2,2-diphenyl butyric acid **39**, the dimethyl amide derivative **41** is obtained via the addition of dimethylamine on the acyl chloride **40**. The first step is carried out using thionylchloride in chloroform in the presence of catalytic amounts of dimethylformamide (DMF), the amounts of chloroform used are quite high due to the low solubility of the reactant **39**. The following step involves the reaction of chloride **40** with dimethylamine, usually as water[51] or THF solution,[52] operating at low temperature due to the exothermicity of this reaction. The amide **41** ring-closes to yield the five membered ring by nucleophilic displacement of bromine. The main drawbacks of this reactions are: *i*) the use of large amounts of light chlorinated solvents, chloroform in particular.[53] *ii*) The use of thionylchloride ($SOCl_2$) for acyl-chloride preparation. The preparation of this intermediate represents an added derivatisation step, contrary to the principles of green chemistry.[54] In addition $SOCl_2$ is an undesirable reactant itself. It reacts violently with water and causes severe burns. and its use leads to the formation of stoichiometric amounts of corrosive gaseous HCl as well as SO_2. Even the use of dimethylformamide (DMF), although in very small amount (less than 1% molar), could be assessed as a drawback of this synthetic methodology, as it is itself undesirable.



Furanimium bromide **42**

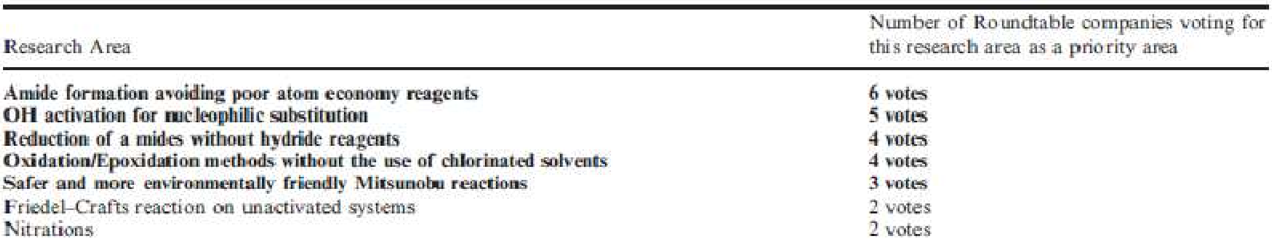
Scheme 5.20 Synthetic route to Furanimium bromide.

However these issues are common to all the amide preparation methods.[55] The preparation of compounds that exhibit this functional group often requires drastic conditions and/or use of highly reactive promoters.[56] The use of coupling reagents such as carbodiimide, extensively used in the synthesis of peptides[57] drastically reduces the atom economy of the amides preparations.[58] In addition this give rise to unwanted by-products requiring additional purification steps, thus compromising the yield of the process and representing serious sources of environmental impact. Since the formation of amides require the removal of a water molecule (Scheme 5.21) all the coupling reagents are essentially dehydrating agents.



Scheme 5.21 Direct amidation generates water as the sole by product.

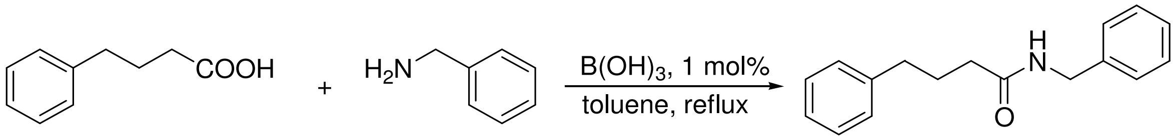
For these reasons the "ACS GCI Pharmaceutical Roundtable"[59] in 2005 underlined the urgency of implementing new synthetic strategies for the preparation of amides, avoiding the use of low atom economic reactants (Figure 5.15).



Research Area	Number of Roundtable companies voting for this research area as a priority area
Amide formation avoiding poor atom economy reagents	**6 votes**
OH activation for nucleophilic substitution	**5 votes**
Reduction of amides without hydride reagents	**4 votes**
Oxidation/Epoxidation methods without the use of chlorinated solvents	**4 votes**
Safer and more environmentally friendly Mitsunobu reactions	**3 votes**
Friedel–Crafts reaction on unactivated systems	2 votes
Nitrations	2 votes

Figure 5.15 Amide formation is an urgent issue for pharmaceutical companies.

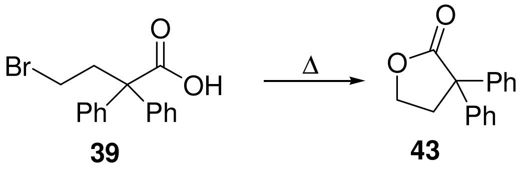
Highly atom economic processes like the thermal direct condensation of acids and amines[60] could be accomplished, nevertheless this method is not widely applicable. An important step towards a green preparation of amides is the relatively recent development of a methodology that uses boric acid in catalytic amounts for the preparation of amides directly from the corresponding carboxylic acids and amines.[61] (Scheme 5.22).



Scheme 5.22 Boric acid catalysed direct amide formation.

This method is very interesting, because the direct condensation of acid with the amine generates only water as the by-product which is removed by azeotropic distillation. In addition it uses boric acid as the catalyst, a compound relatively inexpensive, available and non toxic. However, the procedure has an important limitation *i.e.* the relatively high temperature. Actually the reaction takes quite a long reaction time (15-20 h) at 110 °C. The by-produced water is removed by azeotropic distillation. This causes this method to be inapplicable to thermally unstable substrates. In addition volatile amines cannot be used under these conditions. However the studies on boric acid derivated organo-catalysts able to work at lower temperature represent a very promising field of recent studies on amide formation procedures.[62]

Unfortunately in the case of the preparation of furaniminium bromide it is not possible to conduct the amidation through a condensation under these conditions, because the reactant **39** decomposes at high temperature to the lactone **43** (Scheme 5.23). In addition dimethylamine is gaseous and the competitive nucleophilic substitution of bromine in position 4 would have a detrimental effect.



Scheme 5.23 Thermal cyclisation of **39** to yield the lactone **43**.

5.4.2 Aim of the research

We searched for a method for the preparation of furaniminium bromide - and more generally of amides - that could avoid the use of noxious solvents and of coupling agents. As previously mentioned the use of dehydrating agents can be avoided by carrying out the condensation reaction at high temperature (pyrolysis of the ammonium carboxylate salts[60]). This approach is not suitable when **39** is used as the starting material due to its thermal lability. This particular reactant requires mild conditions, but at the same time it is poorly reactive, due to the steric bulk of the two phenyl groups close to the carboxylic group. In addition dimethylamine is a volatile amine, therefore reaction temperature has to be necessarily low.

A strategy to develop a process for the preparation of furaniminium bromide using environmental compatible solvents reactants and procedures, could have been to avoid the use of toxic, corrosive and poorly atom economical thionyl chloride. However, since we sought for a process which could be rapidly implemented by our industrial partner, we decided to focus primarily on the solvent issue.

Since the target compound **42** hydrolyses in water under basic conditions, we sought for a procedure in which the target product will not be in contact with water. This could also allow to avoid the use of chloroform to extract furaniminium bromide from the aqueous phase. Chloroform is in fact the only organic solvent (among the ones tested) able to extract the product from water. As an example we imagined to implement a process of the type schematised in Figure 5.16.

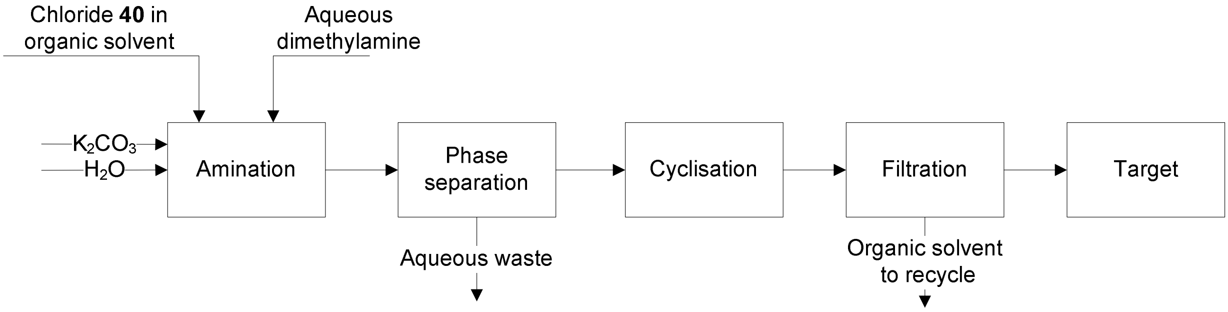


Figure 5.16 Process as we imagined it.

With the same aim we tried to develop a procedure in which water was avoided at all, by using anhydrous dimethylamine instead of its aqueous solution.

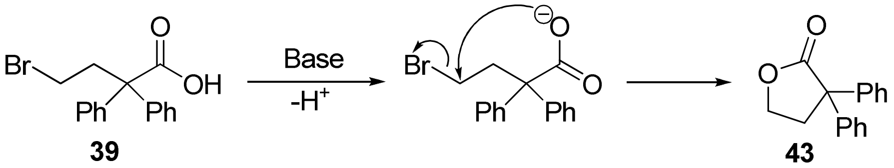
As it usually happens during the study we reconsidered our plans once the chemistry of the compounds we were using was deeper understood. Here below are reported the preliminary studies on the main properties of the involved species.

5.4.3 Results and discussion

Some preliminary observations and experiments were carried out, in order to acquire information on the chemistry of the compounds involved in this synthetic process, in particular regarding lactone **43** that is the most undesirable by-product.

Acid **39** was poorly soluble in chloroform, toluene and dimethylcarbonate at room temperature. However at the reaction temperature (60 °C) the solubility was estimated around 50 mg/mL in chloroform. On the other hand the corresponding chloride derivative **40** proved more soluble (>300 mg/mL) than the carboxylic acid **39** in all the solvents tested.

As previously reported the reactant is prone to cyclisation to yield the lactone **43**. Attempts to analyse compound **39** by CG/MS failed due to formation of **43** in the injector. Lactone formation takes place also at room temperature in the presence of a base (Scheme 5.24). Treating the acid **39** suspended in chloroform with 10% aqueous K_2CO_3, the acid was completely converted to the lactone in less than 3 hours.



Scheme 5.24 Base catalysed decomposition of **39**

The target Furaniminium bromide **42** also decomposes to yield the lactone by hydrolysis. A qualitative evaluation of the hydrolysis rate of furaniminium bromide was carried out by dissolving **42** in water at different pH values. The formed **43** was insoluble in water and precipitated as a white solid (Figure 5.17). After 10 minutes at pH = 10, all the furaniminium was converted to lactone, while at pH = 6 the precipitation of **43** was observed only after 4 hours. In acidic environment **42** was stable for more than 24 hours (no precipitation was observed).

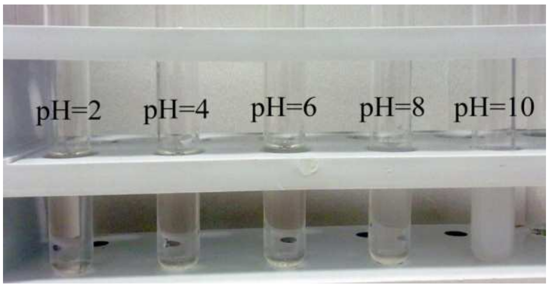
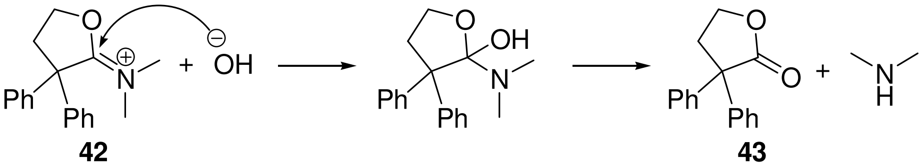


Figure 5.17 In basic aqueous solution furaniminium bromide **42** hydrolised yielding the lactone **43**. The latter precipitated as a white solid.

Hydrolysis was fast in basic conditions, allowing to propose a base catalysed mechanism of the type reported in Scheme 5.25.



Scheme 5.25 Furaniminium bromide **42** hydrolysis mechanism under basic condition.

This preliminary information was extremely useful for the successive study.

5.4.3.1 Reaction with thionyl chloride in different alternative solvents

First we tried to conduct the synthesis in a solvent other than chloroform. Since in the subsequent phases of Galentis' process toluene is used in large quantities, the latter was tested as the solvent for this step of the preparation as well. Since in the original paper[51] the reaction with thionyl chloride was conducted without the addition of DMF, we tried to carry out the chlorination step without the addition of this substance.

Some preliminary tests were conducted by adding thionyl chloride on a suspension of **39** in toluene and heating the resulting mixture at 60 °C (Table 5.12). The reaction was extremely slow without DMF as the catalyst, in particular when a large amount of solvent was used (entry 2), indicating that the reaction rate was very sensible to thionyl chloride concentration. In addition, the absence of DMF addition required a large excess of $SOCl_2$ to increase conversion. On the other hand, by adding DMF conversion was complete after only 4 hours (entry 4) using a slight excess of thionyl chloride (1.25 equivs) and toluene as the solvent (10 equivs).

A shorter reaction time is important not only because it is an advantage in terms of cost of operations, but also because maintaining the reaction mixture at high temperature for a long time favours the formation of the undesired lactone **43** (cf. Scheme 5.23). The latter was the main impurity at this stage, consequently the minimisation of this side reaction was crucial for the overall yield.

Table 5.12 Effect on conversion of dilution of **39** and $SOCl_2$:**39**.[a]

#	Toluene (eq)	$SOCl_2$ (eq)	Conversion (by NMR, %)
1	10	1.25	30
2	50	1.25	15
3	10	2	45
4	10	1.25	>95[b]

[a] Conditions: 60 °C, nitrogen atmosphere, 20 hours.

[b] Catalytic amount of DMF, reaction time:4 hours.

Since the boiling point of toluene is higher than that of chloroform, we also tried to improve conversion by increasing the temperature from 60 to 70 °C. Disappointingly conversion decreased. Probably this temperature causes thionyl chloride to be mainly distributed in the condenser, lowering its concentration in the flask.

Since DMC proved a good solvent in the chlorination of paracyclophane by molecular chlorine (see this chapter, paragraph 5.2.2.5), and is resistant to an extremely acidic environment, we decided to try this solvent also as reaction medium for the chlorination of **39** with thionyl chloride. Surprisingly DMC as the solvent not only allowed to carry out the reaction, but also accelerated it. Under the best condition tested for toluene, the reaction in DMC was almost complete in only 2 hours. The effect of the temperature was tested also in this case varying the temperature from 40 to 70 °C.[63] Results thus obtained are reported graphically in Figure 5.18.

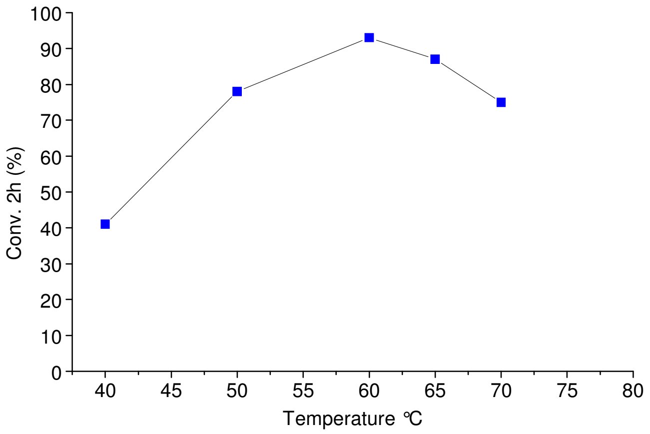


Figure 5.18 Temperature effect on conversion after 2 hours. Conditions: Reagent **39** (10 mmol) in 10 mL of DMC in the presence of 1.25 equivs of $SOCl_2$ and 1 drop DMF.

Looking at Figure 5.18 it appeared clearly that the best temperature for the reaction is 60 °C, therefore this value was chosen for all the successive tests.

The short reaction times required by the reaction in DMC allowed to obtain the chloride **40** in high purity, avoiding the formation of the side product **43** (Table 5.13).

Table 5.13 Lactone formation in different solvents

Entry	Solvent	Time (h)	Lactone (% by NMR)
1	Toluene	4	4
2	$CHCl_3$	3.5	3
3	DMC	2	2

Furthermore, The reaction in DMC is globally endothermic: particularly during the first hour of reaction during which a significant evolution of gaseous by-products was observed. When the same reaction is carried out in chloroform the process is exothermic and the addition of thionyl chloride allows to maintain the mixture at the reflux temperature. To confirm this observation we conducted a simple test: **39** was suspended in DMC and thionyl chloride was added. The resulting mixture was heated to 60 °C without adding DMF. As reported in Table 5.12 the reaction proceeds very slowly under these conditions. A catalytic amount of DMF was then added and the reaction started vigorously, as was apparent by the evolution of gaseous HCl and SO_2. At the same time, the temperature in the flask dropped to 50 °C in only 10 minutes confirming the process to be endothermic. While the reaction of the carboxylic acid and thionylchloride was exothermic, as observed using chloroform as the solvent, onthe contrary the dissolution of **39** in DMC was an endothermic process. Using DMC the energy required to bring the reactant in solution (where it actually reacts) overwhelmed the energy released by the reaction. An accurate measure of the thermodynamic parameters of this process needs to be studied in details.

5.4.3.2 Amide formation using aqueous dimethylamine in different solvents

The second step, *i.e.* the reaction with aqueous dimethylamine was studied. As expected the reaction was fast and exothermic. The reported procedure[51,52] requires a reaction temperature between 5 and -5 °C in the presence of K_2CO_3 to neutralise the co-formed HCl.

As already mentioned in paragraph 5.4.2, at the very beginning we tried to trap the neutral amide **41** in organic solution (using toluene or DMC) and then to obtain the compound **42** by heating the solution (Figure 5.16) after removing the aqueous phase to avoid the target product to distribute in the latter.

Unfortunately amide cyclisation occurred even at - 5 °C, immediately after its formation. As already stated the furaniminium bromide was soluble in water and distributes in the organic phase immediately. This ruled out any possibility of using toluene, DMC or any other organic solvent, to obtain the amide and successively the target compound as planned. This represented a problem not only because a solvent to extract **42** from water was required (e.g. chloroform), but also because the hydrolysis of the product in water under basic condition (Figure 5.17) dramatically compromised the yield of the target compound. In addition the chloride intermediate **40** could also hydrolyse, especially under basic conditions.

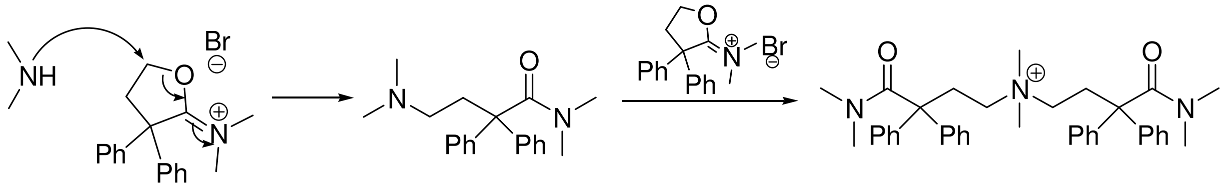
This was puzzling, however a solution was found.

5.4.3.3 Amide formation using anhydrous amine in DMC

To avoid the use of water, we chose to use anhydrous dimethylamine (DMA). This compound is a gas at room temperature, and it is sold in cylinders. The vapour pressure of dimethylamine at 20 °C is 1277 mmHg,[64] hence it is quite simple to handle (see experimental section for further details).

The simplest protocol was to directly bubble the gas in the chloride **40** solution in the organic solvent obtained by the first step described previously. The addition of dimethylamine to toluene solution of **40** caused immediate precipitation of a white solid.

However product **42** was highly impure due to the presence of the impurities **45** and **46**[65] derived from the addition of dimethylamine to **42** as described in Scheme 5.26:



Scheme 5.26 Main impurities formed in presence of anhydrous dimethyl amide.

The formation of these impurities was ascribed to the lack of control of the temperature due to the excessively high rate of addition of the amine.

To more accurately control the addition of amine, a solution of this reactant in DMC was preparared and then added to a DMC solution of **40** by means of a dropping funnel. It was therefore possible to carry out the addition very slowly keeping the temperature carefully under 5

°C. This expedient allowed to obtain the desired **42** as a white solid in almost quantitative yield, maintaining the amount of impurities under 5 % molar (by NMR).

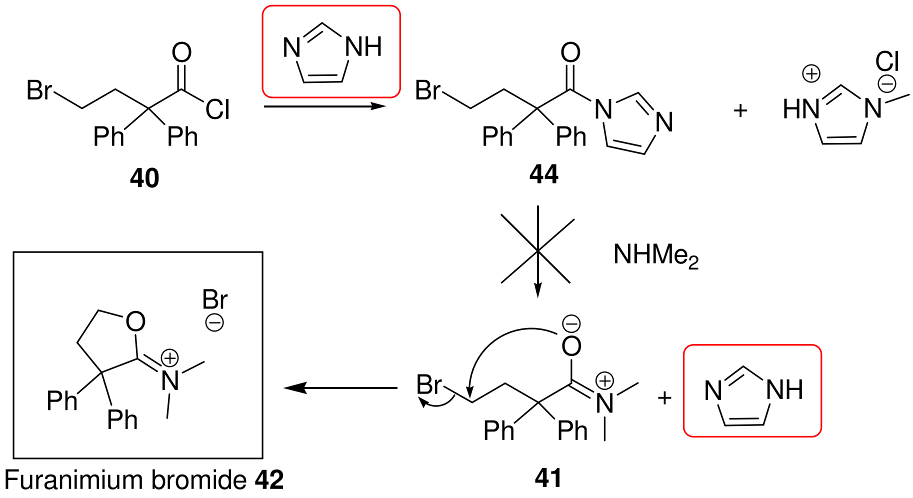
Unfortunately since K_2CO_3 was not present in this reaction mixture, the co-formed HCl reacted with DMA causing the co-precipitation of ammonium chloride. The isolation of **42** from the mixture proved difficult. A procedure for the separation of the two salts avoiding the use of chloroform is currently under investigation by Galentis.

Some scale-up tests were carried out in the Galentis R&D laboratories (Figure 5.19), confirming the lab-scale results obtained in Venice.

Figure 5.19 Scale up tests in Galentis.

5.4.3.4 Amide formation through the imidoyl derivative

Since the removal of the co-formed ammonium hydrochloride salt proved difficult, we sought for an alternative amide formation procedure in order to avoid this drawback. To achieve this result we took inspiration from the Basil™ process for the synthesis of alkoxy phosphines.[66] In that case methylimidazole is used as an acid scavenger. We imagined a process (Scheme 5.27) in which imidazole has not only this function, but also generates the imidoyl derivative **45**. The latter could react with dimethylamine[67] yielding the desired product. The by-product would be neutral imidazole which is slightly soluble in the chosen organic solvent, while the solid **42** should be simply isolated by filtration. Theoretically imidazole could be recovered and recycled.



Scheme 5.27 Proposed Furaniminium synthesis through imidoyl derivative **45**.

Unfortunately the nucleophilic displacement of imidazole by DMA did not occur, even increasing the reaction temperature. Only the formation of undesired side products was observed

5.4.4 Conclusions

A study on the preparation of furaniminium bromide through a more environmental compatible process was carried out. Particular attention, in agreement with the aim of this thesis, was posed on the choice of the solvent for the reaction and on the purification steps, as well as on the use of safer reactants and auxiliaries.

The tests conducted on the first step of the reaction (e.g. the chlorination of the carboxylic acid using thionyl chloride) demonstrated that is possible to avoid the use of an undesirable solvent like chloroform. This toxic and pollutant light chlorinated solvent could be replaced simply with a solvent like toluene with no particular drawback. This solvent was chosen because it was used by Galentis in the successive stripping of the excess of thionyl chloride and by produced HCl. The higher boiling point of this solvent allowed to verify the behaviour of the reaction mixture at higher temperature (>60 °C, *i.e.* the boiling point of chloroform). However an increase of the temperature did not yield any advantage. On the contrary lower conversion and higher amount of impurity (lactone **43**) were observed.

Since DMC was tested in the chlorination of paracyclophane (see this chapter, paragraph 5.2.2.5) with good results, this solvent was tested for the reaction of **39** with $SOCl_2$. Remarkably the reaction proceeded faster than in both chloroform and toluene. The quite high boiling point of DMC allows to strip the excess thionyl chloride and by-products simply removing the reaction solvent, avoiding the use of an additional, higher boiling solvent. Another surprising experimental behaviour was the apparent endothermic character of the reaction due to the energy demanding solvation of the reactant in DMC. This reduces the risk of a runaway reaction and allows to add the thionyl chloride avoiding excessive precautions that are needed in the case of chloroform.

To reduce the formation of impurities a procedure avoiding the contact with water was sought. A procedure using DMC as the sole solvent and anhydrous dimethylamine was developed. The described process simplifies the procedures, but unfortunately did not permit to obtain the product in pure form, because furaniminium bromide was obtained as a mixture with dimethylammonium chloride. The separation of this two salts proved extremely difficult and is currently under investigation by Galentis. To prevent the formation of the chloride salt a different procedure was proposed (Scheme 5.27). The preparation of an imidoyl derivative **46** could in principle allow to obtain the target compound with no formation of side products except imidazole which is more soluble than **42** in DMC. Unfortunately the displacement of imidazole was not possible under mild conditions, therefore this route proved inapplicable.

5.4.5 Experimental section

5.4.5.1 Acid chloride preparation in chloroform

4-Bromo-2,2-diphenylbutyrric acid **39** (3.19 g, 10.0 mmol), thionylchloride (0.90 mL, 12.4 mmol) and chloroform (40 mL) were introduced in a 100 mL round bottomed flask equipped with a reflux condenser and a $CaCl_2$ stopper under the conditions of Table 5.12. To the obtained suspension a drop of DMF was added when required. The mixture thus obtained was heated to 60 °C for 24 hours under nitrogen atmosphere. At the end of the reaction solvent was removed under vacuum and the remaining oil was analysed by NMR spectroscopy to evaluate its composition.

5.4.5.2 Acid chloride preparation in toluene

4-Bromo-2,2-diphenylbutyrric acid **39** (3.19 g, 10.0 mmol), thionylchloride (0.90 – 1.45 mL, 12.4 – 20.0mmol) and toluene (10-50 mL, 94-470 mmol) were introduced in a 100 mL round bottomed flask equipped with a reflux condenser and a $CaCl_2$ stopper under the conditions of Table 5.12. To the obtained suspension a drop of DMF was added when required. The mixture thus obtained was heated to 60 °C for 24 hours under nitrogen atmosphere. At the end of the reaction solvent was removed under vacuum and the remaining oil was analysed by NMR spectroscopy to evaluate its composition.

5.4.5.3 Acid chloride preparation in dimethylcarbonate

4-Bromo-2,2-diphenylbutyrric acid **39** (3.19 g, 10.0 mmol), thionylchloride (0.90 mL, 12.4 mmol) and dimethylcarbonate (10 mL) were introduced in a 100 mL round bottomed flask equipped with a reflux condenser and a $CaCl_2$ stopper. To the obtained suspension a drop of DMF was added. The mixture thus obtained was heated to 60 °C for 4 hours under nitrogen atmosphere. At the end of the reaction solvent was removed under vacuum and the remaining oil was analysed by NMR spectroscopy to evaluate its composition.

5.4.5.4 Furaniminium bromide preparation in dimethylcarbonate

First step: chlorination. In a three neck 500 mL flask equipped as reported in Figure 5.20 4-bromo-2,2-diphenylbutyric acid **39** (47.9 g, 150 mmol) was suspended in 60 mL of dimethylcarbonate.

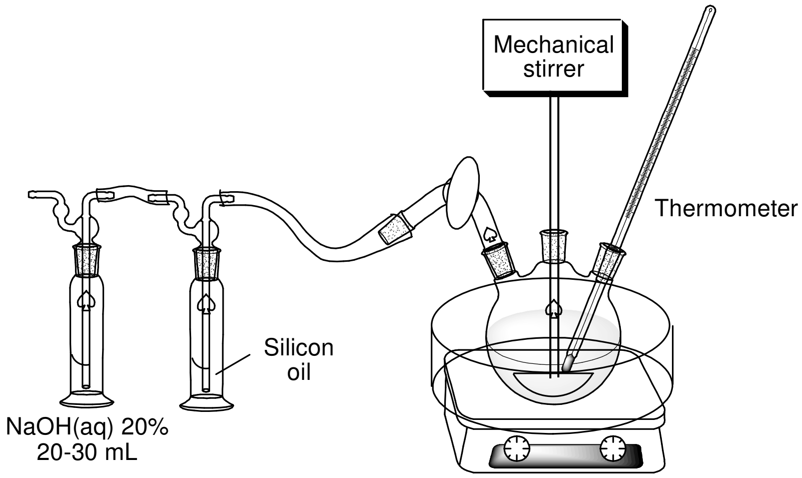


Figure 5.20

Dimethylformamide (0.5 mL, 6.46 mmol, 4.3 % molar) and thionylchloride (13.5 mL, 186 mmol) were then added. The resulting mixture was heated to 60 °C by means of an oil bath. The mixture was kept at that temperature for 2,5 h with stirring. After approximately 1 hour the mixture appeared like a clear yellow solution. Successively the solvent, excess $SOCl_2$ and by produced SO_2 and HCl were removed at reduced pressure keeping the oil bath temperature at 55-60 °C. The resulting yellow oil was dissolved in 30 mL of dimethylcarbonate and cooled to 0 °C by means of an ice bath.

Second step: amination. Using a dropping funnel a solution obtained bubbling dimethylamine (14.7 g, 325 mmol) in 50 of DMC was slowly added to the chloride **40** solution vigorously stirred, keeping the temperature of the mixture below 5 °C. Suddenly a white solid precipitated from the solution. The addition took about 2 hours. When all the amine was added the resulting suspension was kept at 0 °C with stirring for additional 20 minutes. After that time the solid was filtered on a büchner funnel, washed with ethyl acetate (2 x 10 mL) and dried in (essiccatore?) to constant weight. 62.0 g of white solid composed by a mixture of furaniminium bromide and ammonium chloride (1:1.2 molar ratio by NMR) was obtained. The estimated yield of furaniminium at this stage was approximately 90 %.

Third step: purification. In a 500 mL flask water (100 mL), $NaHCO_3$ (10.0 g, 119 mmol) and chloroform (100 mL) were introduced. The mixture was stirred until complete dissolution of the bicarbonate and cooled to 0 °C. The solid previously obtained was added to the cooled mixture with stirring keeping the temperature below 5 °C. After 15 minutes the organic layer was recovered and the acqueous phase extracted with chloroform (2 x 30 mL). Extracts were collected and the solvent removed by rotary evaporation. The resulting colourless oil was triturated with 40 mL of ethyl acetate. The white solid thus obtained was filtered and washed with ethylacetate (2 x 10 mL) and dried to yield furaniminium bromide **42** (40.0 g, 115 mmol, 77 % yield).

*5.4.5.5 Imidazole derivative **44** synthesis and reaction with dimethylamine*

To the oil obtained by the preparation described in the paragraph 5.4.5.3 was dissolved in 6 ml of DMC. The obtained solution was cooled at 10 °C and a solution of imidazole (1.38 g, 20 mmol) in 8 mL of DMC was slowly added with vigorous stirring. During the addition a white solid separated from the solution. The resulting suspension was filtered and the compound 44 solution in DMC was used as it is for further investigations.

*5.4.5.6 Reaction of imidazole derivate **44** with dimethylamine*

To the compound **44** solution in DMC a solution of dimethylamine obtained bubbling the gaseous amine (540 - 910 mg, 12.0 - 20.2 mmol) in 6 mL of DMC was added.

The mixture was kept at room temperature for 20 hours. No reaction occurs. The mixture was then heated at 40 °C and kept at that temperature for 10 hours. Reaction did not occur even at this temperature while some uncharacterised compounds were detected by NMR.

5.4.5.7 Characterisation data

4-bromo-2,2-diphenylbutyric acid 39. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.23 (m, 10H), 3.13 – 2.92 (m, 4H).

4-bromo-2,2-diphenylbutanoyl chloride 40. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.29 (m, 10H), 3.05 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 138.4, 129.1, 128.7, 128.3, 69.8, 42.5, 27.4.

Dimethyl-(tetrahydro-3,3-diphenyl-2-furylidene)-ammonium bromide 42 ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.27 (m, 10H), 4.73 (t, J = 5.7 Hz, 2H), 3.67 (s, 3H), 3.33 (t, J = 6.5 Hz, 3H), 2.85 (s, 3H). 13C NMR (100 MHz, CDCl3) δ 180.6, 135.2, 129.9, 129.2, 127.9, 75.4, 62.9, 45.7, 43.0, 41.7.

Dihydro-3,3-diphenylfuran-2(3H)-one 43 ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.25 (m, 243H), 4.30 (t, *J* = 6.5 Hz, 63H), 2.99 (t, *J* = 6.5 Hz, 69H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 140.7, 128.8, 127.7, 127.6, 65.2, 56.5, 37.6.

4-bromo-1-(1H-imidazol-1-yl)-2,2-diphenylbutan-1-one 44. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.37 – 7.25 (m, 10H), 7.09 (t, J = 1.5 Hz, 1H), 6.72 (d, J = 1.1 Hz, 1H), 3.01 – 2.87 (m, 4H).

5.5 References

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[1] See Chapter 1, paragraph 1.1.2.

[2] From Galentis website.

[3] Chlorinated solvents, the most used dichloromethane in particular are effective but undesirable solvents, whose presence in consumer products is beginning to be regulated by the European Parliament (Decision No. 455/2009/EC of the European Parliament and of the Council, 6 May 2009) since since most of them are suspected human carcinogens.

[4] Galxyl brochure, by Galentis S.r.l.

[5] http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682280.html

[6] (a) D. J. Cram, H. Steinberg, *J. Am. Chem. Soc.*, 1951, **73**, 5691–5704. (b) D. J. Cram and J. Abell, *J. Am. Chem. Soc.*, 1955, **77**, 1179–1186; (c) J. Cram, N. L. Allinger, *J. Am. Chem. Soc.*, 1955, **77**, 6289–6292; (d)

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[9] The chemistry of paracyclophanes was connected to the formation of the poly-xylilene polymer since the discovery of [2.2] paracyclophane in 1949 when Brown and Farthing isolated for the first time this compound studying poly-xylilene. See: C. J. Brown and A. C. Farthing, *Nature*, 1949, **164**, 915-916.

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of chlorine gas at 25 °C d and the chlorine molecular weight MW, the flux of chlorine in mL per minute can be calculate as follows:

$$flux\ Cl_2(mL\ min^{-1}) = \frac{flux\ Cl_2\ (mol\ min^{-1}) * MW}{d}$$

$$flux\ Cl_2\ (mL\ min^{-1}) = \frac{flux\ Cl_2\ (mol\ min^{-1}) * 70.906\ g\ mol^{-1}}{0.003214\ g\ ml^{-1}}$$

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6 Concluding remarks

In this PhD work the development of new eco-friendly methodologies for the preparation of fine chemicals and Active Pharmaceutical Ingredients (API) is reported. In particular the use of solvents with reduced environmental impact was investigated.

In Chapter 2 the synthesis and the properties of a series of new onium ionic liquids (OILs) are reported. The preparation of these salts was achieved by the use of dimethylcarbonate as methylating agent yielding directly methylcarbonate ionic liquids. This allowed to avoid the use of common alkylating agent such as dimethylsulfate or methylhalide, which are toxic and poorly atom economic reagents. This procedure also allowed to obtaine halide free materials. In addition the obtained methylcarbonate salt could be anion exchanged in a very simple way, just by adding an equimolar amount of a Brönsted acid. Interestingly water did not behave like a Brönsted acid, the conjugated base OH^- was so strong that evoluton of CO_2 was not observed and bicarbonate anion was obtained. On the contrary the hydrophobic ionic liquids bearing $[NTf_2]^-$ as the anion were prepared following a previously reported procedure, since the conjugated acid $HNTf_2$ was difficult to handle and very expensive.

Once prepared, the application of these ionic liquids in the field of organic synthesis as solvents and/or catalysts was investigated and the results thus obtained are reported in Chapter 3. Carbonate ionic liquids (CILs) in particular have been used as base catalysts for the condensation of aldehydes and ketones with nitroalkanes.

In this study, basic ionic liquids as catalysts have been compared to conventional organic base catalysts, for example, diazabicycloundecene (DBU), tetramethylphenylguanidine (PhTMG), triethylamine (NEt_3) and dimethylaminopyridine (DMAP).

CILs proved very efficient catalysts and their use allowed to develop a synthetic procedure for the preparation of a series of nitroaldols from the corresponding aldehydes without using any additional solvent. Carbonate ionic liquids were used to catalyse the condensation of nitroalkane with ketones as well. Furthermore these catalysts proved extremely active allowing to obtain selectively dinitro adducts by double addition of nitromethane on cyclic ketones.

Also anion exchanged ionic liquids were useful as catalyst in organic reactions, nitrate ILs in catalytic amounts were profitably employed for the oxychlorination of aromatic substrates. The procedure described in Chapter 3 allowed to obtain mono and dichlorinated aromatic compounds using HCl as chlorine source and atmospheric oxygen as the oxydant. Avoiding the use of molecular chlorine or poorly atom economic reactants such as N-Chloro succinimide render this procedure safe and green, since the only by-product is water. This procedure does not need any added solvent since reactions are carried out in the ionic liquid itself (added in equimolar amont with respect to the substrate).

Our study also demonstrated the catalytic nature of the nitrate ionic liquid allowing us to propose a machanism in which the oxydant is atmospheric oxygen.

As an example of an API preparation we studied the preparation of the well know drug Tadalafil (commercially named Cialis, ™ a drug for man erectile dysfunction) through a more enviromental compatible route. The results we obtained are discussed in Chapter 4. In collaboration with QUILL (Queen's University Ionic Liquid Laboratories) at the Queen's University of Belfast, an alternative synthetic procedure using an hydrophobic ionic liquid and dimethylcarbonate as solvents was developed. The use of DMC in a crucial step of the preparation, in which the stereoselectivity has to be as high as possible, allowed to replace the commoly used nitromethane. On the other hand the use of an hydrophobic ionic liquid (i.e. [C_4dmim]NTf_2) allowed to carry out two synthetitc steps in a single flask without any intermediate purification step. This lowered considerably the amount of solvents used, increasing sensibly the reaction mass efficency of the overall preparation.

In Chapter 5 our investigation on alternative synthetic methodologies, in partnership with Galentis S.r.l., a fine chemical manufacturer located in Marcon (VE), is discussed. In particular our aim was to reduce amounts of solvent (especially chlorinated ones) needed for the preparation of some fine chemical produced by Galentis and/or to implement the use of more environmental acceptable solvents and reagents.

Three different preparations were considered:

Dichloro-[2.2]-p-cyclophanes

The implementation of alternative solvent systems for the chlorination of [2.2]-*p*-clyclophanes. Different solutions such as solventless condition, nitrate ionic liquid mediated oxychlorination and chlorination by gaseous chlorine in alternative eco-friendly solvents were tested. Unfortunately solventless conditions and the use of nitrate ionic liquids did not allow to develop an alternative effective procedure. However data collected during our studies, in particular carrying out the reaction in a number of alternative solvents were extremely interesting for our industrial partner for future R&D work.

Trimethylorthoesters

A study on the preparation of trimethylorthoesters via the Pinner procedure using alternative solvent systems was performed.

The avoidance of chlorinated volatile solvents (e.g. dichloromethane) was our main objective, therefore the viability of the use of methanol as solvent/reagent (without any additional solvent) was considered. A preparation following this protocol was described. It should be underlined that the preparation in solventless conditions allowed to improve the process productivity (low volume reactors are needed). However the separation of product from the mixture proved unachievable without the addition of an organic solvent for the extraction of target compound from the by produced ammonium chloride salt.

At the same time the preparation of trimethylorthobenzoate (TMOB) via the Pinner method was investigated. This product cannot be obtained using this protocol due to the formation of large amounts of benzamide as by-product. TMOB is therefore industrially prepared by nucleophilic displacement of chlorine substituent by methoxide anions. By adding a anion exchange step, we developed a procedure for the preparation of this particular product using the Pinner synthetic route. This allowed to use benzonitrile (harmful) instead of trichloromethylbenzene (carcinogen) as starting material.

Furanimium bromide

The title compound is used as intermediate in the synthesis of loperamide. Its preparation requires large amounts of chloroform used in both the synthetic steps in which consist its preparation.

The replacement of chloroform required the re-thinking of the process. Very interesting results were obtained using dimethylcarbonate as the solvent and anhydrous dimethylamine instead of its aqueous solution.

6.1 Paper originated from this thesis

Overall topics investigated during this PhD thesis led to the drafting of seven scientific papers and of a patent. A list follows:

- M. Fabris, V. Lucchini, M. Noè, A. Perosa and M. Selva, “Ionic Liquids Made with Dimethyl Carbonate: Solvents as well as Boosted Basic Catalysts for the Michael Reaction”, *Chem. Eur. J.*, 2009, **15**, 12273-12282.
- M. Noè, A. Perosa, M. Selva and L. Zambelli, " Phosphonium nitrate ionic liquid catalysed electrophilic aromatic oxychlorination ", *Green Chem.*, 2010, **12**, 1654–1660.
- M. Selva, M. Fabris, V. Lucchini, A. Perosa and M. Noè, “The Reaction of Primary Aromatic Amines with Alkylene Carbonates for the Selective Synthesis of bis-N-(2-hydroxy)alkylanilines: the Catalytic Effect of Phosphonium-Based Ionic Liquids”, *Org. Biomol. Chem.*, 2010, **8**, 5187-5198.
- V. Lucchini, M. Fabris, M. Noè, A. Perosa, M. Selva, “Kinetic Parameter Estimation of Solvent Free Reactions Monitored by 13C NMR Spectroscopy. A Case Study: Mono- and Di-(hydroxy)ethylation of Aniline with Ethylene carbonate” *Int. J. Chem. Kinet.*, 2010, **43**, 154-160.
- V. Lucchini, M. Noè, M. Selva, M. Fabris and A. Perosa, "Synergic nucleophilic-electrophilic catalysis by ionic liquids", *paper submitted.*
- M. Fabris, M, Noè, A. Perosa, M. Selva and R. Ballini, "Methylcarbonate and Bicarbonate Phosphonium Salts as Catalysts for the Nitroaldol (Henry) Reaction.", *paper submitted.*
- M. J. Earle, M. Noè A. Perosa and K. R. Seddon, "Tadalafil synthesis: new, safe and green protocols using dimethylcarbonate and ionic liquids." *paper in draft.*
- M. Noè, A. Perosa, M. Selva and L. Zambelli, Patent application number VE2011A000049, (June 23, 2011).

6.2 Acknowledgement

I would like to express my gratitude to who gave me the possibility to complete this thesis. A dutiful thank "Regione Veneto" and the "European Social Found" for founding the scolarship I earned and the "Finanziamenti esterni" office for the help in the bureaucracy. I want to thank also Galentis S.r.l. whose partnership allowed us to write down the PhD project and to obtain the financing.

Now that I thanked the institutions I can thank all the people who contribute in many ways to the realisation of this work.

A very special thank goes to my supervisor Dr. Alvise Perosa. He always encouraged me to work in an independent way, but, at the same time, was always ready to give me suggestion and help. His enthusiasm inspired and helped me to overcome all the difficulties.

Another person who contributed strongly to the realisation of this work was Prof. Maurizio Selva, a sort of second supervisor. His experience and dedication to chemistry were precious during these three years working at the Green Organic Synthesis Team in Venice.

I was lucky to have a "third supervisor": Dr. Luca Zambelli, managing director at Galentis S.r.l. He was always willing to contribute in many ways to the research activity and his expertise was extremely useful. I want to thank him especially for his enthusiasm.

I wish to thank my lab mate Dr. Massimo Fabris for his experience (he started his PhD one year before mine) and for our useful discussions. But I have to thank all the people who worked in the lab in venice during the last three years: Alessio Caretto, Marina Gottardo, Vanni Benedet, Valeria Galvan, Marta Meneghello, Andrea Loro, Sandro Guidi. Thank you guys! Without you this period of my life would have been much quieter... too much!

Among the personnel of the Università Ca' Foscari di Venezia, I would like to cite Prof. Vittorio Lucchini, Prof. Stefano Paganelli, and the guys of the group of Prof. Ottorino De Lucchi. Without their support all this work would have been impossible!

A very special thank goes to Dr. Martyn Earle and Prof. Kenneth R. Seddon who had the idea to study the synthesis of Tadalafil and welcomed me at the Queen's University Ionic Liquid Laboratories (QUILL) centre at the University of Belfast. I want also to thank all the people of the QUILL centre who spent time with me, working in the lab and getting drunk at the pub.

Thanks to all the personnel of Galentis S.r.l. who make my periods in the company plants and laboratories fruitful, formative and pleasant.

I want also to thank all my friends with whom I spent time having fun and working on interesting projects... thank you guys!

I thank Sara for her comprehension when I was tired and nervous, her contribution to this thesis was much more important than she could ever imagine.

I want to thank my parents Angela and Maurizio for their support during my studies, my sister Giorgia and my grandma Amabile.

Thanks to whom have had the patience to read all this stuff and to whom I forgot to mention.

Marco Noè

A1. Appendix

A2. Chapter 2

Onium ionic liquids made with dimethylcarbonate: green solvents by a green synthesis

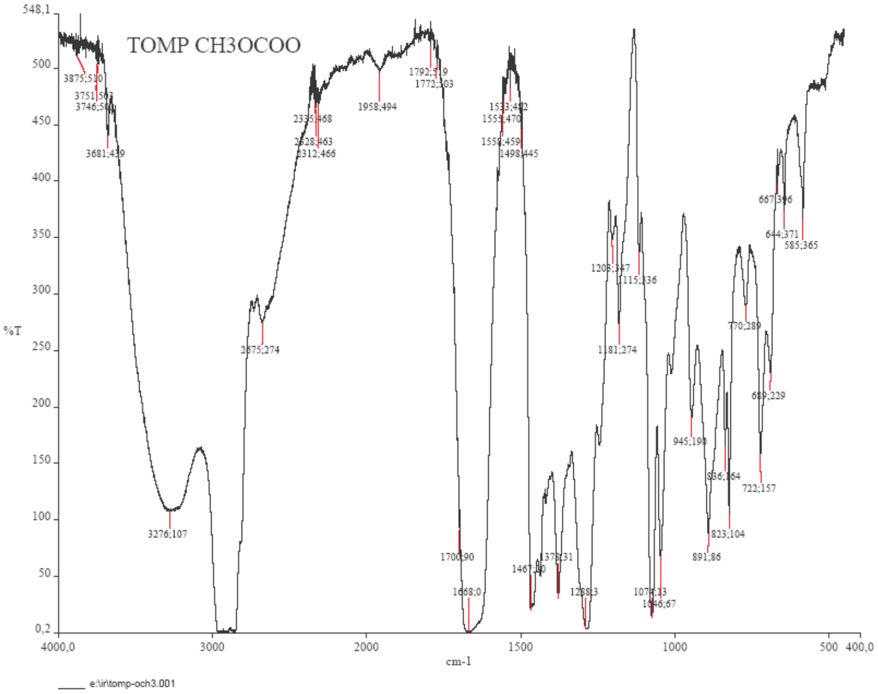

Figure A.2.1. IR spectrum of compound **1a**.

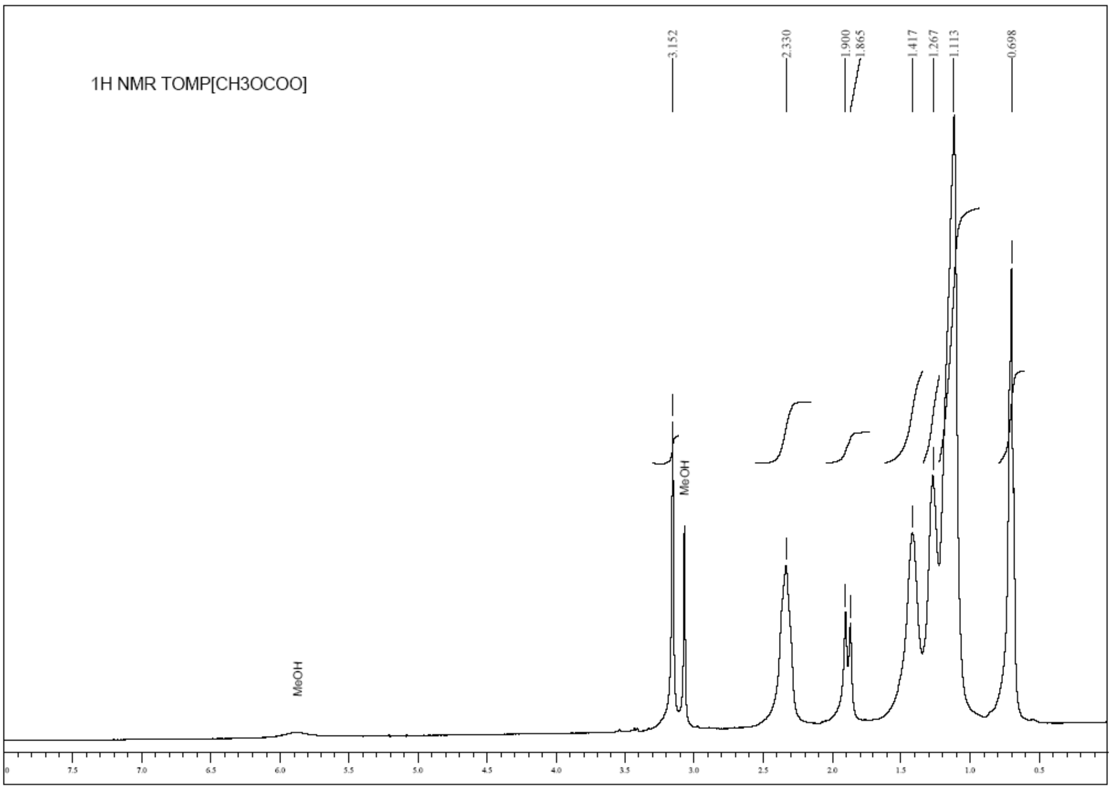

Figure A.2.2. Neat ^{1}H-NMR spectrum of compound **1a**.

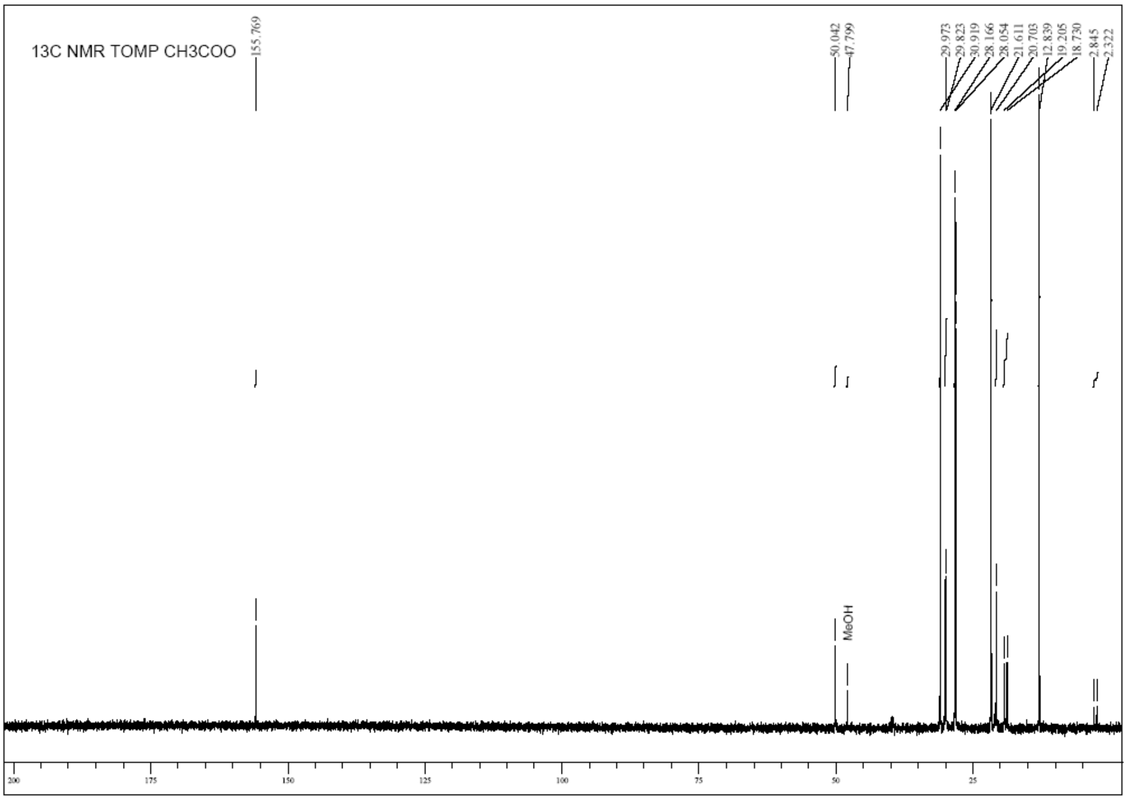

Figure A.2.3. Neat ^{13}C-NMR spectrum of compound **1a**.

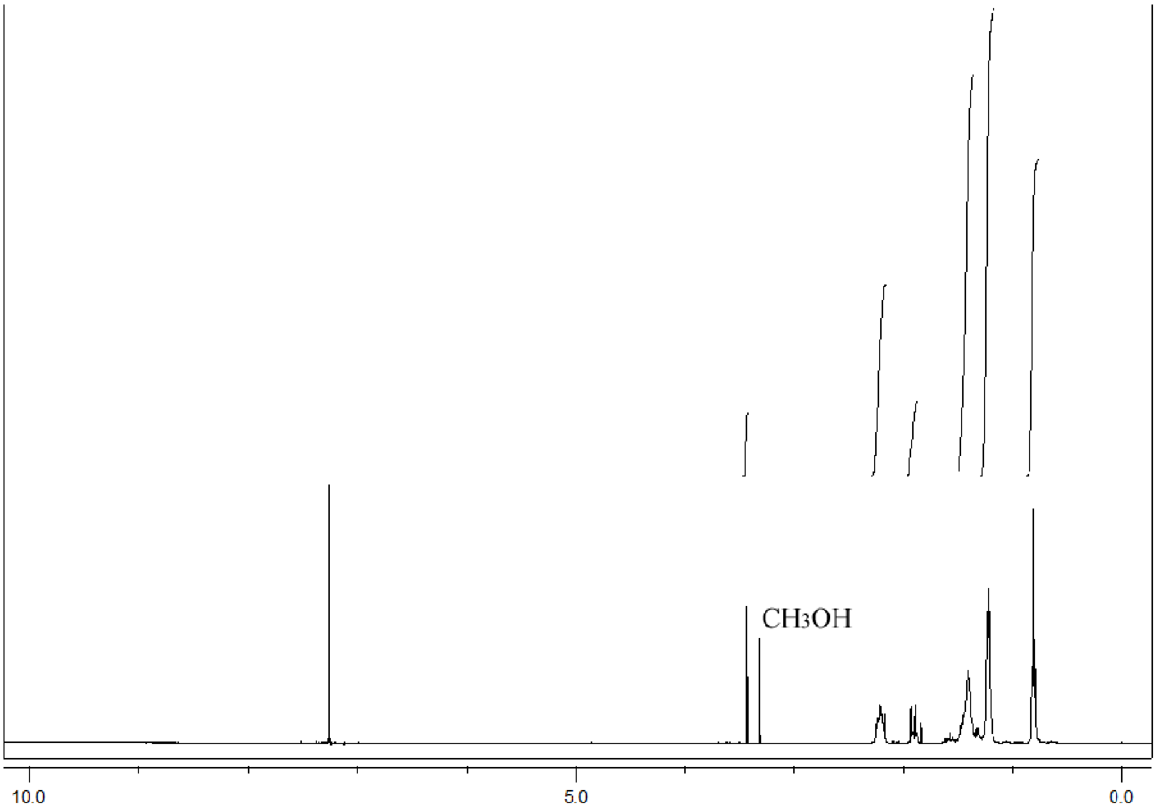

Figure A.2.4. ^{1}H NMR ($CDCl_3$, 400MHz) of compound **1b**.

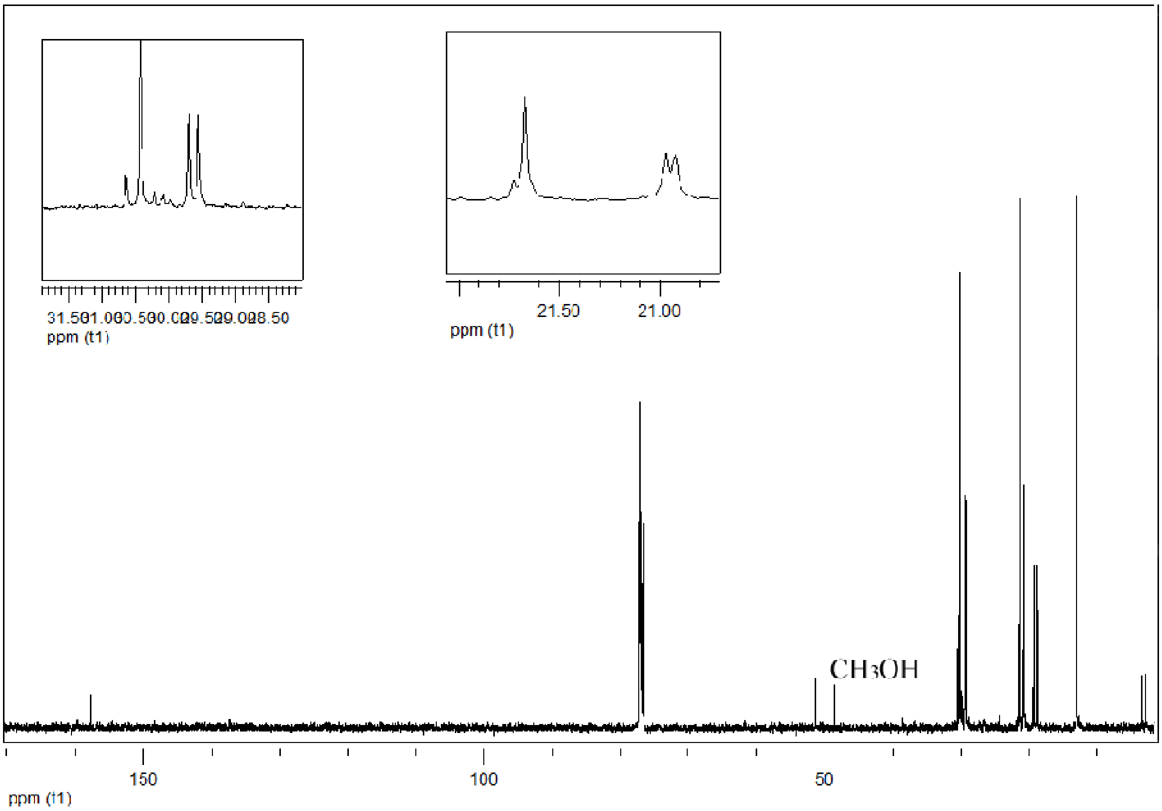

Figure A.2.5 ^{13}C NMR ($CDCl_3$, 100MHz) of spectrum of compound **1b**.

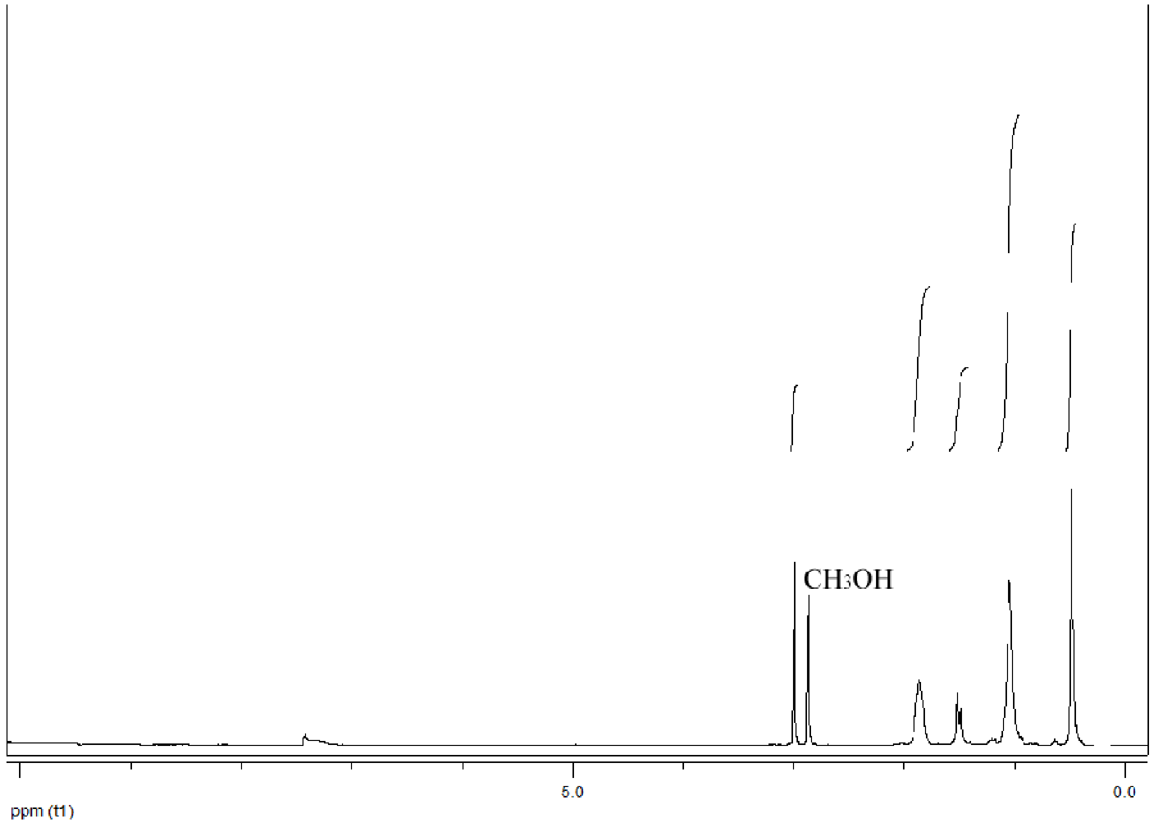

Figure A.2.6. ^{1}H NMR ($CDCl_3$, 400MHz) spectrum of compound **1c**.

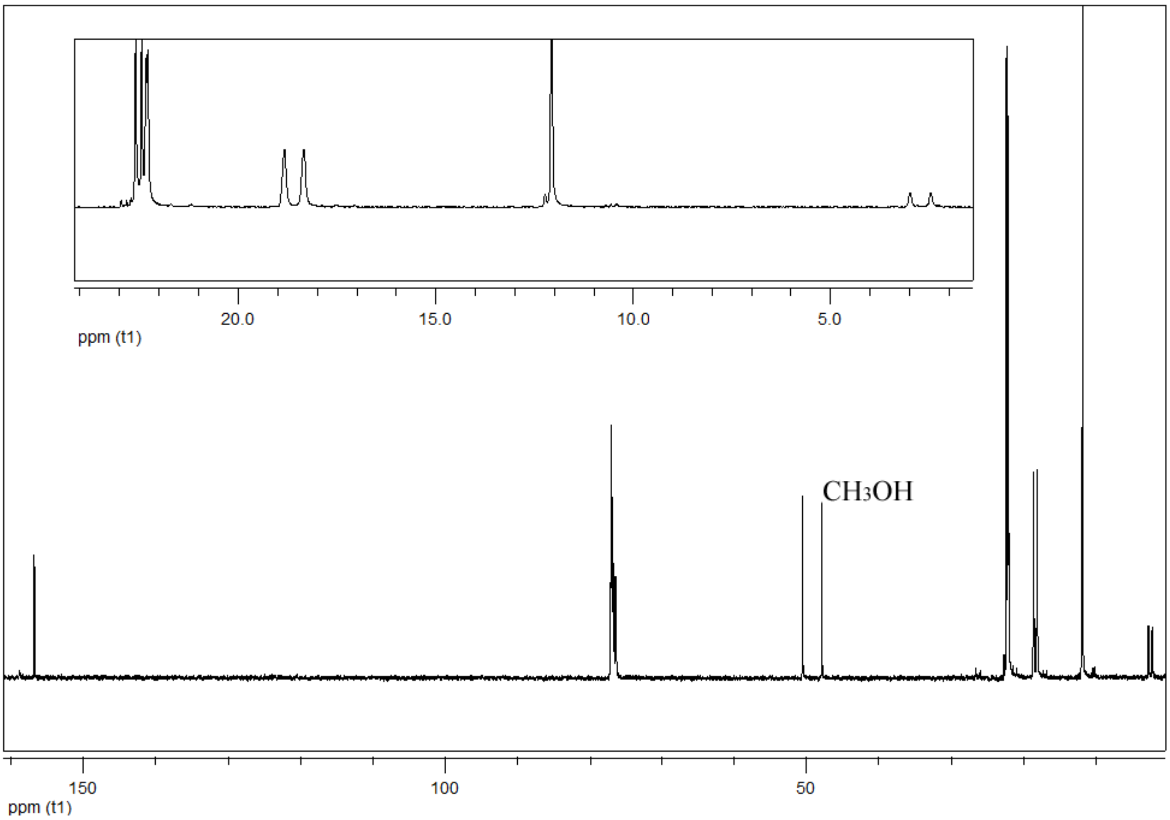

Figure A.2.7. ^{13}C NMR ($CDCl_3$, 100MHz) spectrum of compound **1c**.

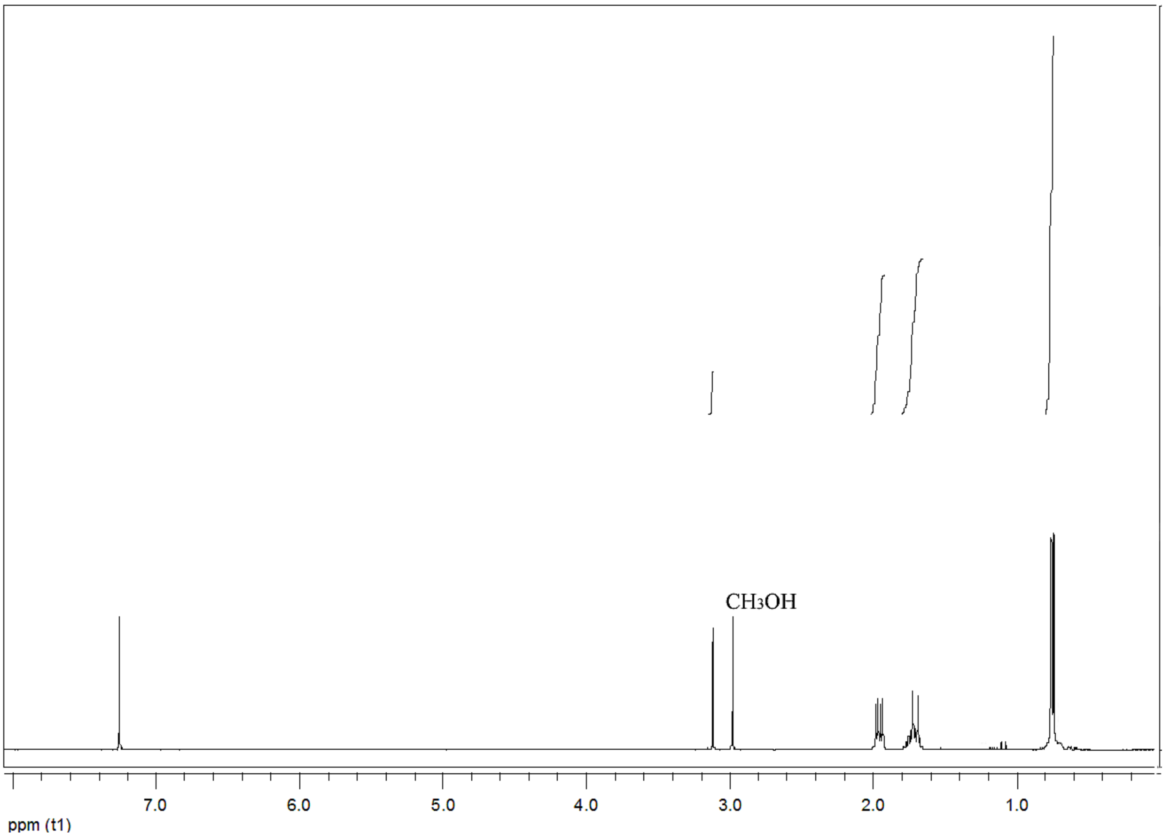

Figure A.2.8. ^{1}H NMR ($CDCl_3$, 400MHz) spectrum of compound **1d**.

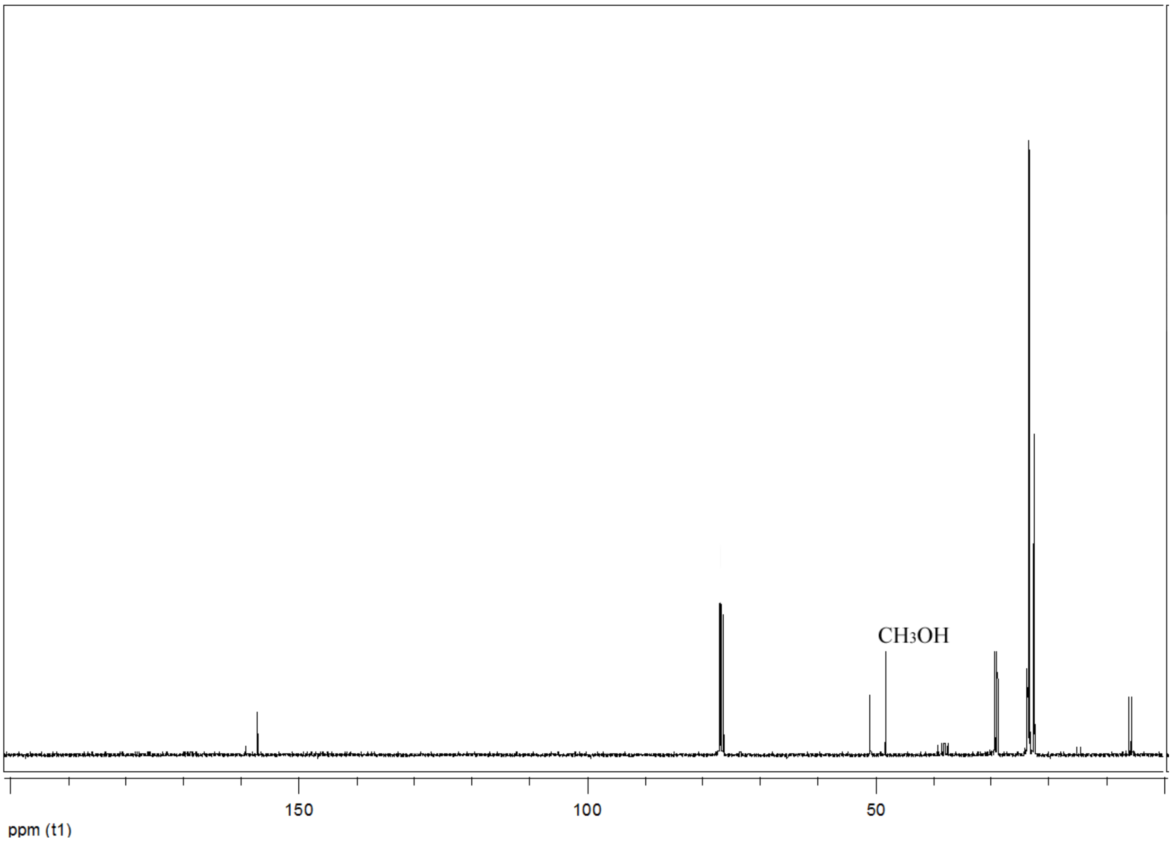

Figure A.2.9. ^{13}C NMR ($CDCl_3$, 100MHz) spectrum of compound **1d**.

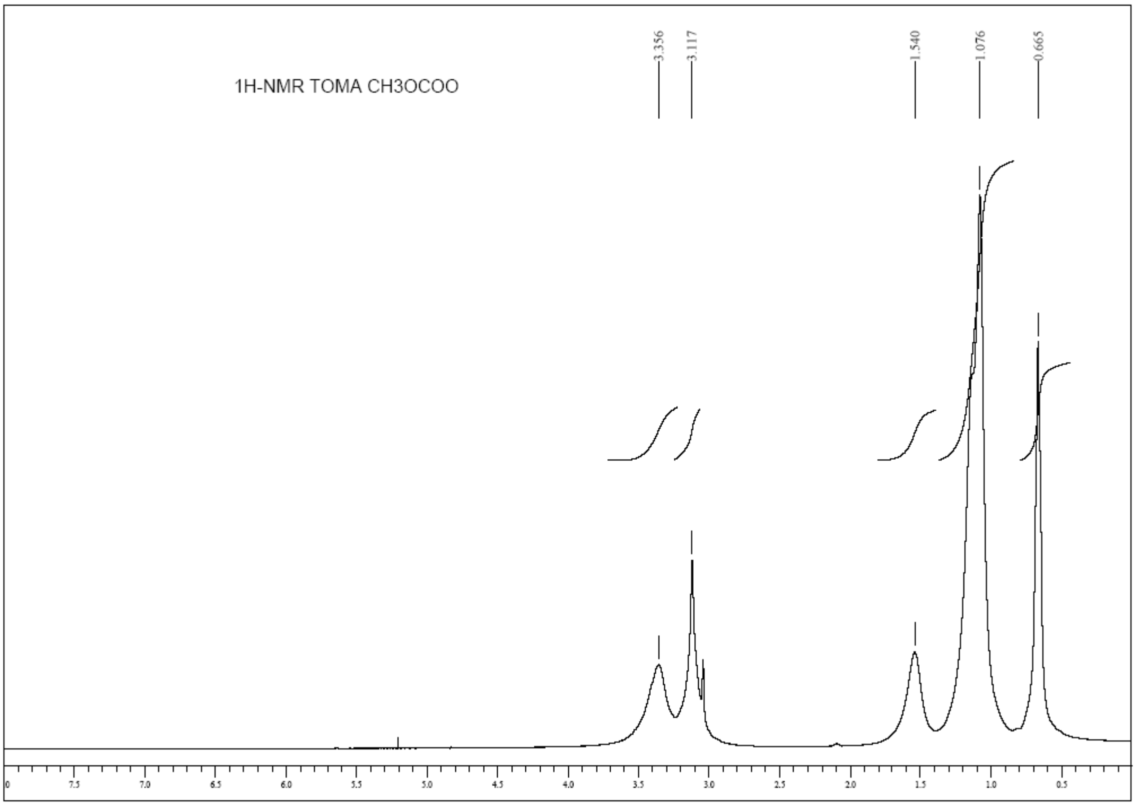

Figure A.2.10. Neat ^{1}H-NMR spectrum of compound **1e**.

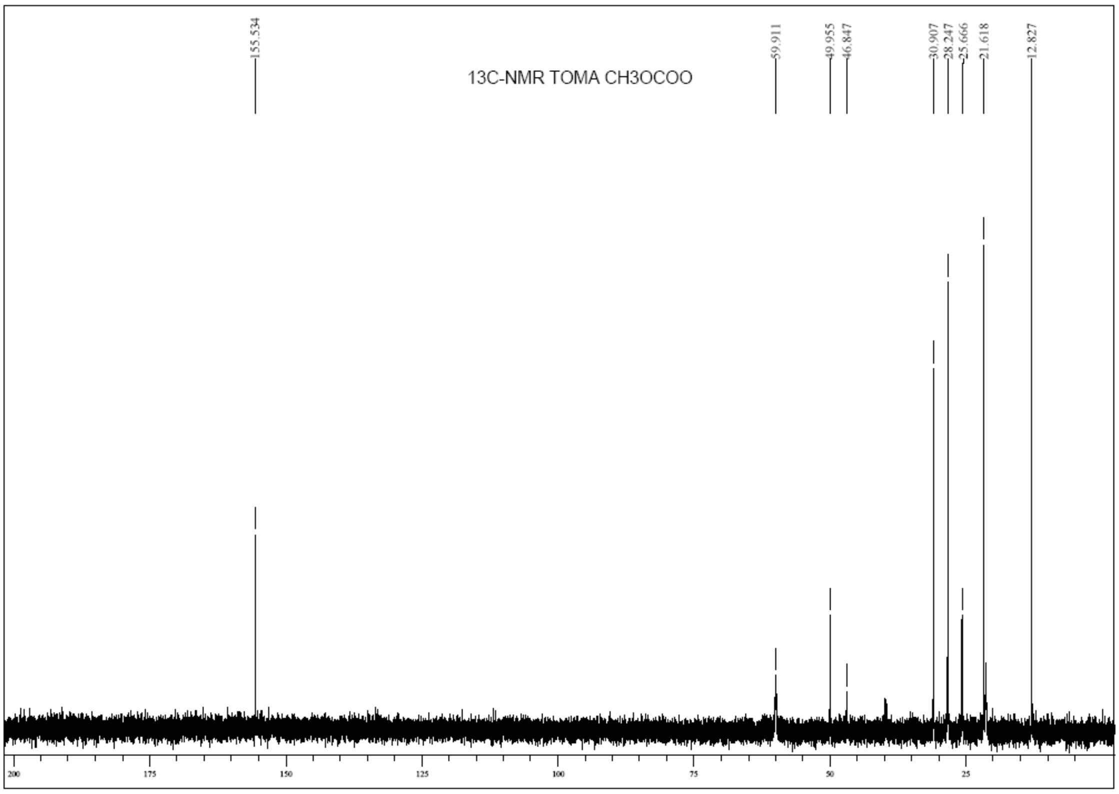

Figure A.2.11. Neat ^{13}C-NMR spectrum of compound **1e**.

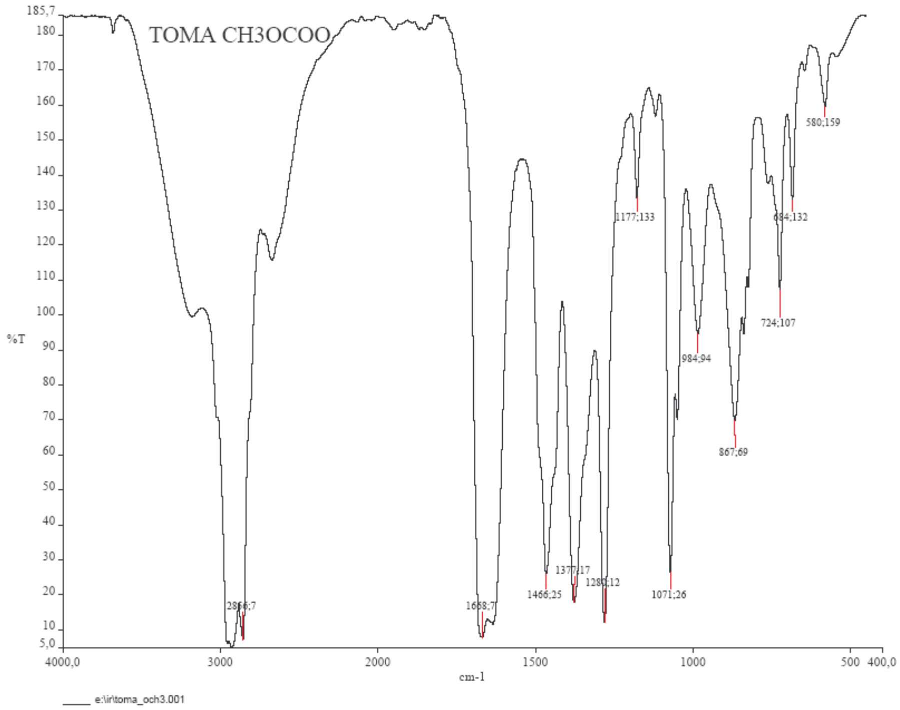

Figure A.2.12. IR spectrum of compound **1e**.

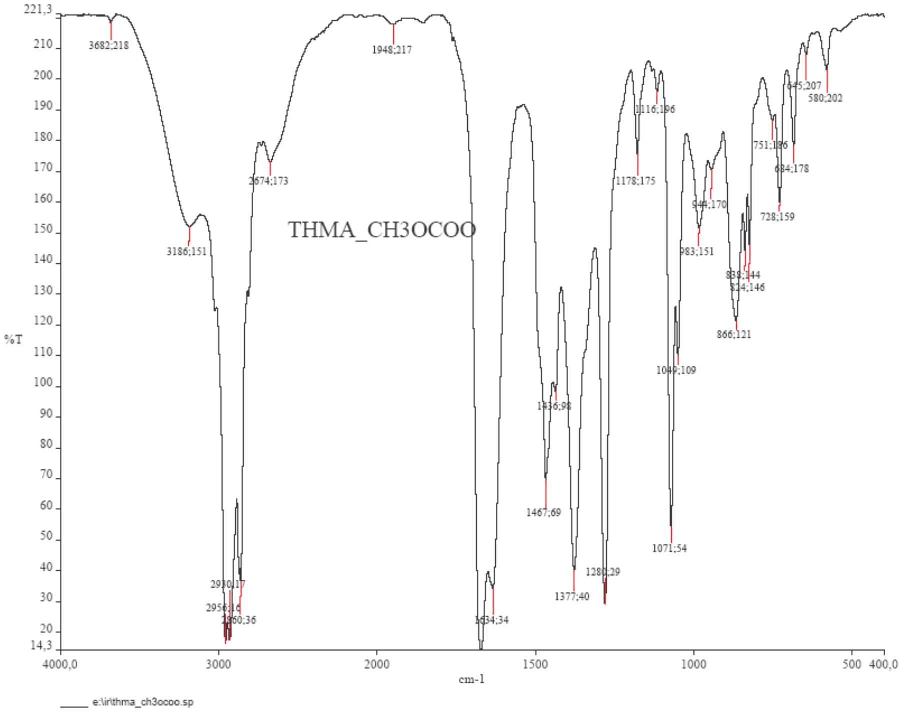

Figure A.2.13. IR spectrum of compound **1f**.

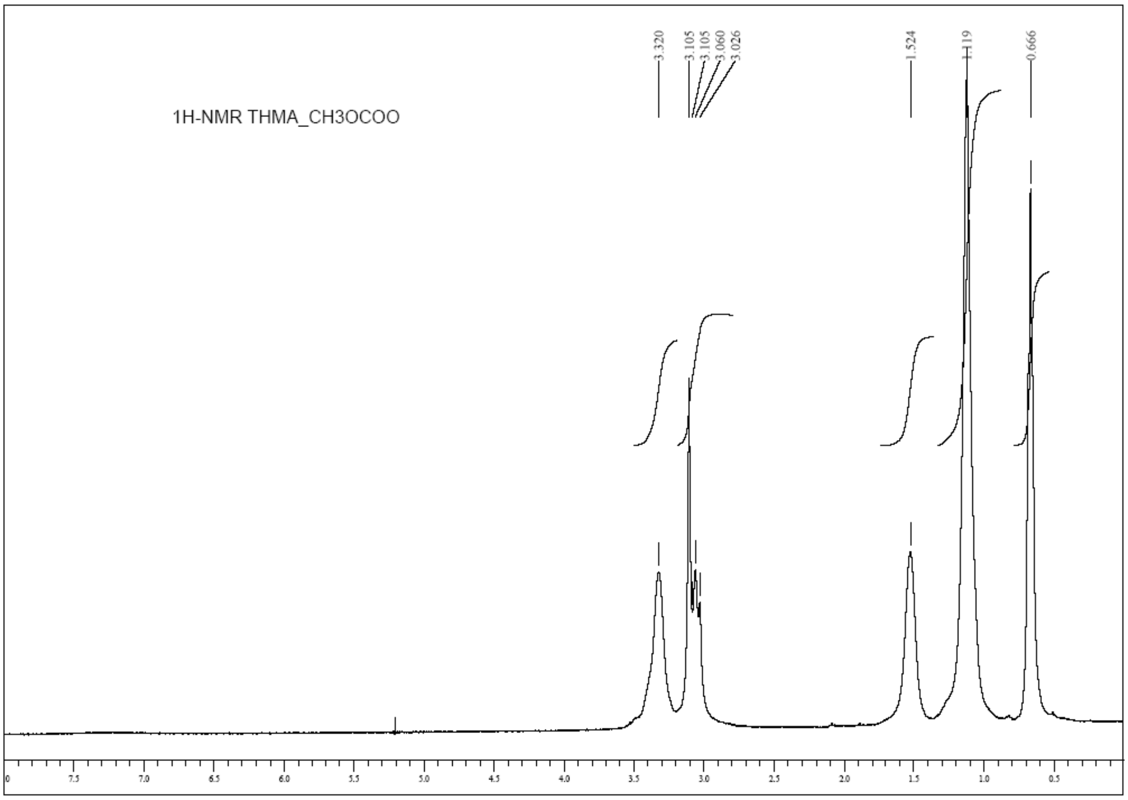

Figure A.2.14. Neat ^{1}H-NMR spectrum of compound **1f**.

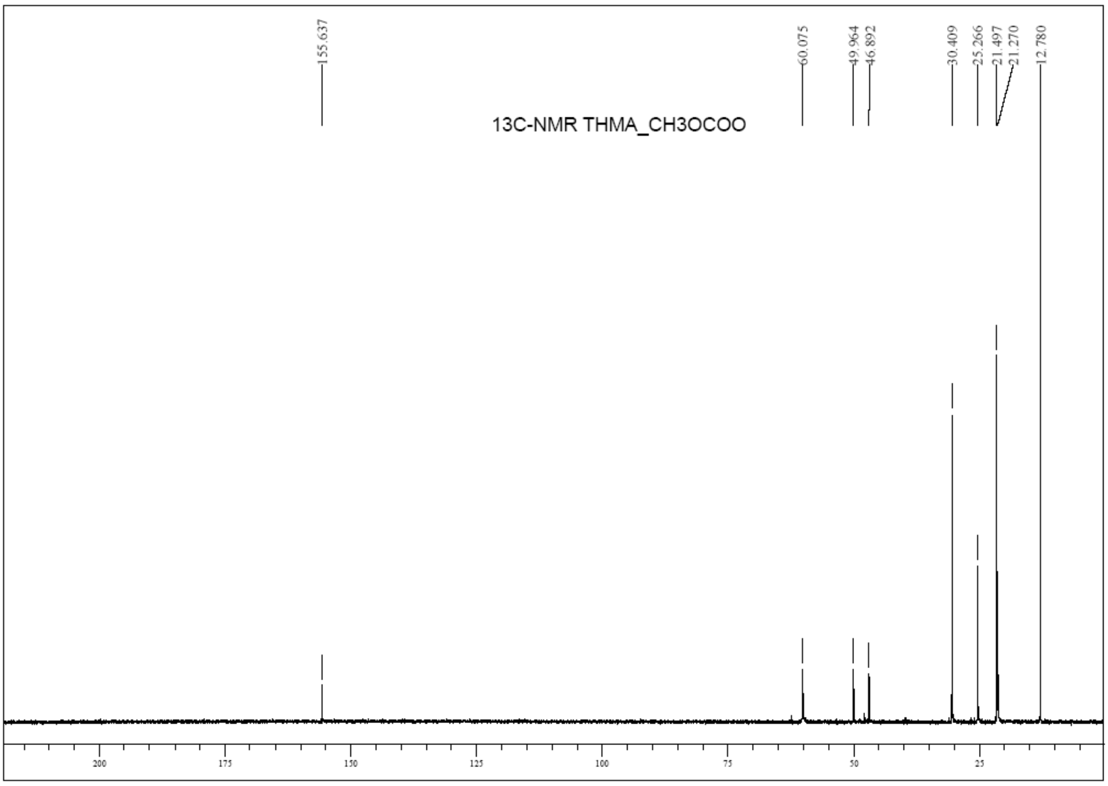

Figure A.2.15. Neat ^{13}C-NMR spectrum of compound **1f**.

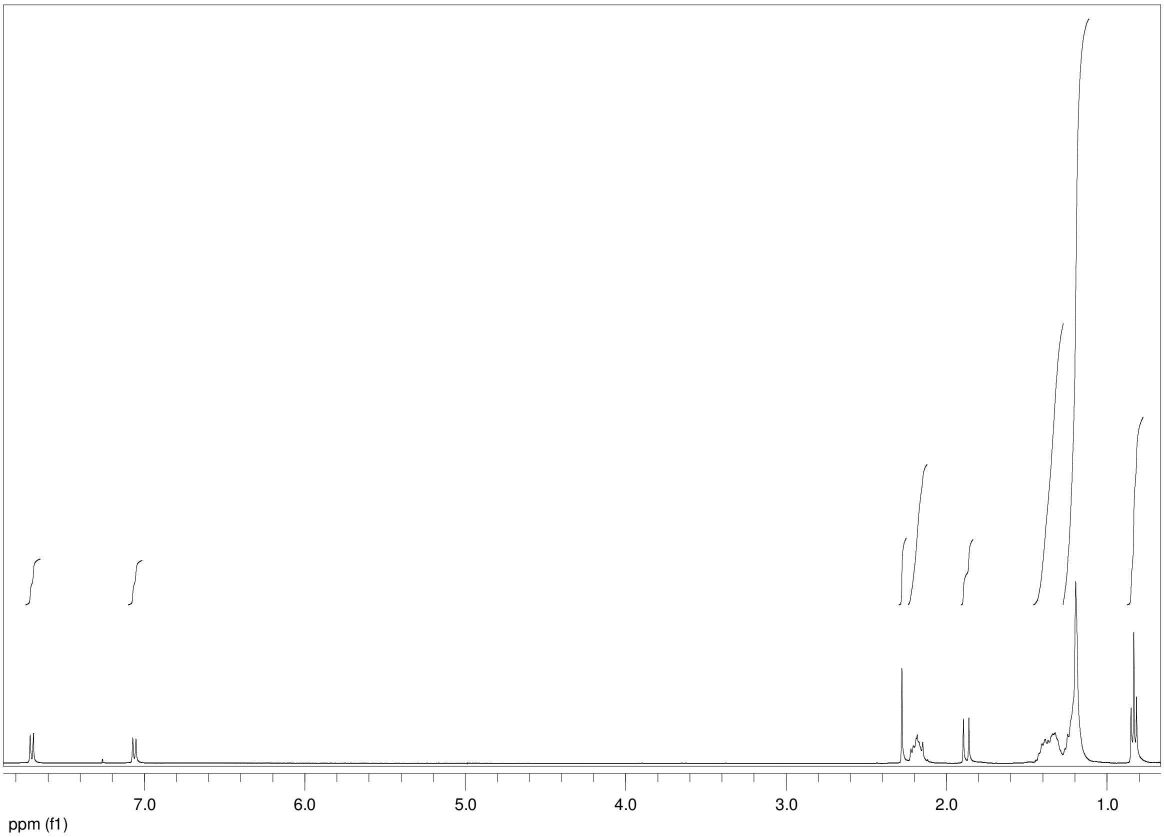

Figure A.2.16. ^{1}H NMR (CDCl$_3$, 400MHz) spectrum of compound **2a**.

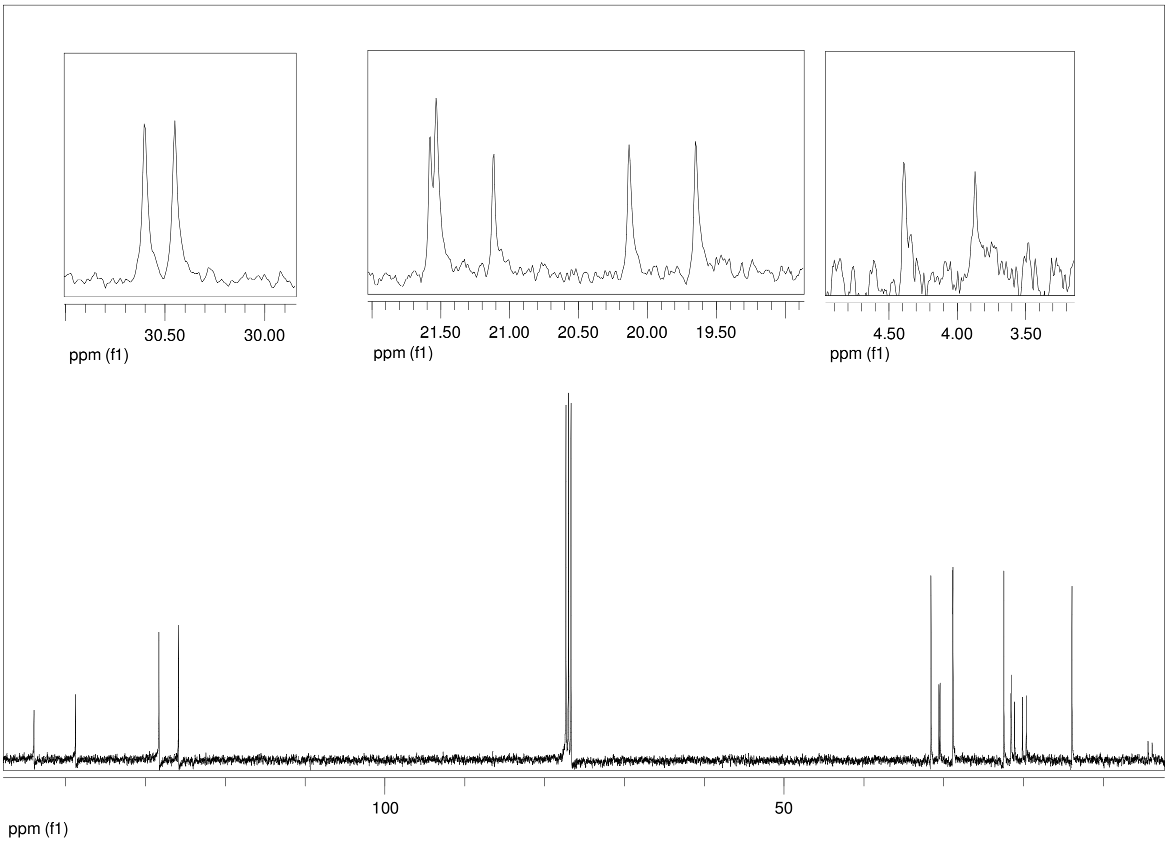

Figure A.2.17. ^{13}C NMR (CDCl$_3$, 100MHz) spectrum of compound **2a**.

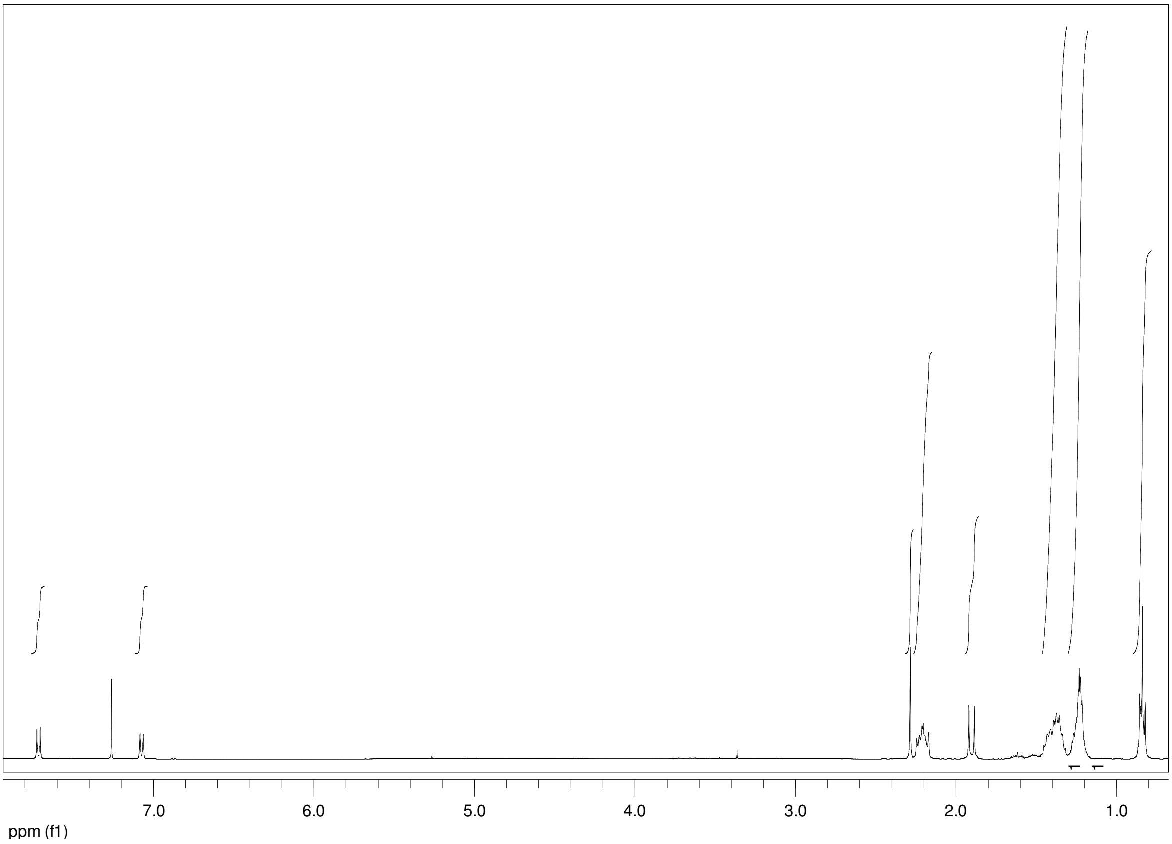

Figure A.2.18. ^{1}H NMR (CDCl$_3$, 400MHz) spectrum of compound **2b**.

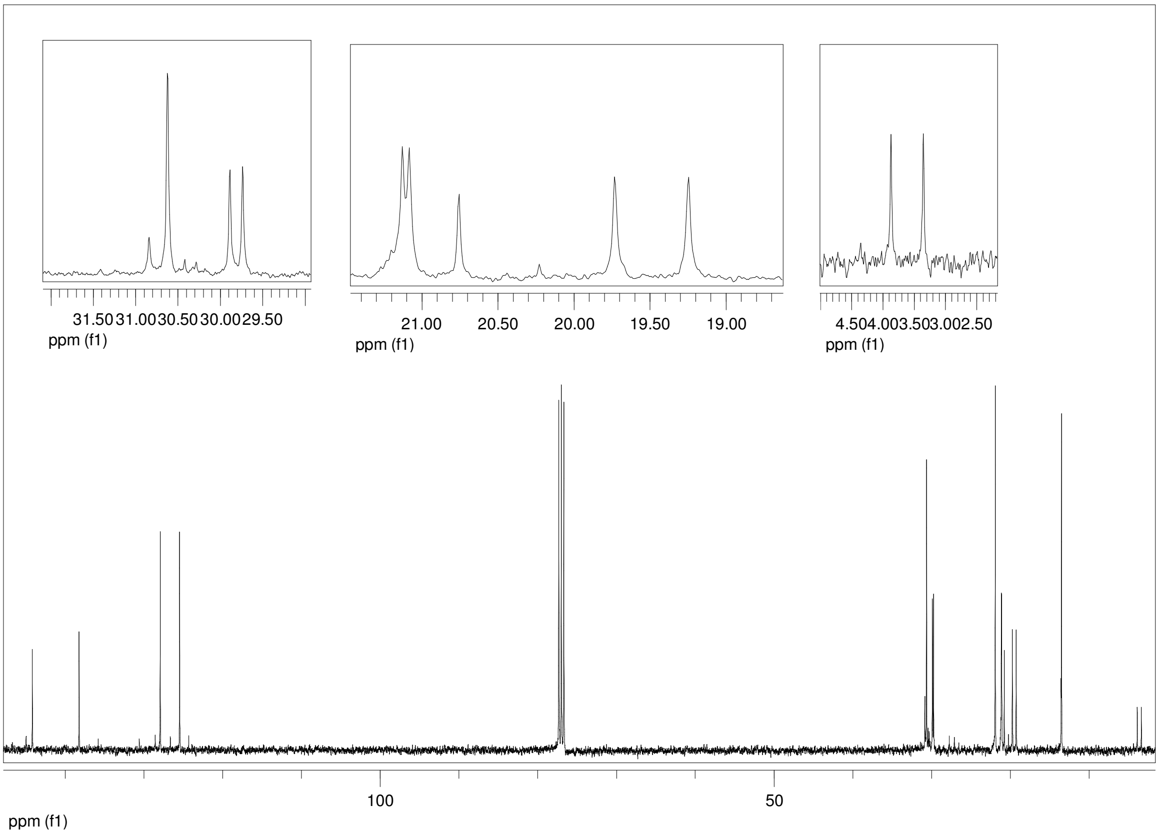

Figure A.2.19. ^{13}C NMR spectrum of compound **2b**.

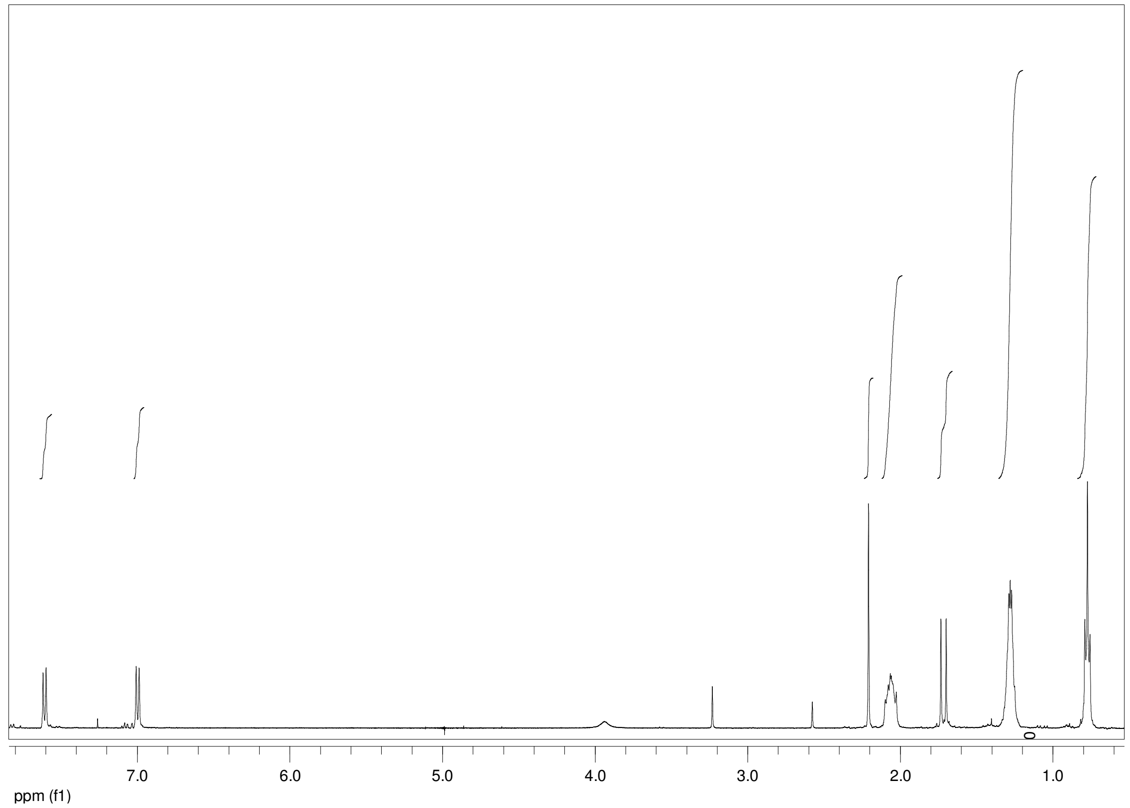

Figure A.2.20. ^{1}H NMR (CDCl$_3$, 400MHz) spectrum of compound **2c**.

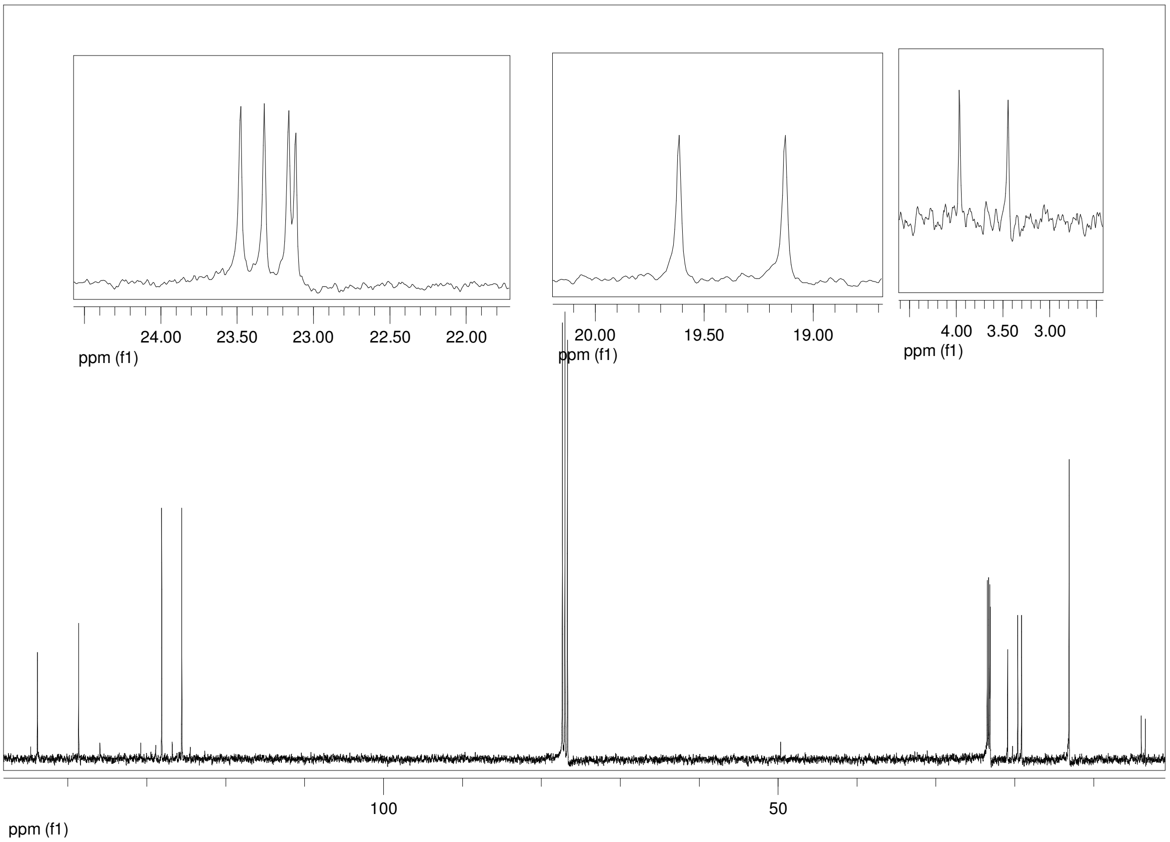

Figure A.2.21. ^{13}C NMR (CDCl$_3$, 100MHz) spectrum of compound **2c**.

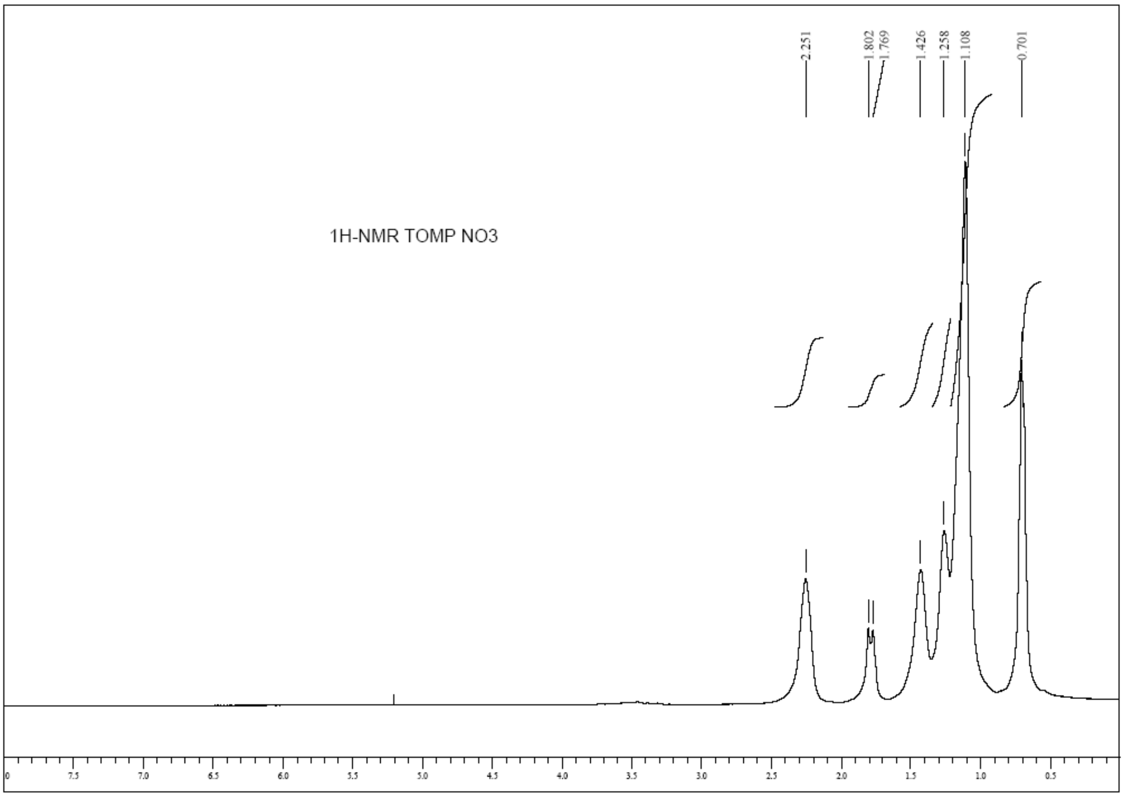

Figure A.2.22. Neat ^{1}H-NMR spectrum of compound **3a**.

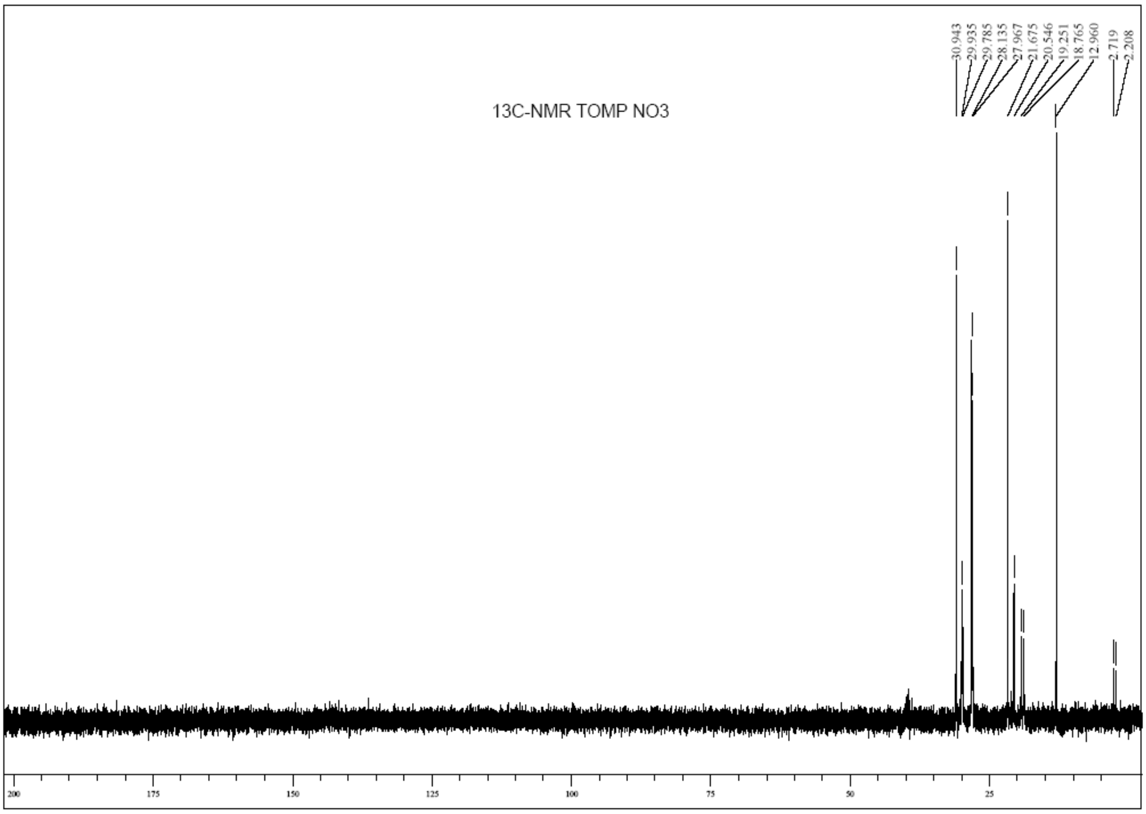

Figure A.2.23. Neat ^{13}C-NMR spectrum of compound **3a**.

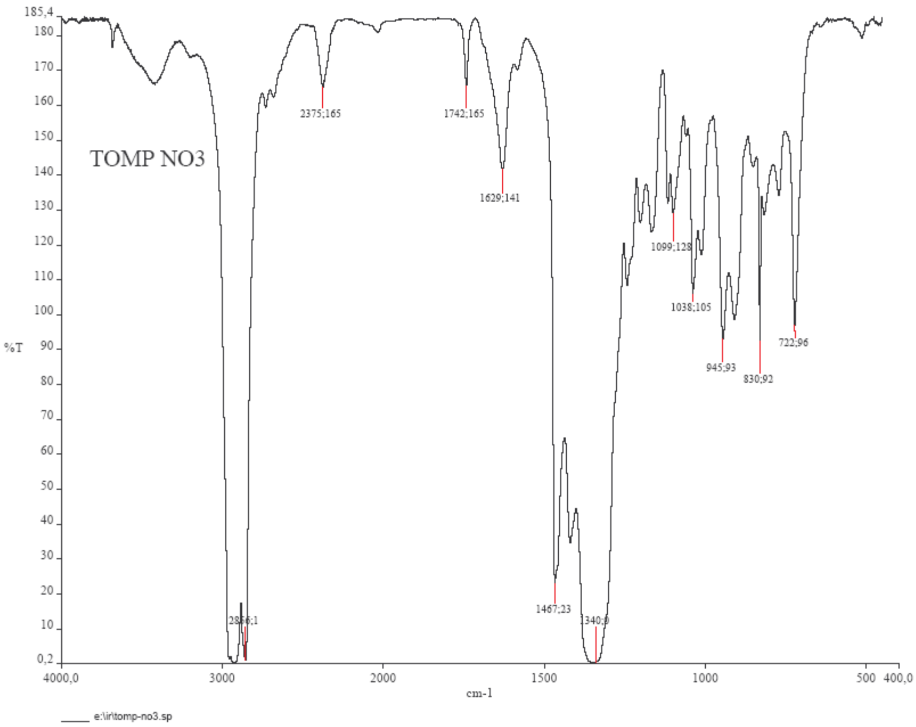

Figure A.2.24. IR spectrum of compound **3a**.

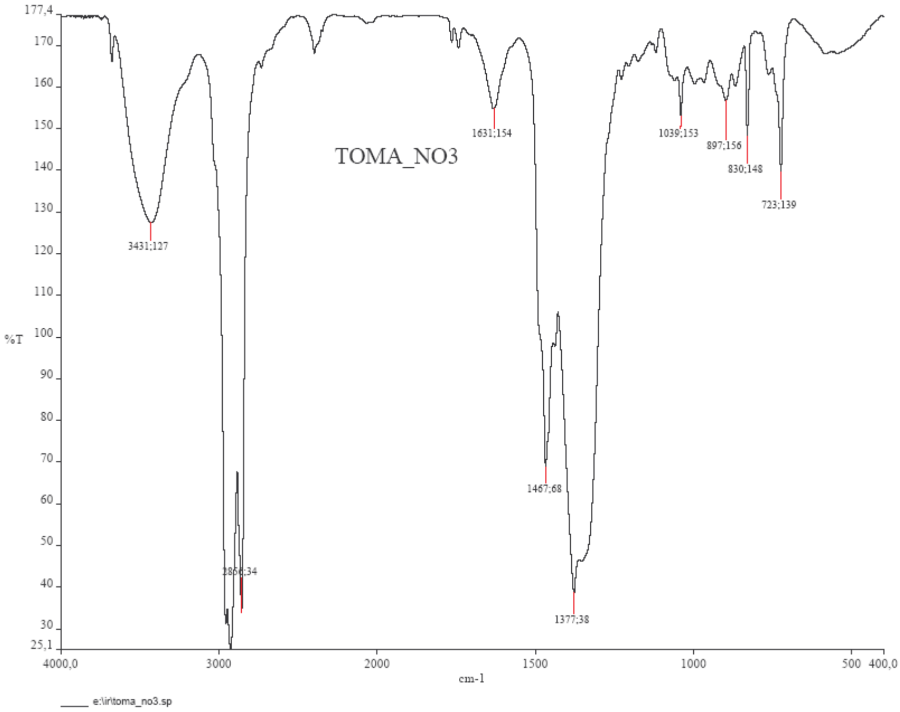

Figure A.2.25. IR spectrum of compound **3e**.

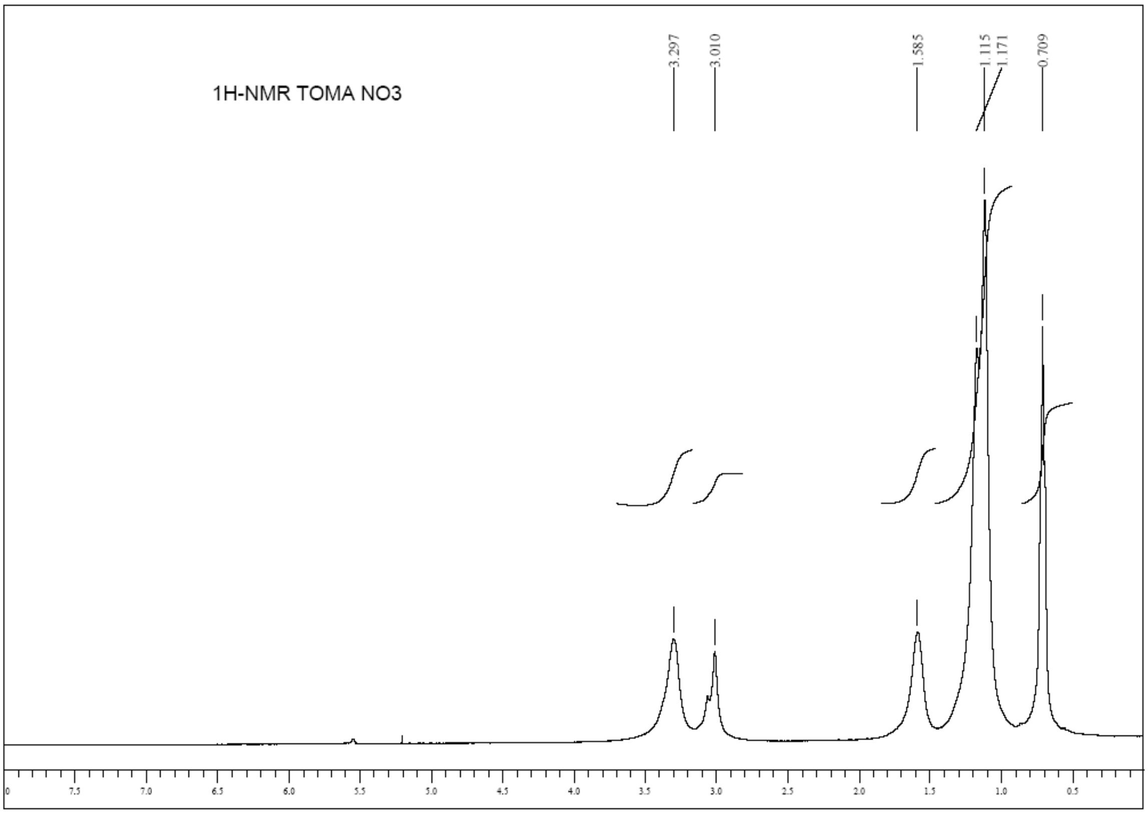

Figure A.2.26. Neat ^{1}H-NMR spectrum of compound **3e**.

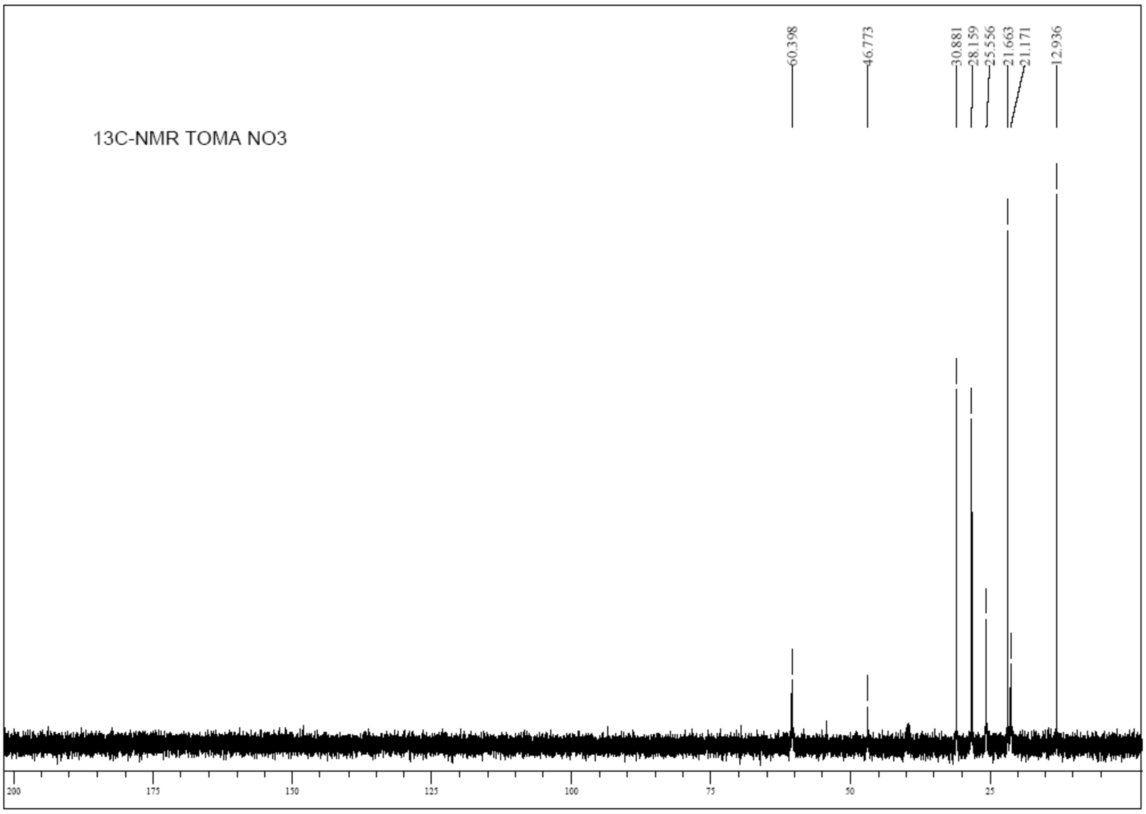

Figure A.2.27. Neat ^{13}C-NMR spectrum of compound **3e**.

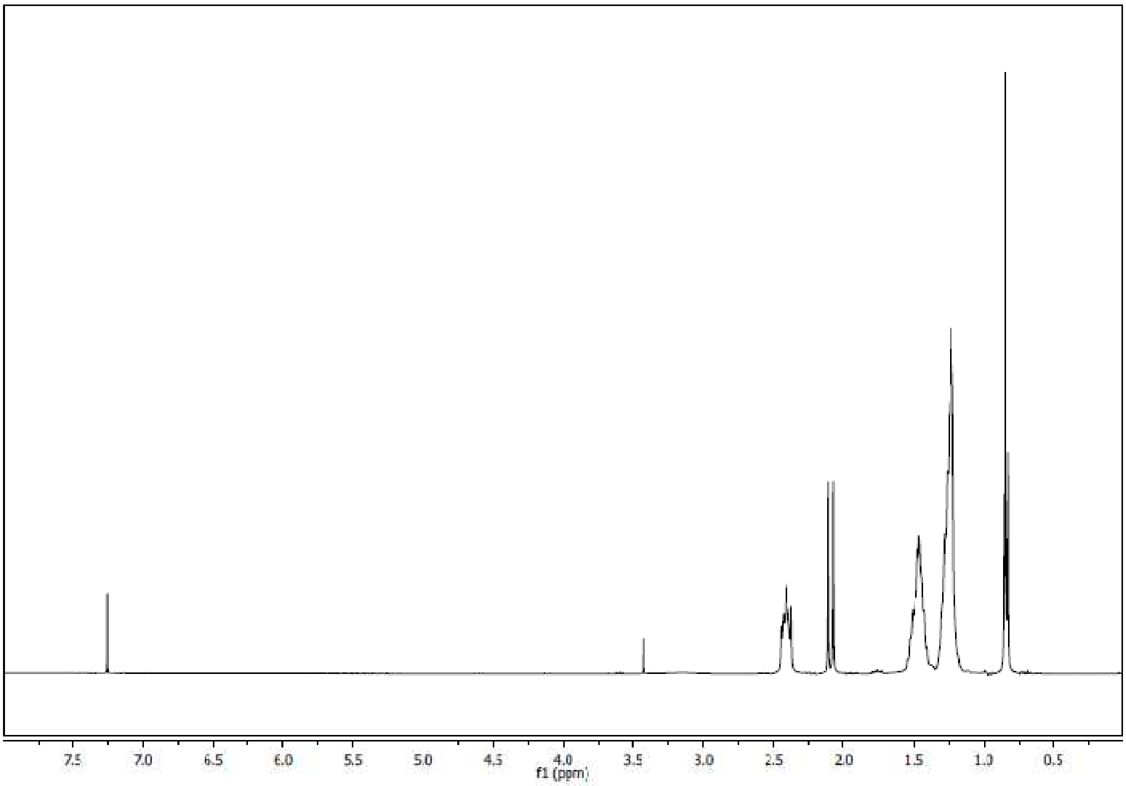

Figure A.2.28. ^{1}H-NMR ($CDCl_3$, 400MHZ) spectrum of compound **4a.**

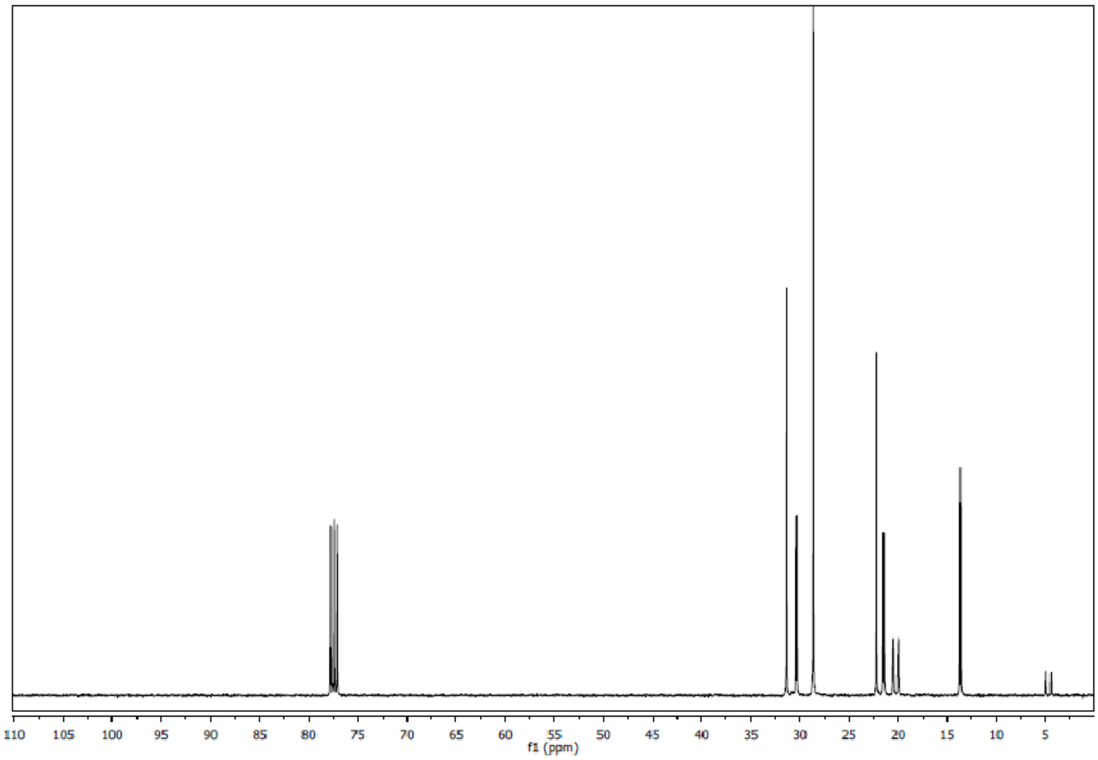

Figure A.2.29. ^{13}C-NMR ($CDCl_3$, 100MHz) spectrum of compound **4a.**

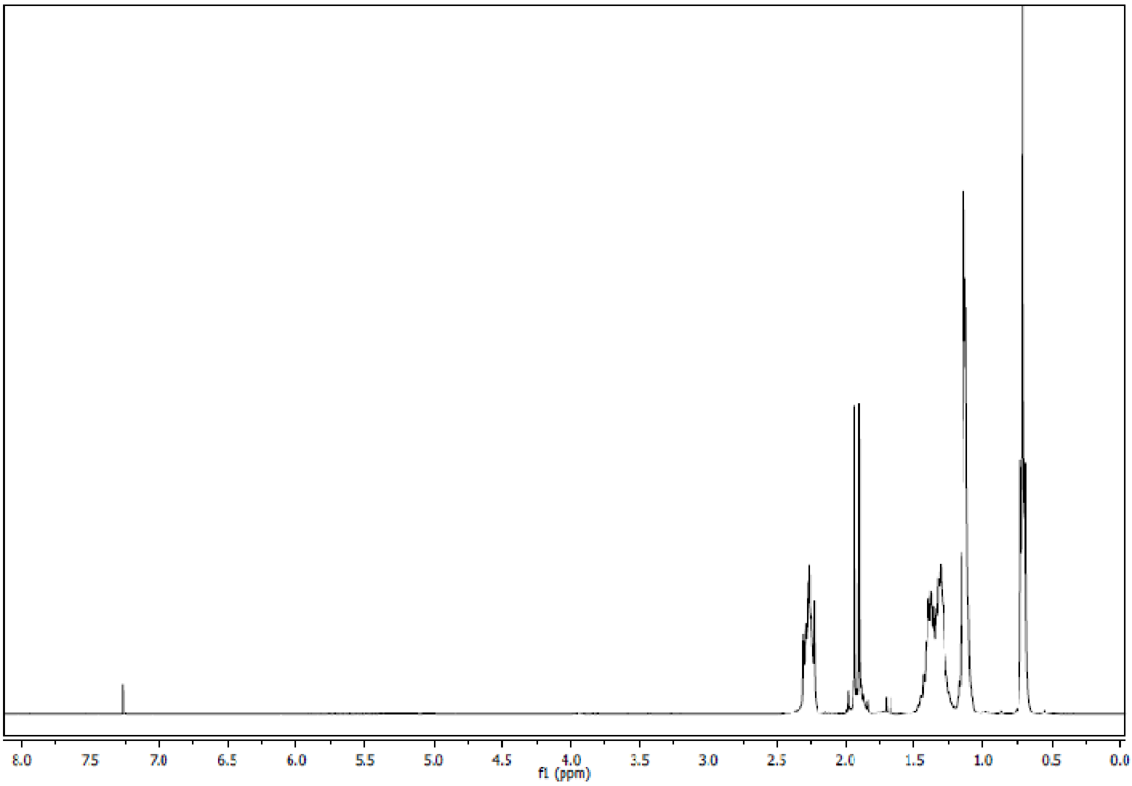

Figure A.2.30 ^{1}H-NMR ($CDCl_3$, 400MHz) spectrum of compound **4b**

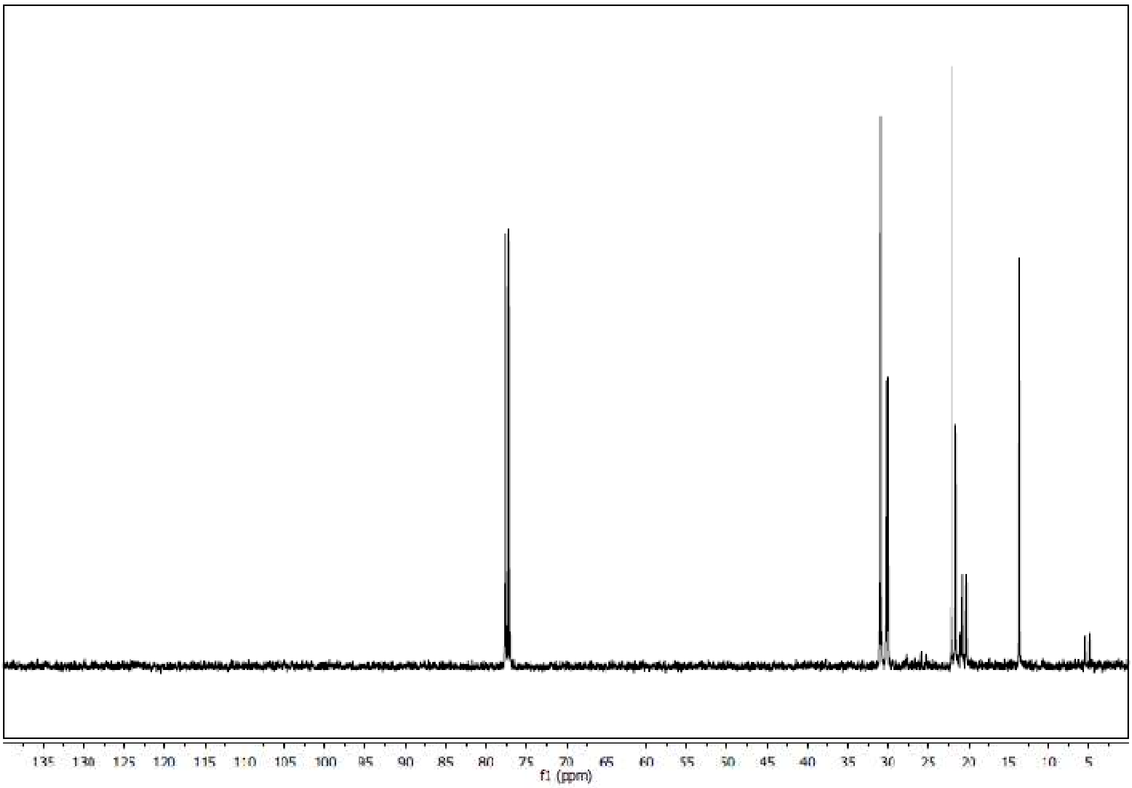

Figure A.2.31. ^{13}C-NMR ($CDCl_3$, 100MHz) spectrum of compound **4b**.

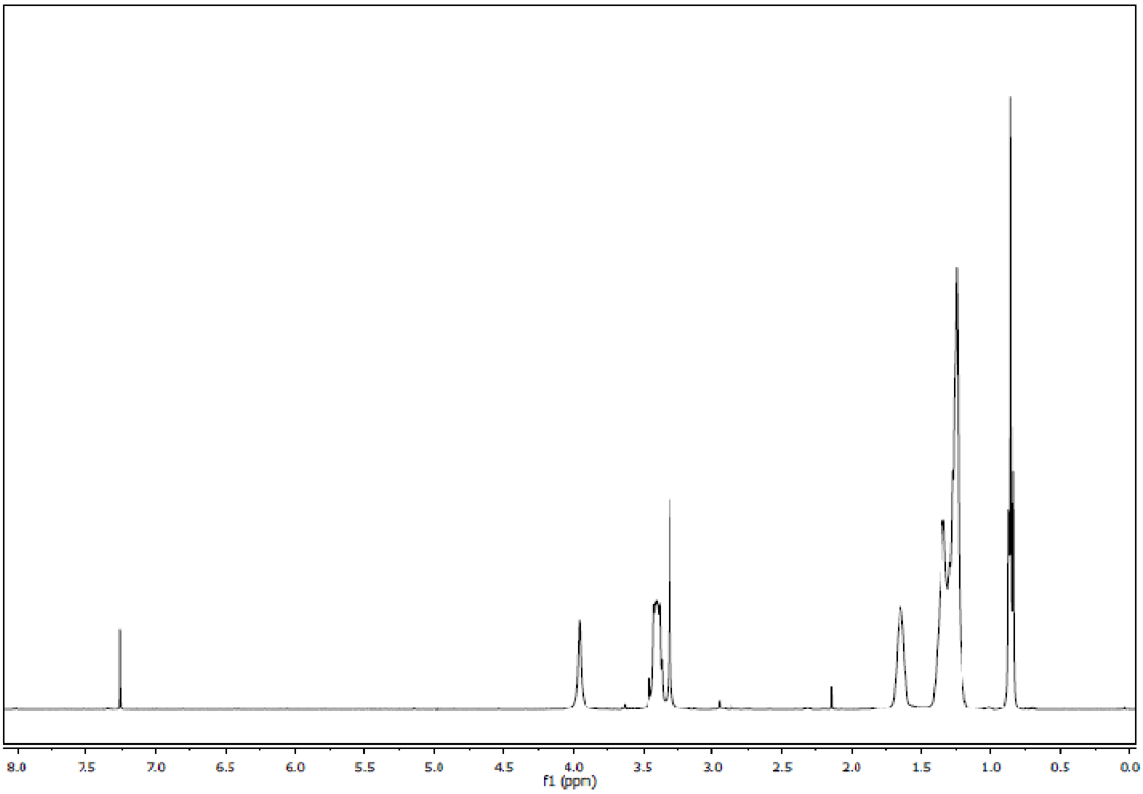

Figure A.2.32. ^{1}H-NMR ($CDCl_3$, 400MHz) spectrum of compound **4e**.

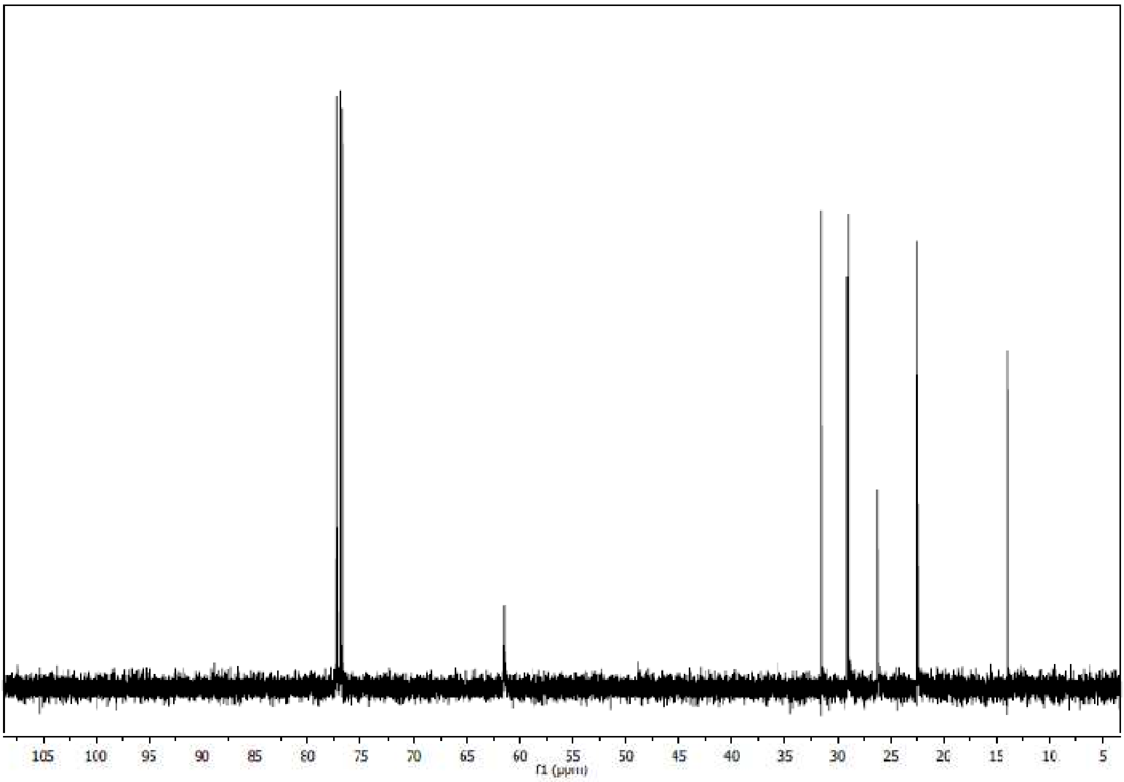

Figure A.2.33. ^{13}C-NMR ($CDCl_3$, 100MHz) spectrum of compound **4e**.

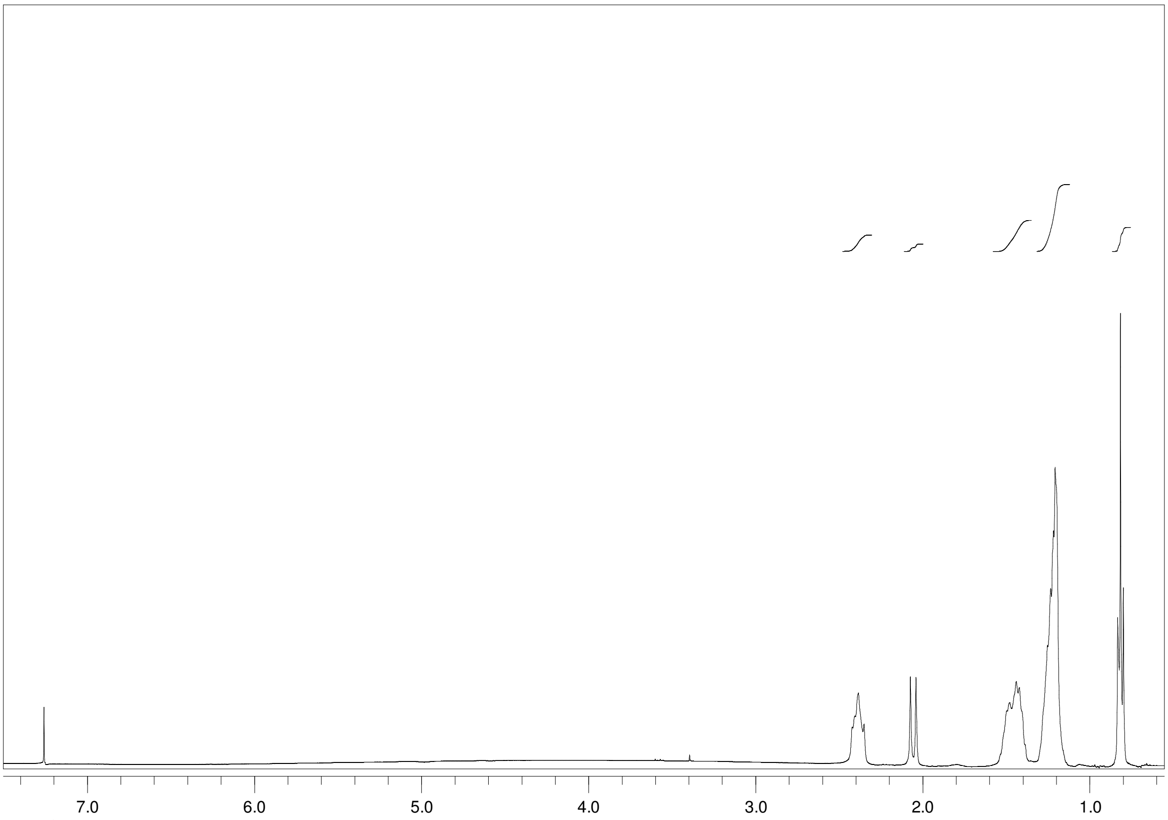

Figure A.2.34. ^{1}H NMR ($CDCl_3$, 400MHz) spectrum of compound **5a.**

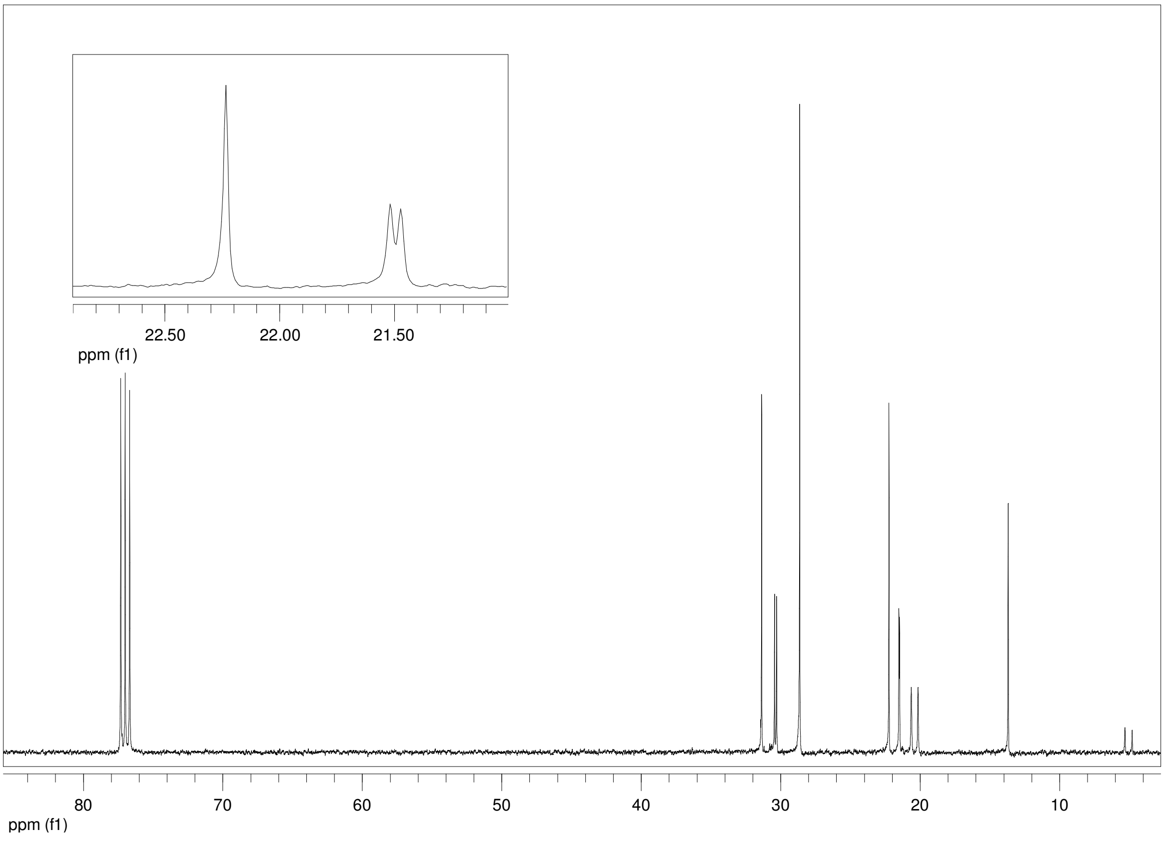

Figure A.2.35. ^{13}C NMR ($CDCl_3$, 100MHz) of spectrum of compound **5a.**

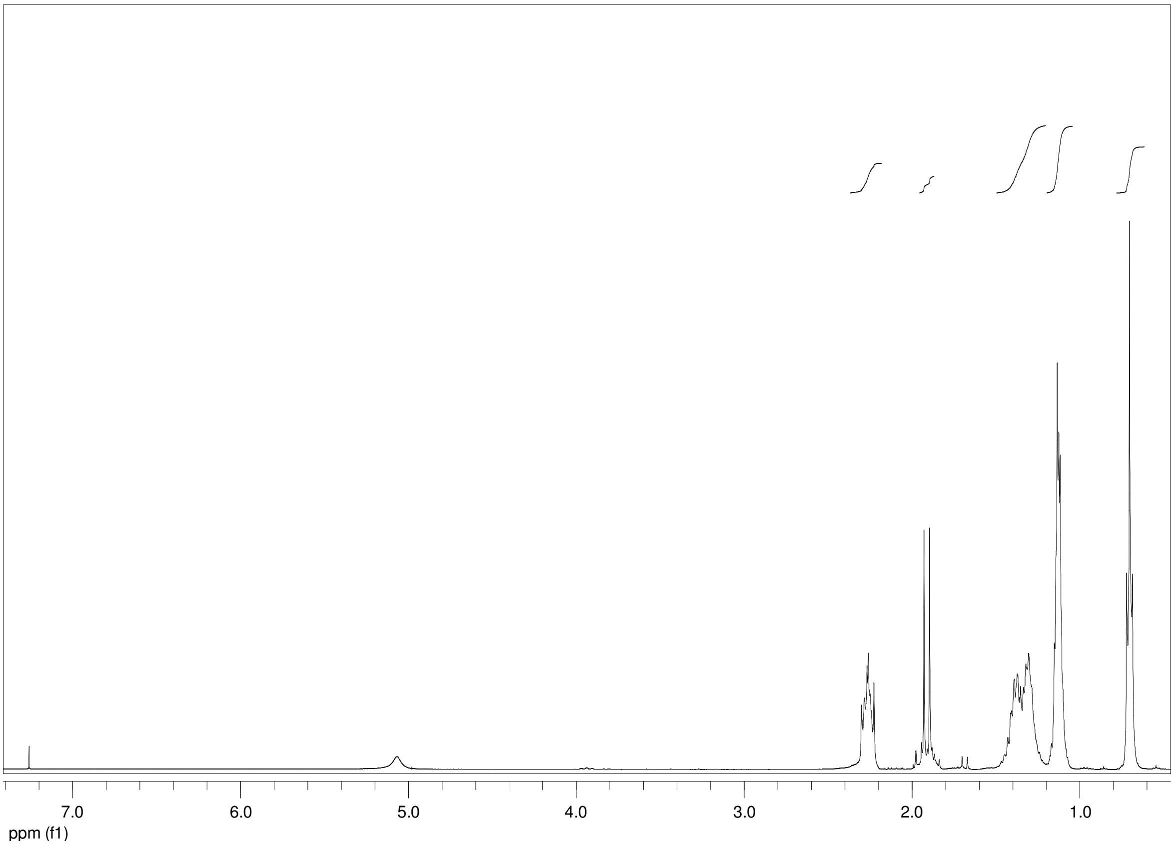

Figure A.2.36. ^{1}H NMR ($CDCl_3$, 400MHz) spectrum of compound **5b**.

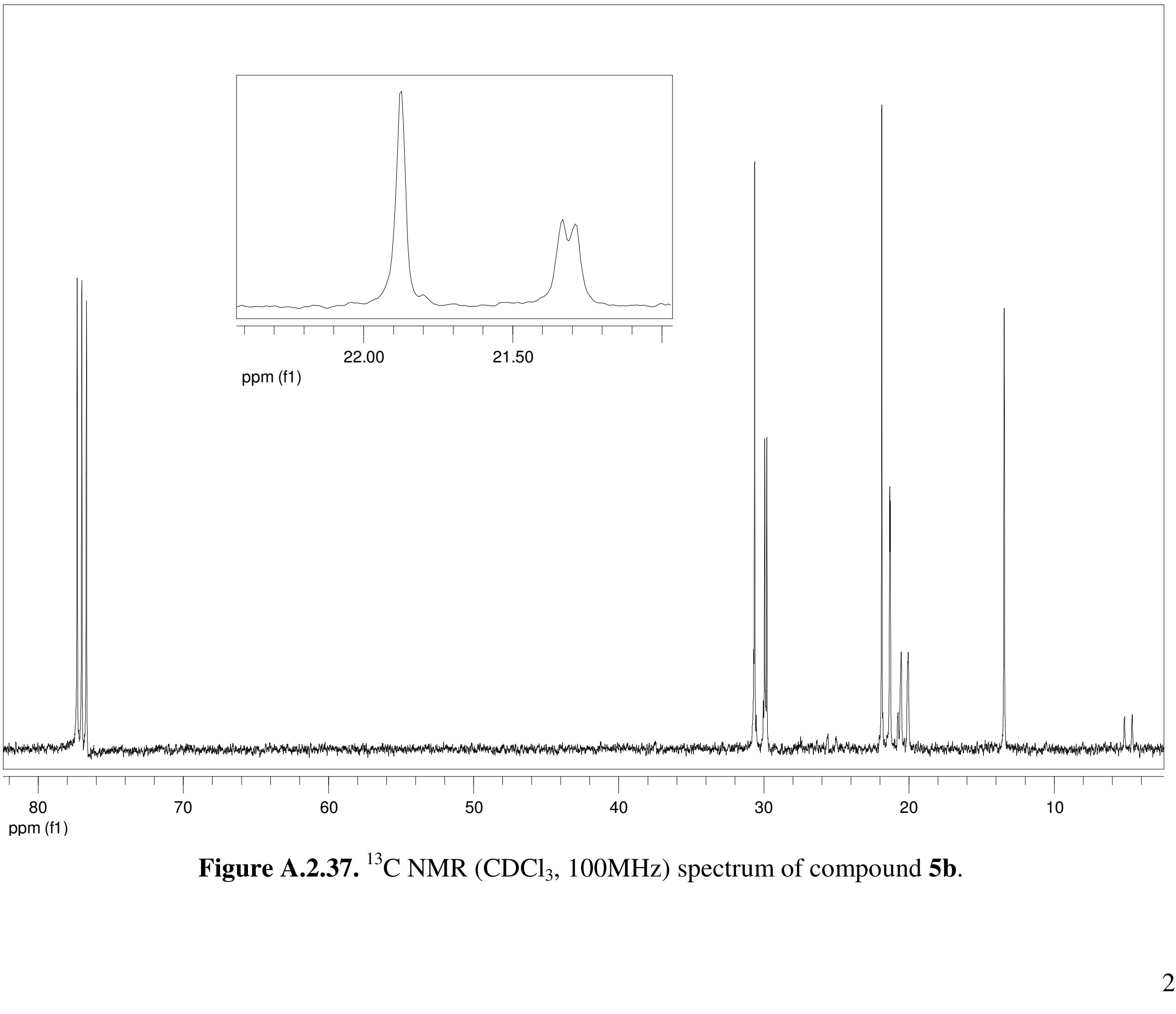

Figure A.2.37. ^{13}C NMR ($CDCl_3$, 100MHz) spectrum of compound **5b**.

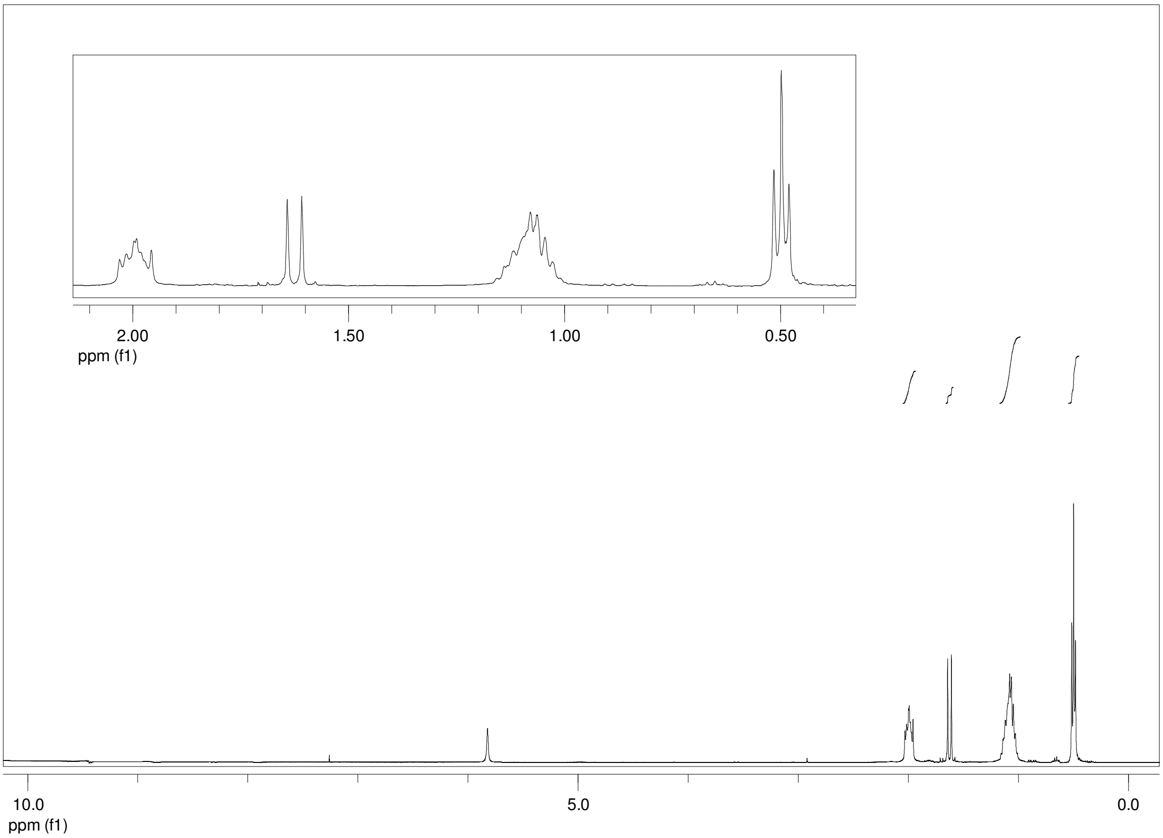

Figure A.2.38. ^{1}H NMR ($CDCl_3$, 400MHz) spectrum of compound **5c**.

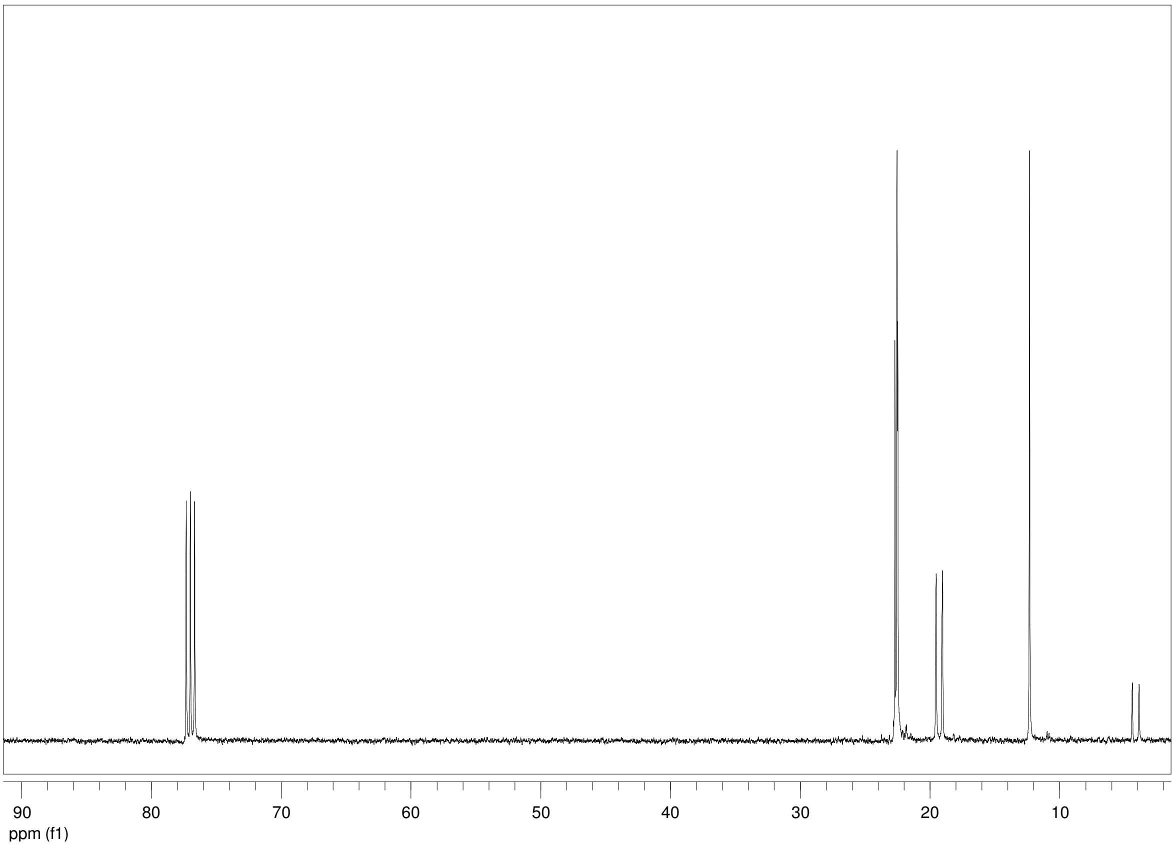

Figure A.2.39. ^{13}C NMR ($CDCl_3$, 100MHz) spectrum of compound **5c**.

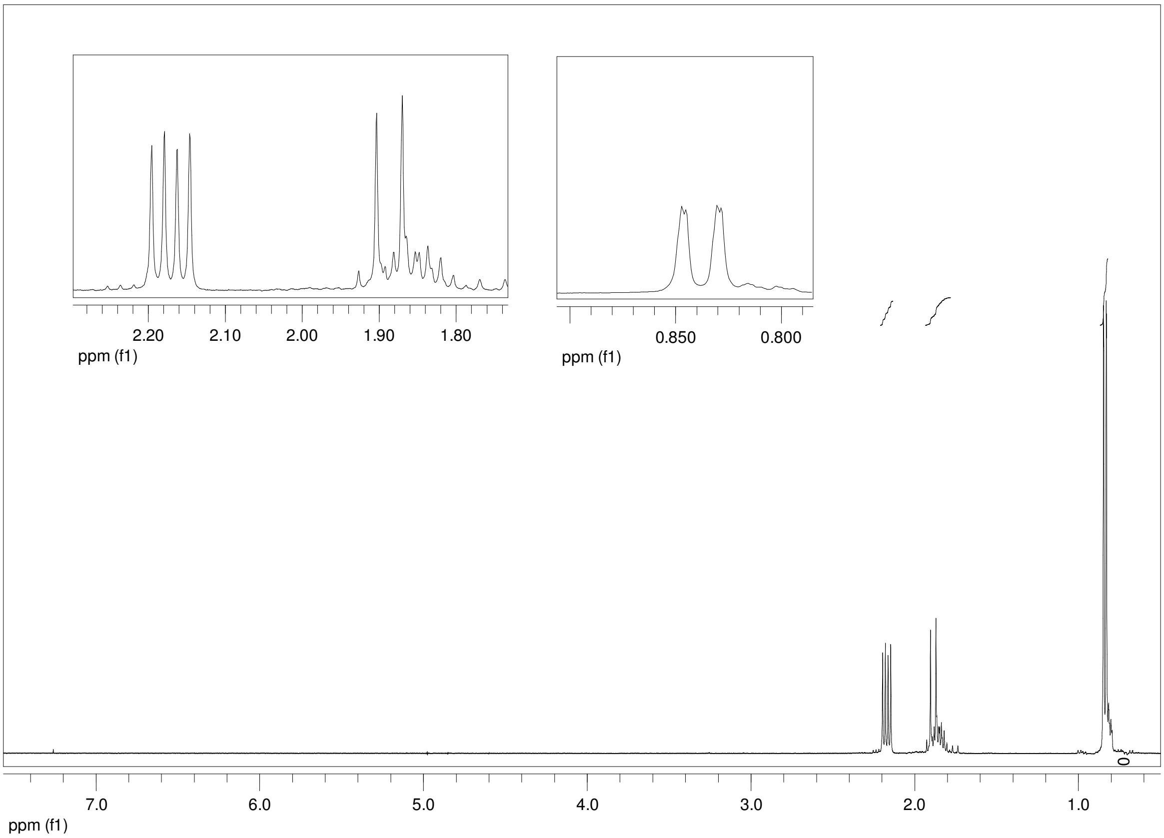

Figure A.2.40. ^{1}H NMR ($CDCl_3$, 400MHz) spectrum of compound **5d**.

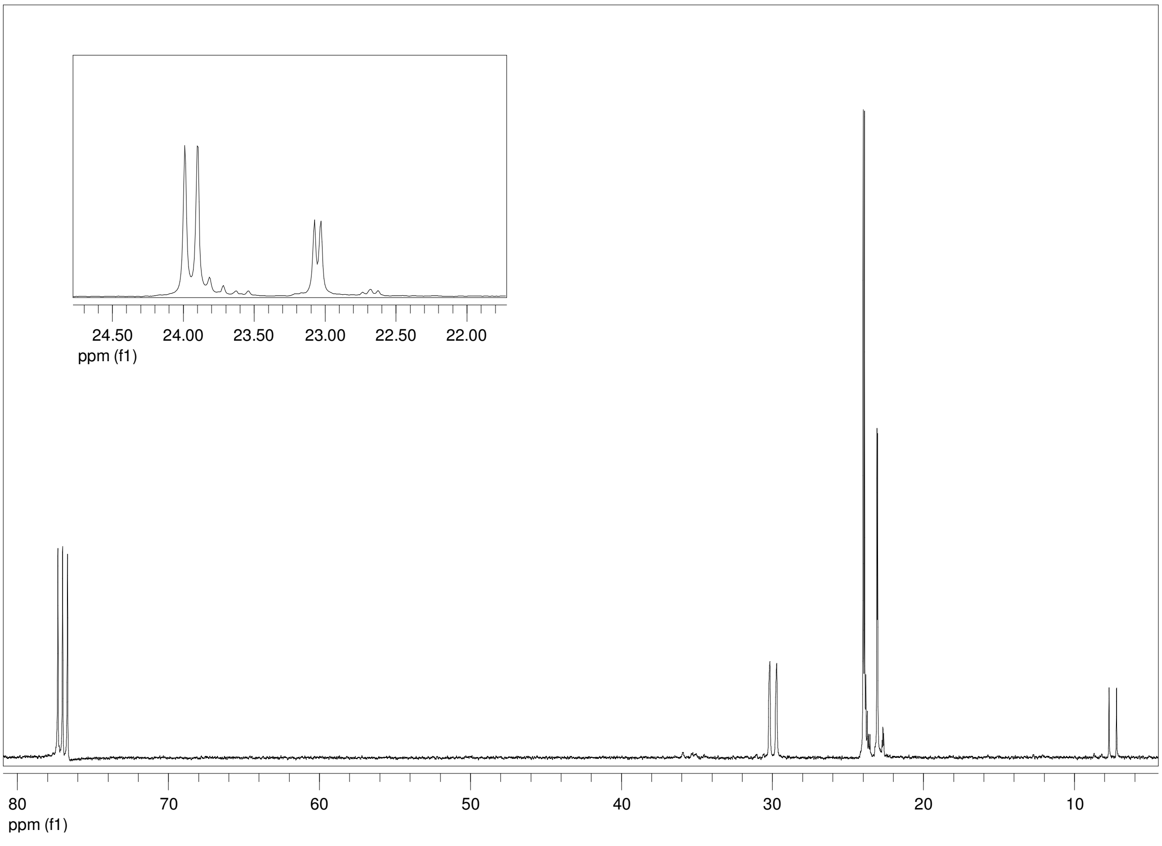

Figure A.2.41. ^{13}C NMR ($CDCl_3$, 100MHz) spectrum of compound **5d**.

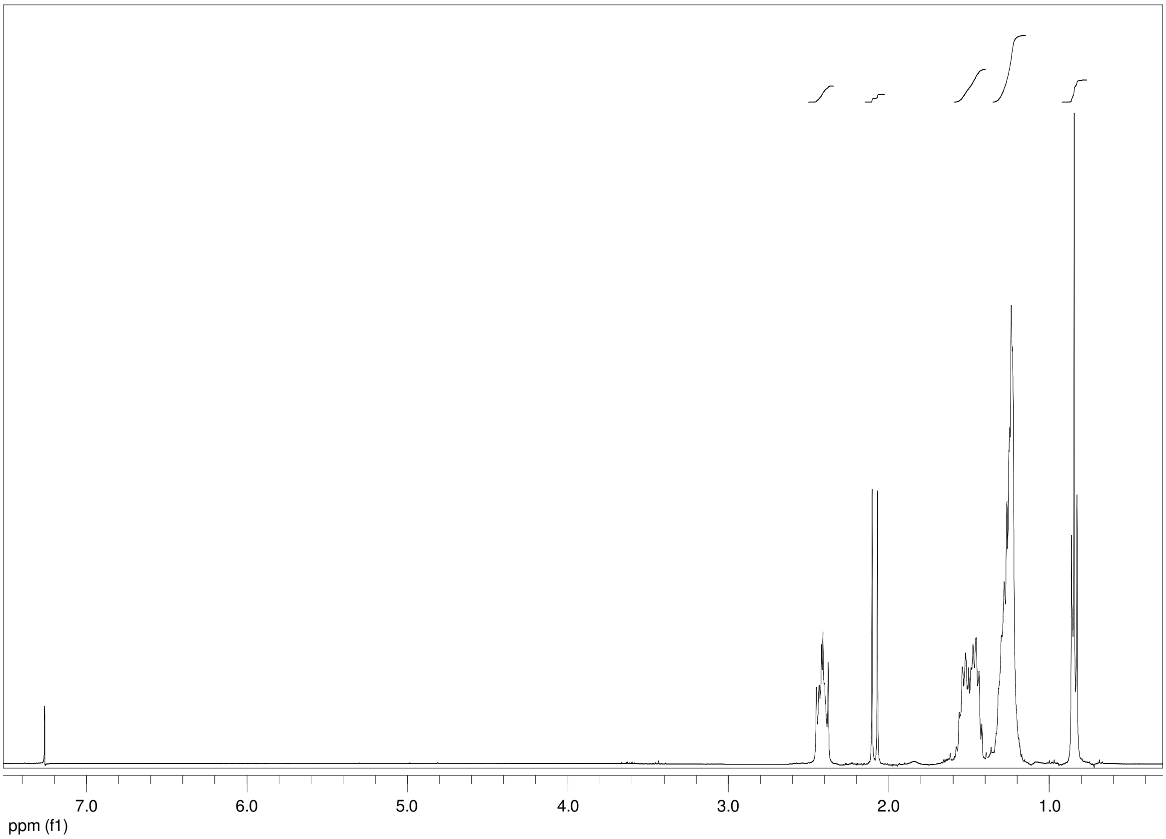

Figure A.2.42. ^{1}H NMR ($CDCl_3$, 400MHz) spectrum of compound **6a**.

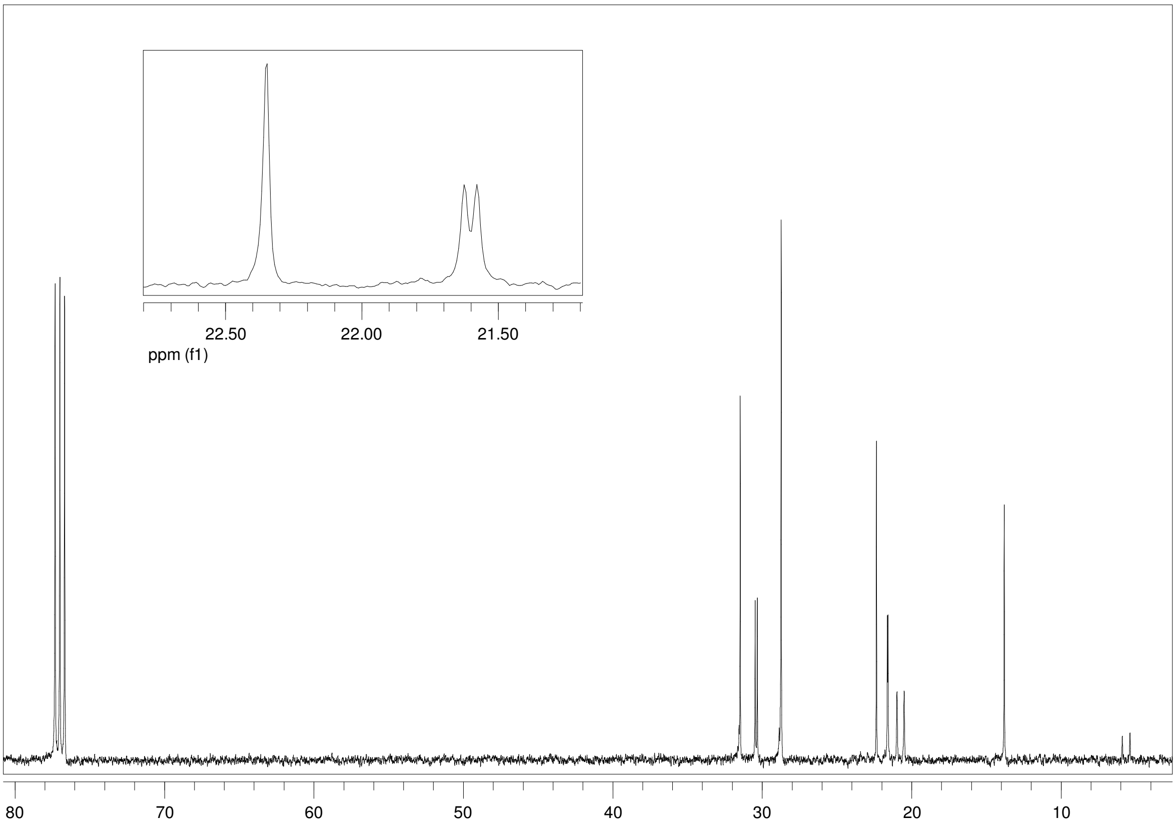

Figure A.2.43. ^{13}C NMR ($CDCl_3$, 100MHz) spectrum of compound **6a**.

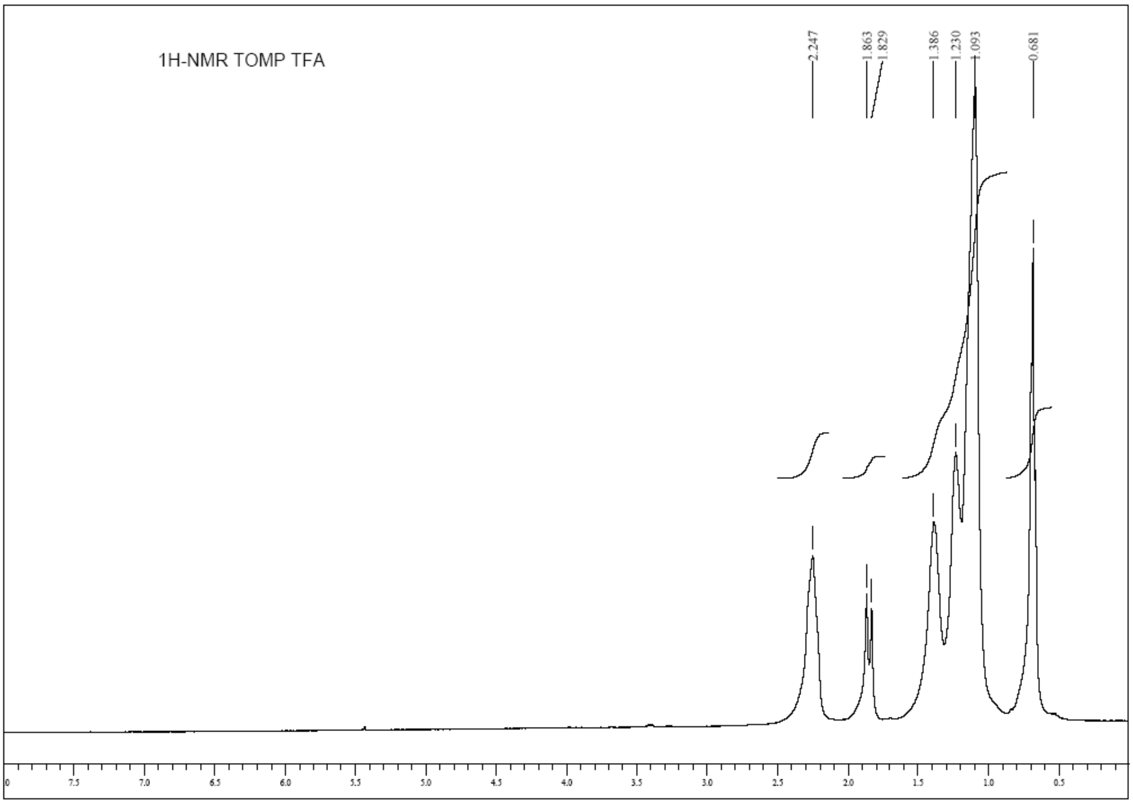

Figure A.2.44. Neat ^{1}H-NMR spectrum of compound **7a**.

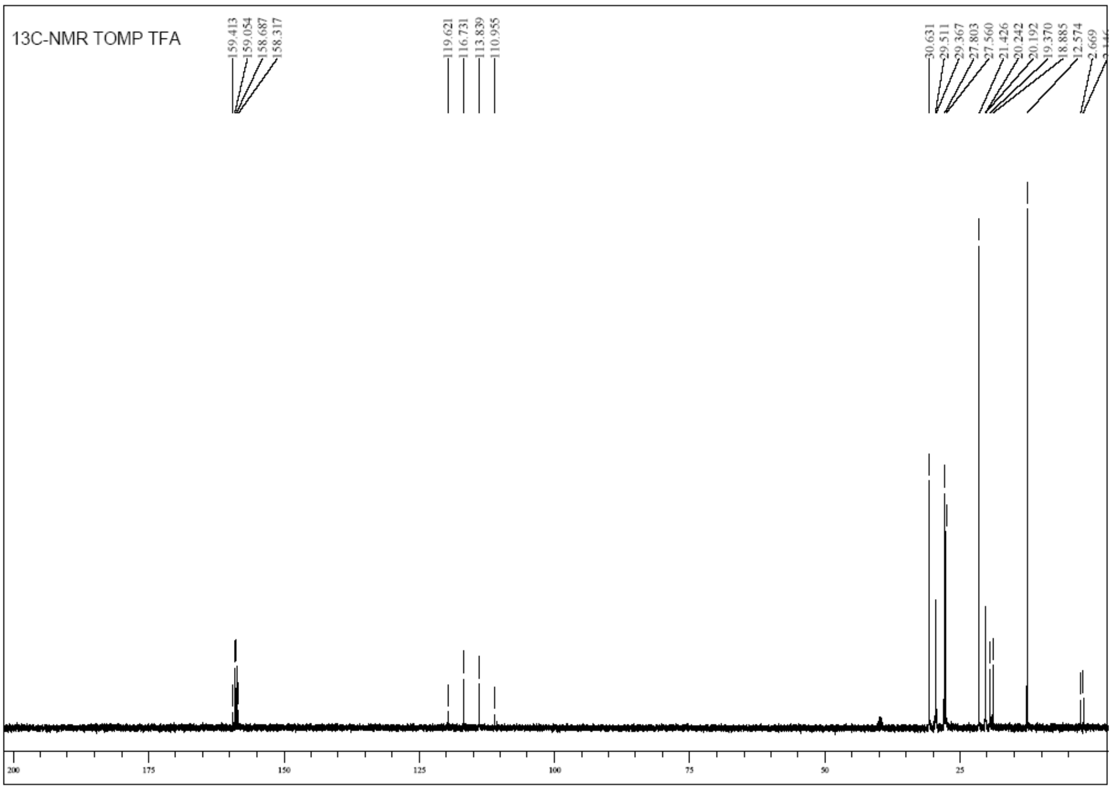

Figure A.2.45. Neat ^{13}C-NMR spectrum of compound **7a**.

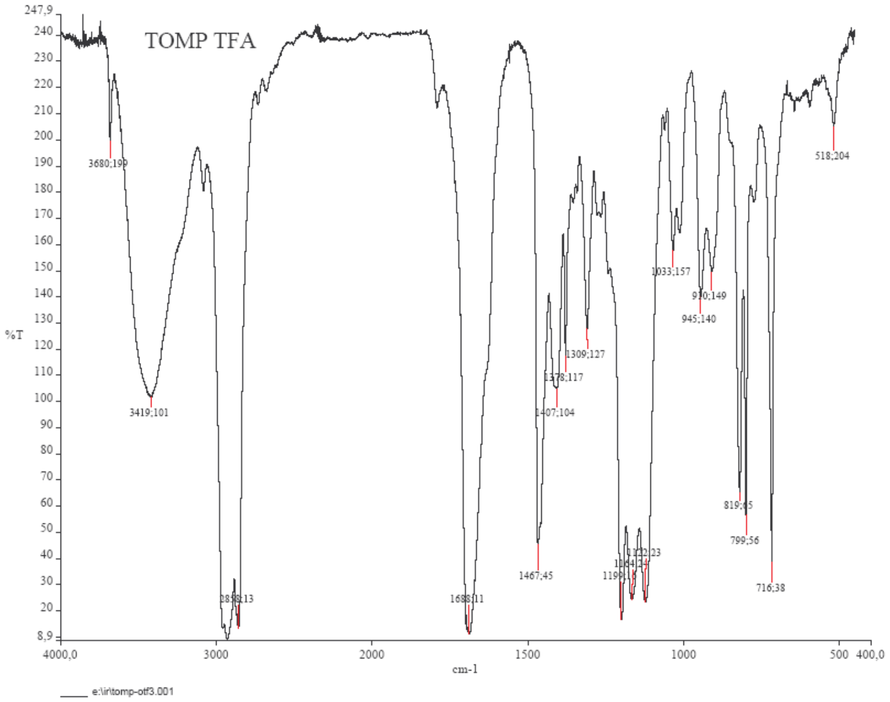

Figure A.2.46. IR spectrum of compound **7a**.

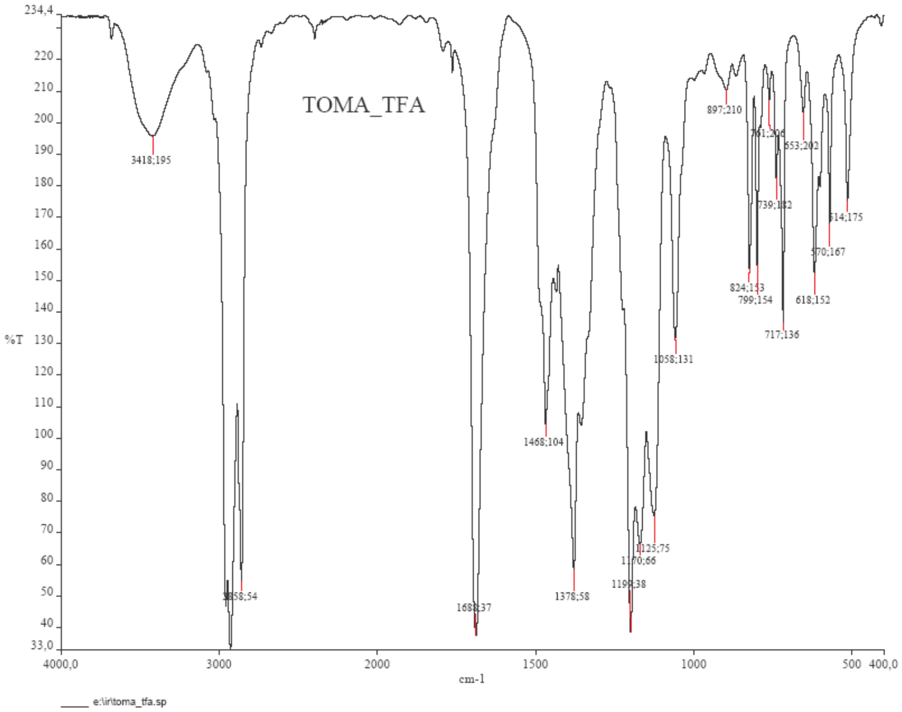

Figure A.2.47. IR spectrum of compound **7e**.

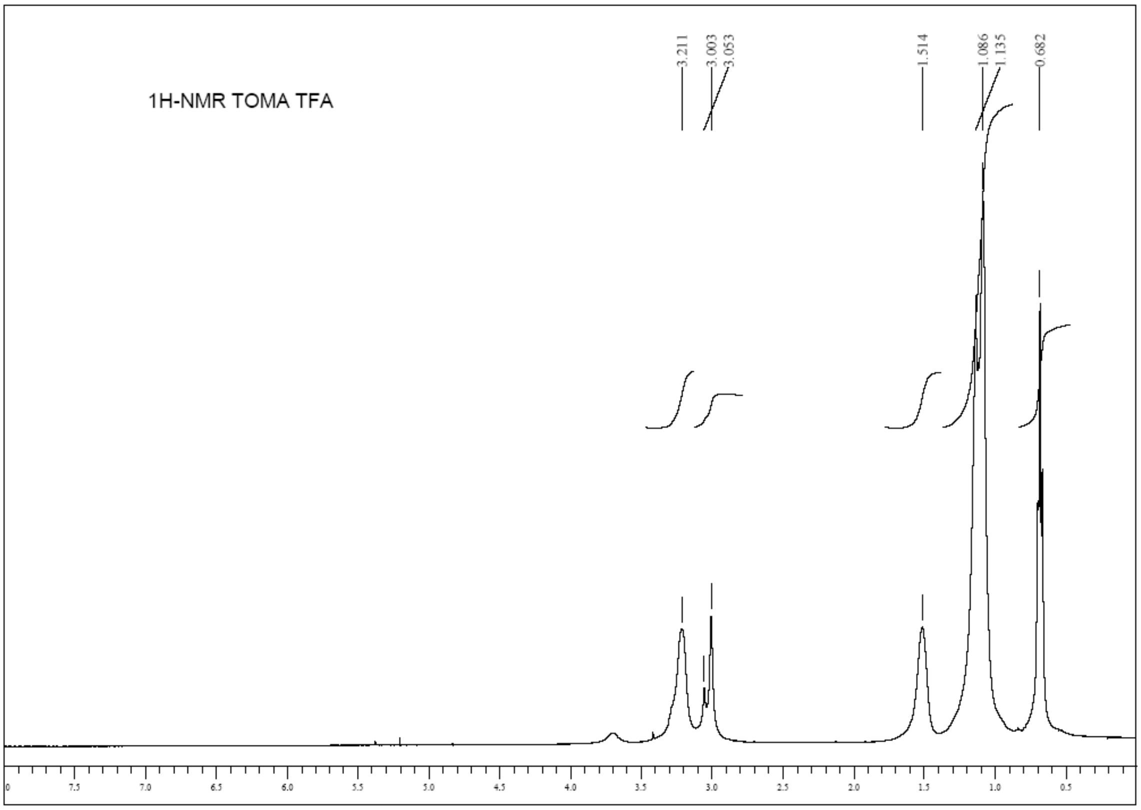

Figure A.2.48. Neat ^{1}H-NMR spectrum of compound **7e**.

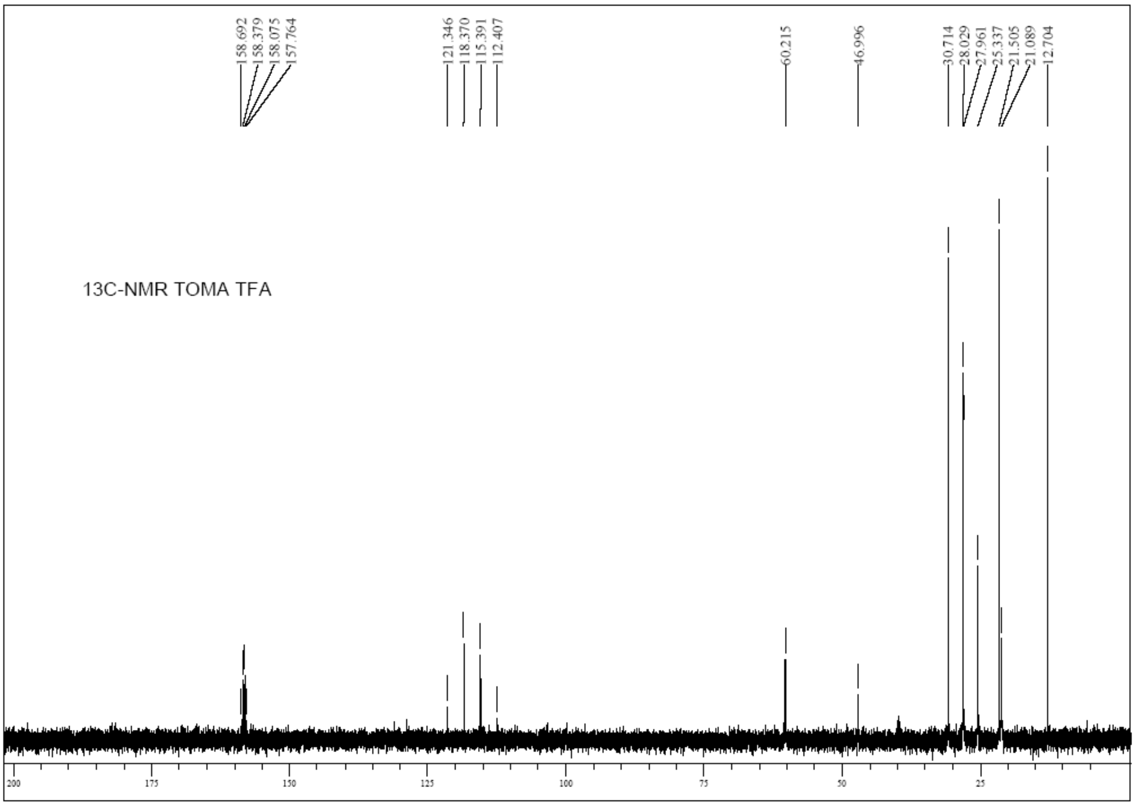

Figure A.2.49. Neat ^{13}C-NMR spectrum of compound **7e**.

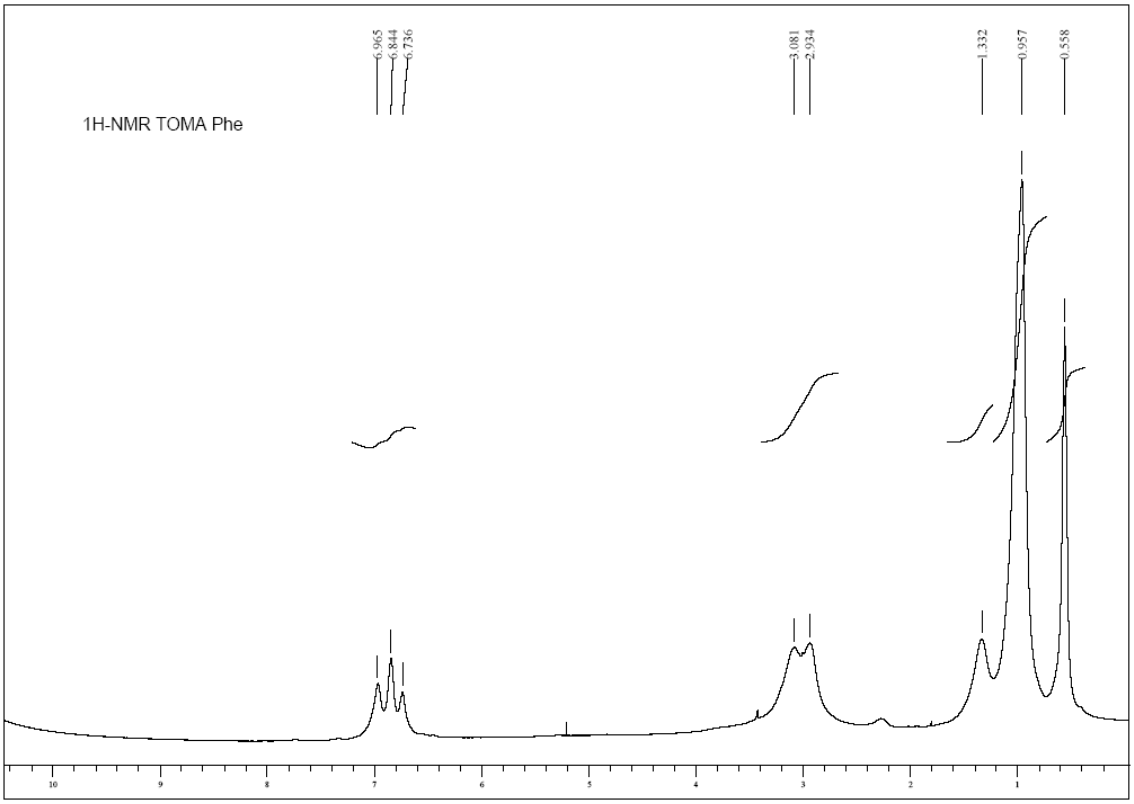

Figure A.2.50. Neat ^{1}H-NMR spectrum of compound **8e**.

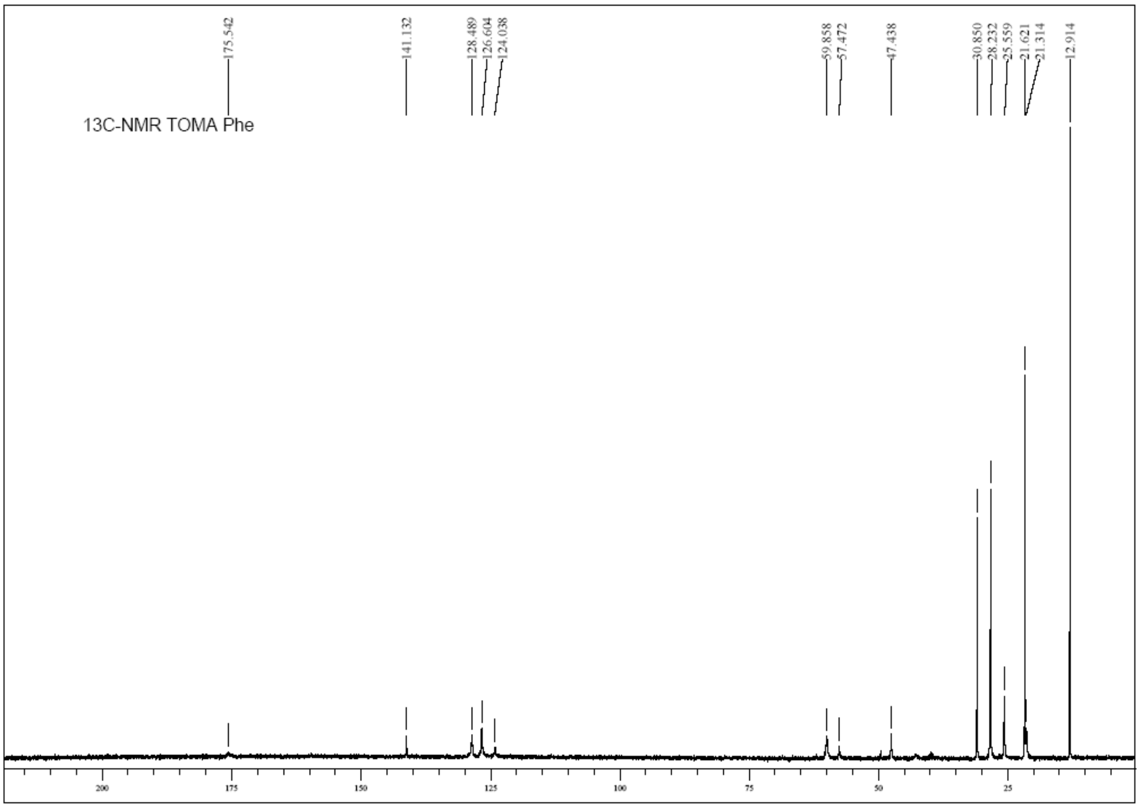

Figure A.2.51. Neat ^{13}C-NMR spectrum of compound **8e**.

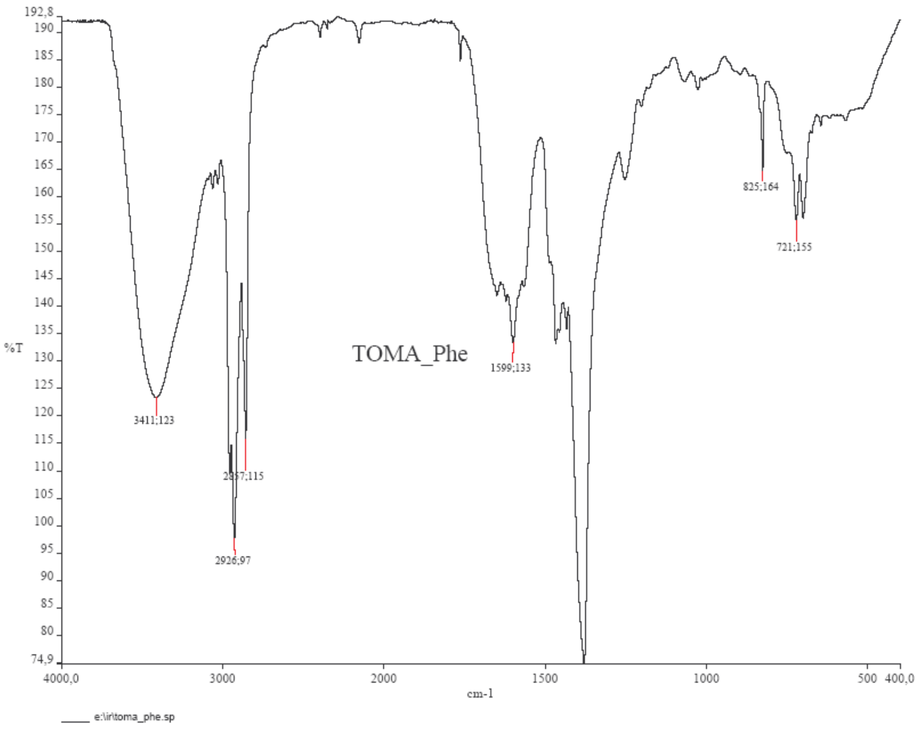

Figure A.2.52. IR spectrum of compound **8e**.

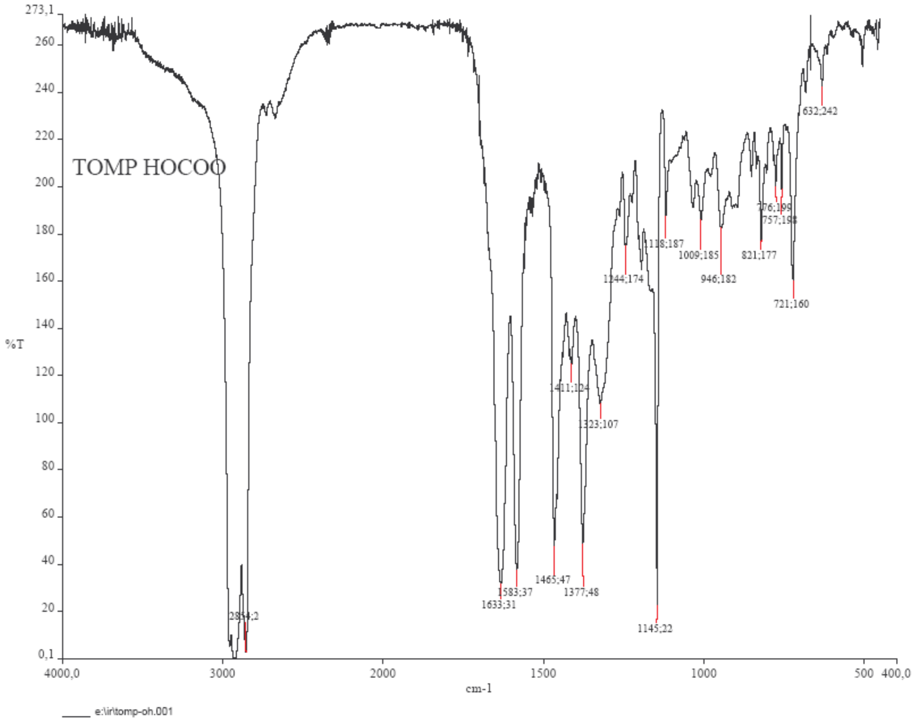

Figure A.2.53. IR spectrum of compound **9a**.

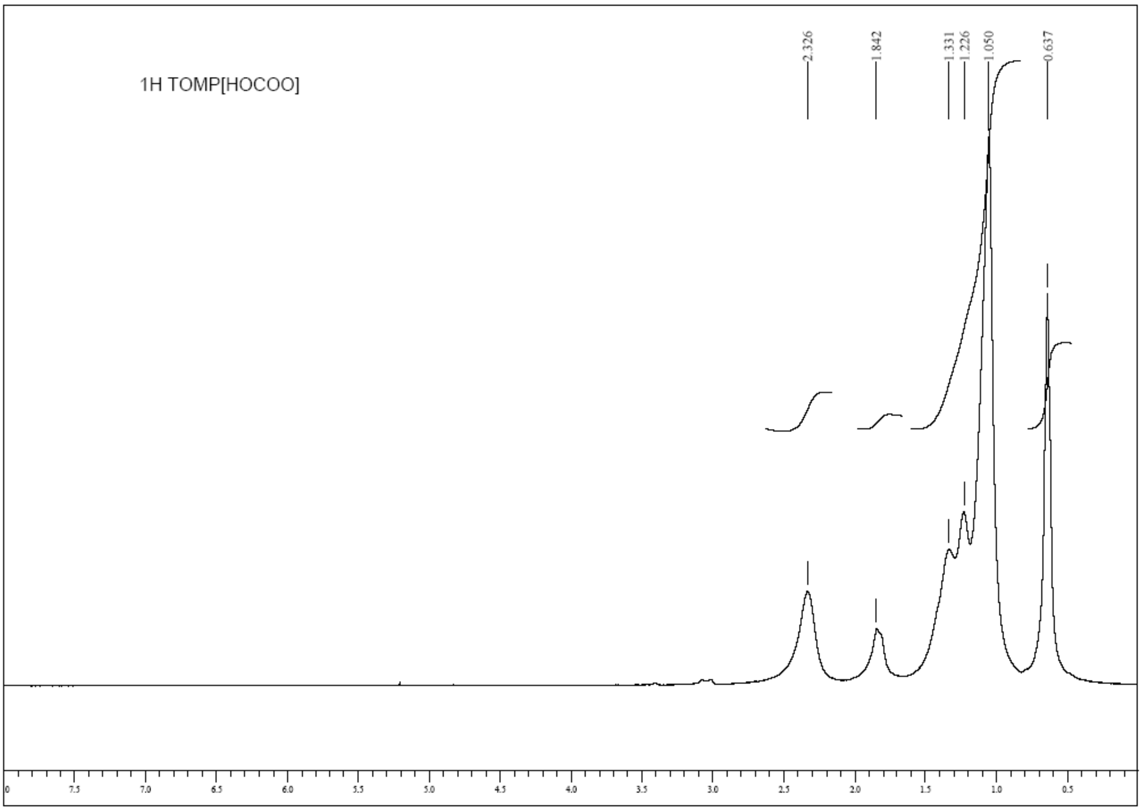

Figure A.2.54. Neat ^{1}H-NMR spectrum of compound **9a**.

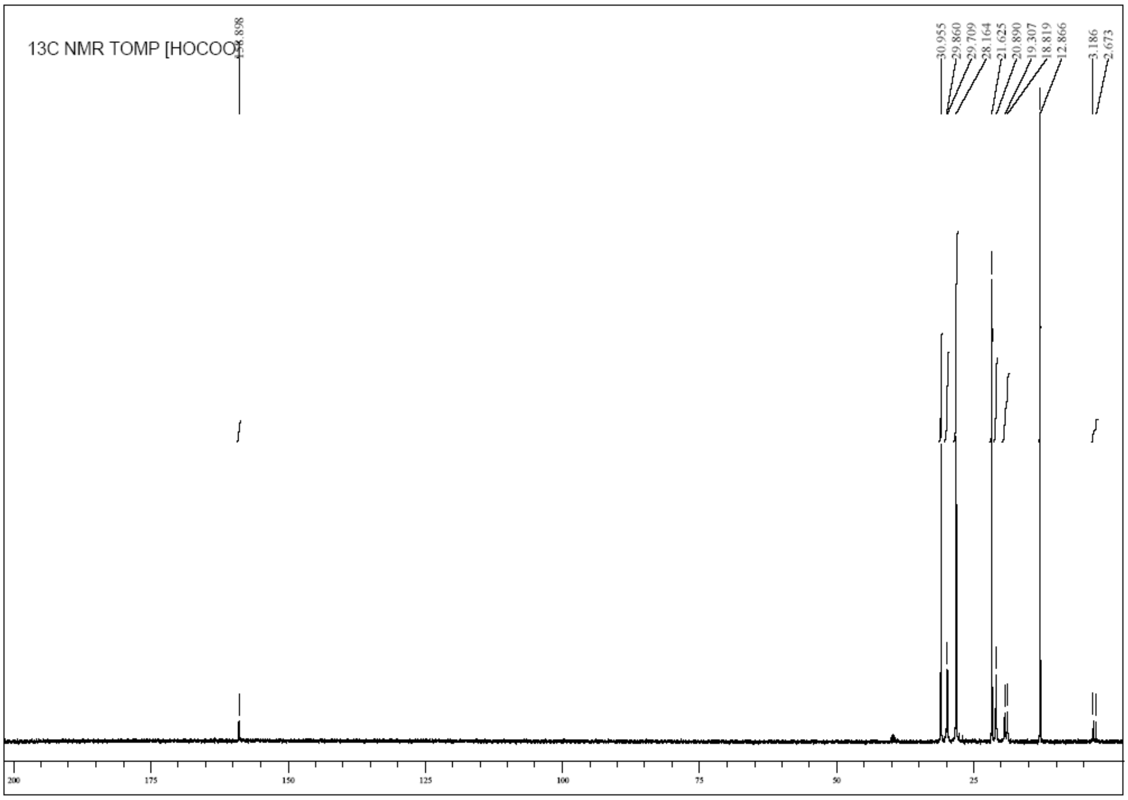

Figure A.2.55. Neat ^{13}C-NMR spectrum of compound **9a**.

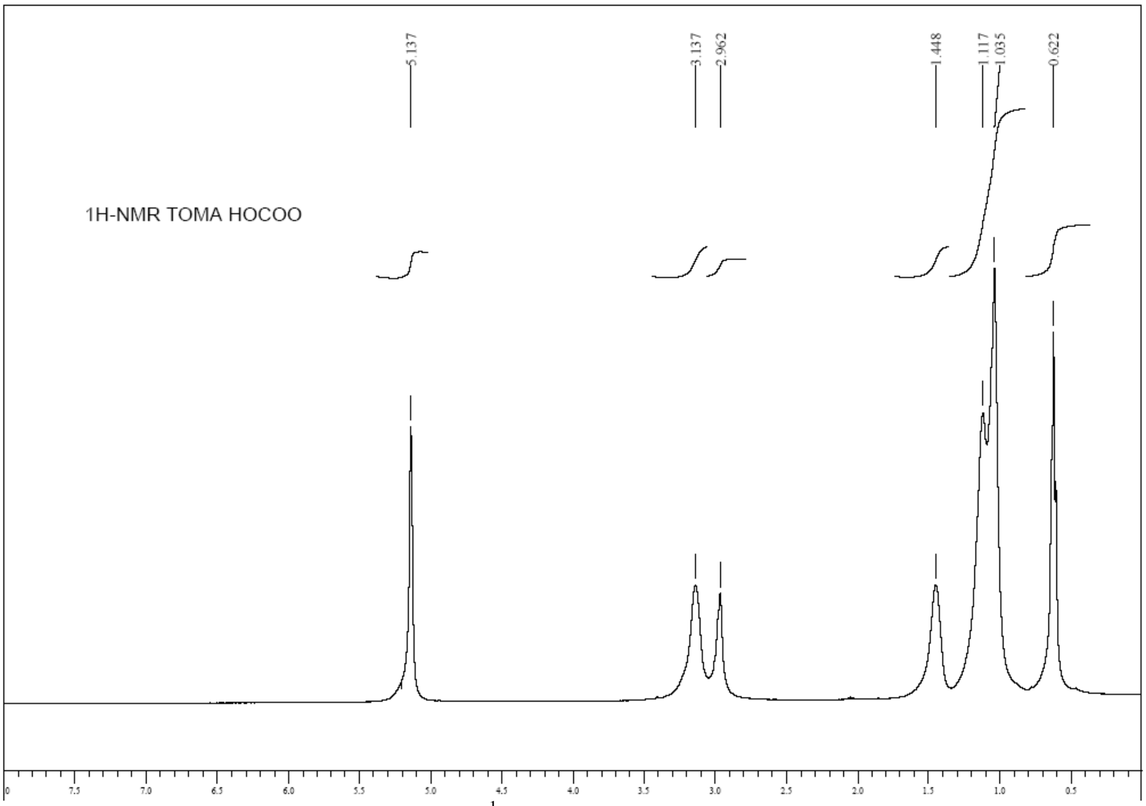

Figure A.2.56. Neat ^{1}H-NMR spectrum of compound **9e**.

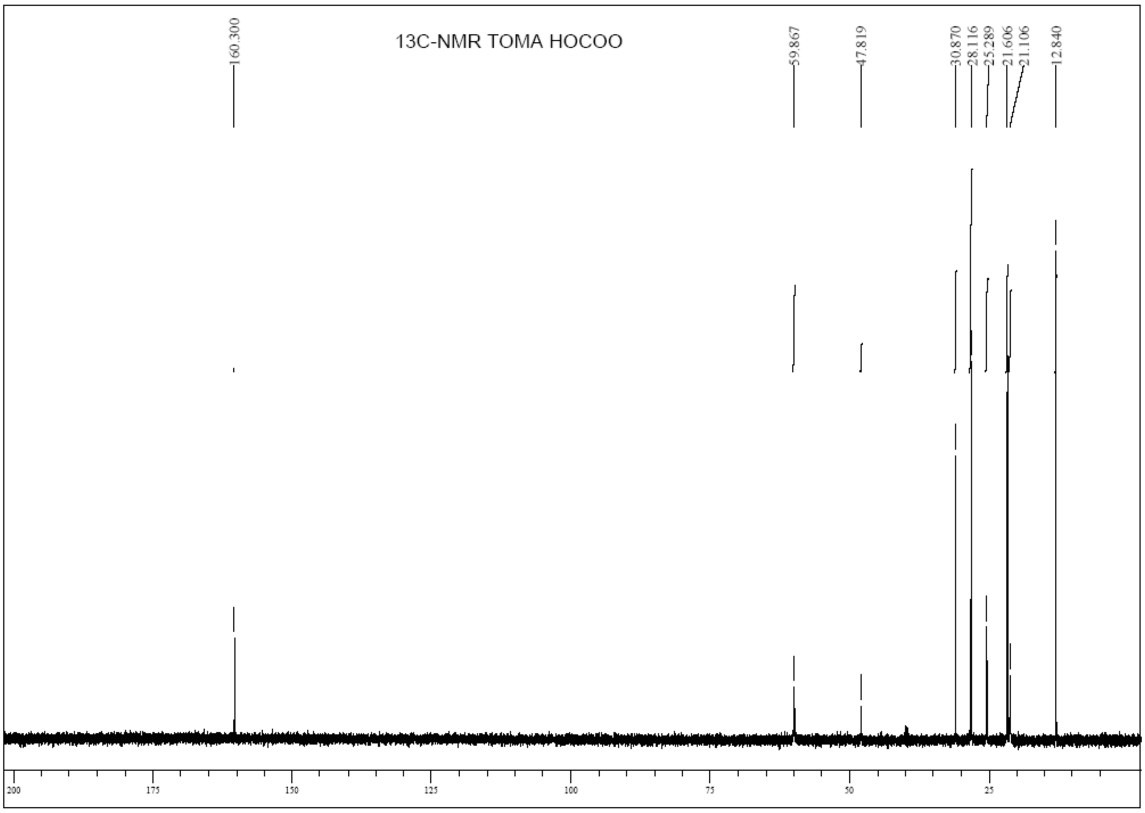

Figure A.2.57. Neat ^{13}C-NMR spectrum of compound **9e**.

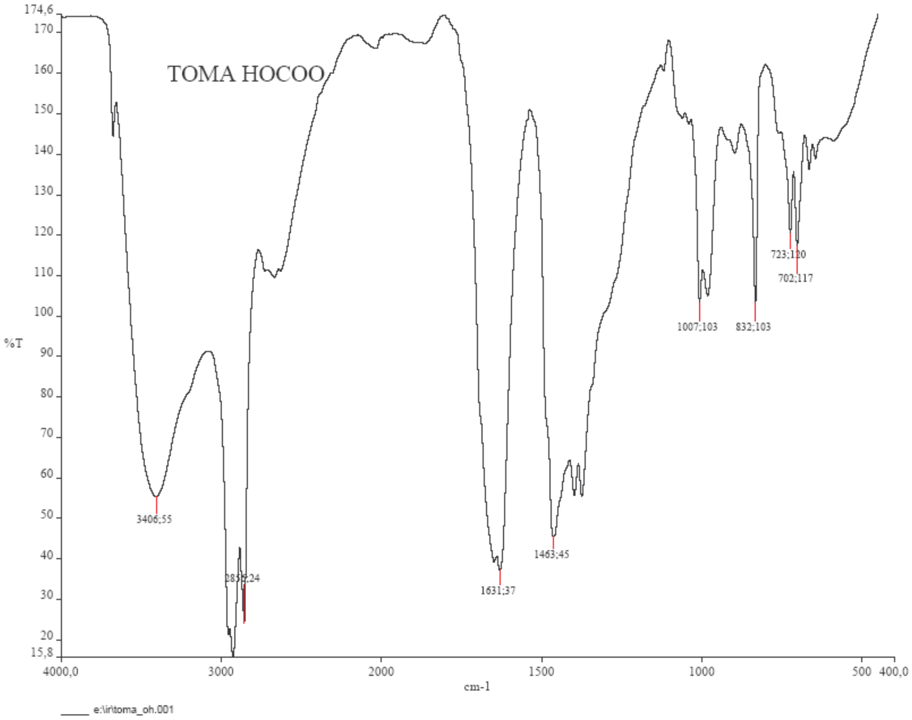

Figure A.2.58. IR spectrum of compound **9e**.

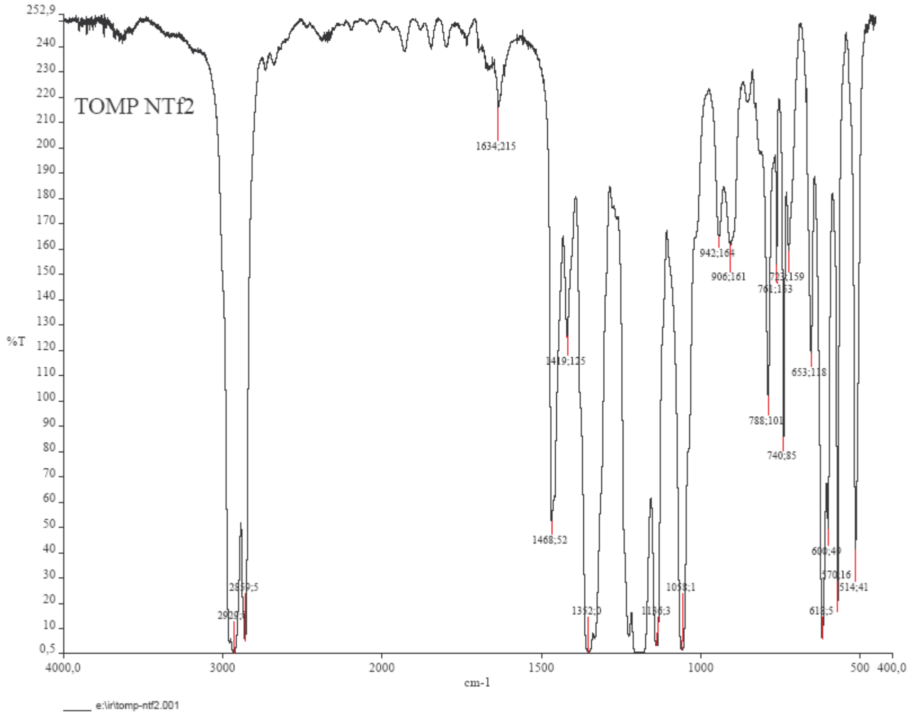

Figure A.2.59. IR spectrum of compound **10a**.

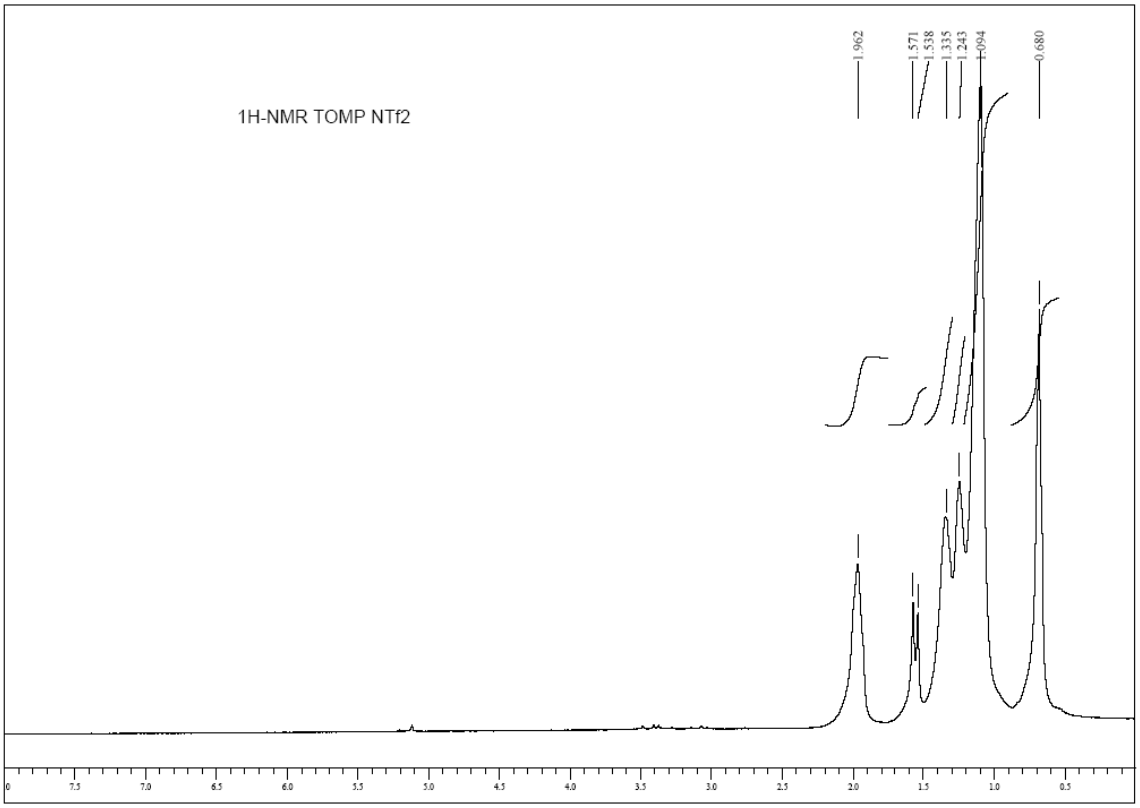

Figure A.2.60. Neat ^{1}H-NMR spectrum of compound **10a**.

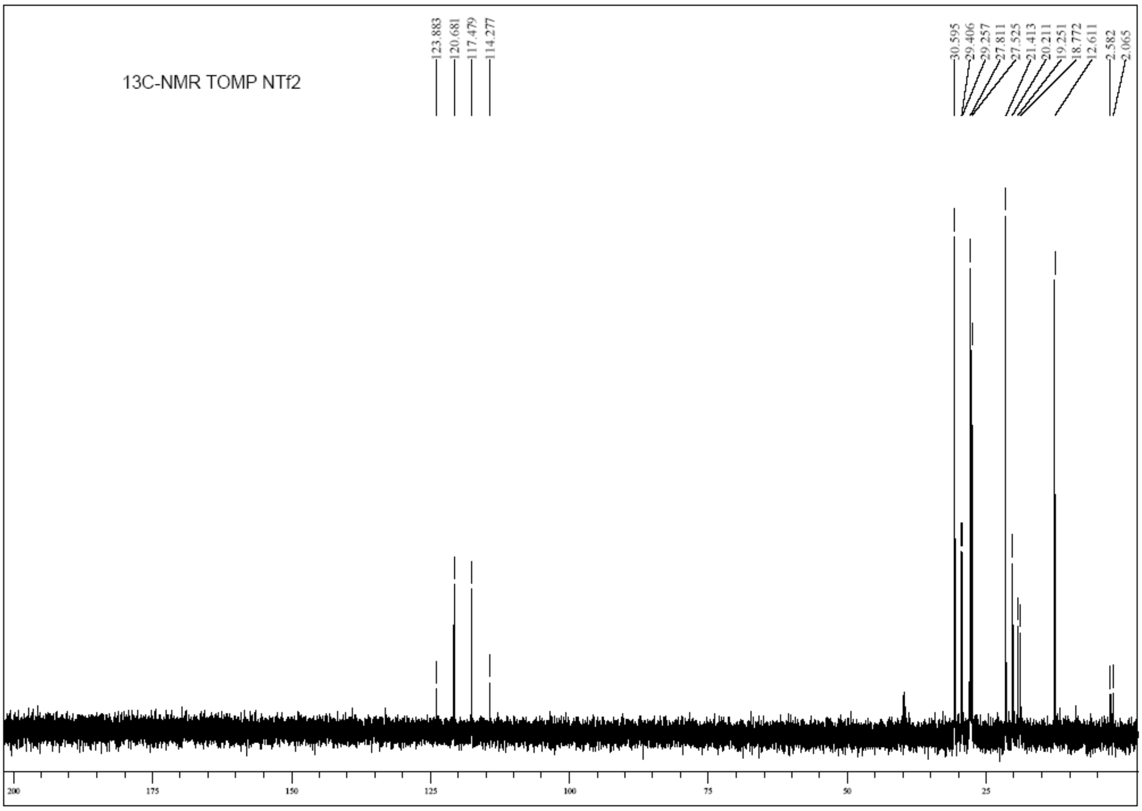

Figure A.2.61. Neat ^{13}C-NMR spectrum of compound **10a**.

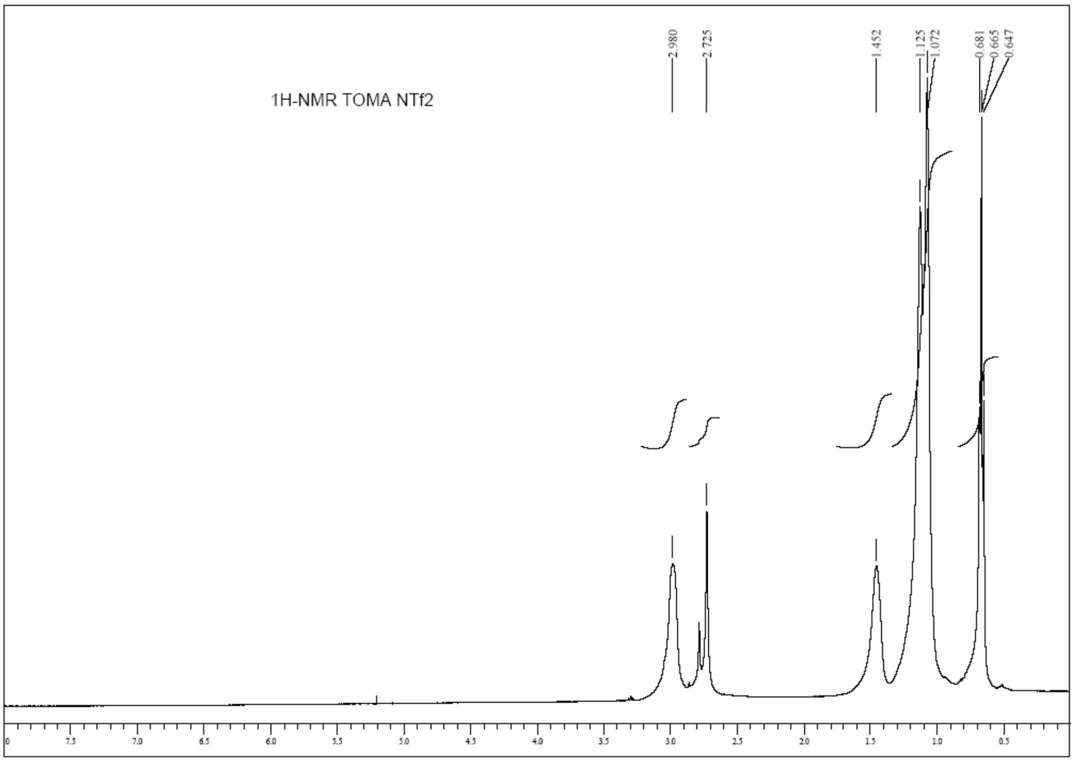

Figure A.2.62. Neat ^{1}H-NMR spectrum of compound **10e**.

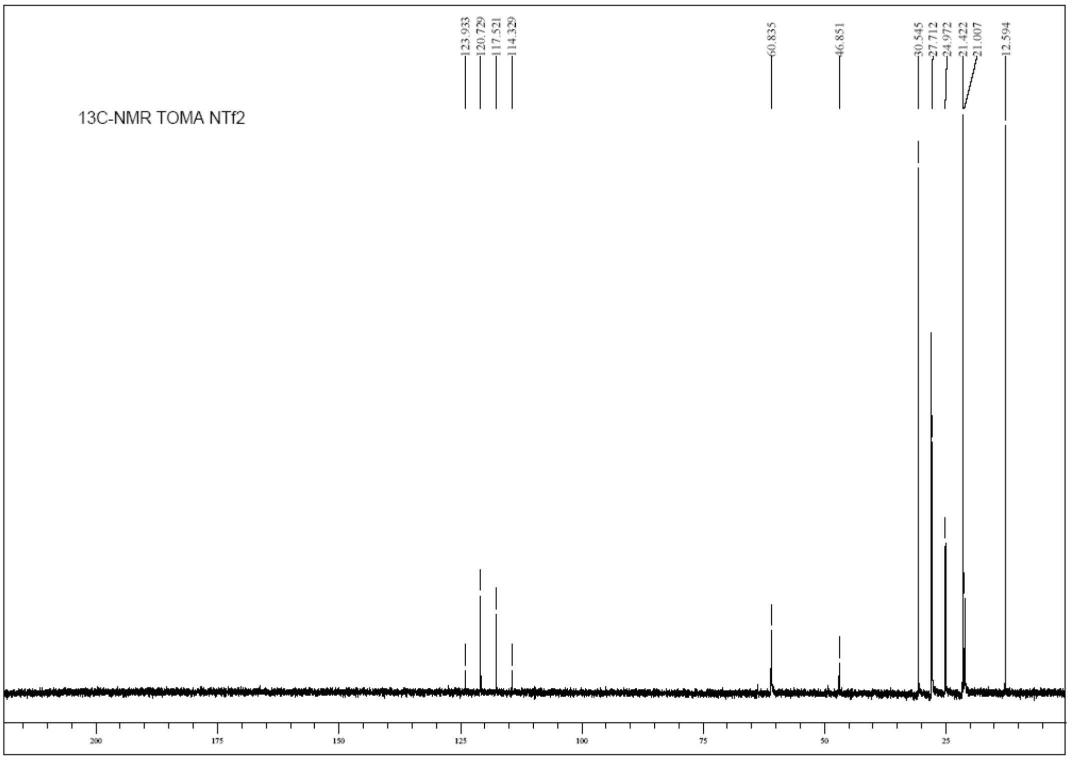

Figure A.2.63. Neat ^{13}C-NMR spectrum of compound **10e**.

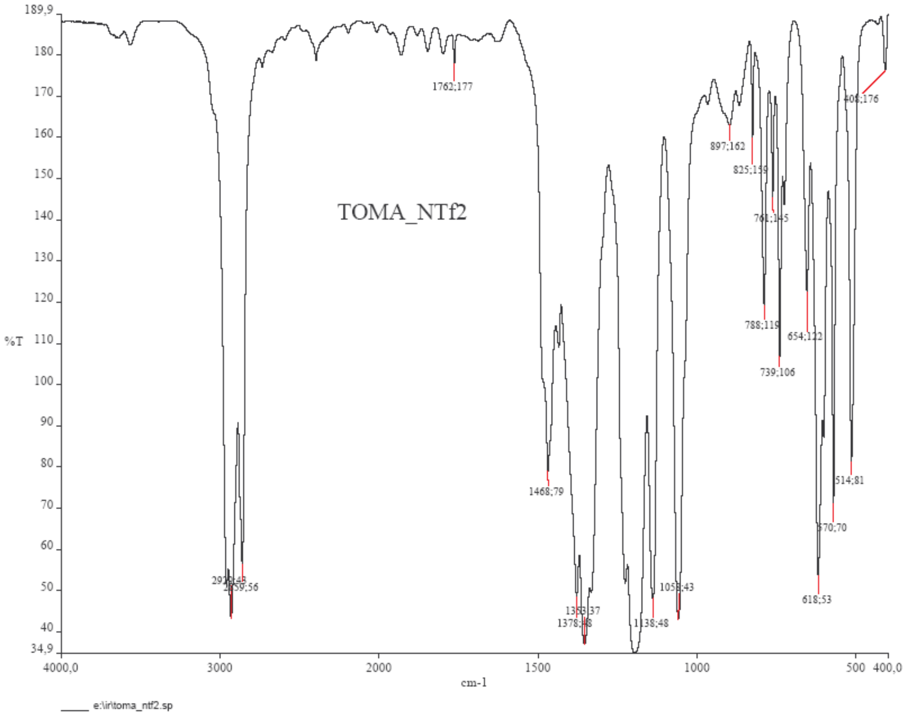

Figure A.2.64. IR spectrum of compound **10e**.

A3. Chapter 3

Onium salts: applications as solvents/catalysts for organic reactions

A.3.1 Basicity of carbonate ionic liquid. A case study: the Henry reaction.

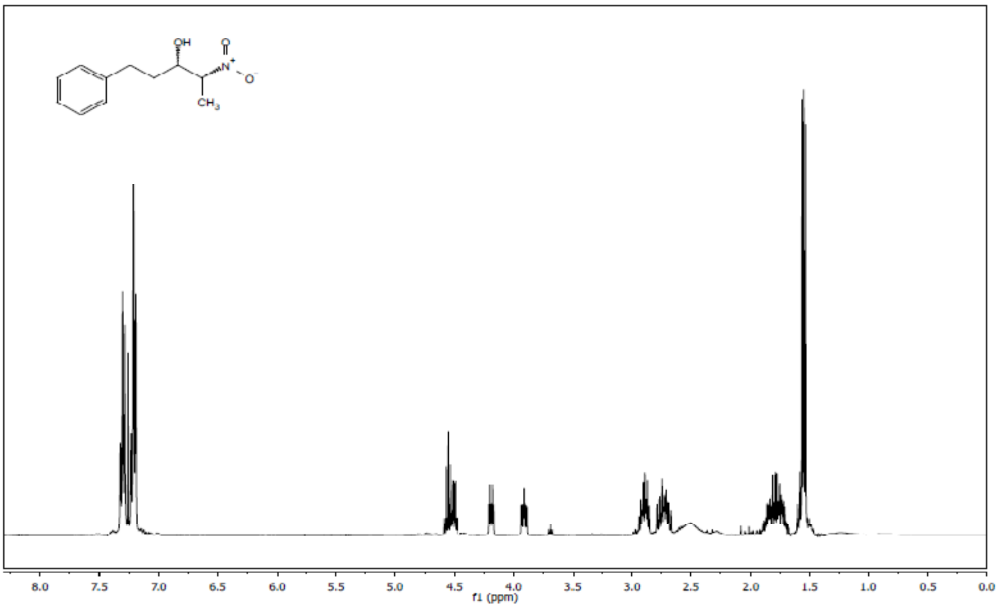

Figure A. 3.1. ^{1}H-NMR ($CDCl_3$, 400MHz) spectrum of compound **12a**.

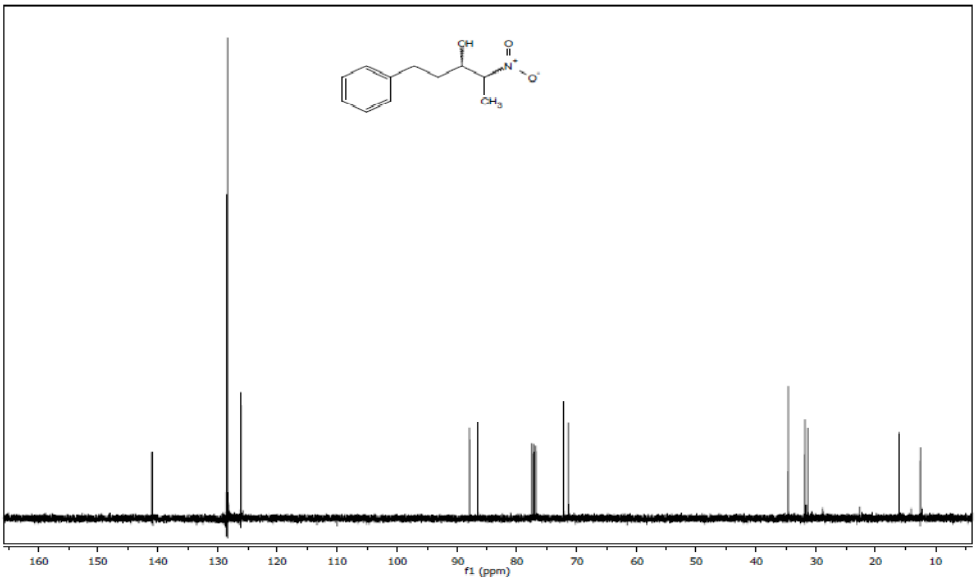

Figure A.3.2. ^{13}C-NMR ($CDCl_3$, 100MHz) spectrum of compound **12a**.

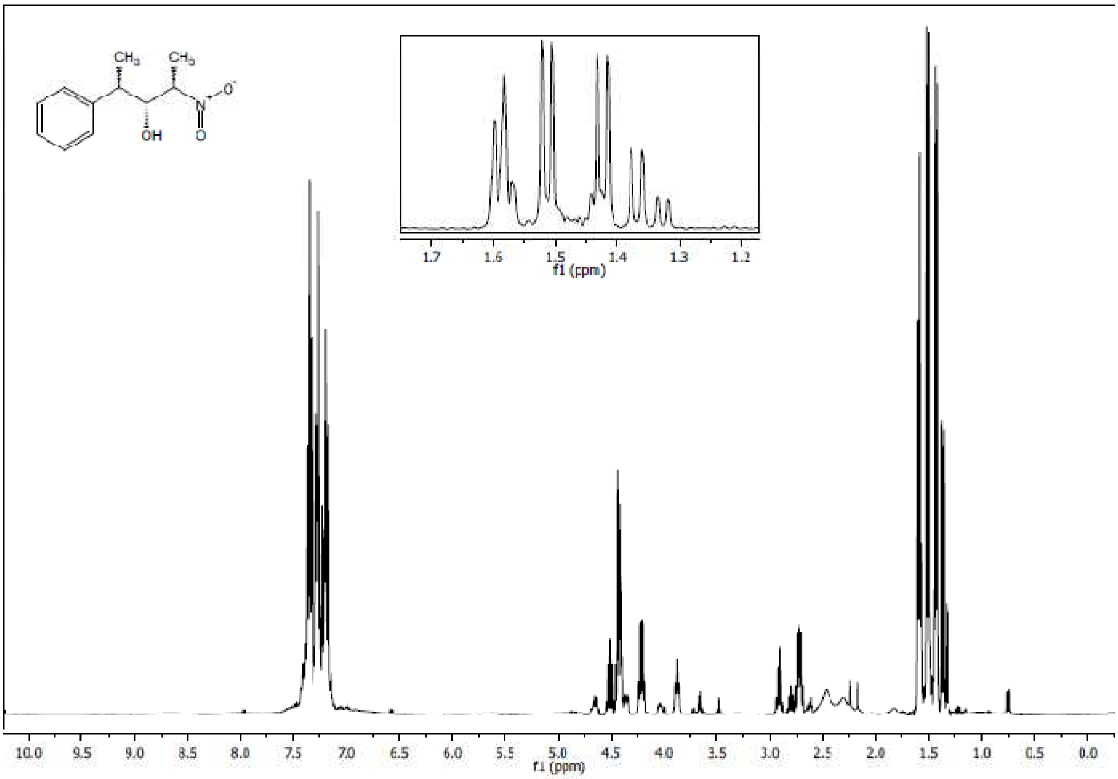

Figure A.3.3. ^{1}H-NMR ($CDCl_3$, 400MHz) spectrum of compound **12b**.

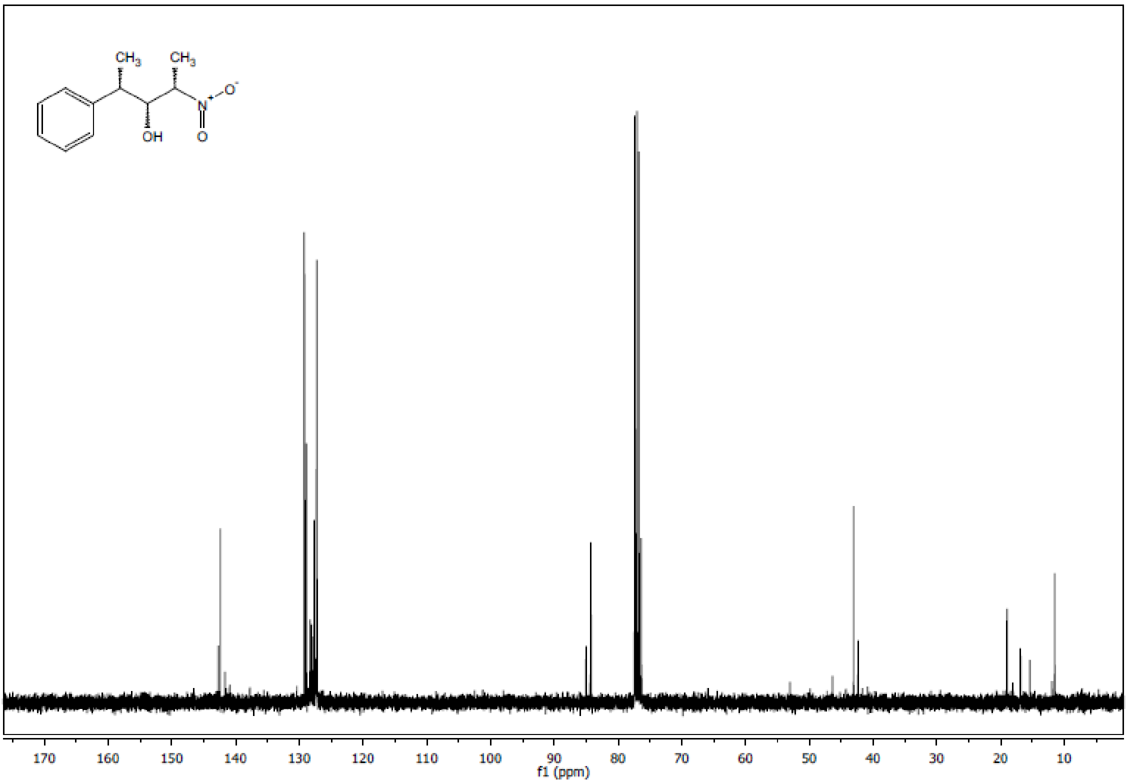

Figure A.3.4. ^{13}C-NMR (CDCl3, 100MHz) spectrum of compound **12b**.

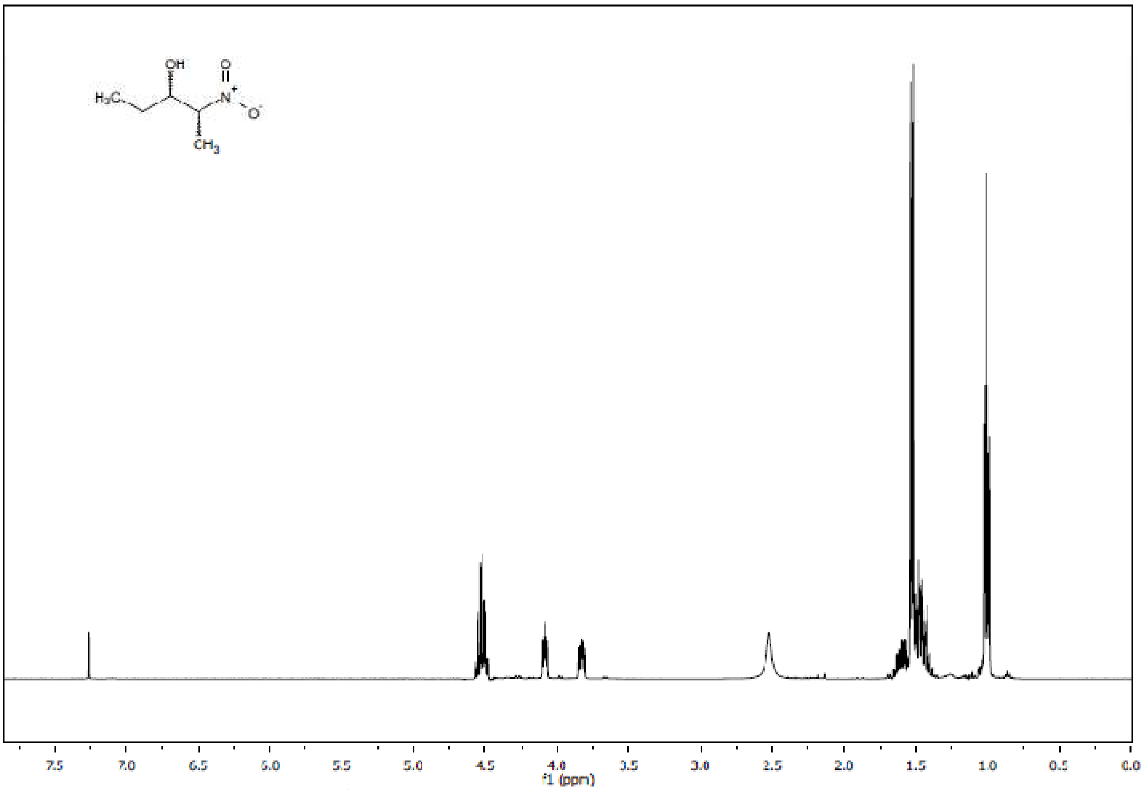

Figure A.3.5. ^{1}H-NMR (CDCl$_3$, 400MHz) spectrum of compound **12c**.

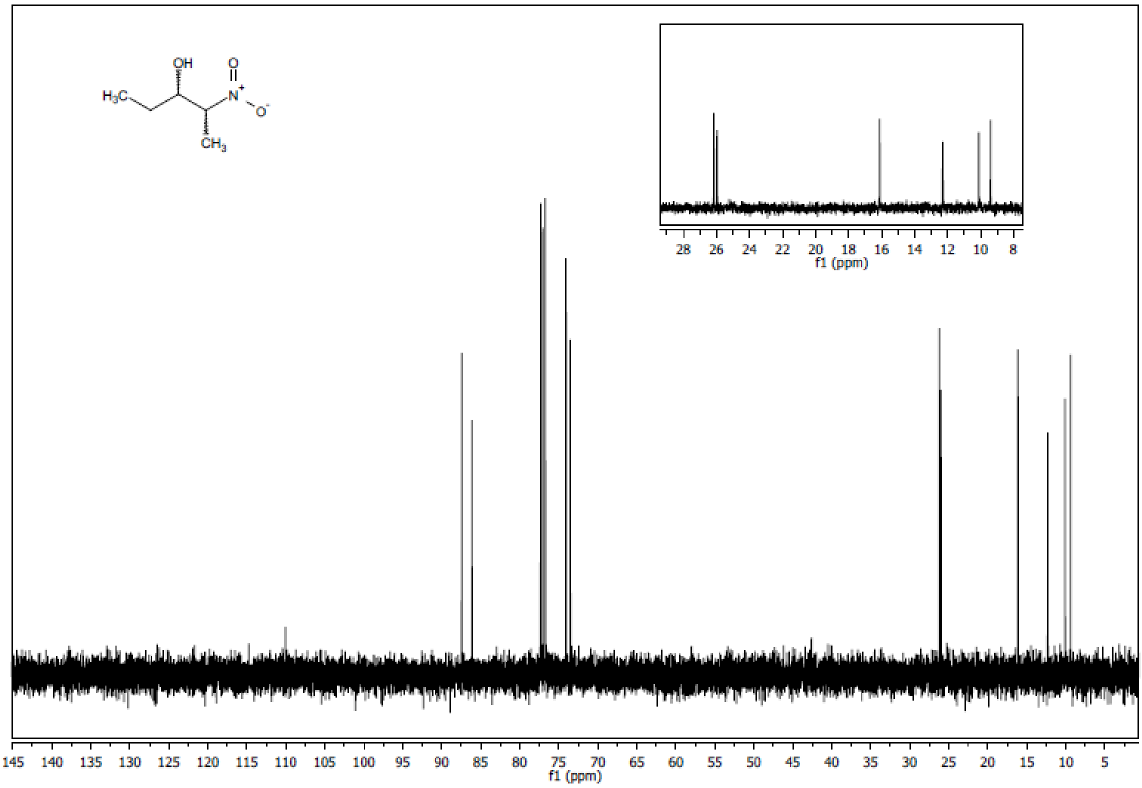

Figure A.3.6. ^{13}C-NMR (CDCl$_3$, 100MHz) spectrum of compound **12c**.

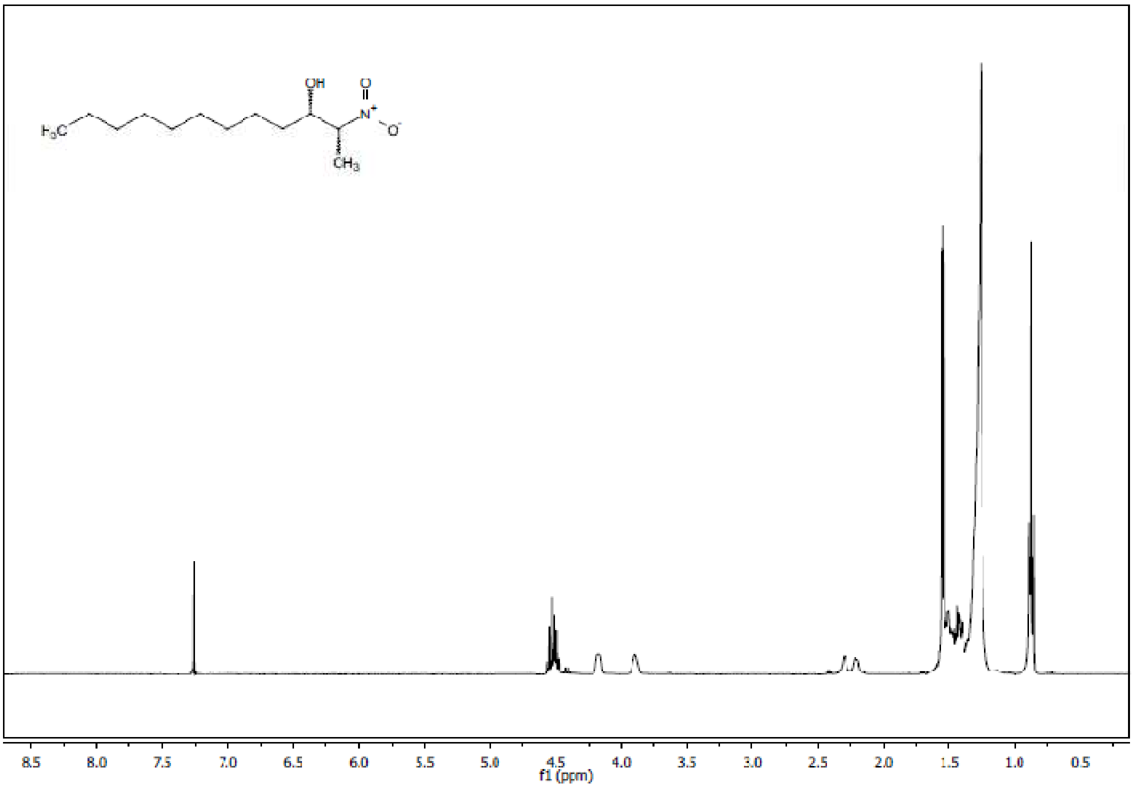

Figure A.3.7. ^{1}H-NMR ($CDCl_3$, 400MHz) spectrum of compound **12d**.

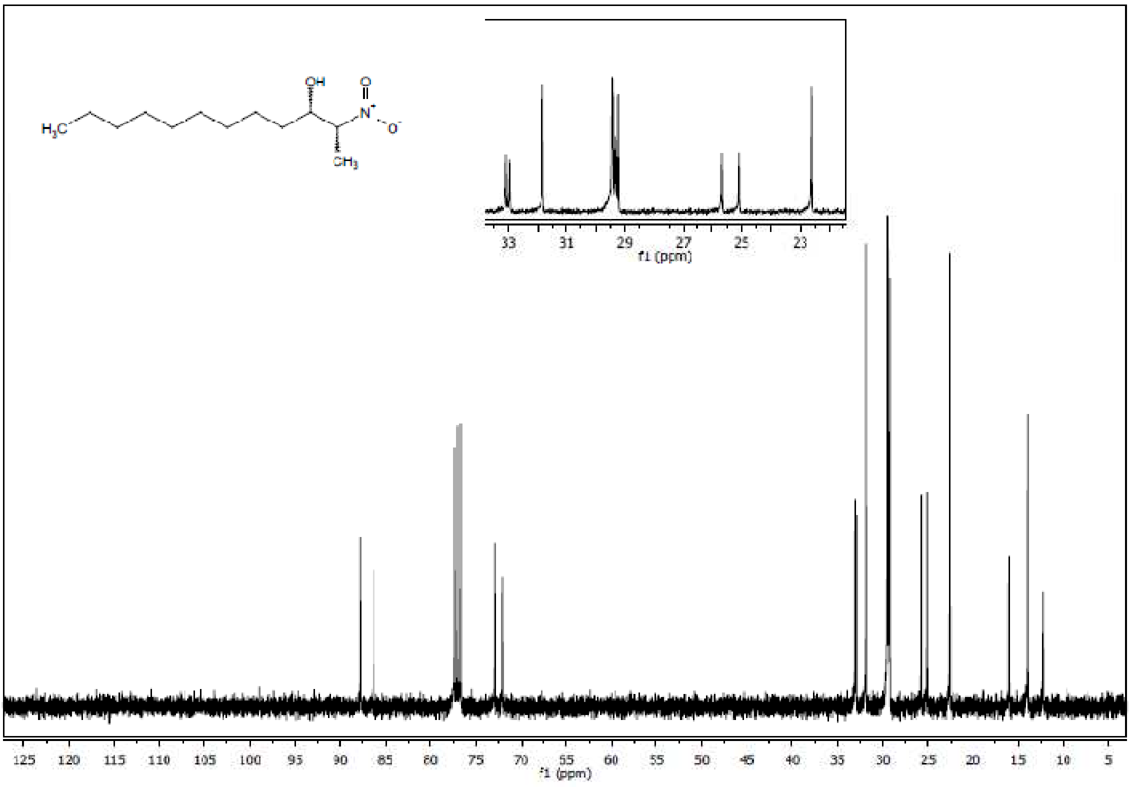

Figure A.3.8. ^{13}C-NMR ($CDCl_3$, 100MHz) spectrum of compound **12d**.

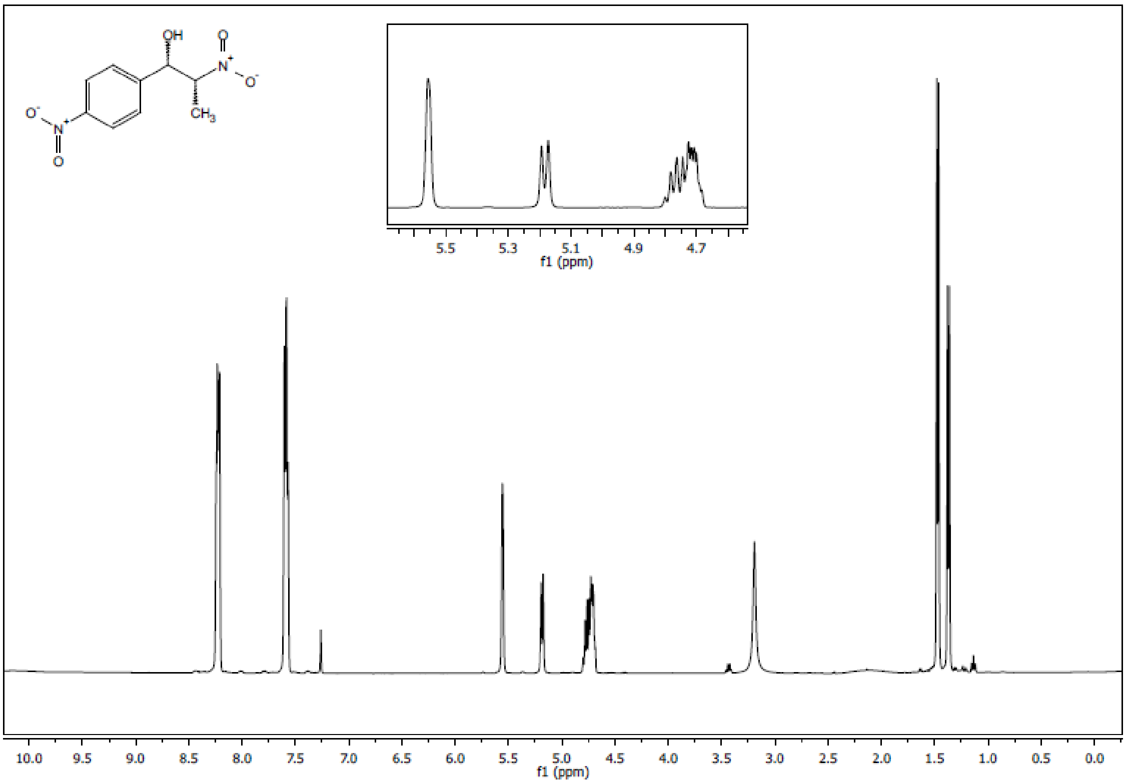

Figure A.3.9. ^{1}H-NMR ($CDCl_3$, 400MHz) spectrum of compound **12e**.

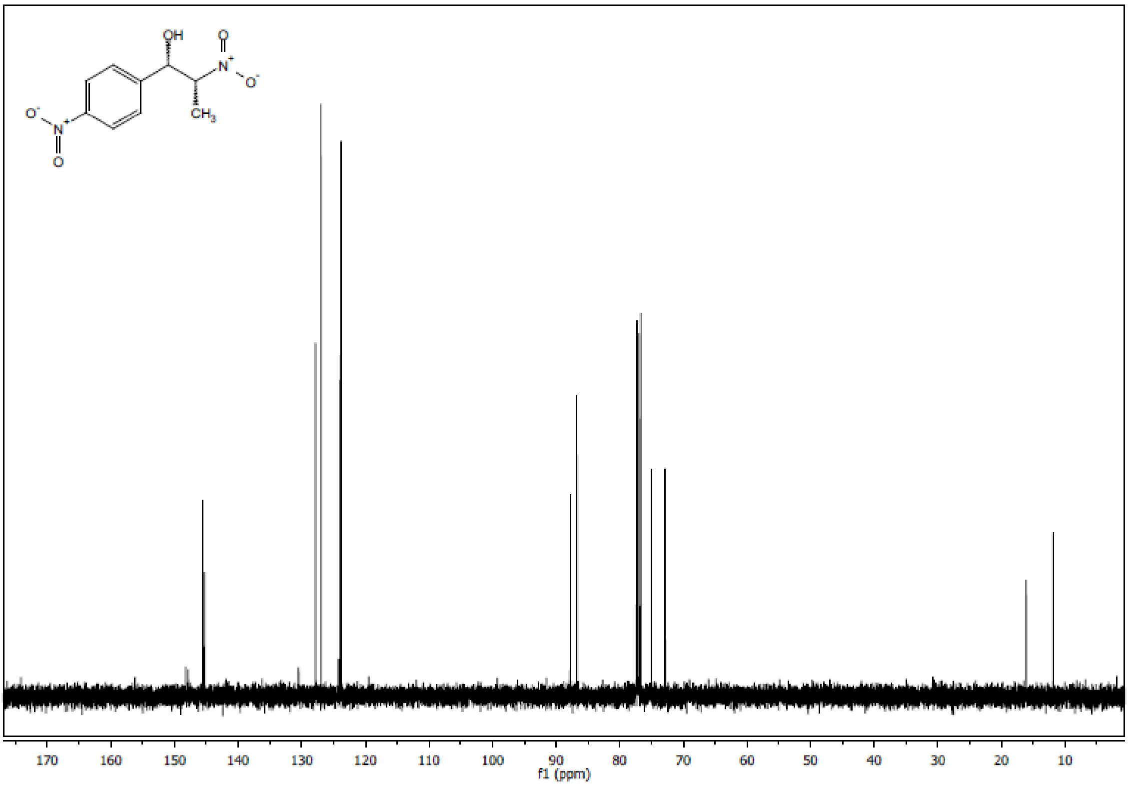

Figure A.3.10. ^{1}H-NMR ($CDCl_3$, 100MHz) spectrum of compound **12e**.

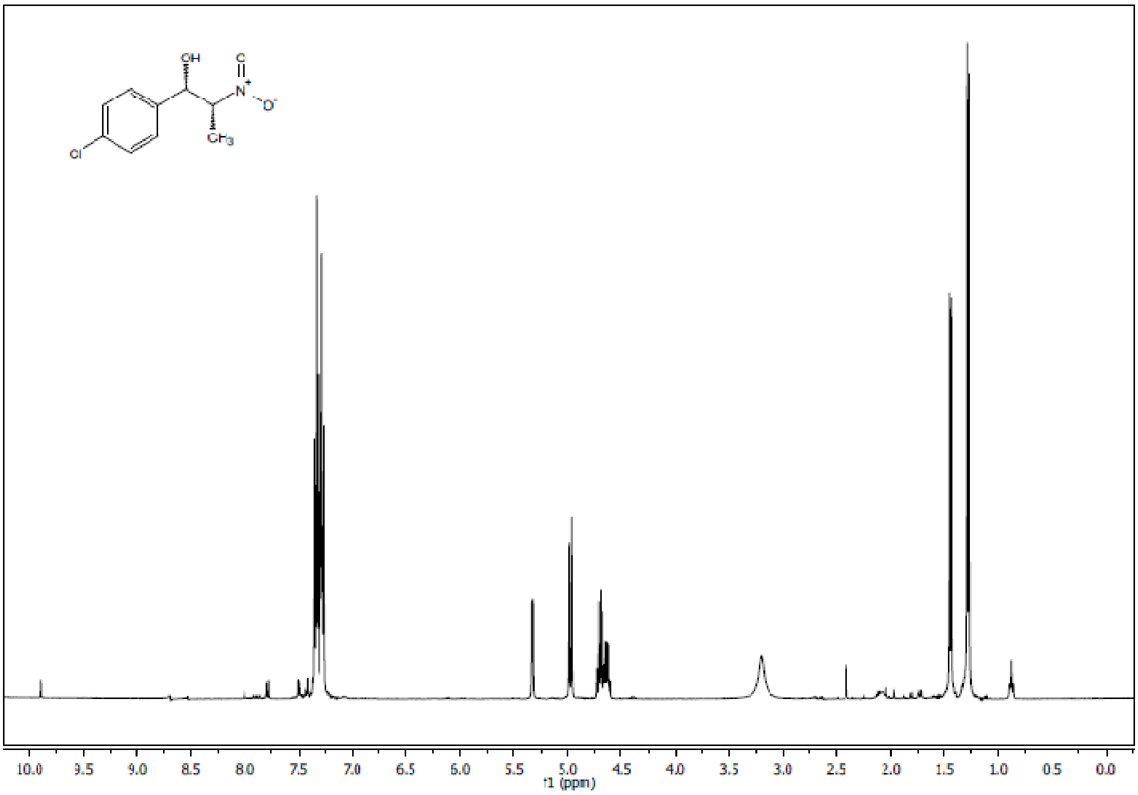

Figure A.3.11. ^{1}H-NMR ($CDCl_3$, 400MHz) spectrum of compound **12f**.

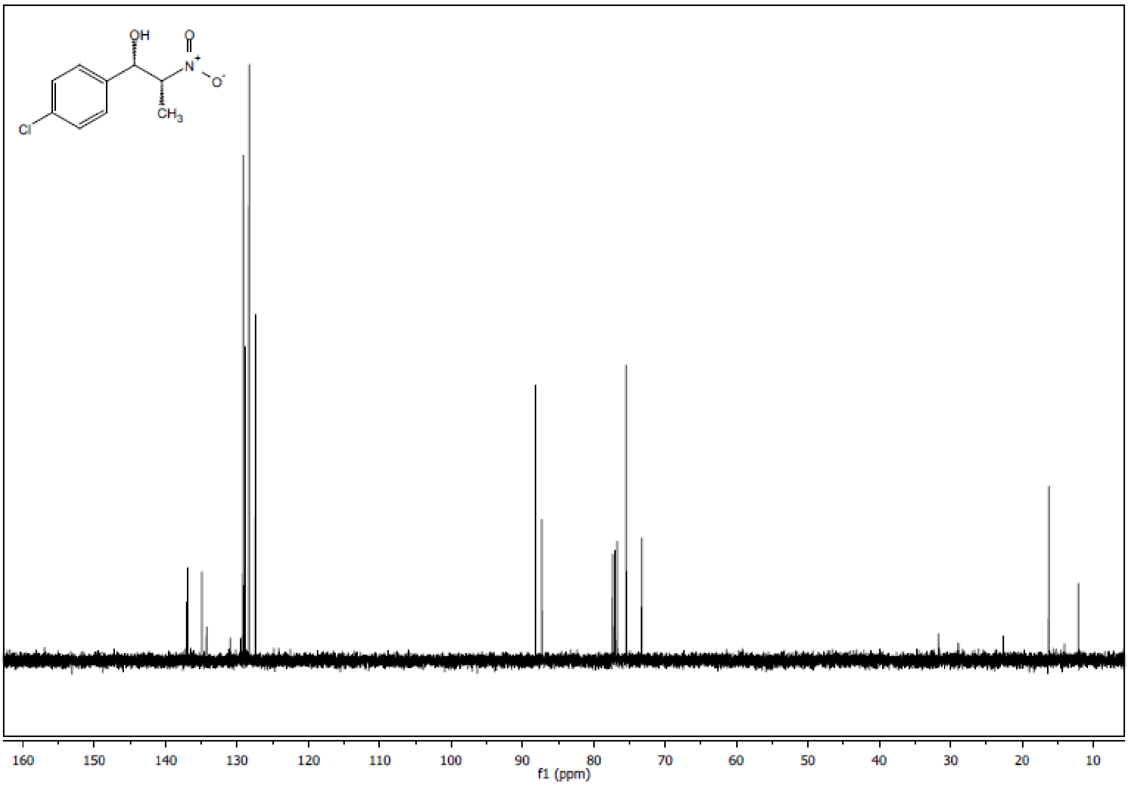

Figure A.3.12. ^{13}C-NMR ($CDCl_3$, 100MHz) spectrum of compound **12f**.

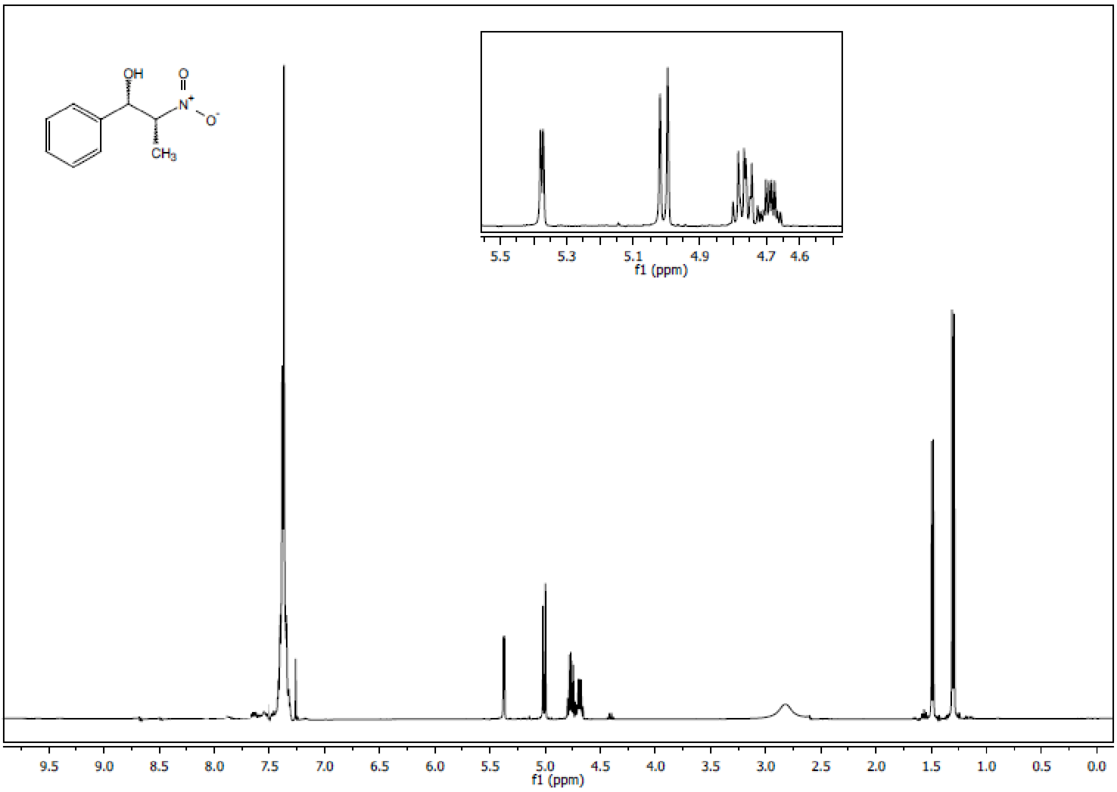

Figure A.3.13. ^{1}H-NMR ($CDCl_3$, 400MHz) spectrum of compound **12g**.

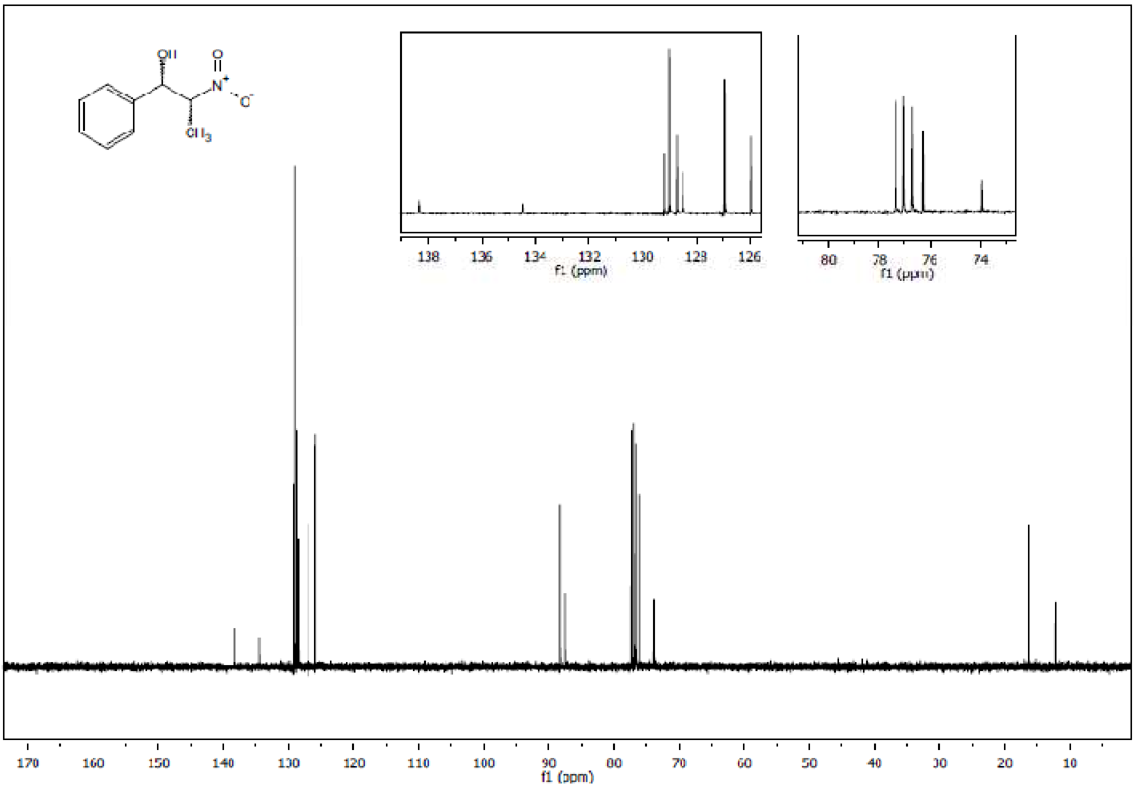

Figure A.3.14. ^{13}C-NMR ($CDCl_3$, 100MHz) spectrum of compound **12g**.

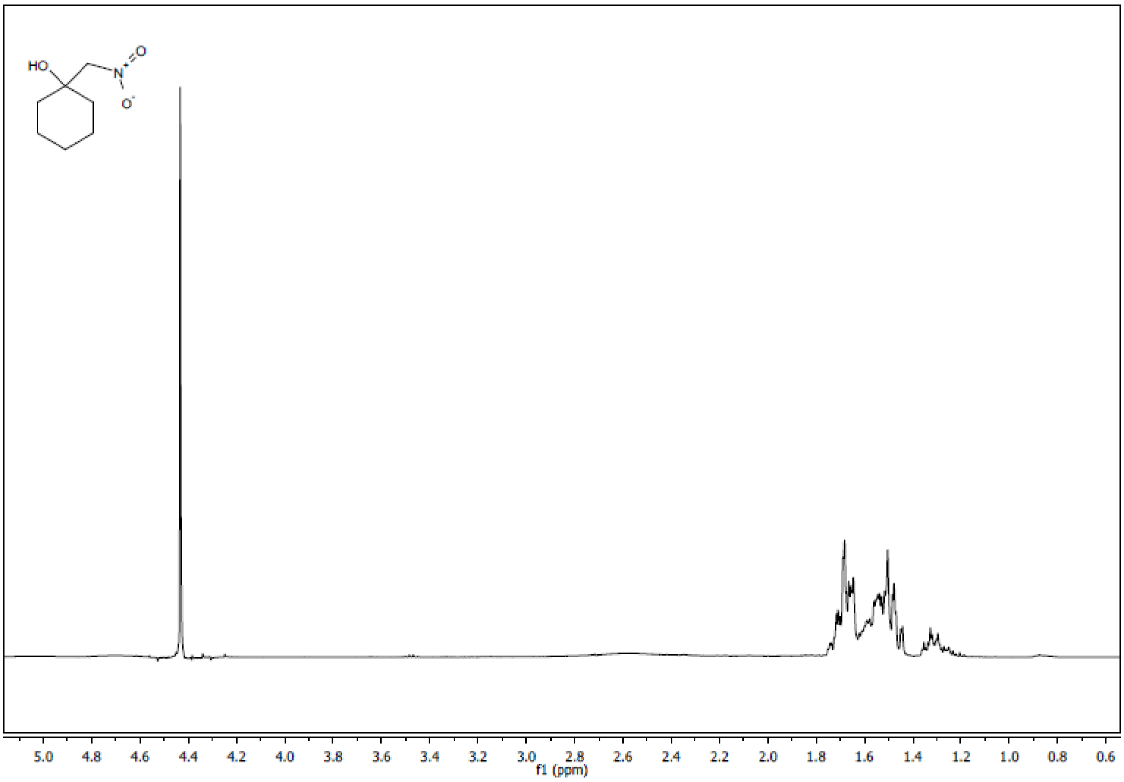

Figure A.3.15. ^{1}H-NMR ($CDCl_3$, 400MHz) spectrum of compound **14a**.

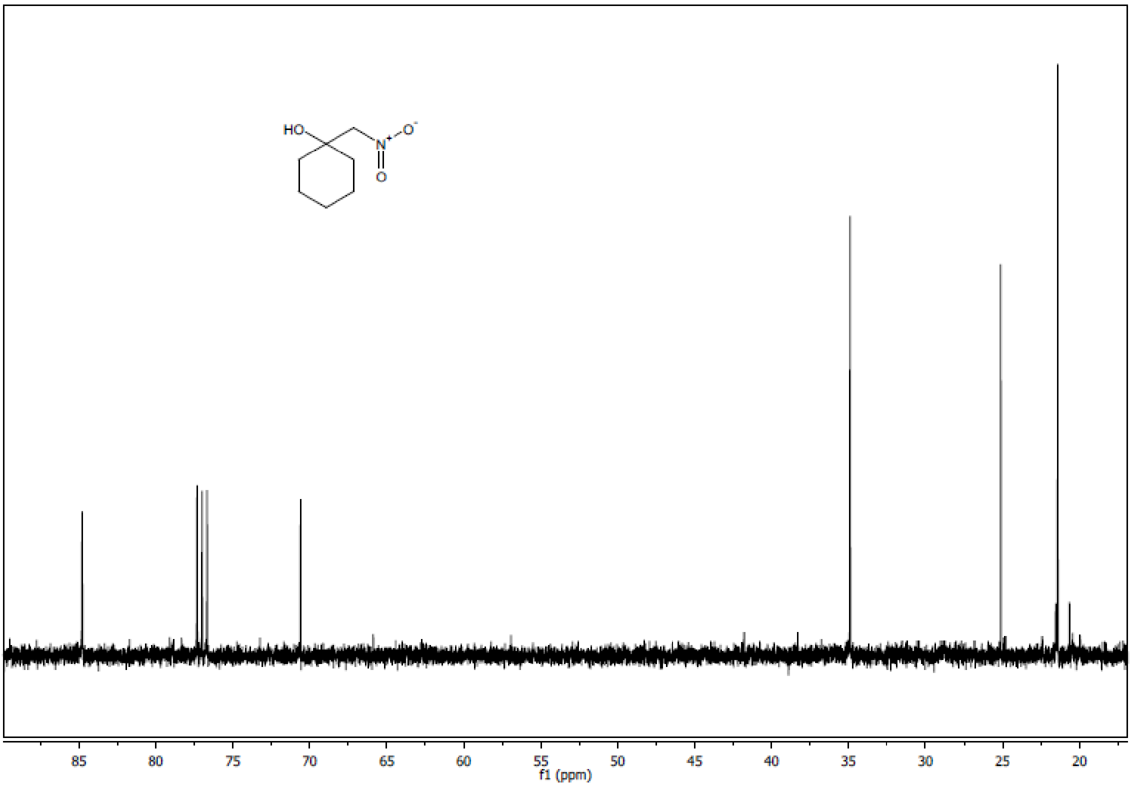

Figure A.3.16. ^{1}H-NMR ($CDCl_3$, 100MHz) spectrum of compound **14a**.

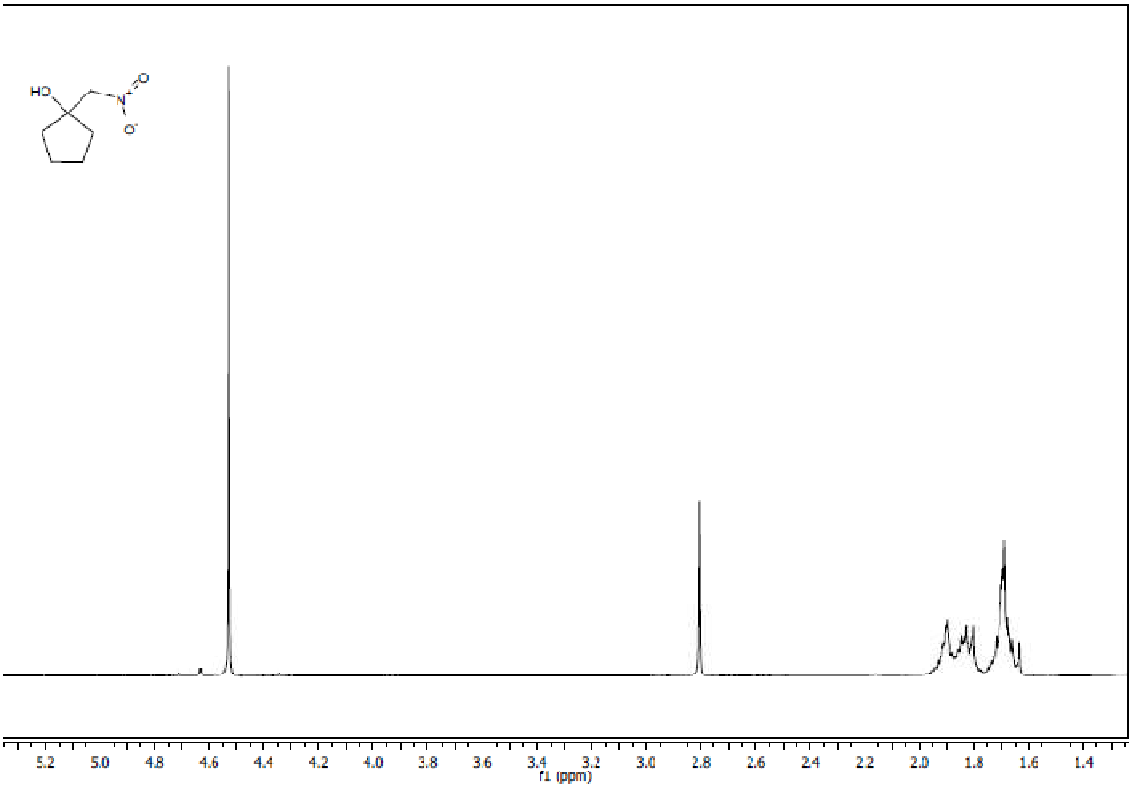

Figure A.3.17. ^{1}H-NMR (CDCl$_3$, 400MHz) spectrum of compound **14b**.

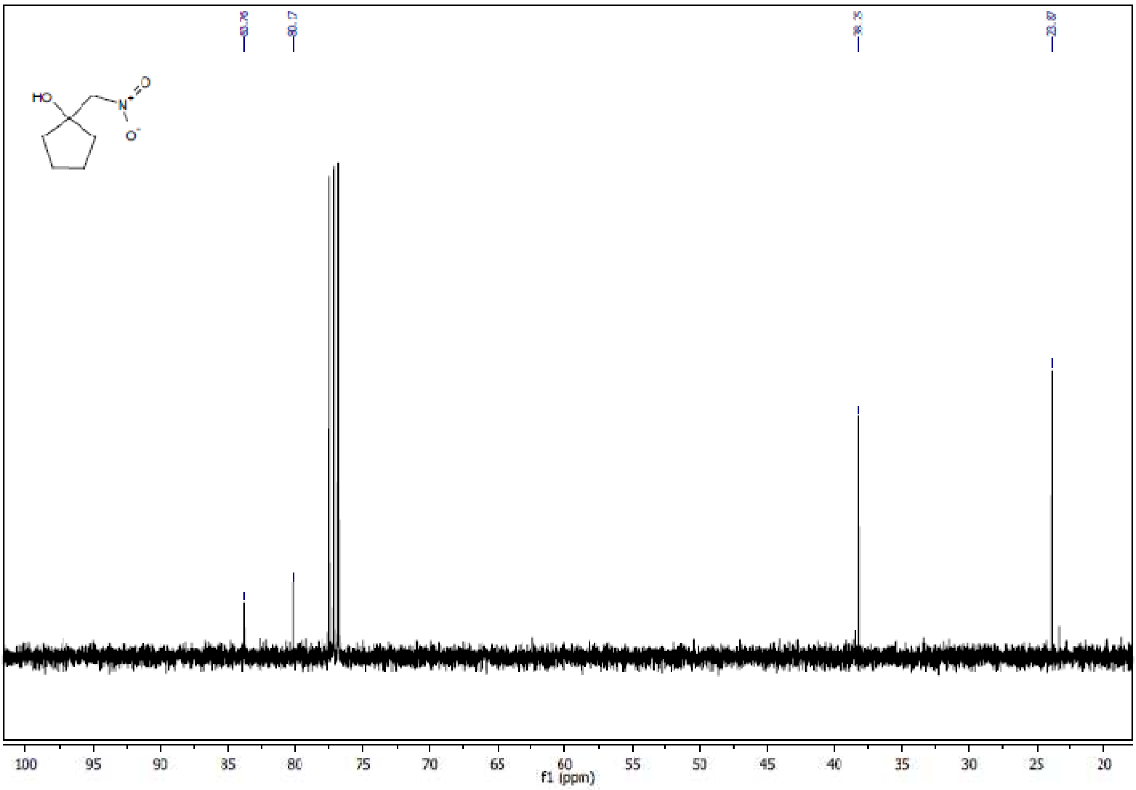

Figure A.3.18. ^{13}C-NMR (CDCl$_3$, 100MHz) spectrum of compound **14b**.

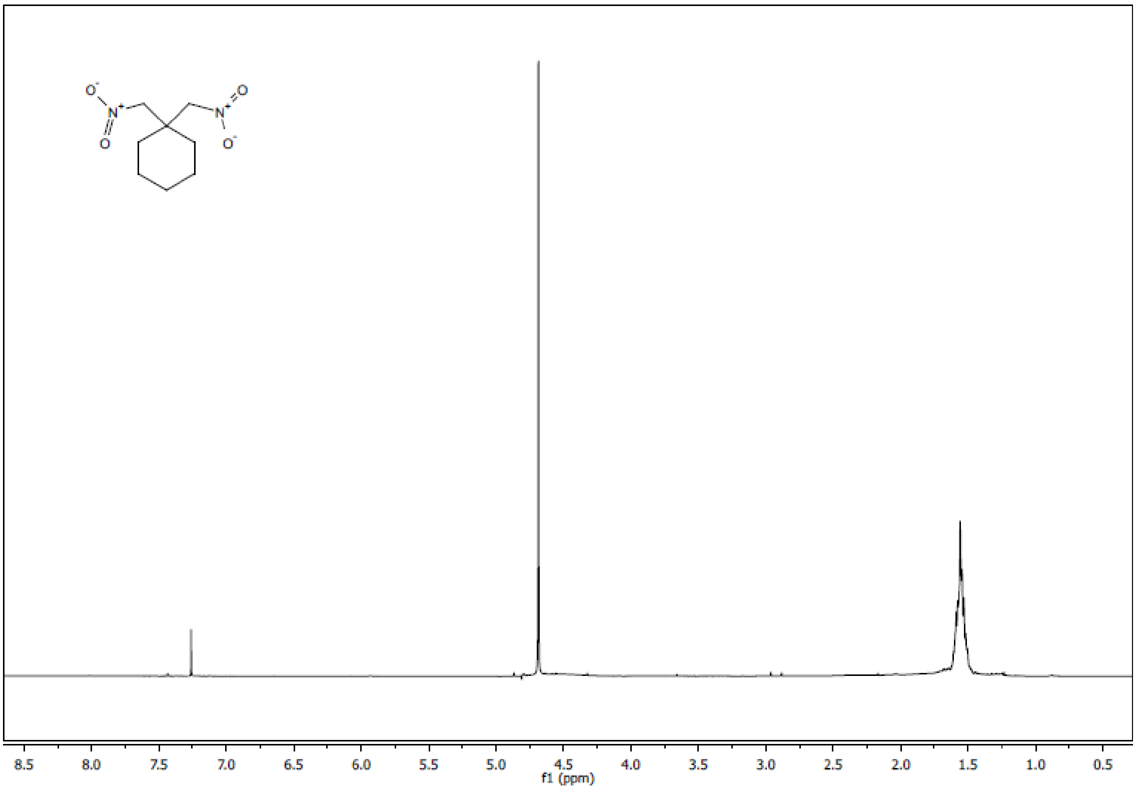

Figure A.3.19. ^{1}H-NMR ($CDCl_3$, 400MHz) spectrum of compound **15a**.

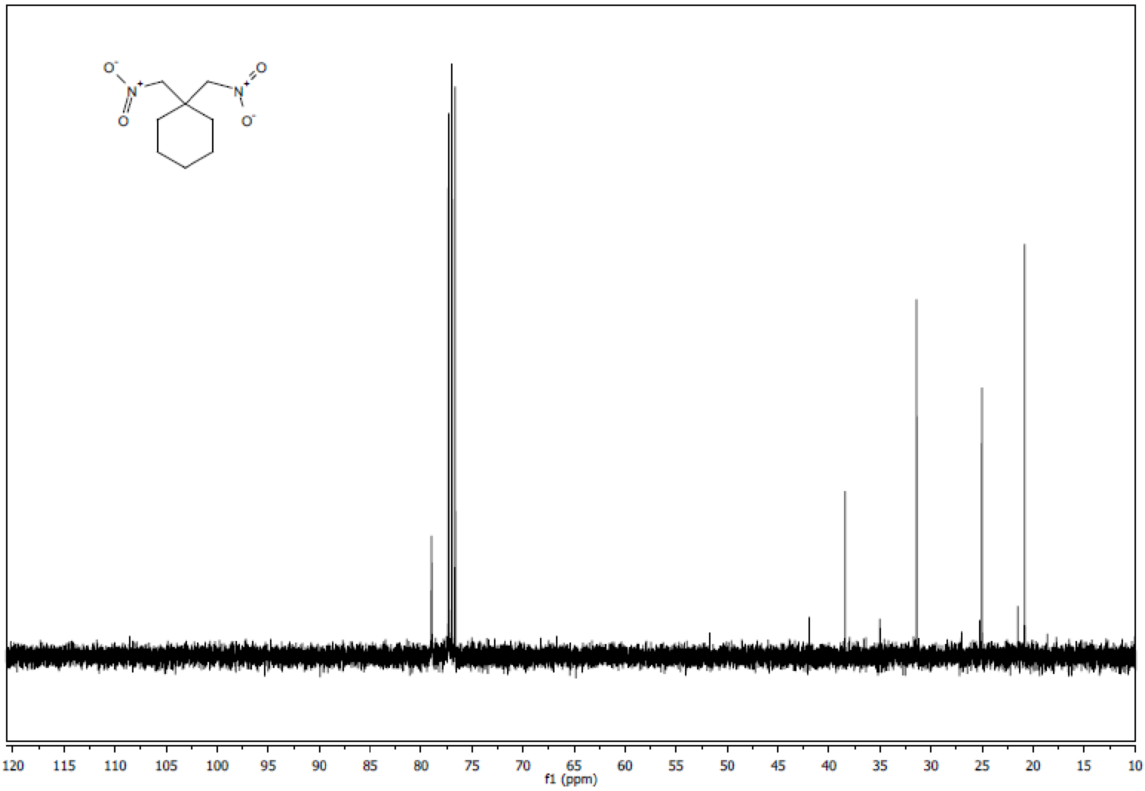

Figure A.3.20. ^{13}C-NMR ($CDCl_3$, 100MHz) spectrum of compound **15a**.

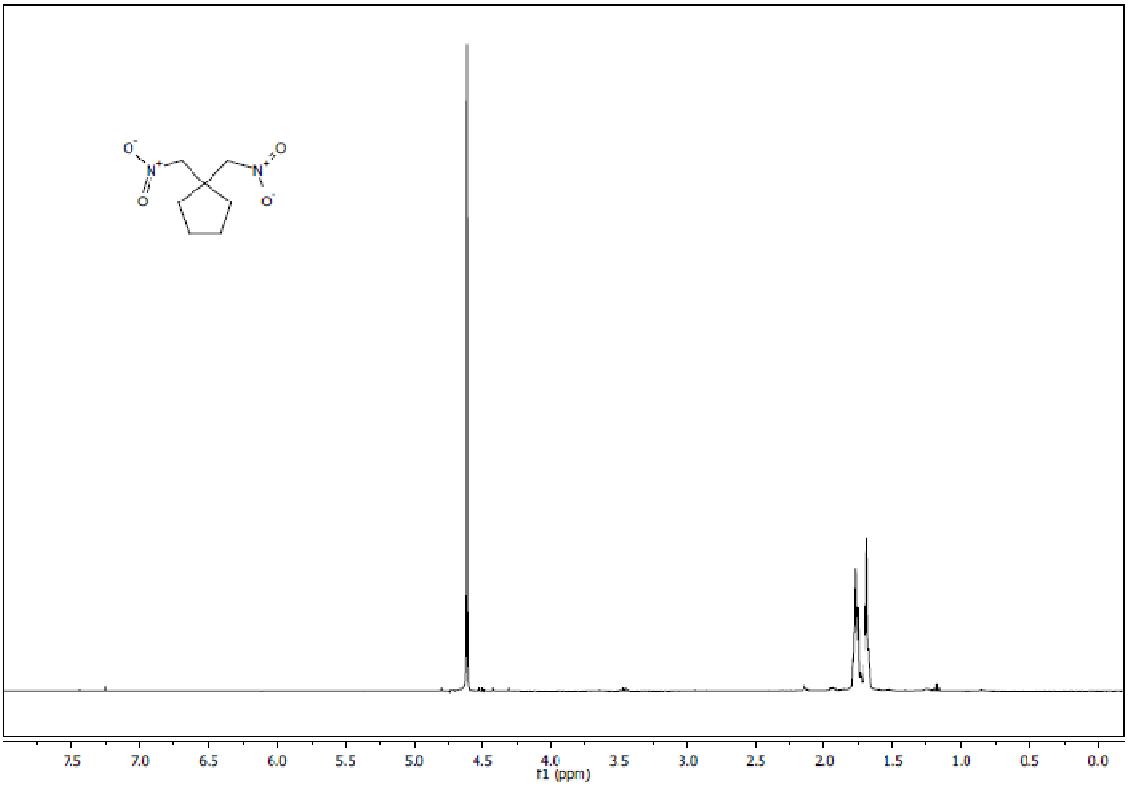

Figure A.3.21. ^{1}H-NMR ($CDCl_3$, 400MHz) spectrum of compound **15b**.

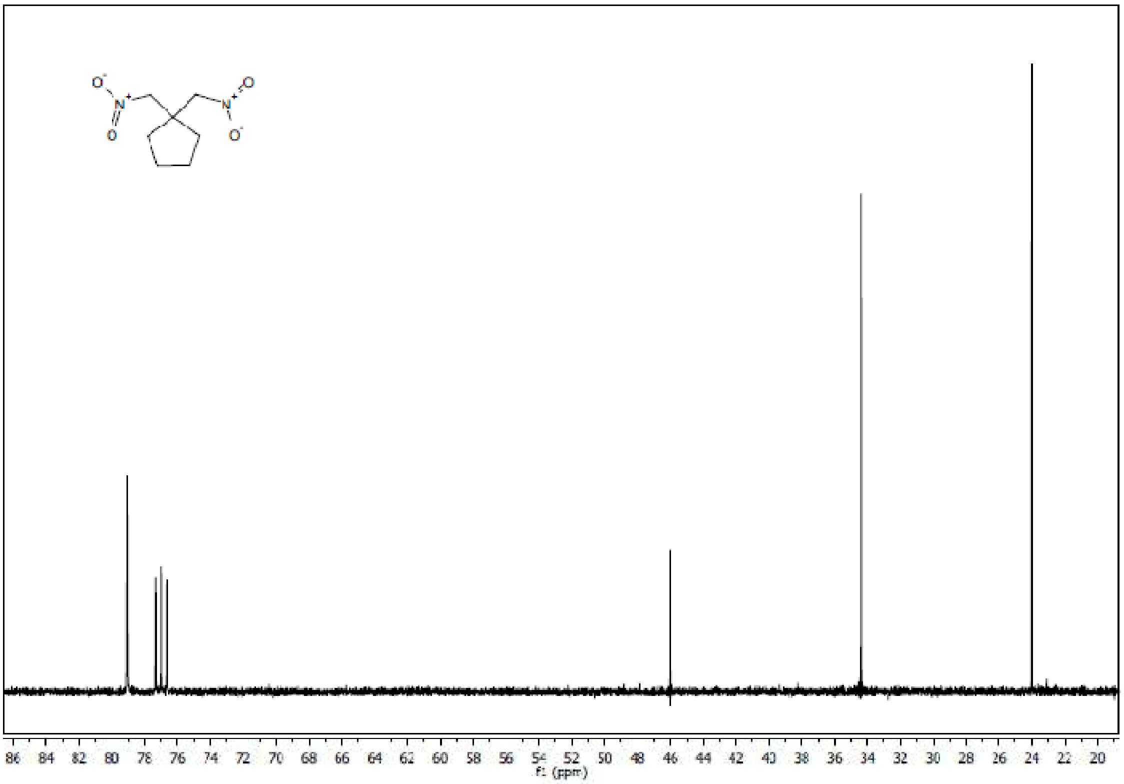

Figure A.3.22. ^{13}C-NMR ($CDCl_3$, 100MHz) spectrum of compound **15b**.

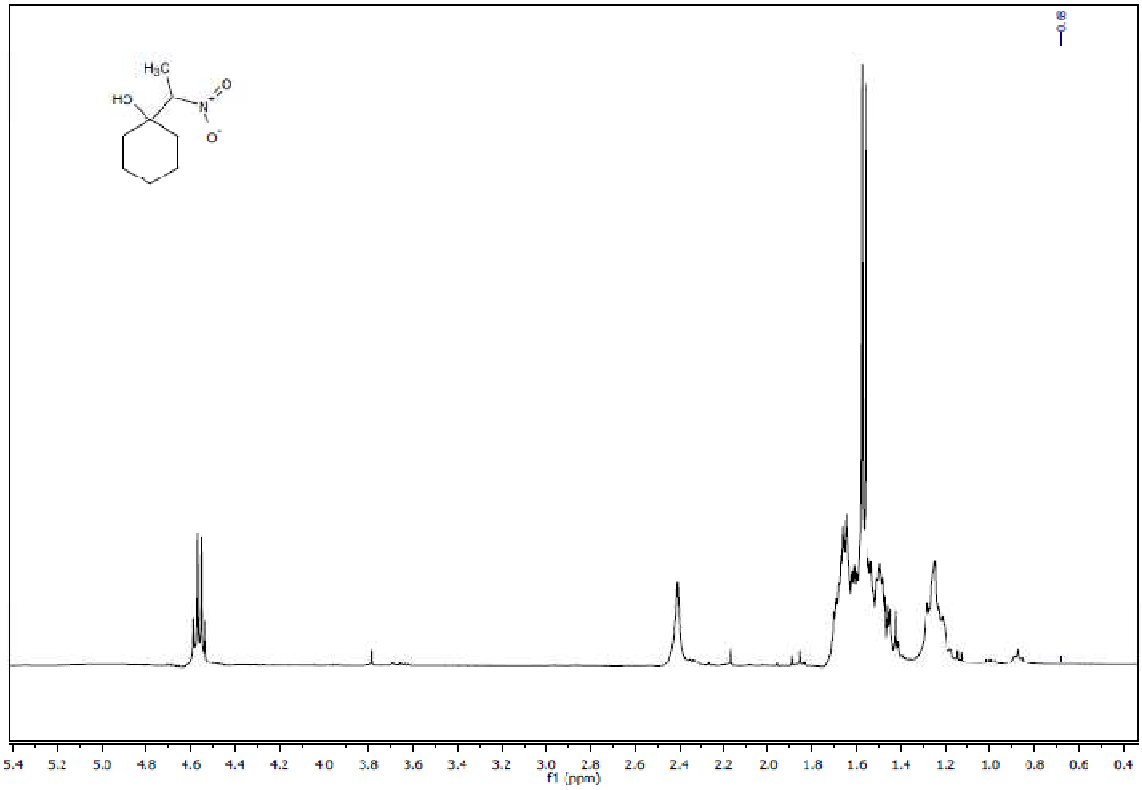

Figure A.3.23. ^{1}H-NMR ($CDCl_3$, 400MHz) spectrum of compound **16a**.

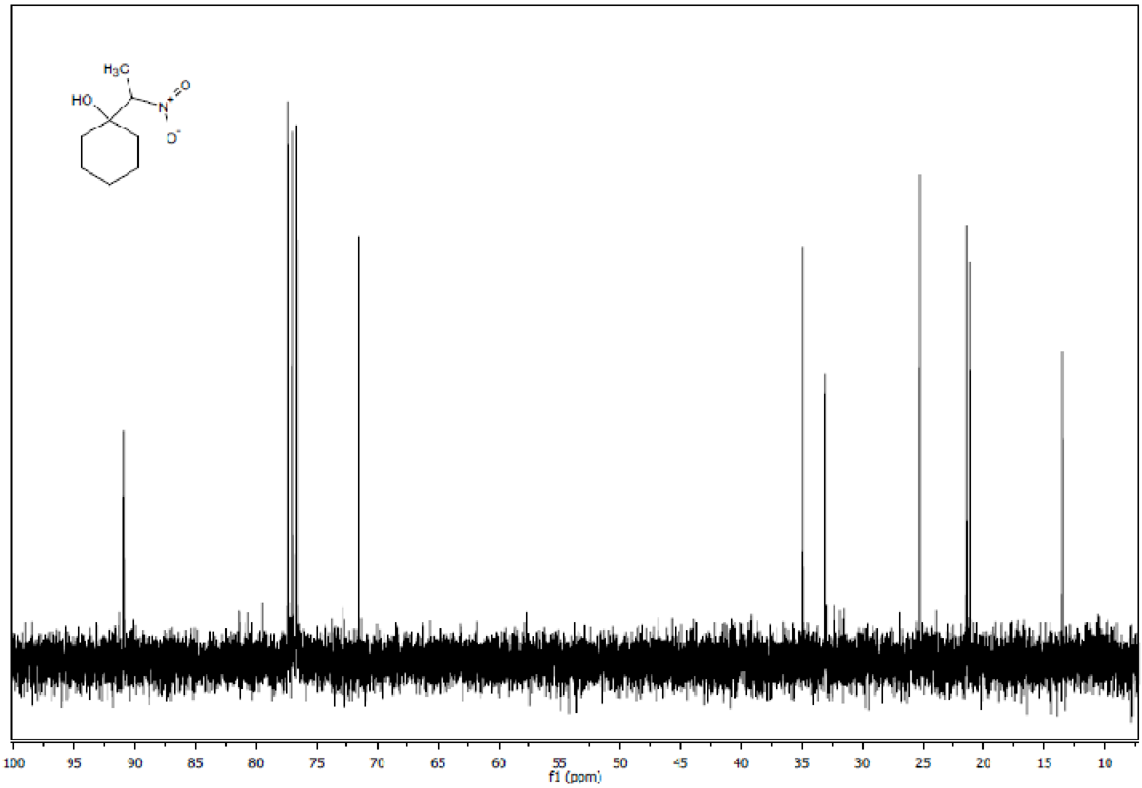

Figure A.3.24. ^{13}C-NMR ($CDCl_3$, 100MHz) spectrum of compound **16a**.

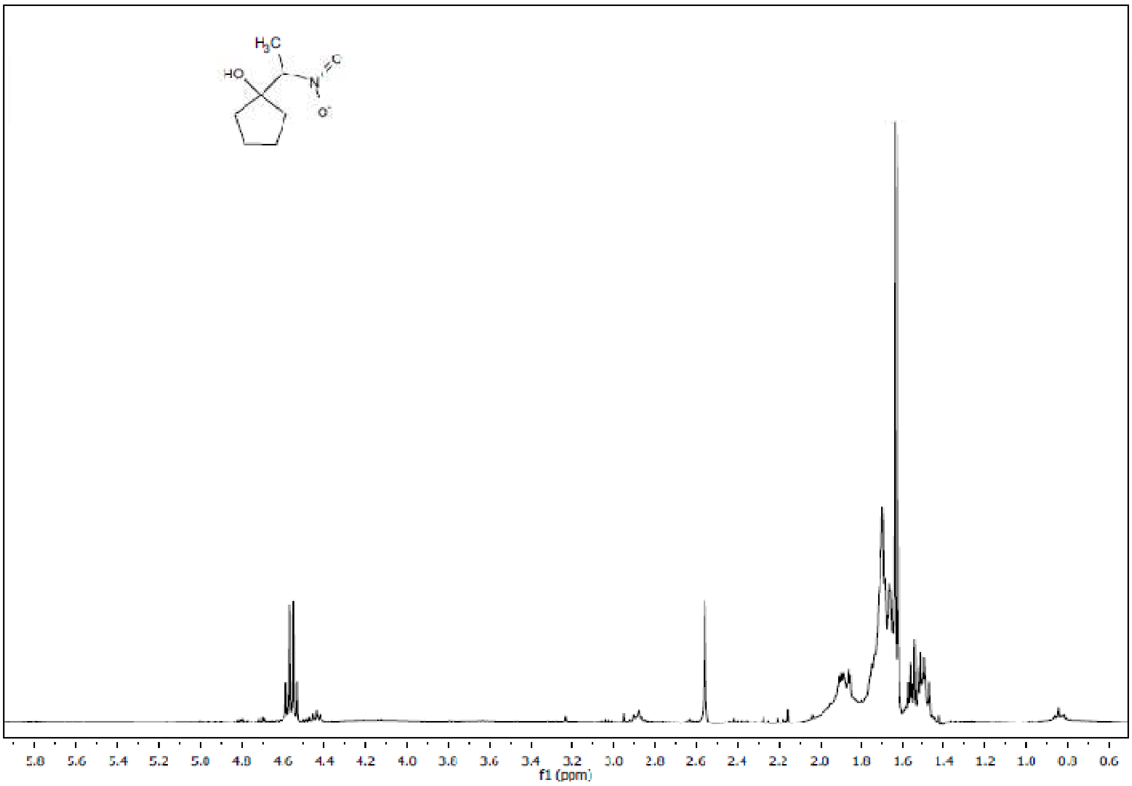

Figure A.3.25. ^{1}H-NMR (CDCl$_3$, 400MHz) spectrum of compound **16b**.

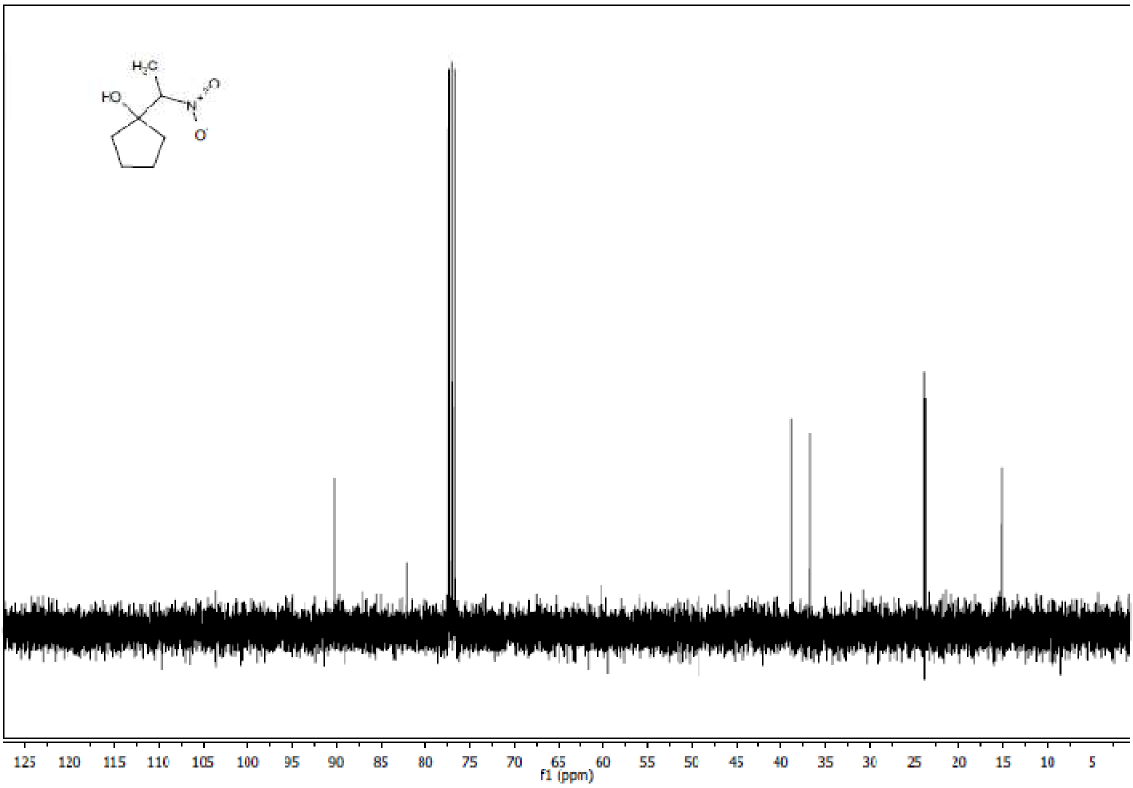

Figure A.3.26. ^{13}C-NMR (CDCl$_3$, 100MHz) spectrum of compound **16b**.

A.3.2 Phosphonium nitrate ionic liquid catalysed electrophilic aromatic oxychlorination.

Figure A.3.27. Reaction mixture before reaction . Upper layer: P8,8,8,1NO3 + Anisole; lower layer: aqueous HCl

Figure A.3.28. Brown fumes evolving at the beginning of reaction

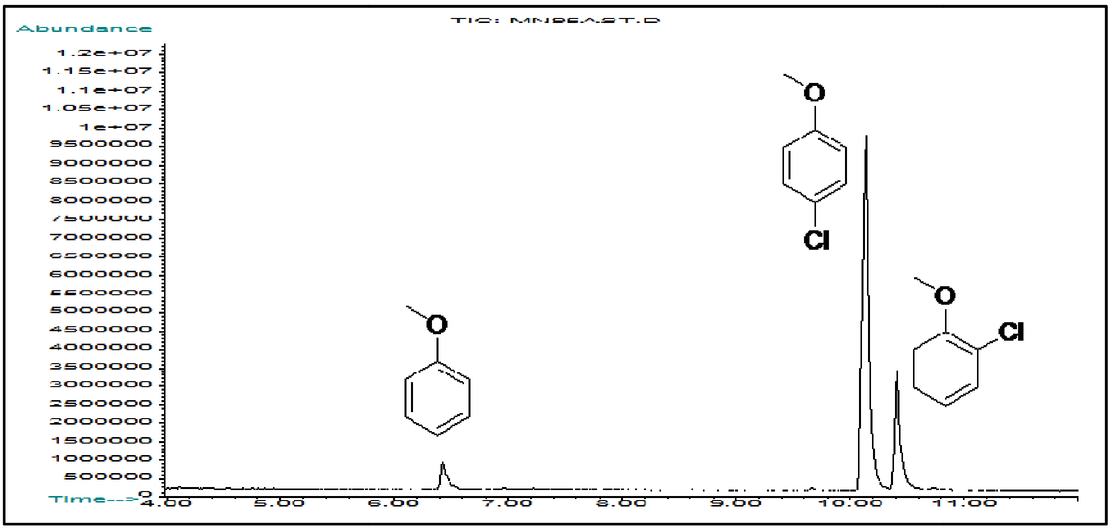

Figure A.3.29. GC of the anisole monochlorination.

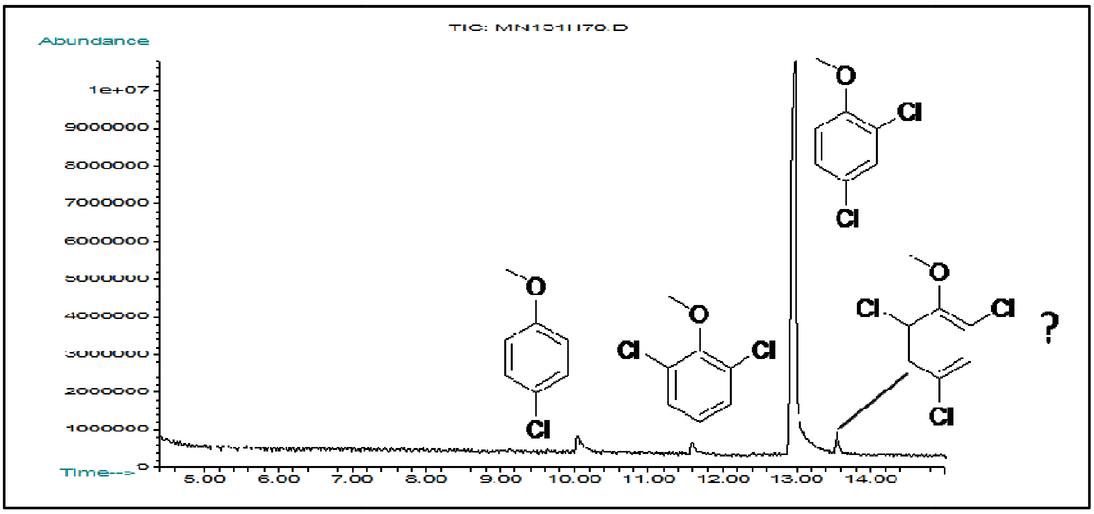

Figure A.3.30. GC of the anisole dichlorination.

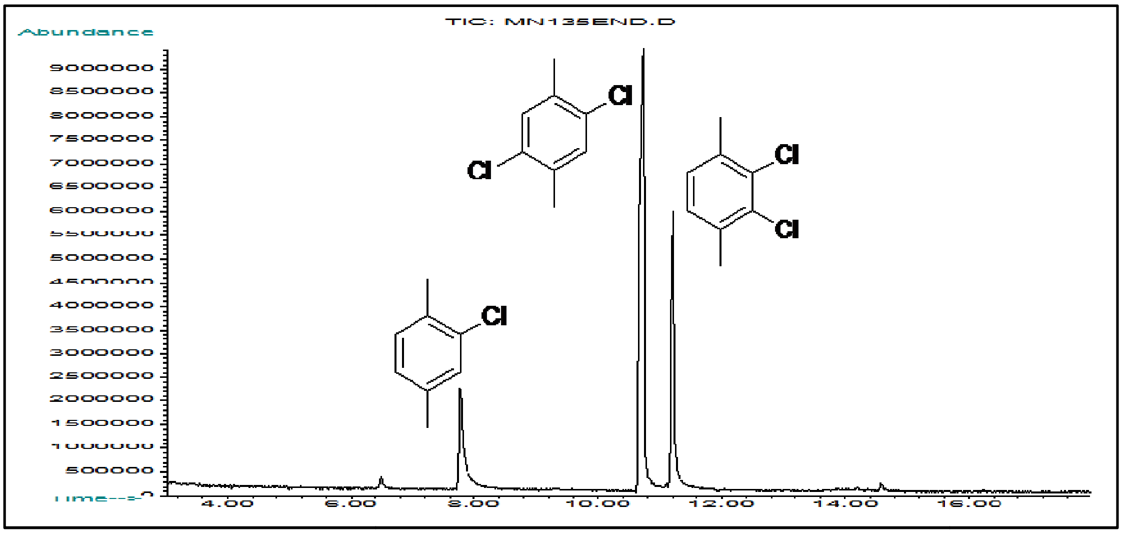

Figure A.3.31. GC of the .*p*-Xylene dichlorination products gas-chromatogram.

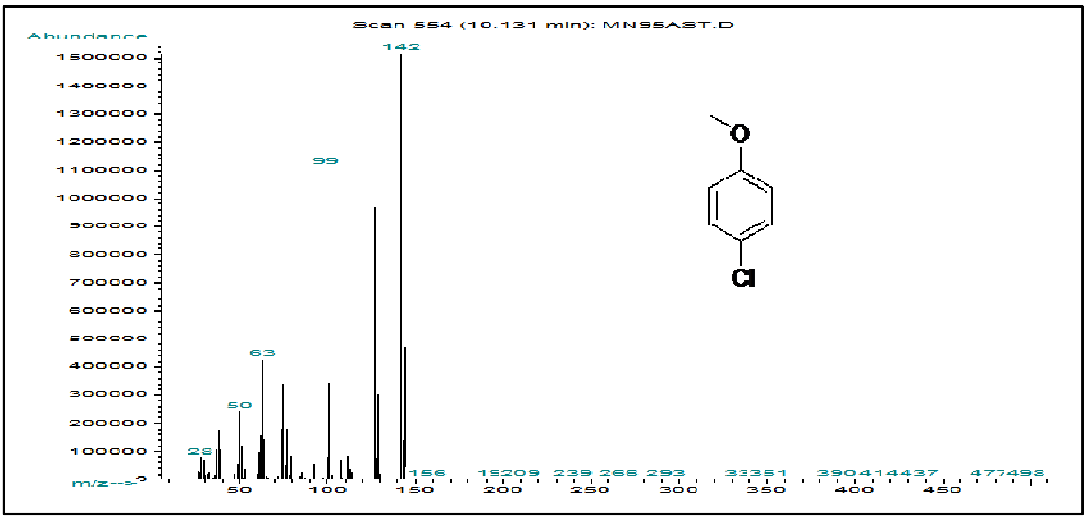

Figure A.3.32. MS spectrum of compound **18a** (*para* isomer).

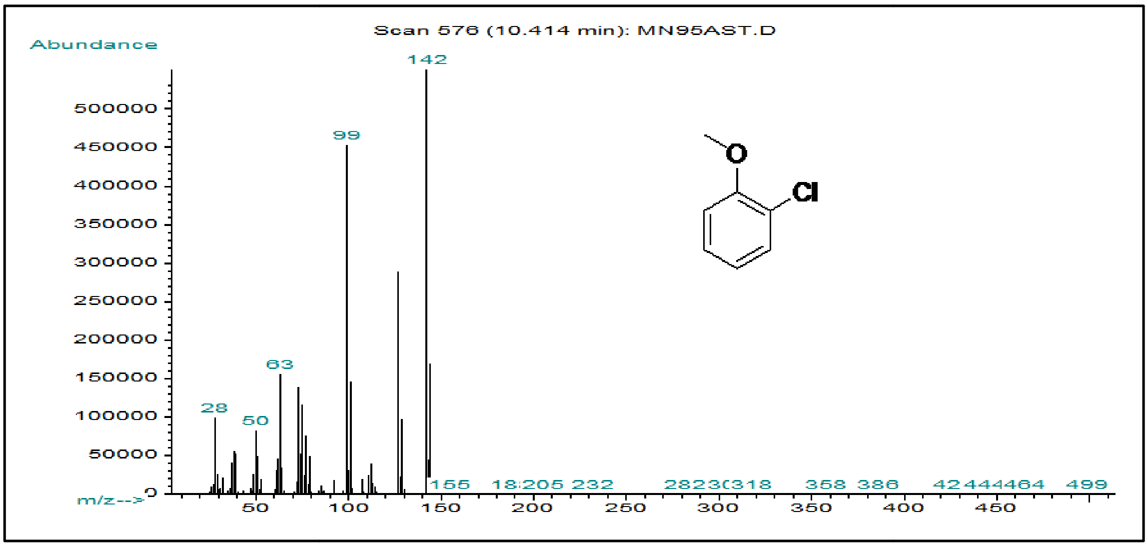

Figure A.3.33. MS spectrum of compound **18a** (*ortho* isomer).

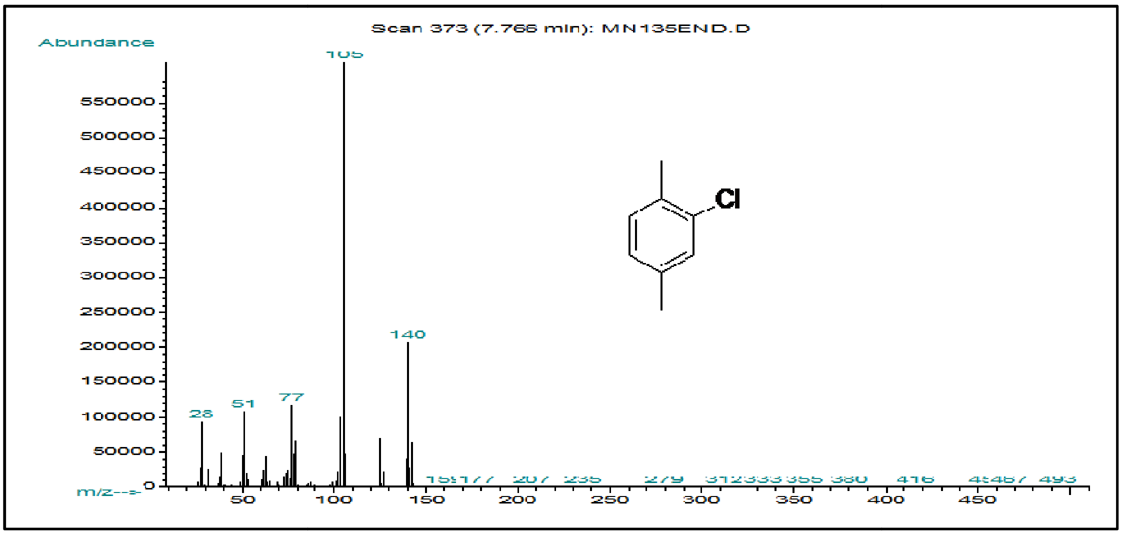

Figure A.3.34. MS spectrum of compound **18b.**

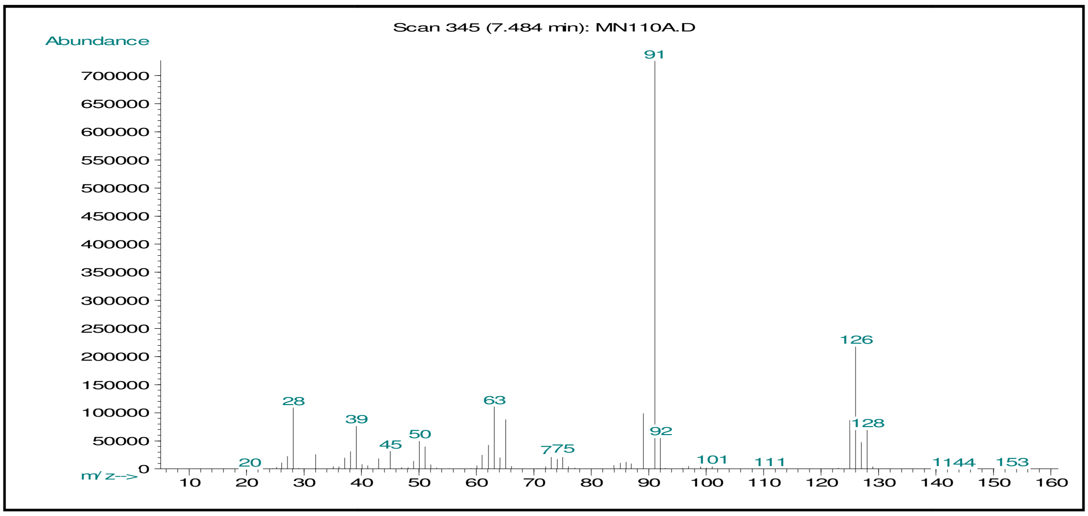

Figure A.3.35. MS spectrum of compound **18c**.

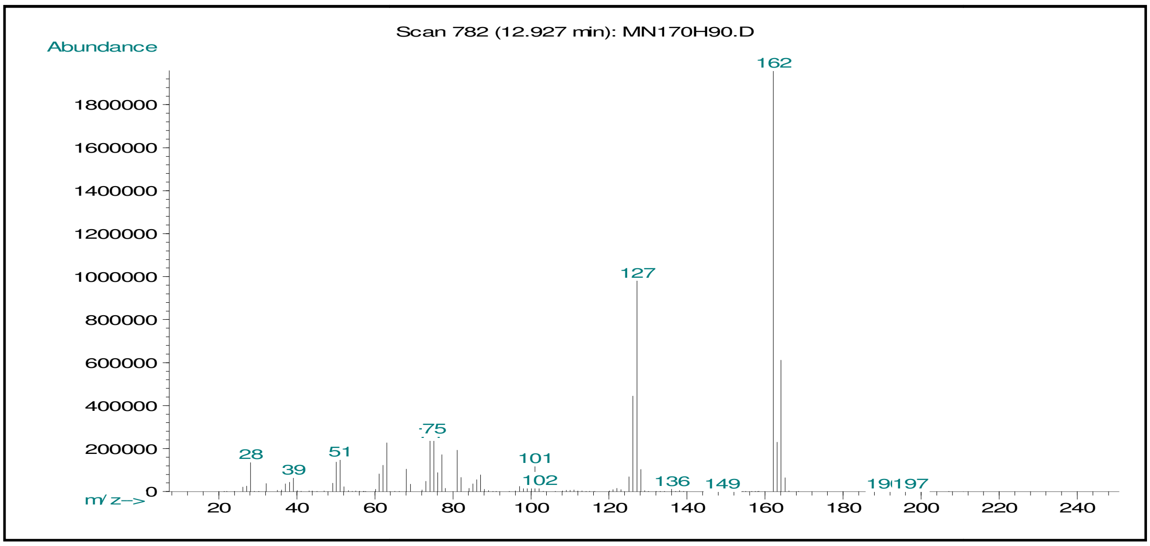

Figure A.3.36. MS spectrum of compound **18d**.

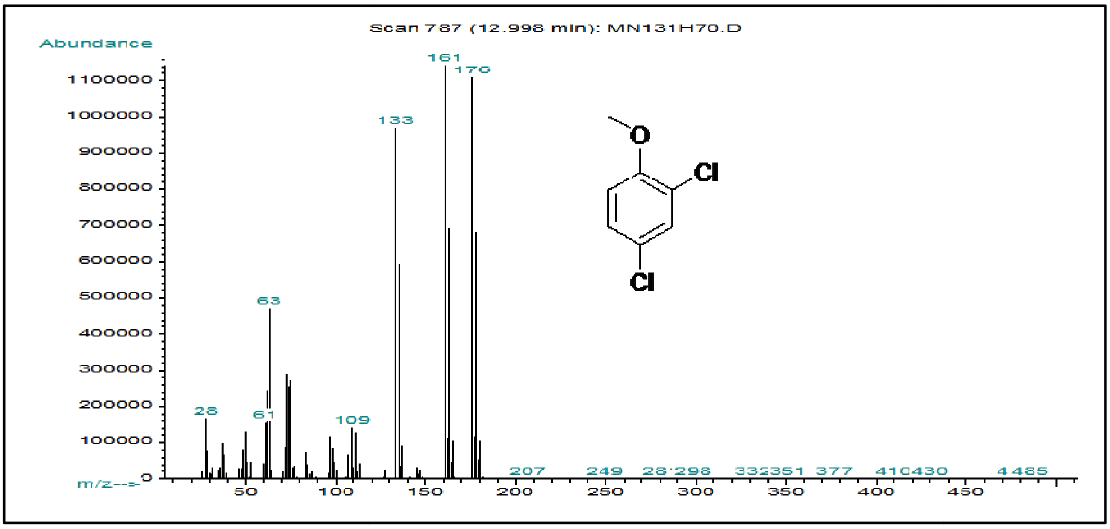

Figure A.3.37. MS spectrum of compound **19a**.

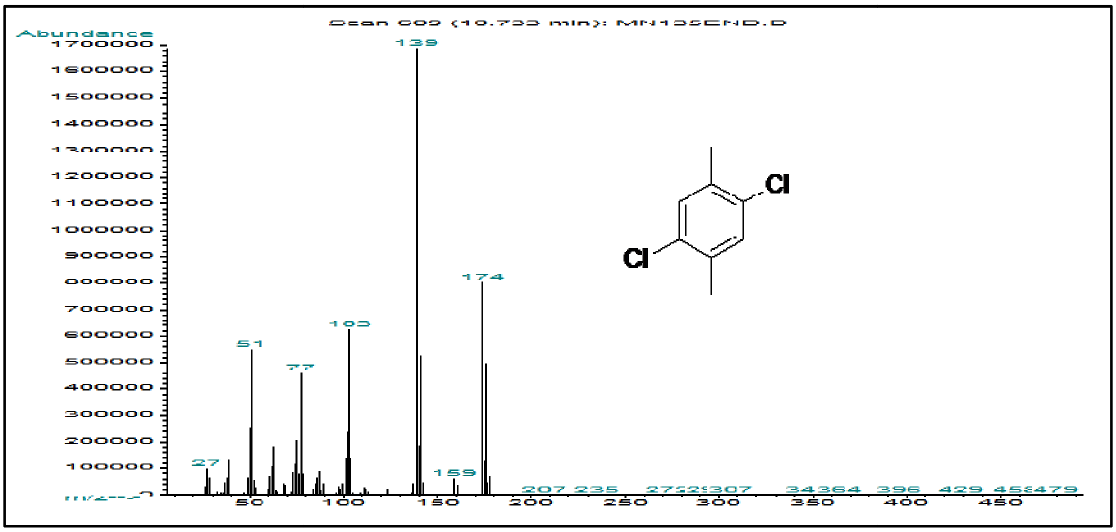

Figure A.3.38. MS spectrum of compound **19b** (2,5 isomer).

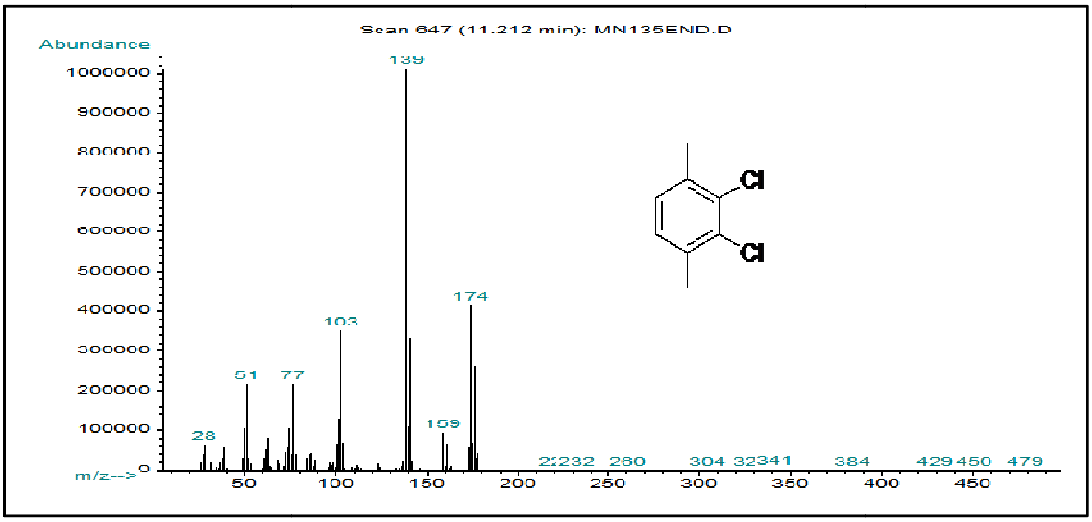

Figure A.3.39. MS spectrum of compound **19b** (2,5 isomer).

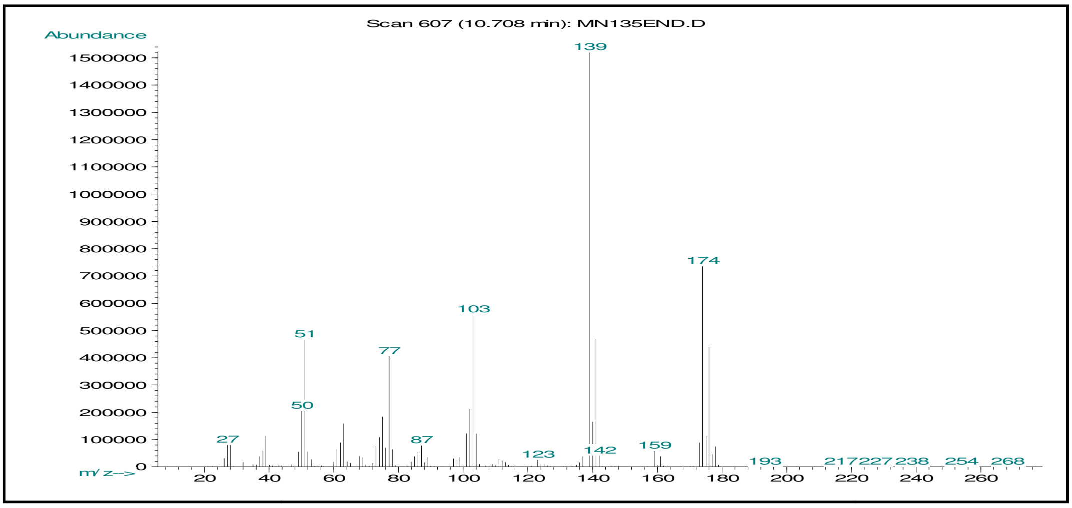

Figure A.3.40. MS spectrum of compound **19c**.

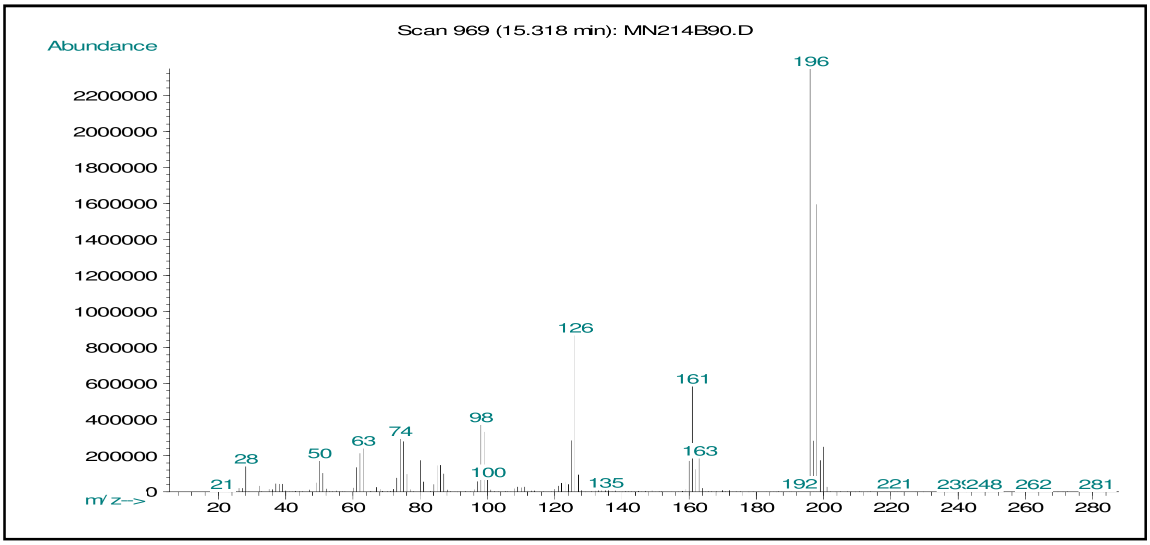

Figure A.3.41. MS sectrum of compound **19d**.

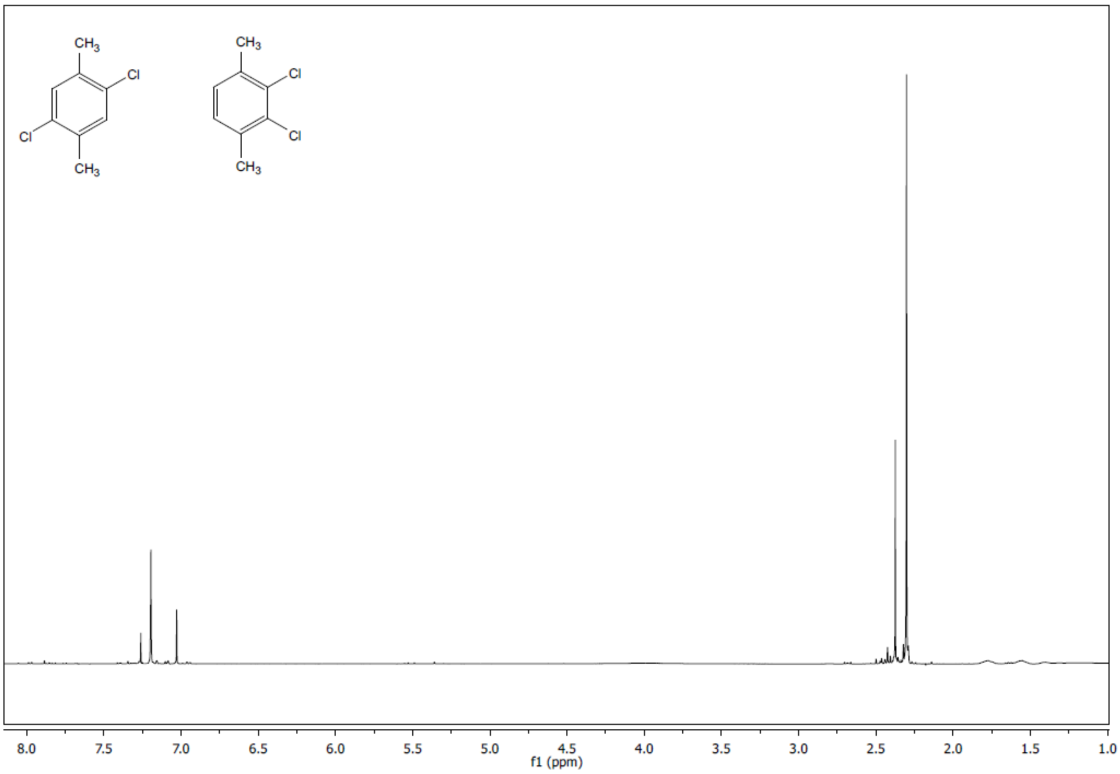

Figure A.3.42. ^{1}H-NMR ($CDCl_3$, 400 MHz) spectrum of compounds **19b**.

A4. Chapter 4

Green alternative procedures for Tadalafil preparation

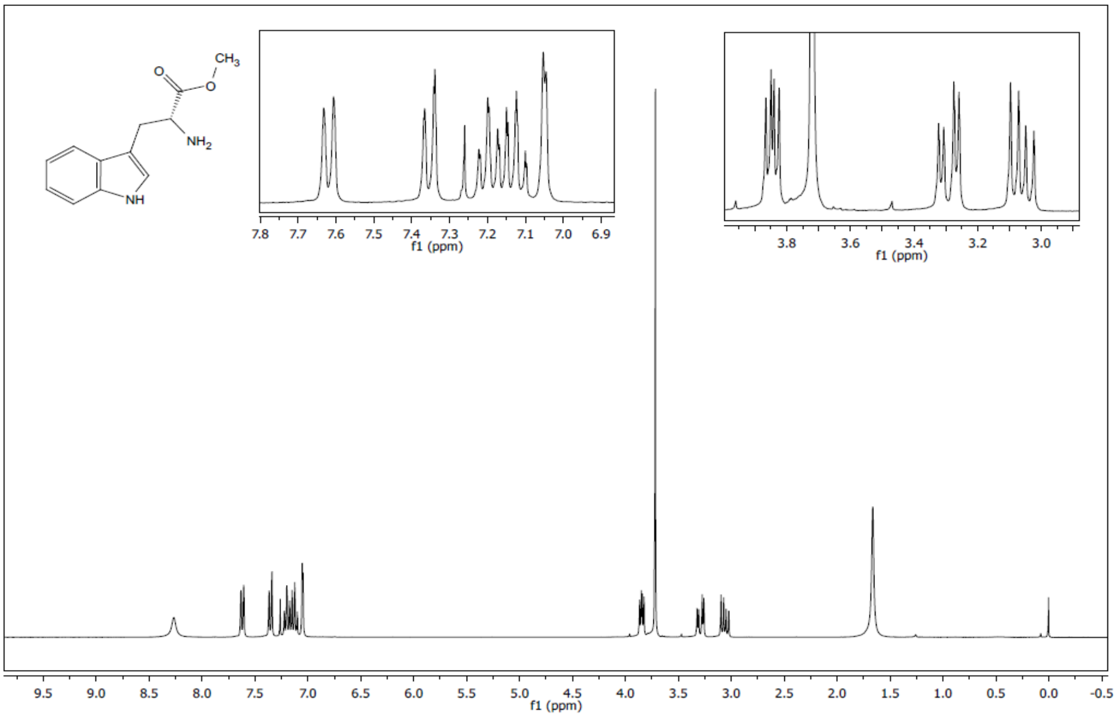

Figure A.4.1. ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of compound **21**.

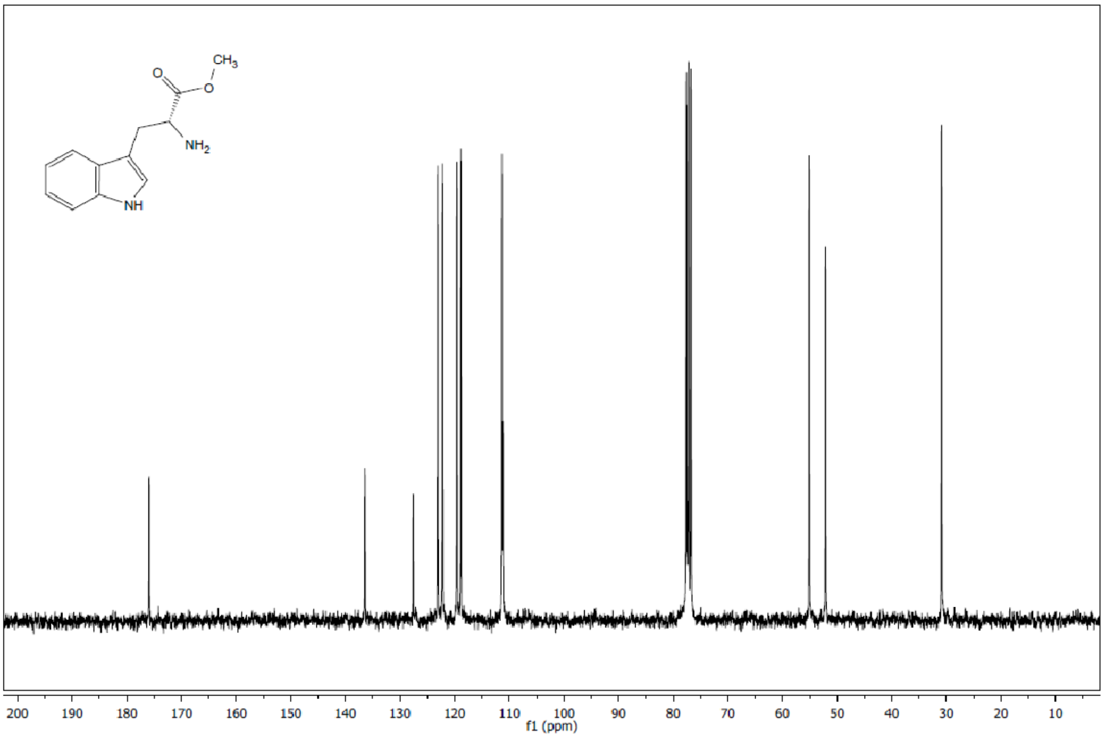

Figure A.4.2. ^{13}C NMR ($CDCl_3$, 75 MHz) spectrum of compound **21**.

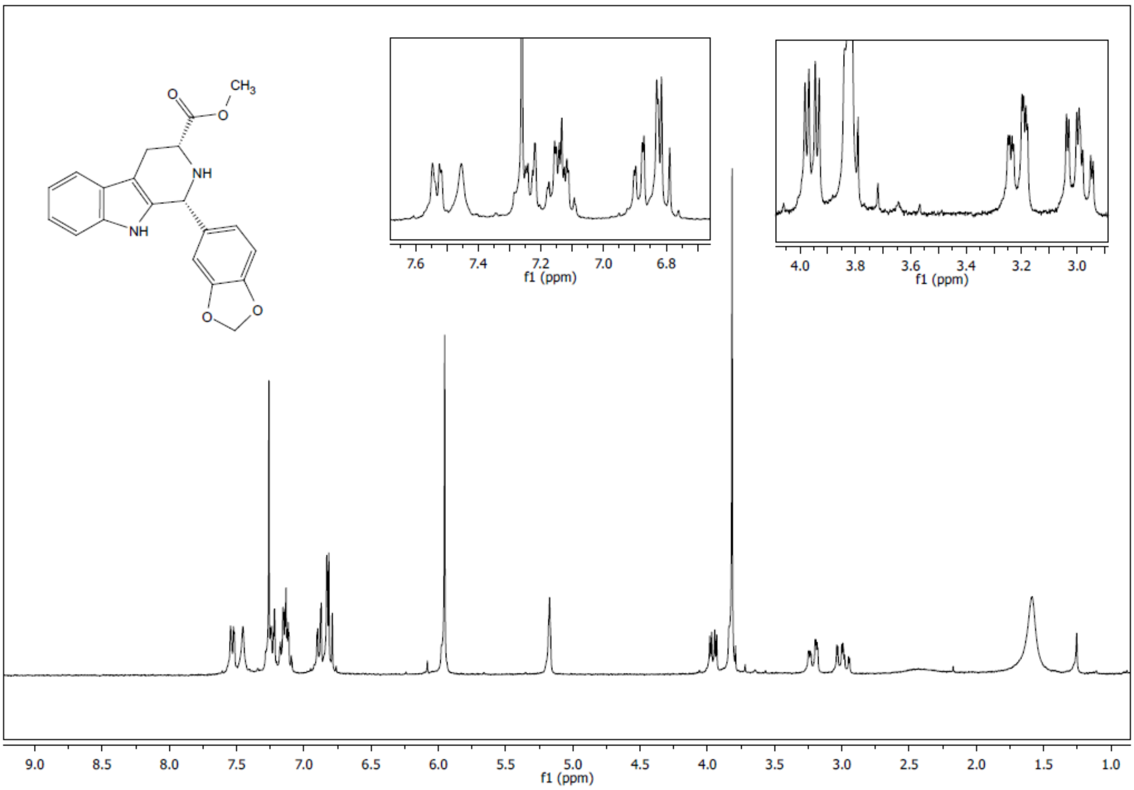

Figure A.4.3. ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of compound **22*cis***.

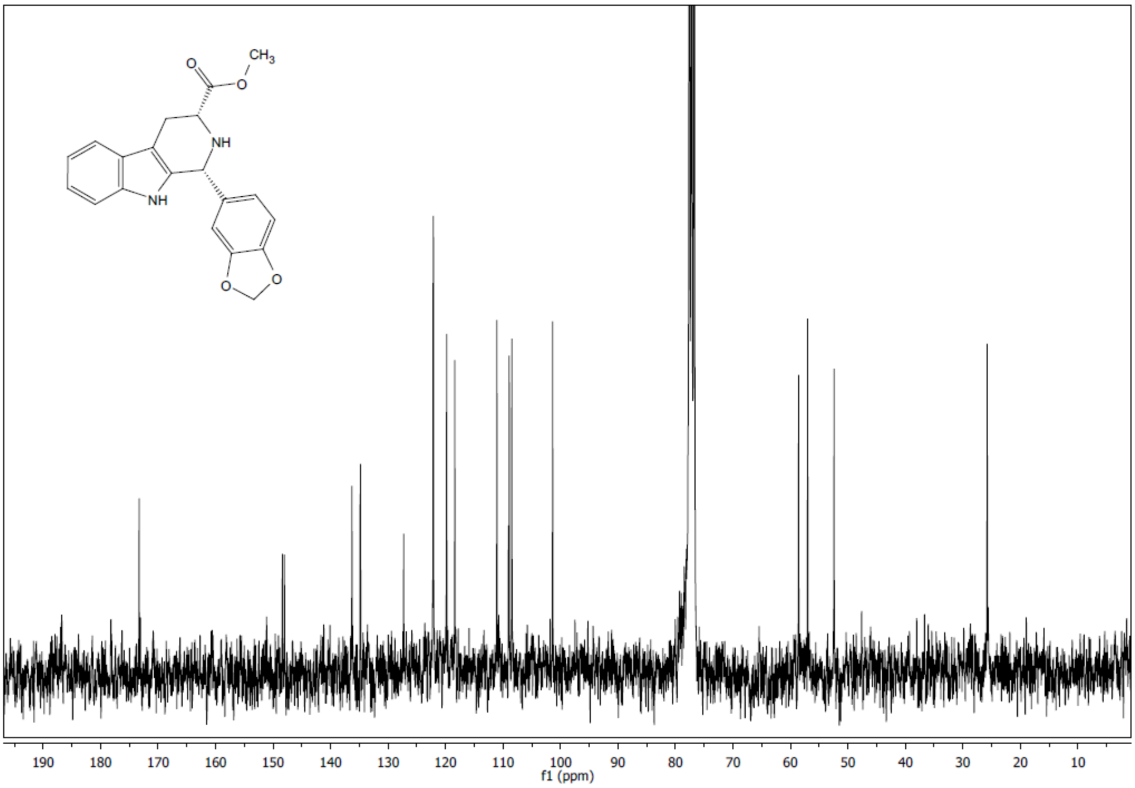

Figure A.4.4. ^{13}C NMR ($CDCl_3$, 75 MHz) spectrum of compound **22*cis***.

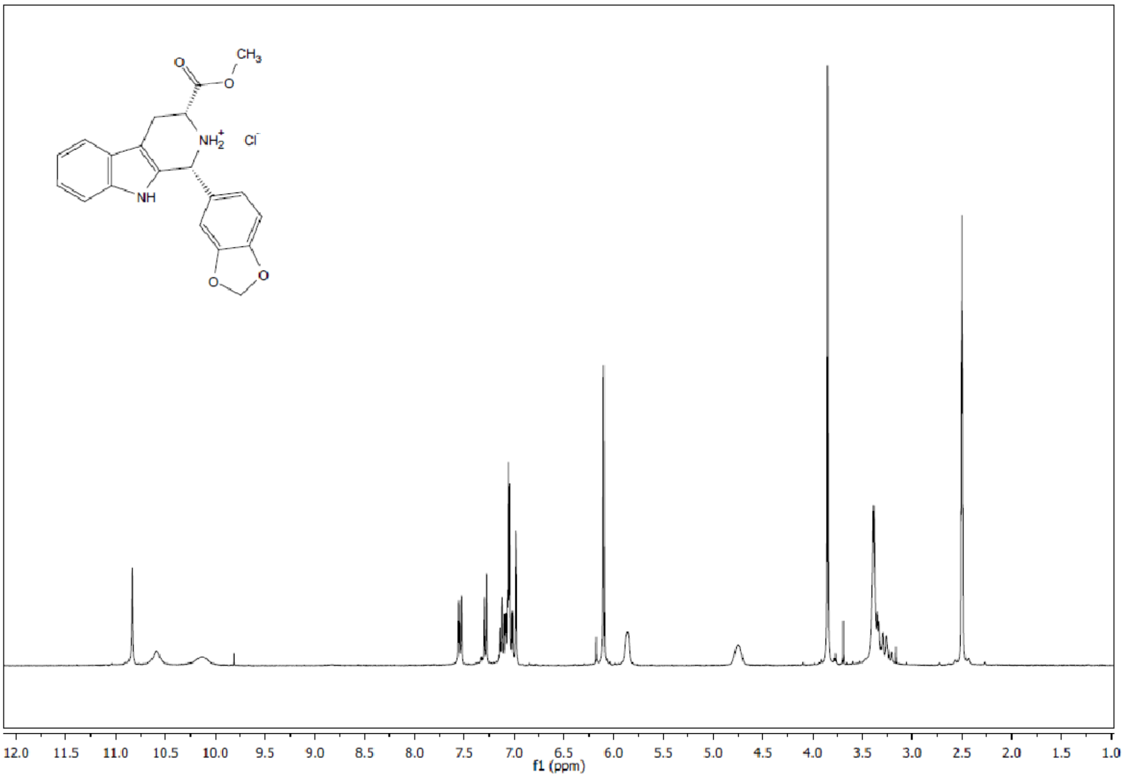

Figure A.4.5. ^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of compound **22*cis*·HCl**.

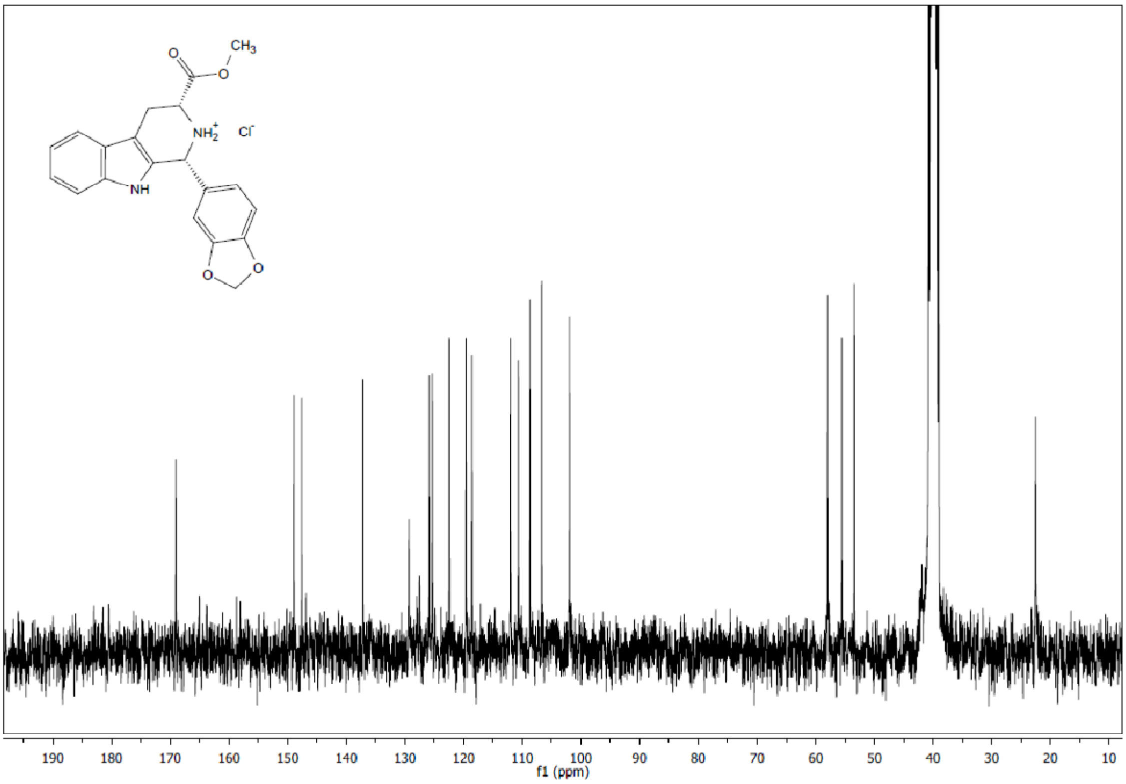

Figure A.4.6. ^{13}C NMR (DMSO-d_6, 75 MHz) spectrum of compound **22*cis*·HCl**.

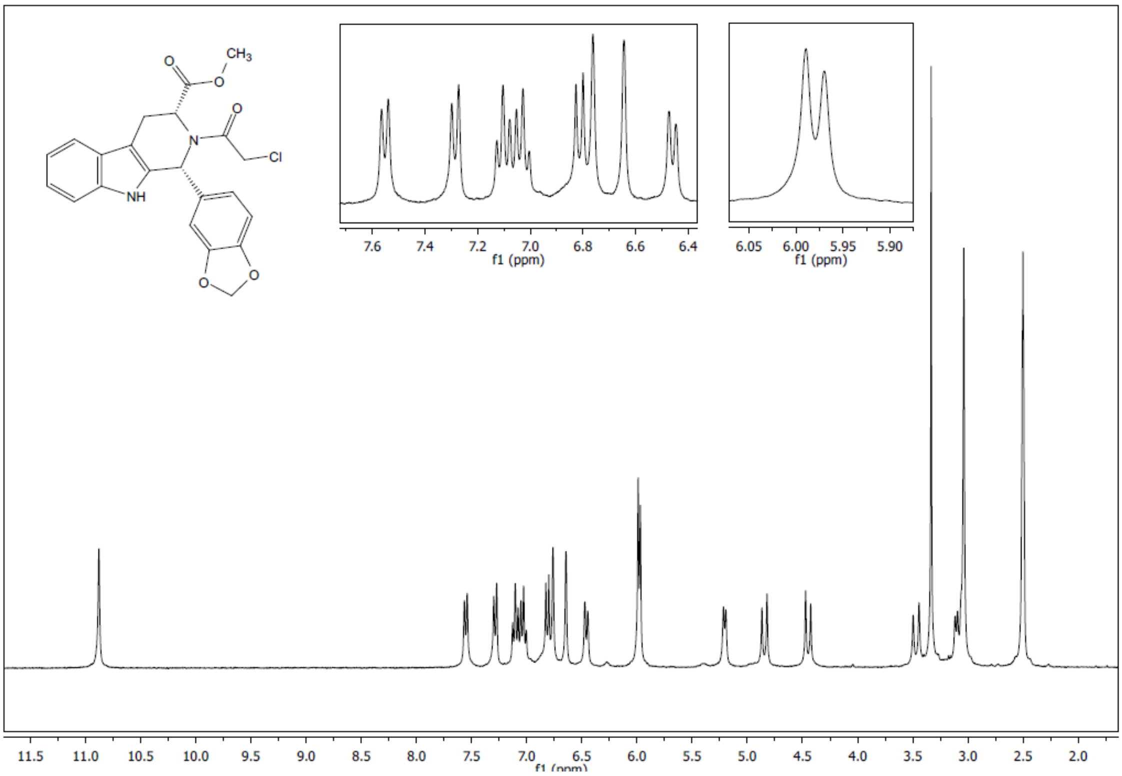

Figure A.4.7. ^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of compound **23**.

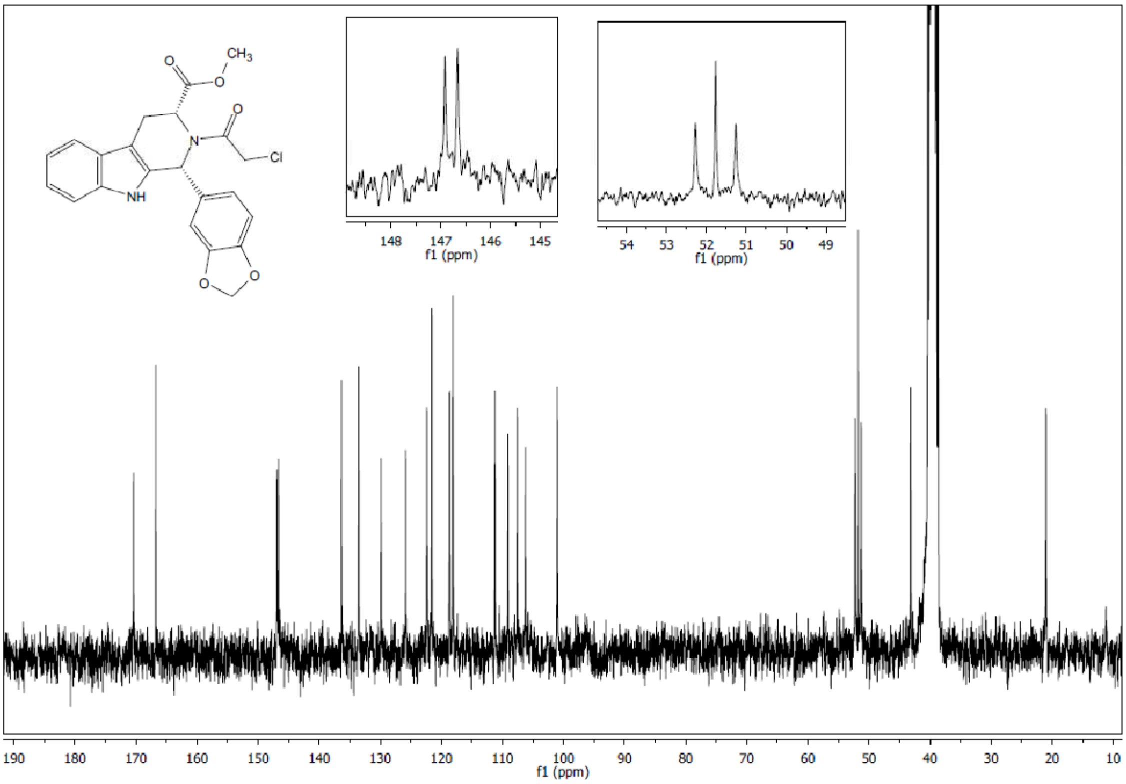

Figure A.4.8. ^{13}C NMR (DMSO-d_6, 75 MHz) spectrum of compound **23**.

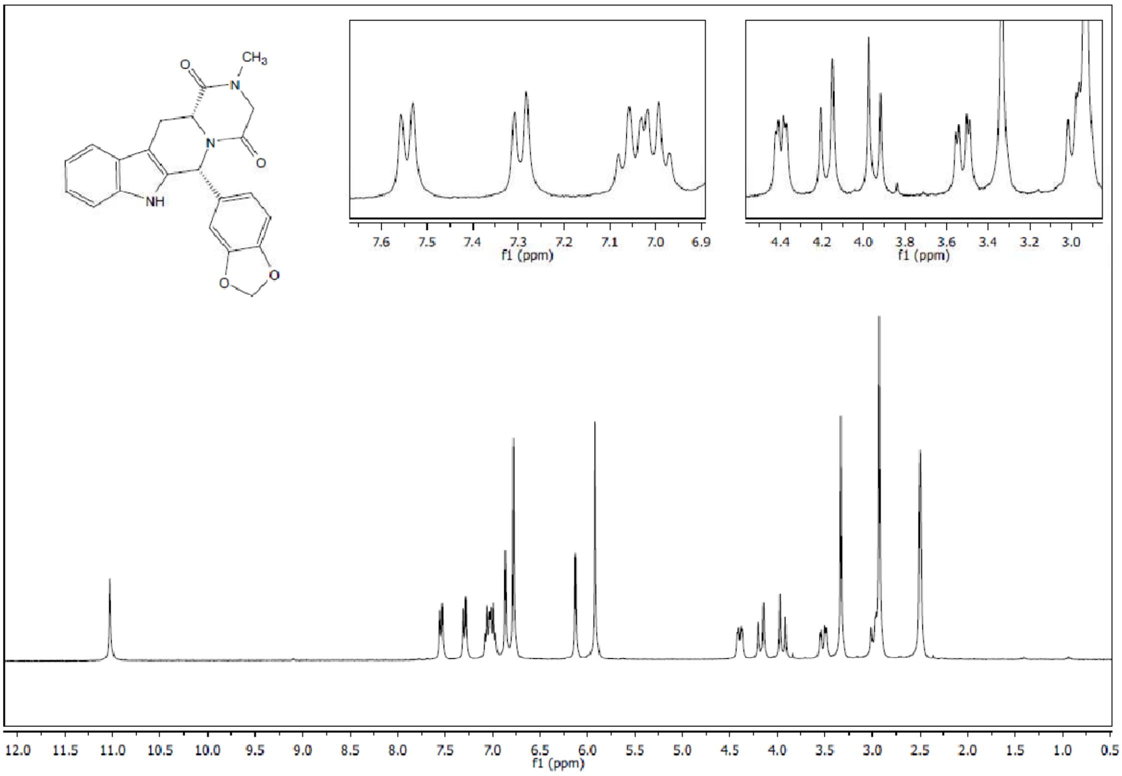

Figure A.4.9. ^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of compound **24**.

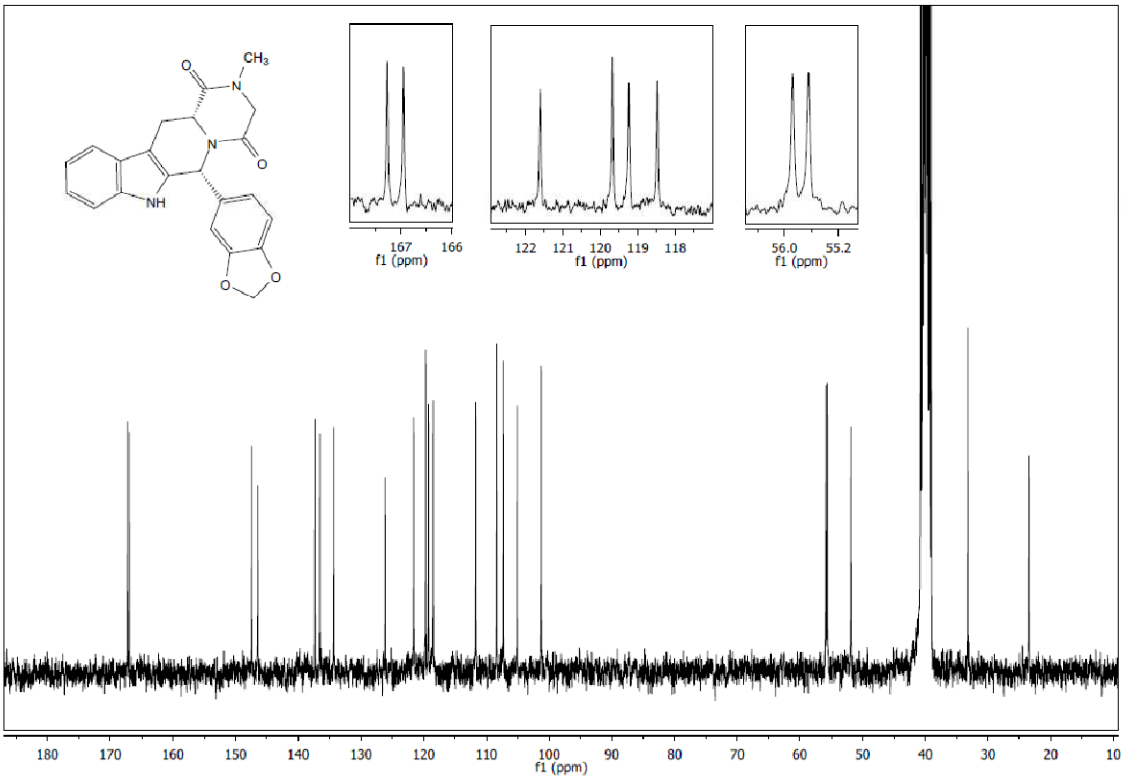

Figure A.4.10. ^{13}C NMR (DMSO-d_6, 75 MHz) spectrum of compound **24**.

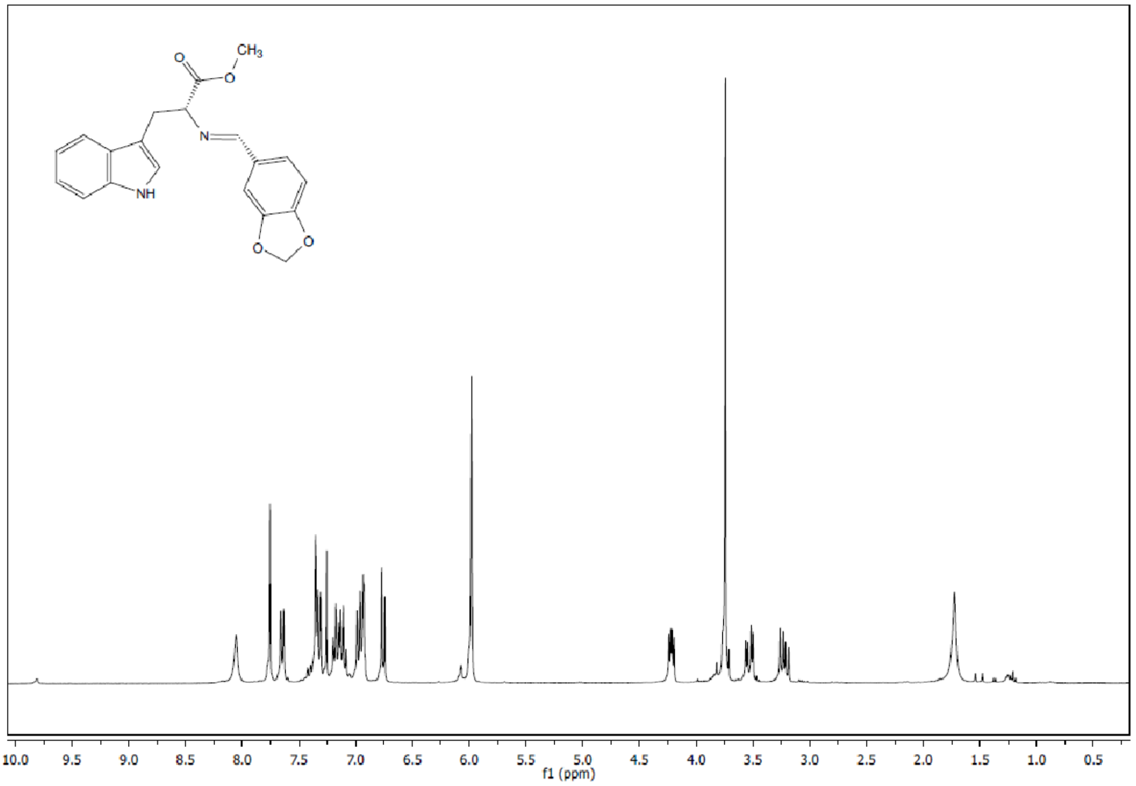

Figure A.4.11. ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of compound **25**.

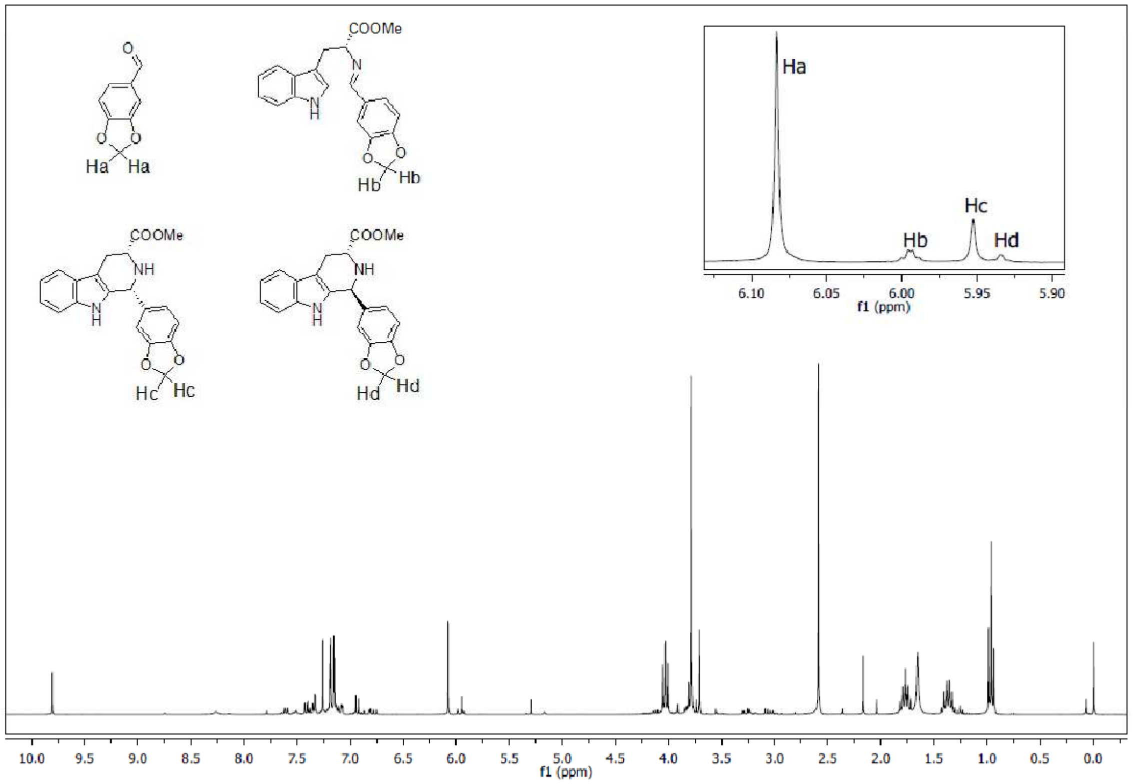

Figure A.4.12. ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of the Pictect-Spengler reaction mixture in [C_4dmim][NTf_2]. Diagnostic signals whose integration was used to evaluate conversion and selectivity of the reaction are highlighted in the expanction box.

A5. Chapter 5

Green synthetic strategies implementation in collaboration with Galentis S.r.l.

A.5.1 Chlorination of [2,2]-paracyclophane in alternative solvents

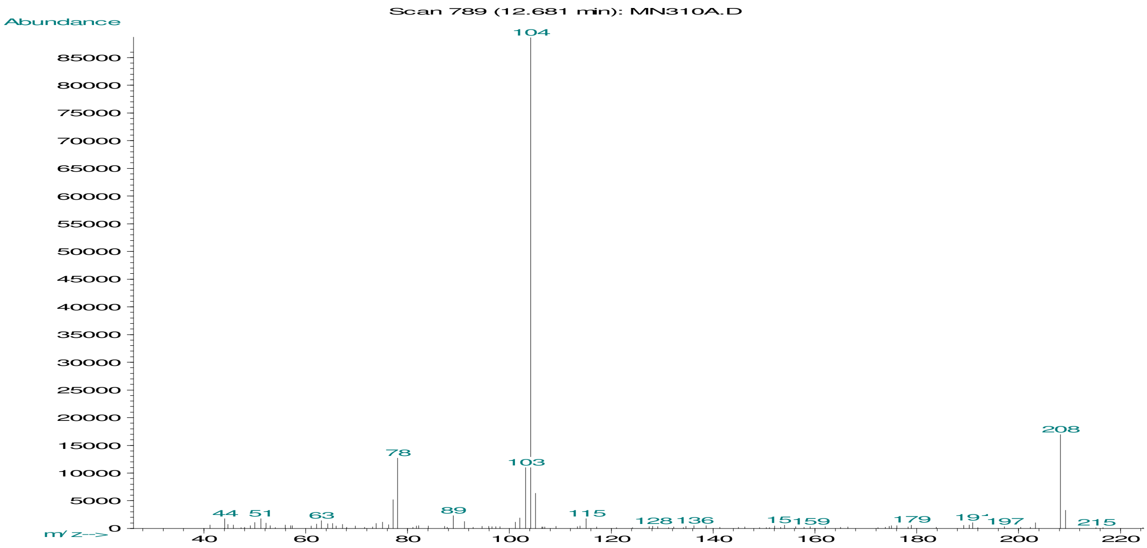

Figure A.5.1. MS spectrum of compound **27**.

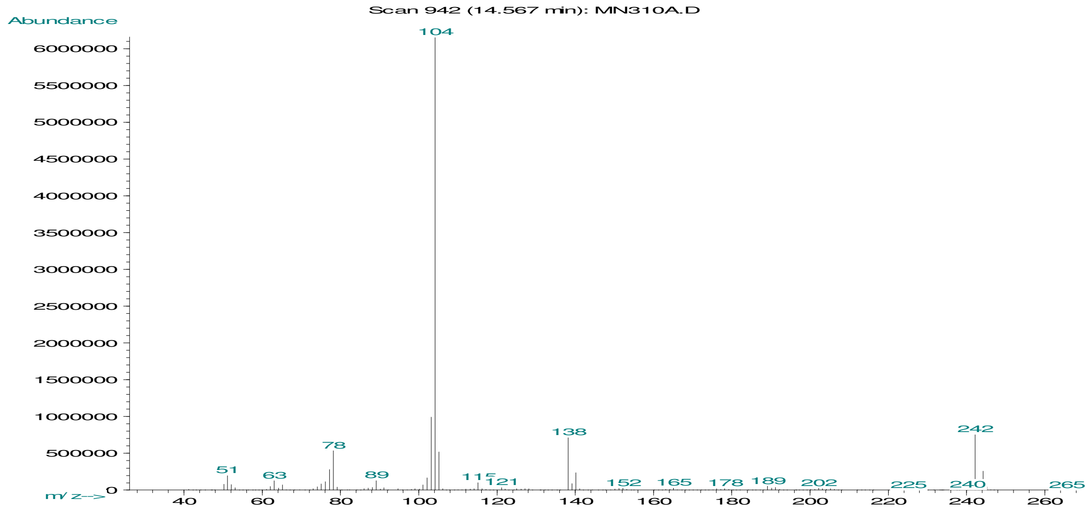

Figure A.5.2. MS spectrum of compound **28**.

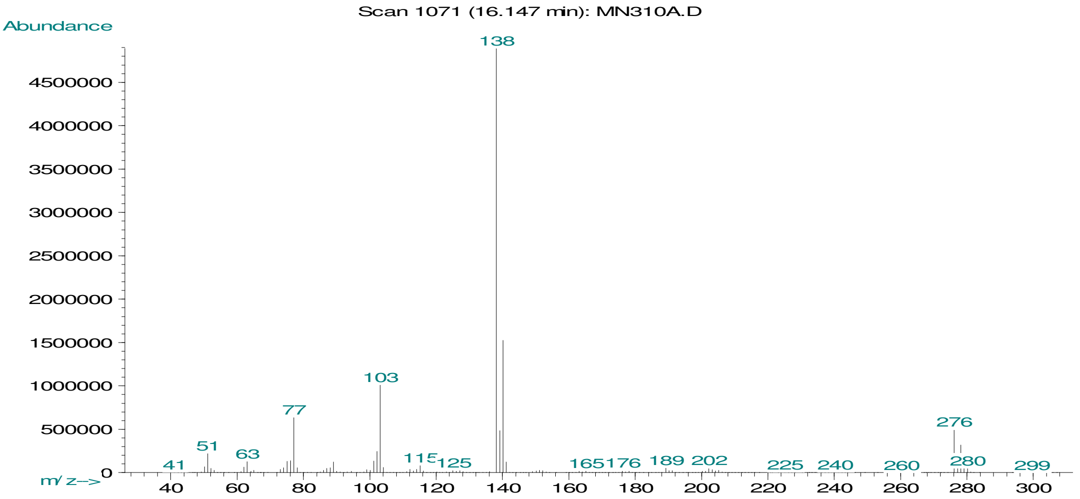

Figure A.5.3. MS spectrum of compound **29**.

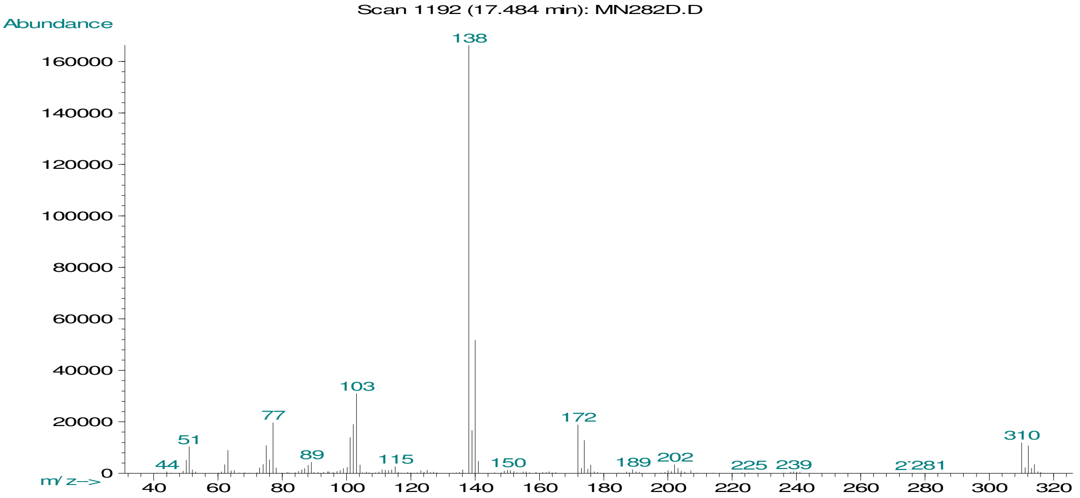

Figure A.5.4. MS spectrum of compound **30**.

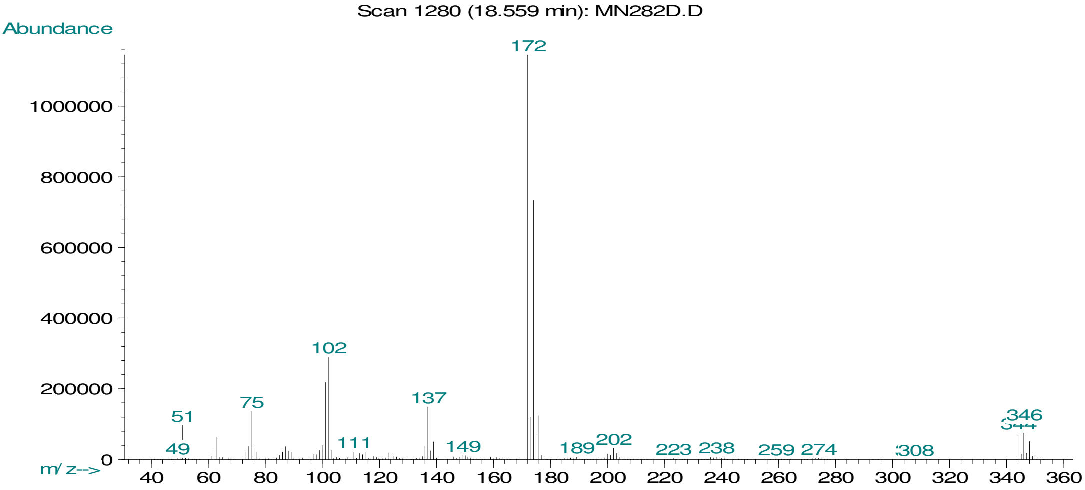

Figure A.5.5. MS spectrum of compound **31**.

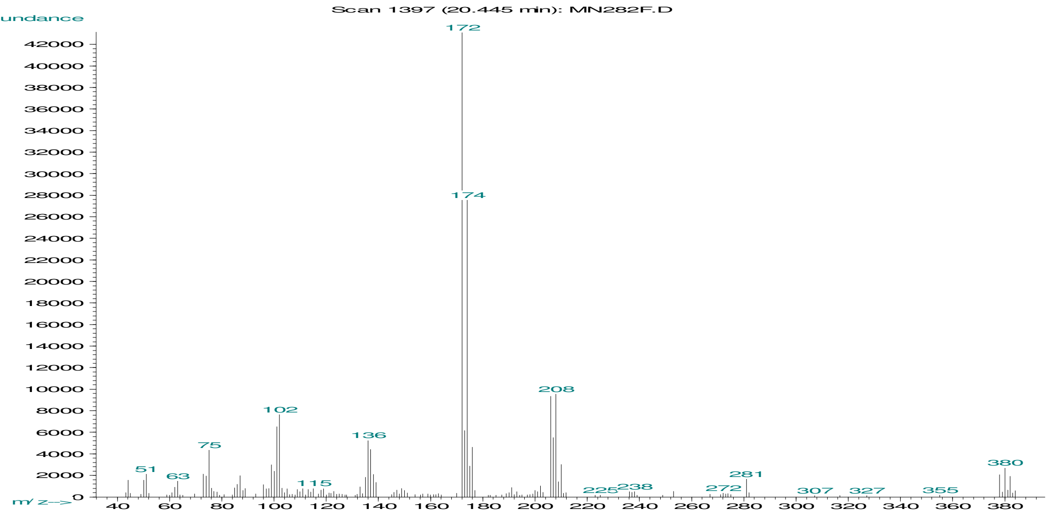

Figure A.5.6. MS spectrum of compound **32**.

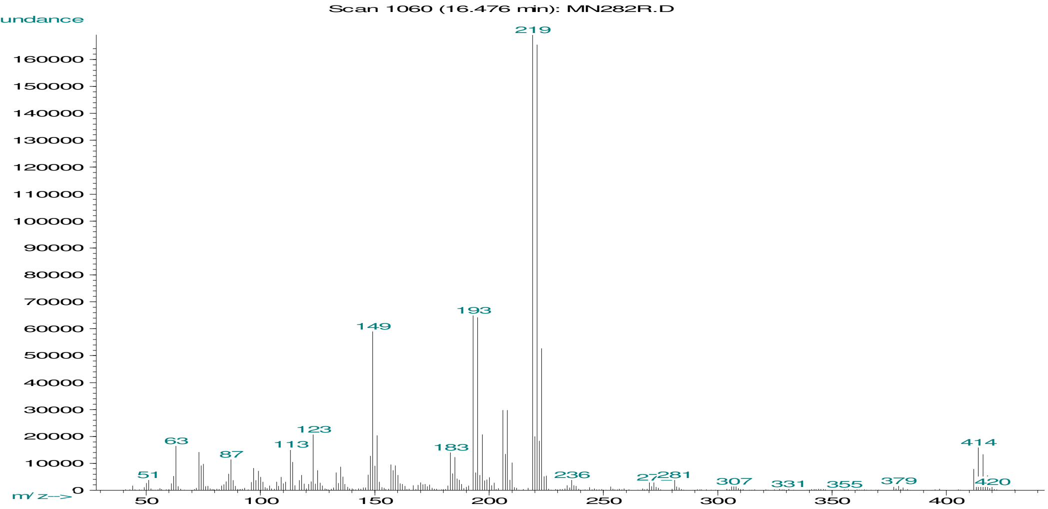

Figure A.5.7. MS spectrum of compound **33**.

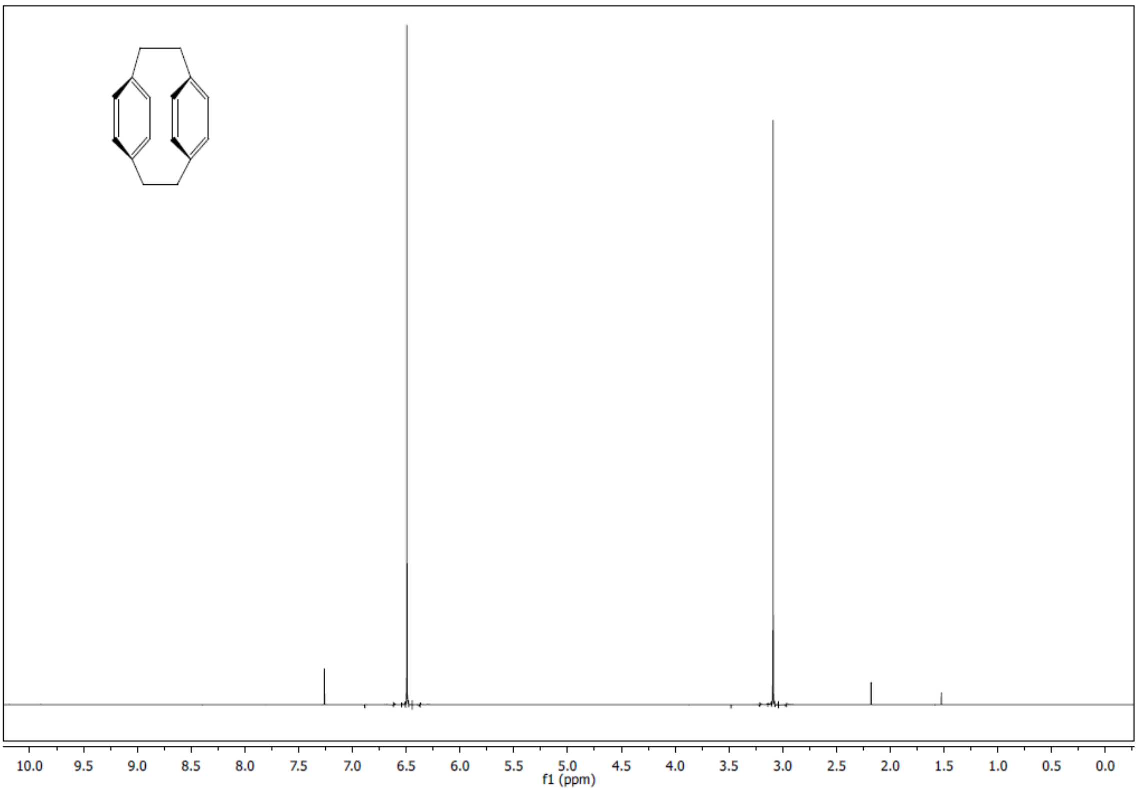

Figure A.5.8. ^{1}H-NMR ($CDCl_3$, 400 MHz) spectrum of compound **27**.

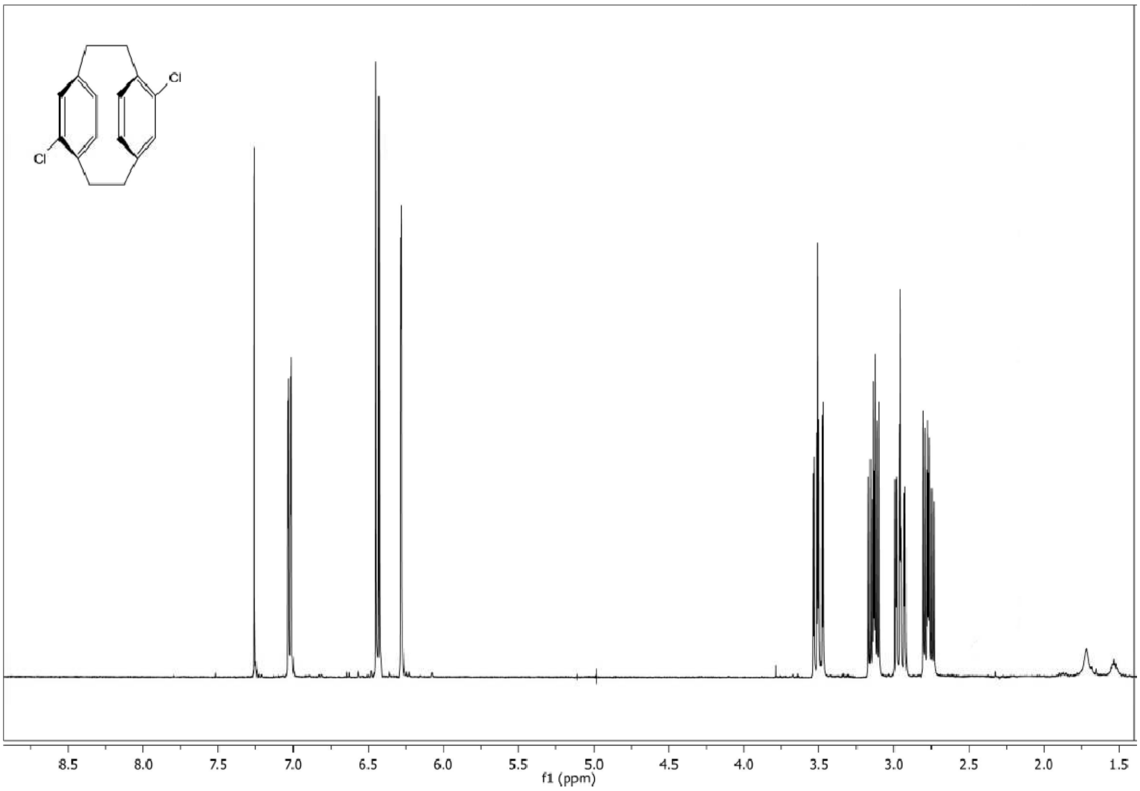

Figure A.5.9. ^{1}H-NMR ($CDCl_3$, 400 MHz) spectrum of 4,16dichloro[2.2]paracyclophane.

A.5.2 Trimethyl Orthoesters preparation

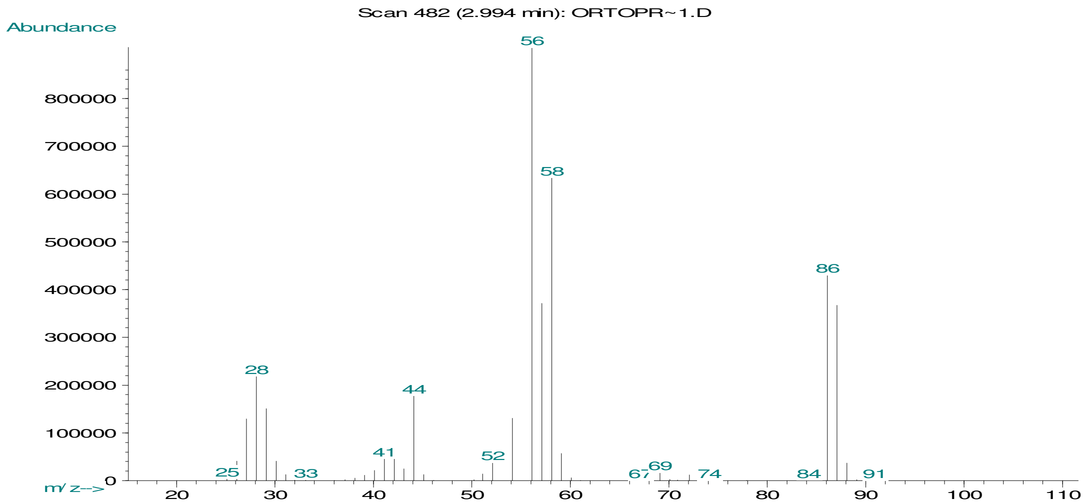

Figure A.5.10. MS spectrum of O-methyl-propioimidate **35a**.

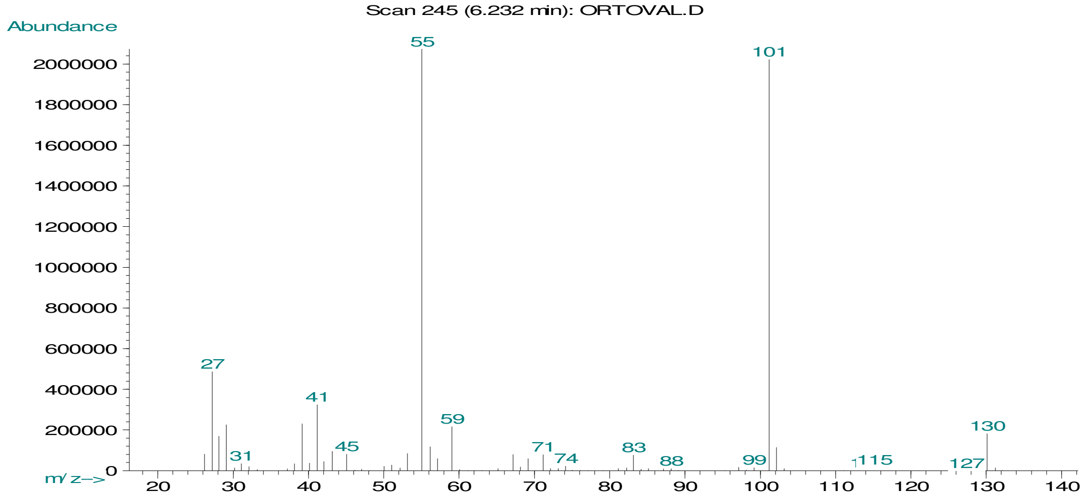

Figure A.5.11. MS spectrum of methyl-pentaneimidate **35b**.

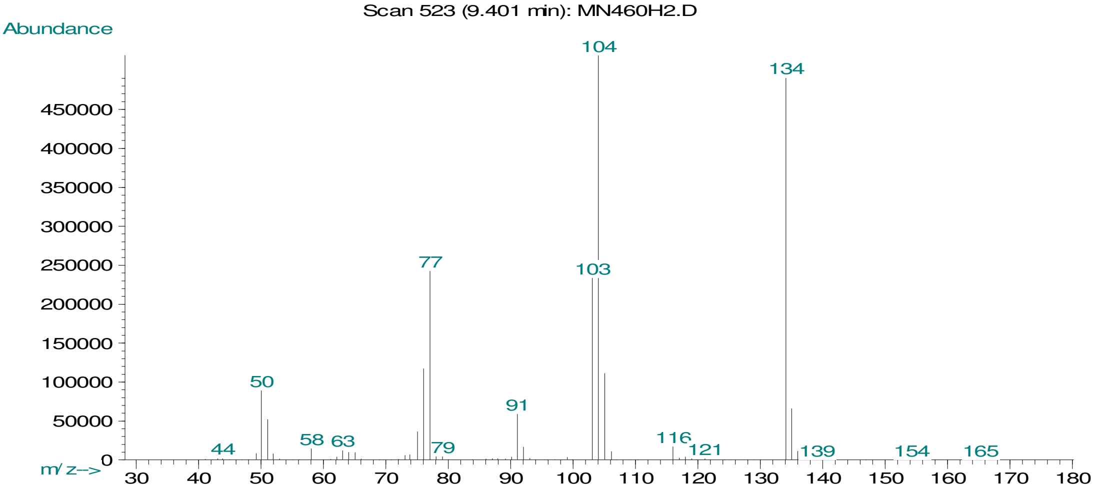

Figure A.5.12. MS spectrum of O-methyl-benzoimidate **35c.**

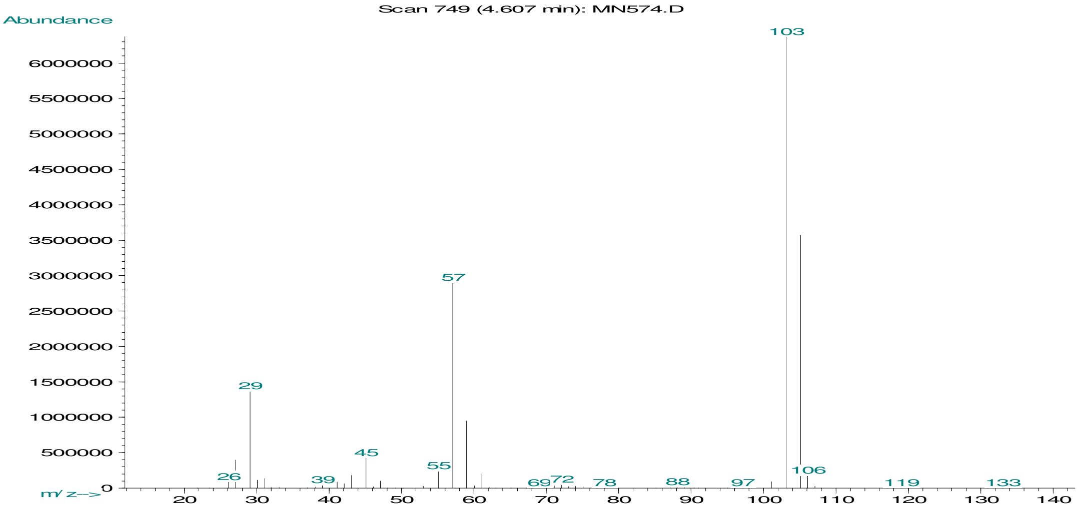

Figure A.5.13. MS spectrum of trimethylrthopropionate **36a**.

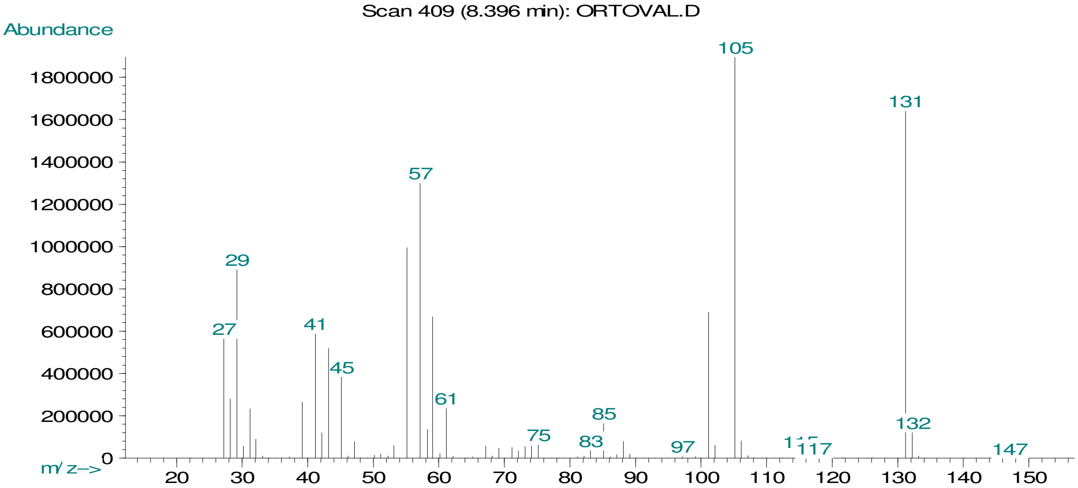

Figure A.5.14. MS spectrum of trimethylorthopentanoate **36b**.

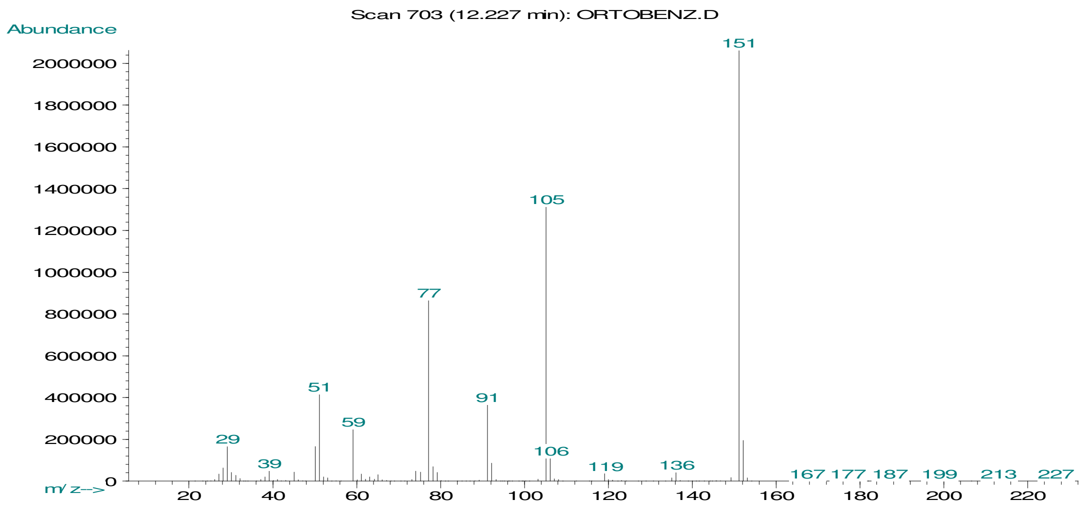

Figure A.5.15. MS spectrum of trimethylorthobenzoate **36c**.

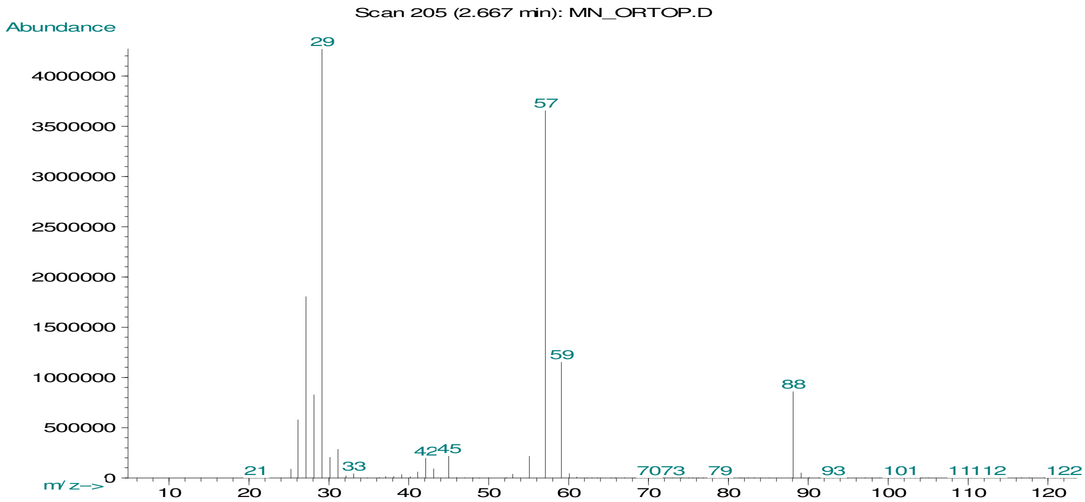

Figure A.5.16. MS spectrum of methyl-propionate **37a**.

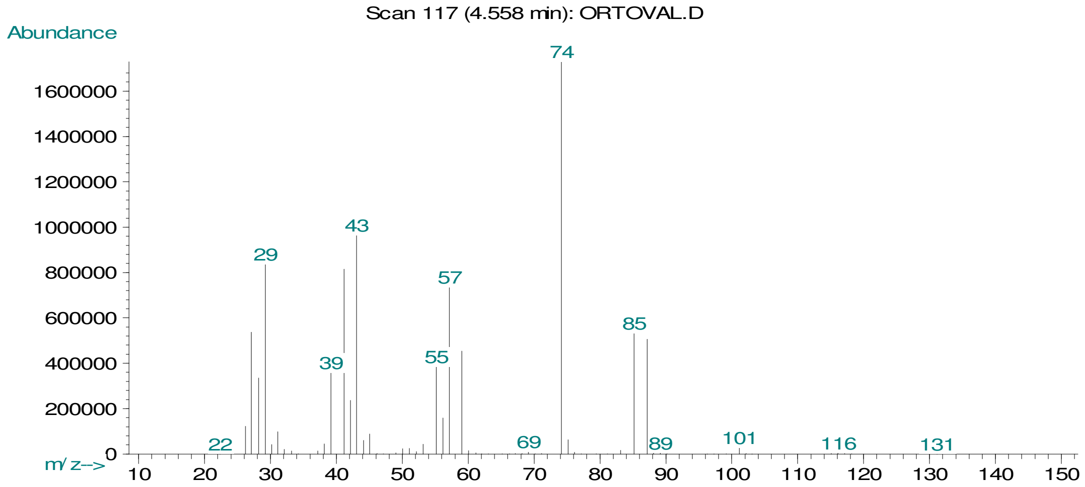

Figure A.5.17. MS spectrum of methyl-pentanoate **37b**.

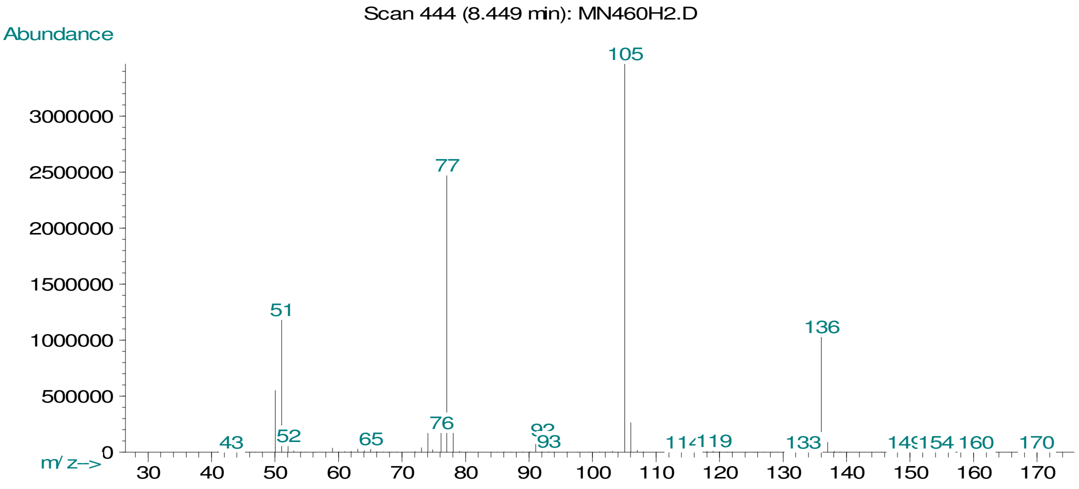

Figure A.5.18. MS spectrum of methylbenzoate **37c**

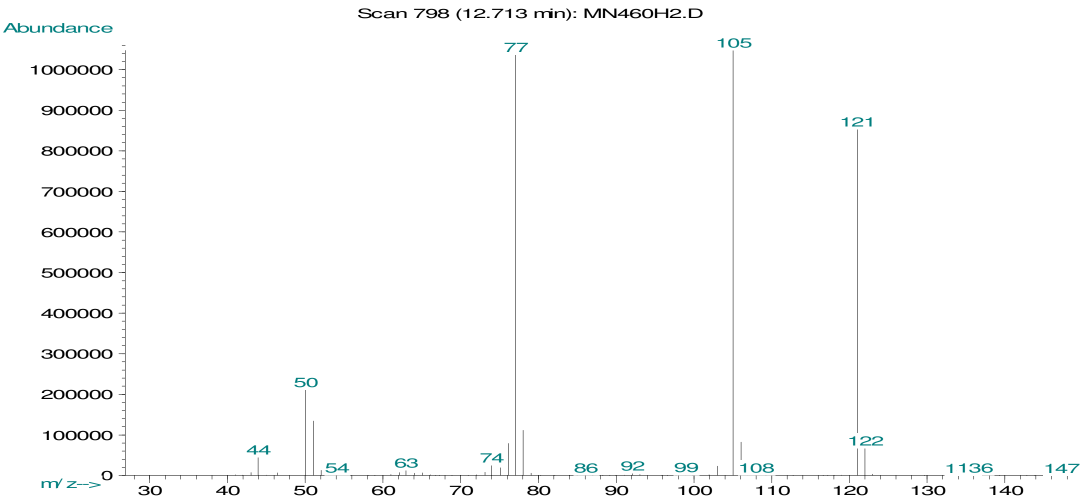

Figure A.5.19. MS spectrum of benzamide **38c**.

A.5.3 Furaniminium bromide preparation

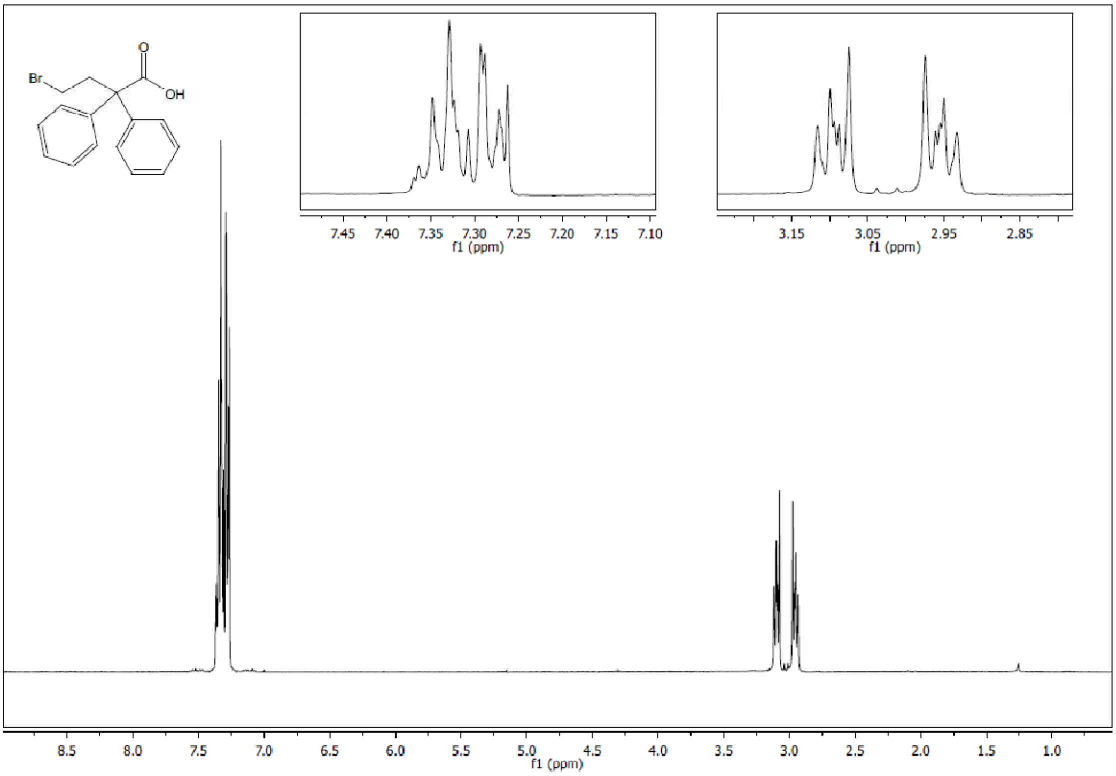

Figure A.5.20. ^{1}H-NMR ($CDCl_3$, 400 MHz) of compound **39**.

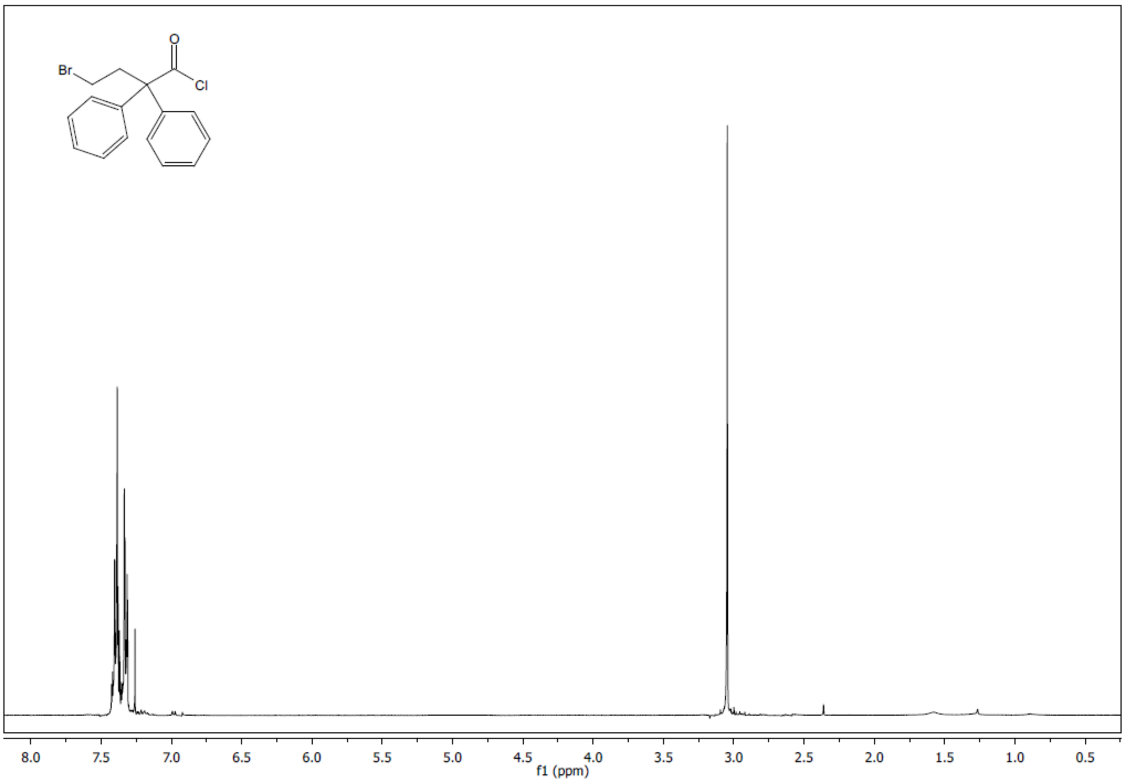

Figure A.5.21. ^{1}H-NMR ($CDCl_3$, 400MHz) of compound **40**.

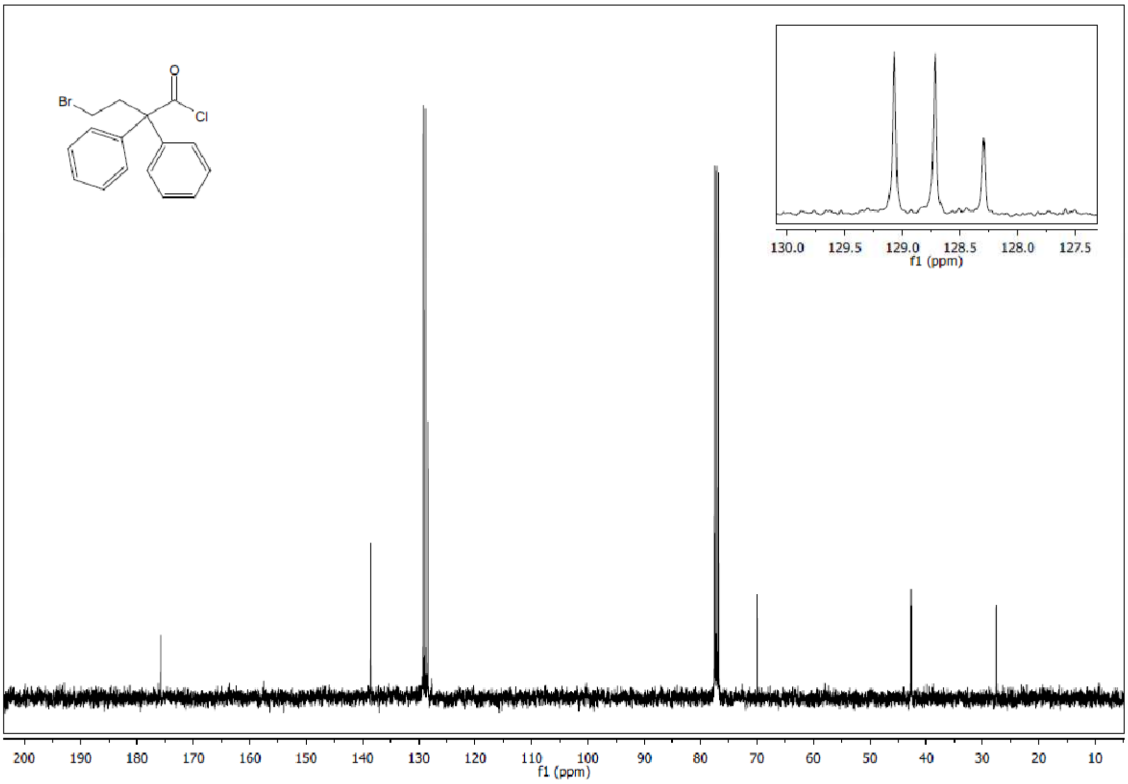

Figure A.5.22. ^{13}C-NMR ($CDCl_3$, 100MHz) spectrum of compound **40**.

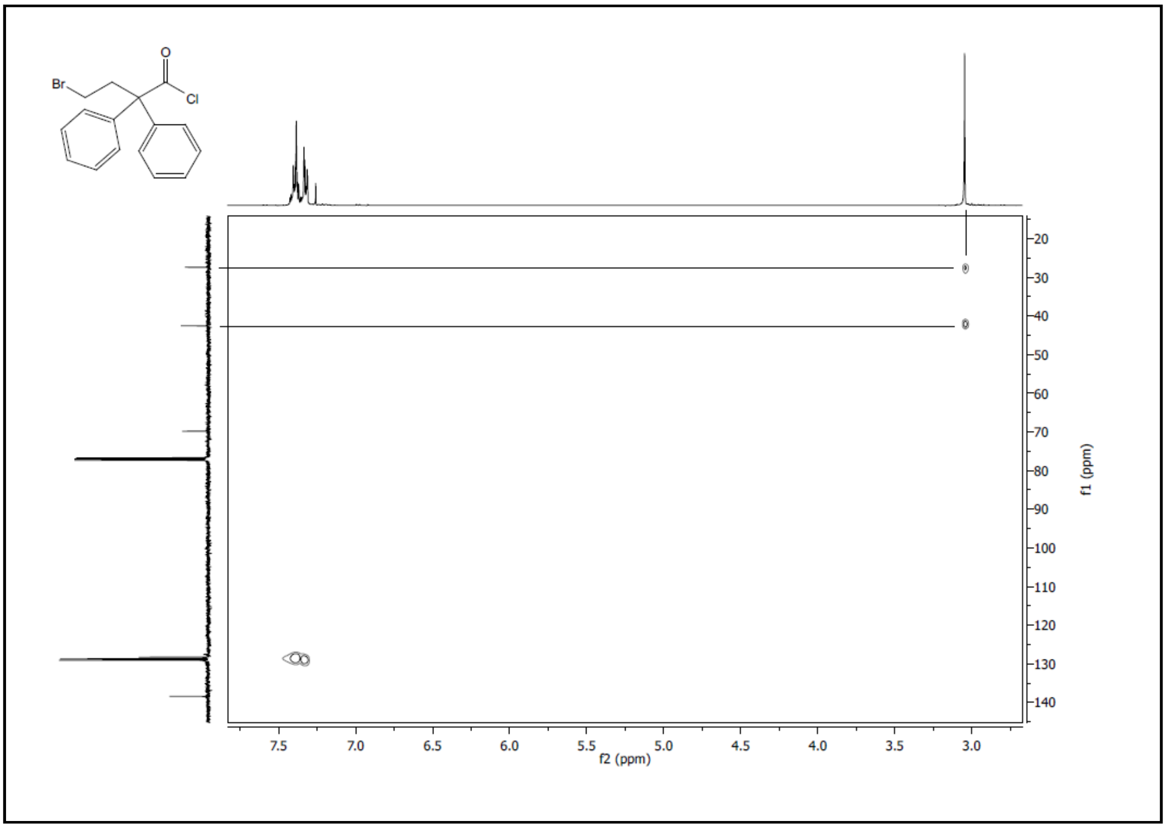

Figure A.5.23. HMQC spectrum of compound **40**.

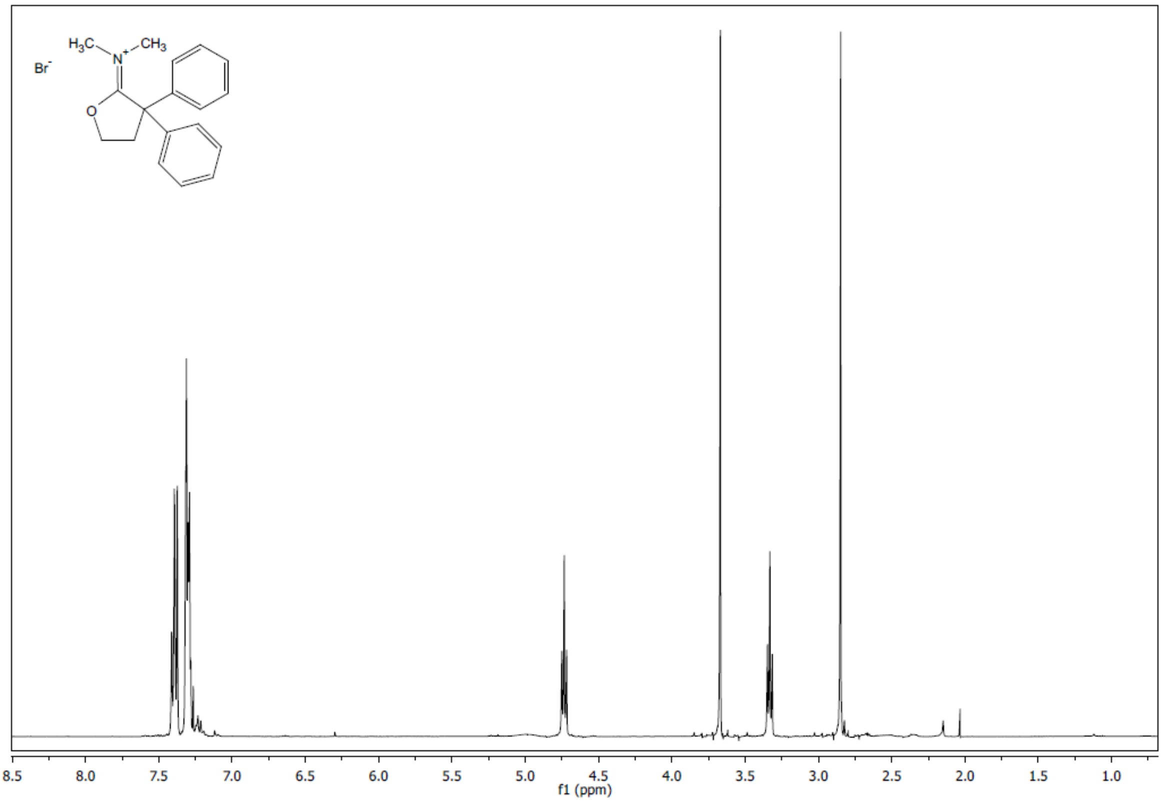

Figure A.5.24. ^{1}H-NMR ($CDCl_3$, 400MHz) spectrum of compound **42**.

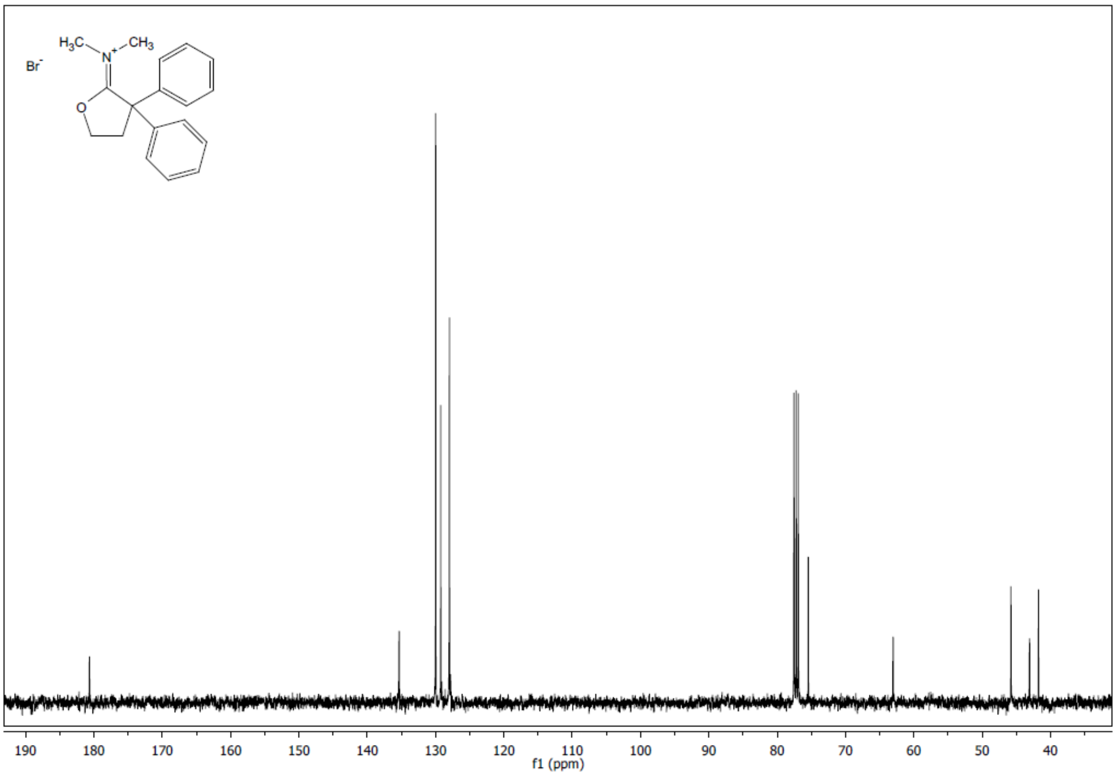

Figure A.5.25. ^{13}C-NMR ($CDCl_3$, 100MHz) spectrum of compound **42**.

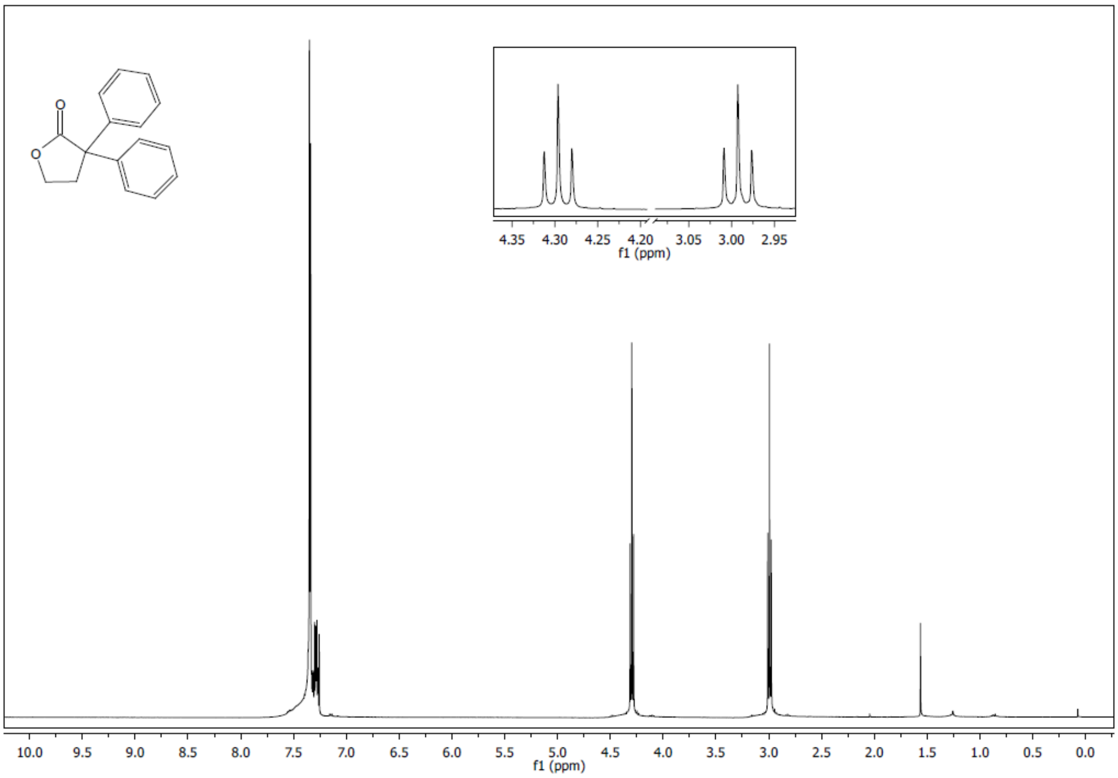

Figure A.5.26. ^{1}H-NMR ($CDCl_3$, 400MHz) spectrum of compound **43**.

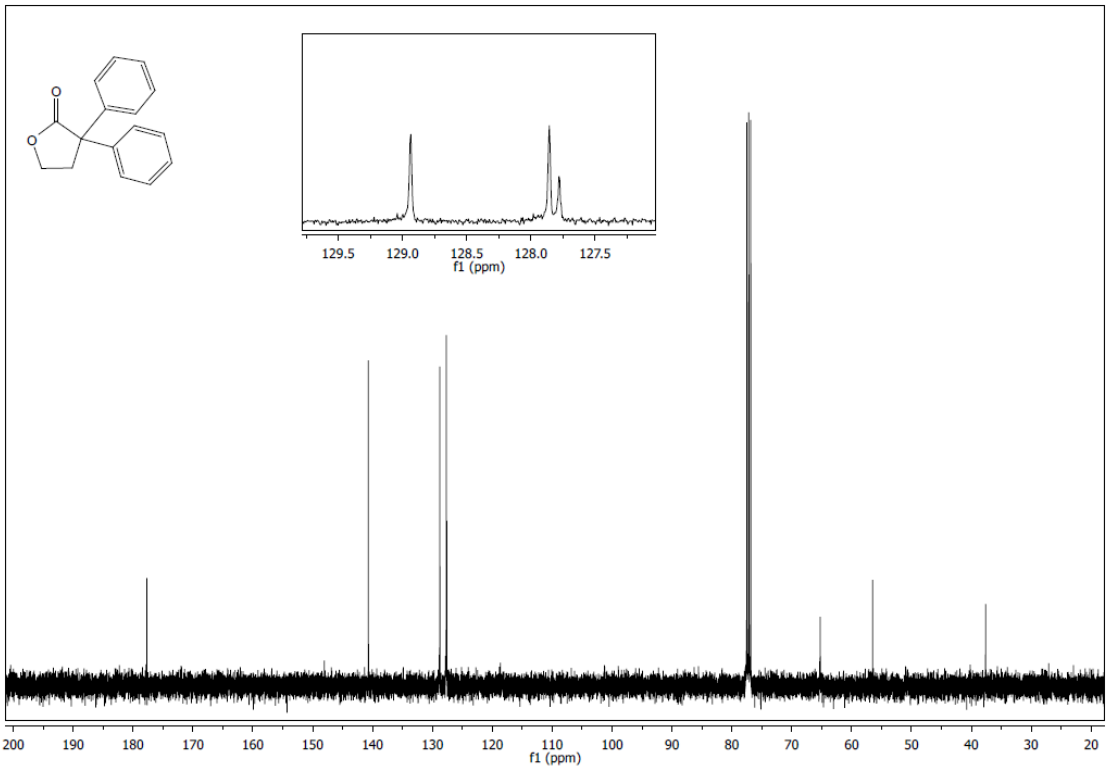

Figure A.5.27. ^{13}C-NMR ($CDCl_3$, 100MHz) spectrum of compound **43**.

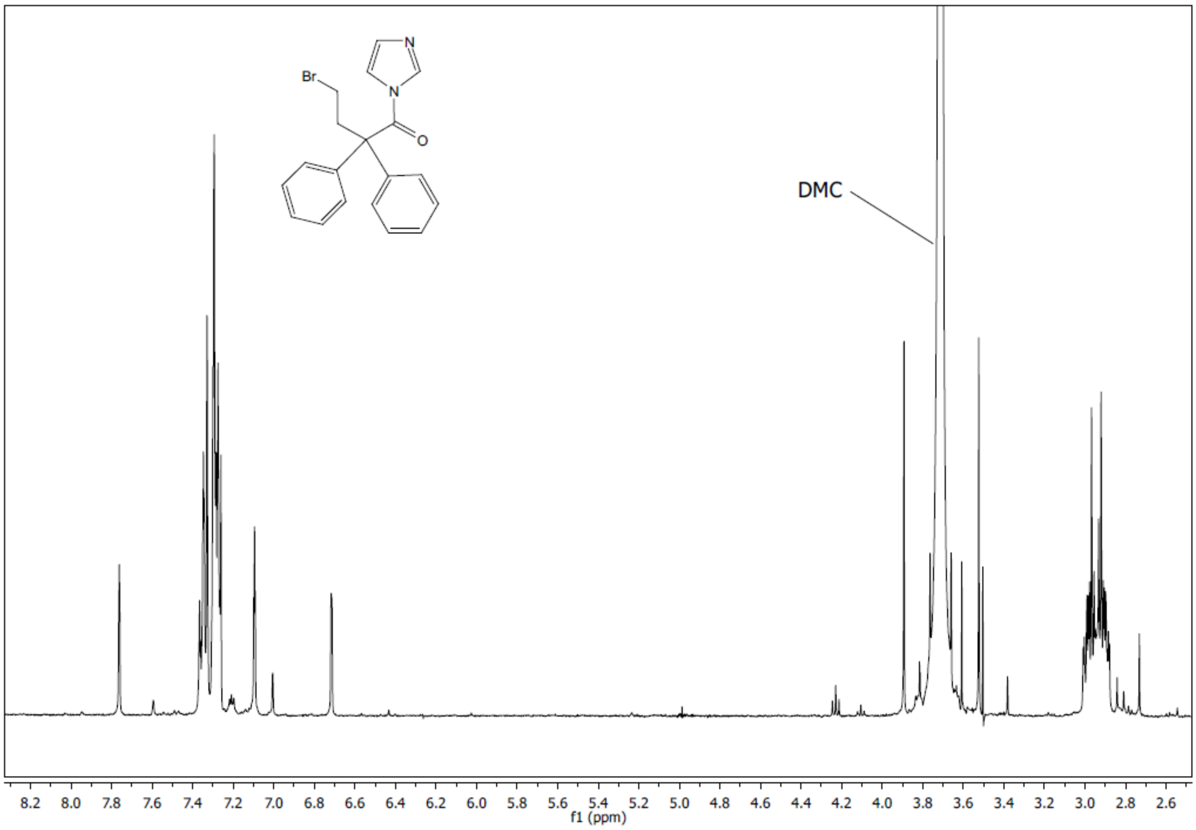

Figure A.5.28. ^{1}H-NMR ($CDCl_3$, 400MHz) spectrum of compound **43** solution in DMC.

Abstract of the PhD thesis

Student: Marco Noè matriculation number: 955619

PhD Course: Scienze Chimiche

Cycle: XXIV°

Title of the thesis : Greener Syntheses & Solvents for Fine and Pharmaceutical Chemicals

Abstract: In this PhD thesis new eco-friendly methodologies for the preparation of fine and pharmaceutical chemicals are presented.

A set of carbonate ionic liquids were prepared using a new green procedure. The obtained CILs have been used as base catalysts for the condensation of aldehydes and ketones with nitroalkanes without the addition of solvent. CILs were further reacted with both water and protic acids to produce anion exchanged ionic liquids. Nitrate phosphonium ionic liquids were able to promote electrophilic aromatic oxychlorination without the addition of solvent.

The preparation of Tadalafil using more enviromental compatible solvents and reactants was studied. The use of ionic liquids and dimethylcarbonate as solvents was considered in order to improve the overall mass index of the preparation.

In partnership with Galentis S.r.l. we sought new synthetic methodologies for the preparations of the following compounds: i) chlorinated [2.2]-p-cyclophanes (polymer intermediates) ii) trimethylorthoesters (used for steroids derivatisation) and iii) furaniminium bromide (intermediate in the Loperamide preparation).

Signature of the student

Estratto per riassunto della tesi di dottorato

Studente: Marco Noè matricola: 955619
Dottorato: Scienze Chimiche
Ciclo: XXIV°

Titolo della tesi : Greener Syntheses & Solvents for Fine and Pharmaceutical Chemicals

Abstract: In questa tesi di dottorato vengono presentate nuove metodologie ecosostenibili per la preparazione di prodotti della chimica fine e farmaceutica.

Una serie di liquidi ionici carbonato (CILs) sono stati preparati utilizzando una nuova procedura "green". I CILs sono stati utilizzati come catalizzatori basici per la condensazione di aldeidi e chetoni. I CILs sono stati fatti reagire con acqua e acidi protici ottenendo nuovi liquidi ionici. Liquidi ionici nitrato sono stati in grado di promuovere ossiclorurazione elettrofila aromatica in assenza di co-solvente.

Viene riportato lo studio sulla preparazione di Tadalafil mediante l'uso di solventi e reagenti più eco-compatibili. L'utilizzo di liquidi ionici e dimetilcarbonato come solventi è stato proposto col fine di ridurre l'impatto ambientale della preparazione.

In collaborazione con Galentis S.r.l. sono state indagate nuove metodologie di sintesi per la preparazione dei seguenti composti: i) [2.2]paraciclofani clorurati (intermedi per polimeri) ii) trimetilortoesteri (utilizzati per derivatizzazione di steroidi) e iii) furaniminio bromuro (intermedio nella preparazione della Loperamide).

Firma dello studente