Ionic Liquid-supported Sulfonyl Hydrazine and Iodine Reagents: Synthesis and Application in Selected Organic Transformations

THESIS

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by

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CERTIFICATE

This is to certify that the thesis entitled **"Ionic Liquid-supported Sulfonyl Hydrazine and Iodine Reagents: Synthesis and Application in Selected Organic Transformations"** submitted by **Ms. Sunita Choudhary** ID No **2011PHXF021P** for the award of Ph. D. Degree of the Institute embodies the original work done by him under my supervision.

Signature in full of the Supervisor:

Name in capital block letters: **Dr. ANIL KUMAR**
Designation: Associate Professor

Date:

Dedicated to
My beloved grandparents
and parents

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ABSTRACT

The thesis entitled **"Ionic Liquid-supported Sulfonyl Hydrazine and Iodine Reagents: Synthesis and Application in Selected Organic Transformations"** deals with the synthesis of functionalized ionic liquids (FILS) and their application in organic reactions. FILs are ionic liquids having functional group tethered with ionic liquids for specific chemical tasks. In these two novel functionalized ionic liquids (a) ionic liquid-supported sulfonyl hydrazine and (b) ionic liquid-supported iodine reagents have been synthesized and utilized for selected organic transformations. The thesis is divided in four chapters.

The **first chapter** of thesis describes a literature overview on use of ionic liquids as soluble support synthesis. In past decades ionic liquids have emerged as alternative soluble support for liquid phase synthesis of small molecules in organic synthesis. Synthesis of several heterocyclic compounds, oligmers and peptides has been achieved using functionalized ionic liquids as a soluble support. Detailed schematic information on these methods have been summarized in this chapter.

The **second chapter** of the thesis describes synthesis and applications of ionic liquid-supported sulfonyl hydrazine. The chapter is divided in three parts. In part-A, ionic liquid-supported sulfonyl hydrazine has been synthesized and used as a soluble support in the synthesis of 1,2,3-thiadiazoles and 1,2,3-selenadiazoles. Ionic liquid-supported sulfonyl hydrazine was reacted with a number of ketones to afford the corresponding ionic liquid-supported hydrazones that were converted to 1,2,3-thiadiazoles (80-91%) in the presence of thionyl chloride. The reaction of ionic liquid-supported hydrazones with selenium dioxide in acetonitrile afforded 1,2,3-selenadiazoles (20-40%). In part-B, ionic liquid-supported sulfonyl hydrazine has been used as a soluble support for the traceless synthesis of highly substituted pyrazoles *via* two different routes. Substituted pyrazoles were achieved in moderate to excellent yield (40-93%). The advantages of this protocol is an easy and convenient purification process that avoids chromatographic separation of products and thus makes the method eco-friendly and economical. In part-C, IL-supported sulfonic acid and sulfonyl hydrazine have been utilized as an efficient acid catalyst and scavenger, respectively for the synthesis of *bis*(indolyl)methane. The employed excess aldehyde for completion of the reaction was scavenged by ionic liquid-supported sulfonyl hydrazine. Purification of products without column chromatography, ease of reaction monitoring, high loading of catalyst/scavenger and shorter reaction time are the salient feature of the developed protocol. The reuse and regeneration of the catalyst and scavenger have been achieved up to 5 times and 2 times, respectively without significant loss of activity.

The **third chapter** of the thesis describes synthesis and applications of ionic liquid-supported hypervalent iodine reagent**.** In part-A, ionic liquid-supported hypervalent iodine reagent, and employed for a 'catch and release' strategy with substituted acetophenones to generate various α-substituted acetophenones in good to excellent yields (50-90%). The use of an ionic liquid-supported hypervalent iodine reagent avoids chromatographic separation for the purification of α-substituted acetophenones and thus makes the method greener. In part-B, ionic liquid-supported hypervalent iodine reagent has been used for the synthesis of aza-heterocycles through a 'catch-and-release' strategy. This strategy provided a combinatorial approach for the synthesis of 2-aminothiazoles and imidazo[1,2-a]pyridines directly from substituted acetophenones in good to excellent yields (58-83%). In part-C, ionic liquid-supported diaryliodonium salt has been synthesized and used in the phenylation of substituted phenols and carboxylic acids, to give the corresponding diaryl ethers and aryl esters, respectively, in good to excellent yields (37-85%) and with high purities.

Finally, overall thesis work and future scope of the research work summarized in the fourth chapter.

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LIST OF ABBREVIATIONS / SYMBOLS

Abbreviation/Symbol	Description
α	Alpha
Å	Angstrom
ADM	2-Azido-1,3-dimethylimidazolinium
ACN	Acetonitrile
ATP	Adenosine triphosphate
[bmim][Br]	1-Butyl-3-methylimidazolium bromide
[bmim][BF_4]	1-Butyl-3-methylimidazolium tetrafluoroborate
[bmim][PF_6]	1-Butyl-3-methylimidazolium hexafluorophosphate
n-BuLi	*n*-Butyl lithium
β	Beta
Bu	Butyl
Calcd.	Calculated
^{13}C	Carbon-13
Cat.	Catalyst
CAN	Cerric ammonium nitrate
Conc.	Concentration
$^{\circ}C$	Degree centigrade
δ	Delta
$CDCl_3$	Deuterated chloroform
d	Doublet
dd	Doublet of doublet

DCE	Dichloroethane
DCM	Dichloromethane
DMA	*N*,*N*-Dimethylacetamide
DMF	*N*,*N*-Dimethylformamide
DMSO-d_6	Deuterated dimethylsulfoxide
EI	Electron ionization
ESI	Electron spray ionization
EtOAc	Ethyl acetate
Equiv.	Equivalent
FILs	Functionalized ionic liquids
G	Gram
h	Hours
HDNIB	[Hydroxy-(2,4-dinitrobenzenesulfonyloxy)iodo]benzene
HRMS	High resolution mass spectrometry
ILs	Ionic liquids
IR	Infrared
Hz	Hertz
J	Coupling constant
Lit.	Literature
MS	Mass spectrometry
M.P.	Melting point
m	Multiplet
mg	Milligram
MHz	Mega hertz

Min.	Minutes
mL	Milliliter
mmol	Millimole
MW	Microwave
N_2	Nitrogen gas
NMR	Nuclear magnetic resonance
ppm	Parts per million
%	Percentage
psi	Per square inch
p-TsOH	*p*-Toluenesulfonic acid
rpm	Revolutions per minute
rt	Room temperature
s	Singlet
t	Triplet
TFA	Trifluoroacetic acid
TfOH	Trifluoromethanesulfonic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
TSIL	Task specific ionic liquid
OTf	Triflouromethanesulfonate
δ	Chemical shift
V	Volume
W	Watt

TABLE OF CONTENTS

Chapter I

Functionalized Ionic Liquids as Soluble Supports in Organic Synthesis: A Review

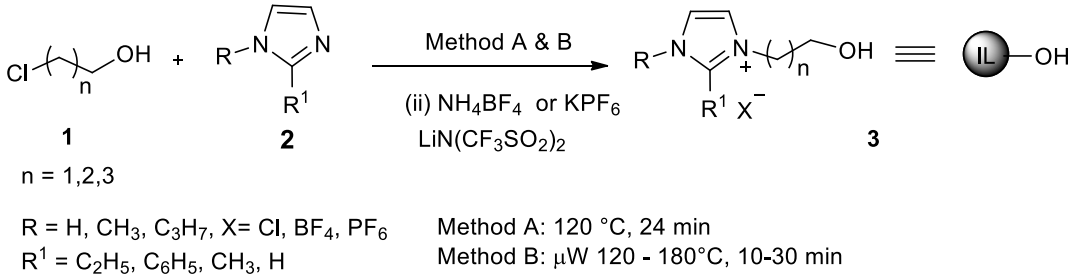
1.1 Introduction

Supported synthesis is a widely employed technique that has greatly assisted the synthesis of several compounds in combinatorial synthesis.[1-3] Traditionally, supported synthesis has employed heterogeneous material such as cross-linked polystyrene to support one of the reactants.[4] The main advantage of the supported material being heterogeneous is that it can be readily separated by simple filtration techniques from the excess reagents and by-products thus minimizes requirement of chromatographic seperation.[5-8] However, the disadvantages of this solid phase synthesis are comparatively long reaction times, low loading capacities of resins, hard to monitor the reaction by spectroscopic technique and solvent compatibility. To overcome these problems, polyethylene glycol (PEG) polymers have been used as soluble support for the synthesis of many pharmacologically important compounds. These polyethylene glycol based supports have good stability, high compatibility and good swelling characteristic with non-polar solvents,[9-11] however, they are also associated with some limitations like swelling of polymer in both non-polar and polar solvents, low loading capacities and difficult automation. 'Fluorous' i.e. highly fluorinated (or perfluorinated) compounds have been used as soluble support for peptide synthesis and other small molecules, however, low solubility in organic solvents and requirement of costly fluorinated solvent are serious concerns in fluorous phase synthesis.[12, 13]

In recent years, ionic liquids have emerged as alternative soluble support for the liquid-phase synthesis of small molecules in organic synthesis.[14-19] The added advantages of these are their tunable chemical properties and greener nature. Ionic liquids as soluble support has been used for the synthesis of novel reagents and catalysts. These soluble supports can easily be separated from the reaction mixture by simple washing with appropriate solvent at each step; reuse of an ionic liquid supported reagent is economical, environmentally benign, time intensive and efficient and progress of reactions can easily be monitored by TLC (thin layer chromatography). This new concept of ionic liquid supported synthesis combines advantages of both soluble support and heterogeneous support such as polymer and silica. The main advantages of ionic liquid supported synthesis are homogeneous reaction conditions, tunable solubility in common solvents, high loading efficiency, easy monitoring of the reactions by TLC and spectroscopic techniques. Recent development in the use of ionic liquid as soluble support in organic synthesis is briefly described in this chapter.

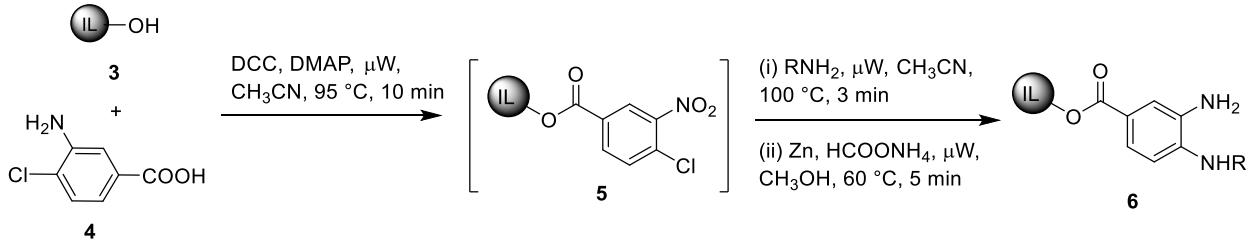
1.2 Synthesis of benzimidazole linked pyrrolo-/pyrido-/isoindolo-benzimidazolones

Chung-Ming Sun and coworkers[20-26] have extensively used ionic liquid as soluble support for the synthesis of various heterocyclic compounds. They have used ionic liquid-supported alcohol, (1-(2-hydroxyethyl)-3-methylimidazolium) tetrafluoroborate (**3**) for the synthesis of various bioactive organic molecules with or without microwave-assisted technique. Ionic liquid-supported alcohol was synthesized from 1-methylimidazole (**2**) by reacting with chloroalkanes (**1**) under conventional heating and microwave irradiation (**Scheme 1.1**).



Scheme 1.1: Synthesis of ionic liquid-supported alcohol

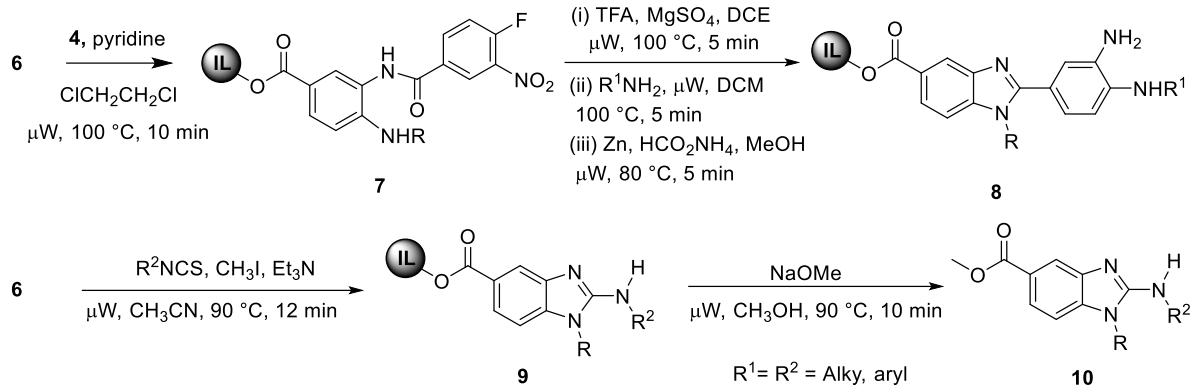
A diverse library of *bis*-heterocyclic compounds has been prepared by cascade cyclization under microwave irradiation. Initially, **3** was chosen as a support and it was esterified with 4-fluoro-3-nitrobenzoic acid **4**. *ipso*-Fluoro substitution with primary amines followed by reduction of nitro group gave ionic liquid-supported *ortho*-phenylenediamine **6** (**Scheme 1.2**).



Scheme 1.2: Synthesis of ionic liquid-supported *ortho*-phenylenediamine **6**

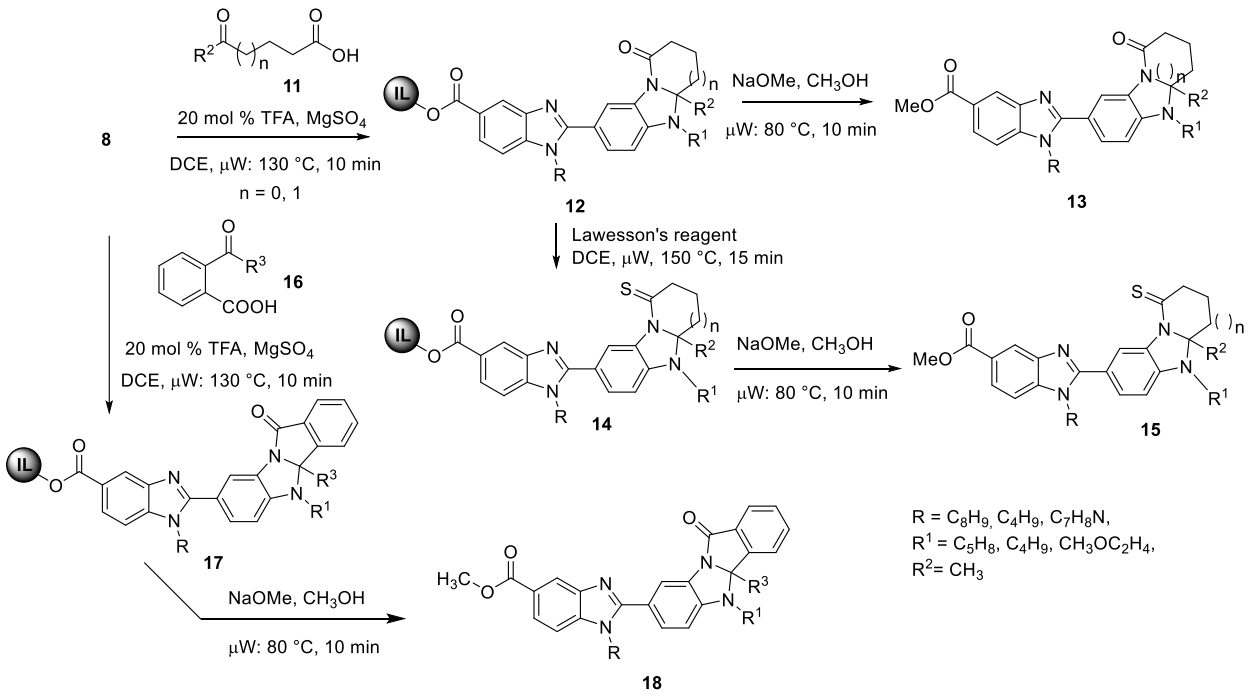
Reaction of **6** with acid **4** under microwave irradiation gave an amide **7** which was cyclized to give ionic liquid supported benzimidazole in presence of trifluoroacetic acid (TFA). Further reaction of ionic liquid supported benzimidazole with various primary amines and reduction of nitro group under microwave irradiation produced ionic liquid supported diamine linked through benzimidazole **8** (**Scheme 1.3**). Further, ionic liquid-supported *ortho*-phenylenediamine **6** was treated with isothiocyanates to give corresponding ionic liquid supported 2-aminobenzimidazoles

9. Reaction of **9** with sodium methoxide in methanol under microwave irradiation provided corresponding 2-aminobenzimidazoles **10** in good to excellent yields (**Scheme 1.3**)



Scheme 1.3: Synthesis of ionic liquid supported diamine **8** and 2-aminobenzimidazoles **10**

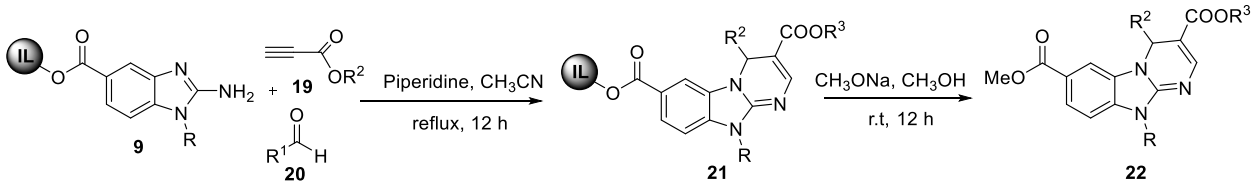
The ionic liquid supported diamines linked through benzimidazole **8** were purified and were further utilized in the one-pot synthesis of *bis*-heterocyclic compounds (**Scheme 1.4**). Reaction of **8** with different keto acids **11** under acidic condition and microwave irradiation resulted in the formation of ionic liquid supported substituted *bis*-benzimidazoles **12**. On the other hand, intramolecular amidation led to formation of ionic liquid-supported benzimidazole linked pyrrolo/pyrido-benzimidazolones **12**. Additionally, the ionic liquid-supported benzimidazole linked pyrrolo/pyrido-benzimidazolone **12** was reacted with Lawesson's reagent under microwave irradiation to produce corresponding thio derivative **14**. Again, treating **12** and **14** with sodium methoxide in methanol under microwave irradiation led cleavage of ionic liquid support to give corresponding pyrrolo/pyrido-benzimidazolones **13** and their thio derivatives **15**, respectively in good yields. The scope was further expanded by reacting **8** with 2-acetylbenzoic acid (**16**) in the presence of TFA (20 mol %) under irradiation to give ionic liquid linked isoindolo-benzimidazolones **17**. The ionic liquid support from **17** was removed by treating it with NaOMe in methanol under microwave irradiation to give corresponding benzimidazole linked isoindolo-benzimidazolones **18** in good to excellent yield (**Scheme 1.4**). The ionic liquid support **3**, obtained after cleavage was reused in all the cases.



Scheme 1.4: Synthesis of benzimidazole linked pyrrolo-/pyrido-/isoindolo-benzimidazolones

1.3 Synthesis of 4,10-dihydropyrimido[1,2-*a*]benzimidazoles

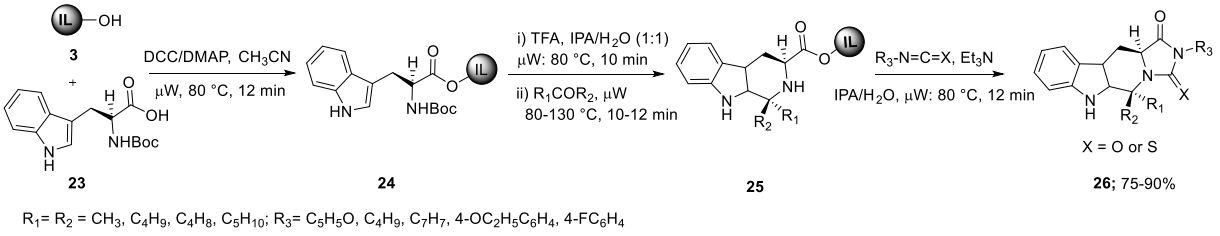
Chung-Ming Sun group[27] utilized ionic liquid-supported 2-aminobenzoimidazole **9** in a multicomponent reaction wherein **9** was treated with olefins **19** and aldehyde **20** in the presence of piperidine in acetonitrile to give corresponding ionic liquid supported benzimidazole-linked dihydropyrimidine **21**. After removing the excess reactants and unwanted products by precipitation in ether, the ionic liquid tag was removed in sodium methoxide to afford 4,10-dihydropyrimido[1,2-*a*]benzimidazole derivatives **22** in good to excellent yields (**Scheme 1.5**). The ionic liquids tag could be recovered and reused for further synthesis.



Scheme 1.5: Ionic liquid phase synthesis of 4,10-dihydropyrimido[1,2-*a*]benzimidazoles

1.4 Synthesis of hydantoin fused tetrahydro-β-carboline

To synthesize the target compound, Boc-protected L-tryptophan (**23**) was coupled to hydroxy functionalized ionic liquid **3** under three different conditions a) room temperature, b) thermal heating, and c) microwave irradiation (**Scheme 1.6**).[22] The reaction time was much lower in case of microwave irradiation. After filtering off the dicyclohexyl urea, ionic liquid-supported tryptophan **24** was precipitated with ether and filtered out. Subsequently, ionic liquid supported β-carbolines **25** were prepared by NHBoc deprotection followed by Pictet-Spengler cyclization with carbonyl compounds under microwave irradiation in the presence of TFA (20 mol %). The progress of the reaction at each step could be easily monitored by proton NMR spectroscopy. Ketones required more severe conditions for cyclization to occur as compared to aldehydes. The products were obtained by removal of aqueous acid media, re-dissolution in CH_3CN, precipitation with ether and finally filtration. Terminal hydantoin moieties were added across the β-carbolines by reaction with isocyanates/thioisocyanates under microwave irradiation *via* traceless approach wherein cleavage of ionic liquid-support and cyclization was achieved in one step using triethylamine to give hydantoin fused tetrahydro-β-carbolines **26** (**Scheme 1.6**). The reaction time was much lesser under microwave irradiation than under refluxing conditions and progress of the reaction could be monitored by TLC. The products were obtained in high yield and purity.

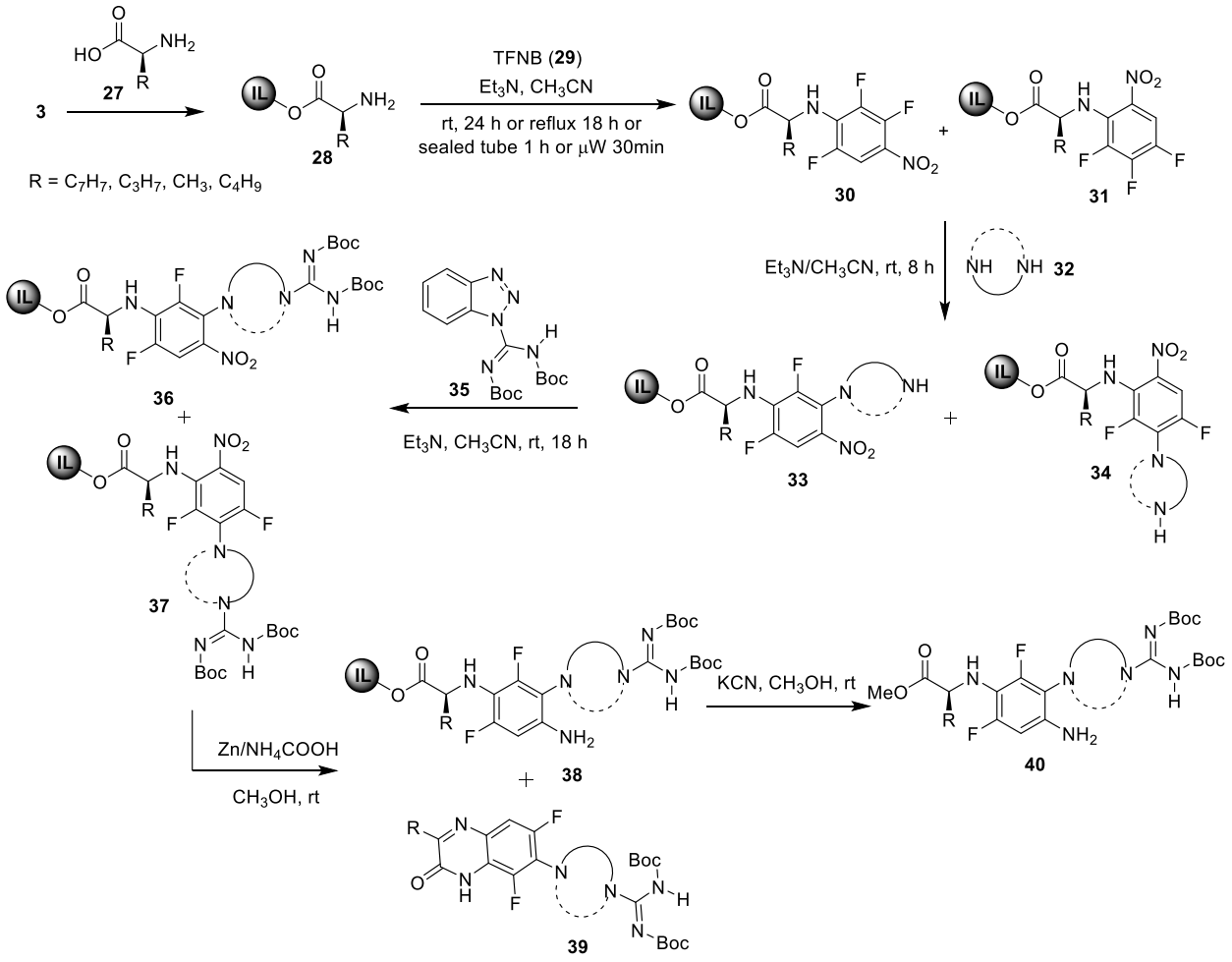


Scheme 1.6: Ionic liquid supported synthesis of hydantoin fused tetrahydro-β-carbolines

1.5 Synthesis of guanidine linked piperazinyl and quinoxalinone

Chen *et al.* established a ionic liquid phase traceless synthetic strategy to prepare guanidine linked piperazinyl, azepanyl, and aminomethylpiperidinylquinoxalinones (**Scheme 1.7**).[28] In this strategy, initially amino acids were supported on hydroxyl functionalized ionic liquid **3** by esterification to give ionic liquid supported amino acid **28** which was then linked with trifluoronitrobenzene (TFNB) (**29**) *via* nucleophilic aromatic substitution to give two isomeric compound **30** and **31**. Reaction of the two ionic liquid supported trifluorbenzenes (**30** & **31**) with

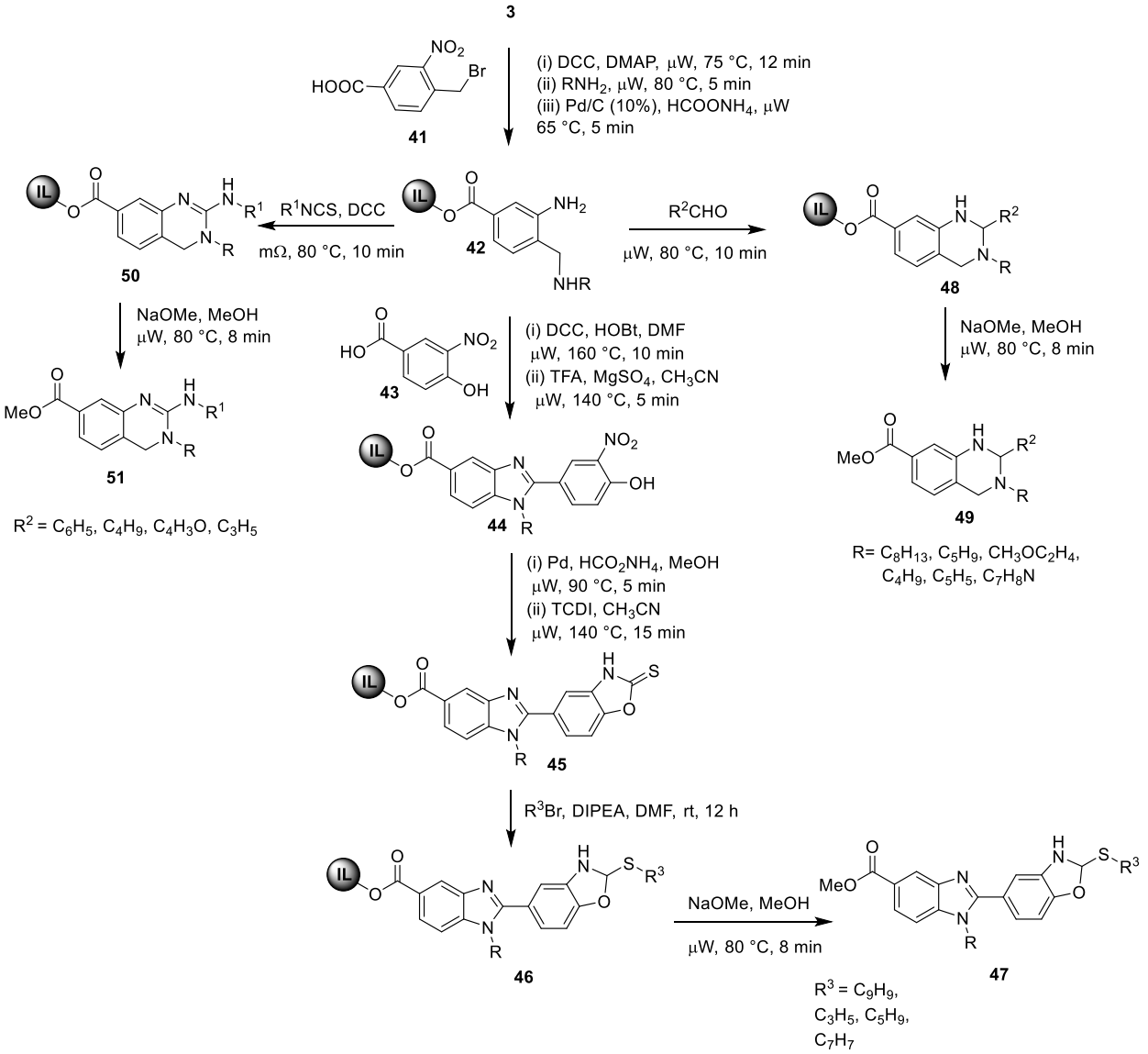
piperazines **32** gave **33** and **34** which then on reaction with Boc-protected benzotriazole activated guanidinyl **35**, gave **36** and **37**. Reduction and cleavage of ionic liquid support from **36** resulted in guanidine linked piperazinyl **40**, whereas reduction of nitro group followed by intramolecular nucleophilic substitution of **37** led to piperidinylquinoxalinones **39**. All the ionic liquid bound intermediates and products were purified by washing with ether. The versatility of the strategy was shown by using different aliphatic, aromatic and heteroaromatic amino acids. The methodology found to be useful for the rapid synthesis of *bis*-heterocyclic libraries containing high structural diversity.



Scheme 1.7: Ionic liquid phase synthesis of guanidine linked piperazinyl and quinoxalinone

1.6 Synthesis of benzo[*d*]oxazol-5-yl-*1H*-benzo[*d*]imidazole, dihydro-quinazolines and tetrahydroquinazoline

Microwave irradiation was employed by Chung-Ming Sun group for the parallel synthesis of benzo[*d*]oxazol-5-yl-1*H*-benzo[*d*]imidazole (**47**) using an ionic liquid as soluble support.[29] Ionic liquid-bounded *ortho*-phenylenediamine **42** was prepared by coupling **3** with 4-(bromomethyl)-3-nitrobenzoic acid (**41**) followed by reaction with amines and reduction of nitro group. Reaction of **42** with 4-hydroxy-3-nitrobenzoic acid **43**, followed by an acid-mediated ring closure reaction produced ionic liquid supported benzimidazole derivatives **44**. The nitro group on the benzimidazole was reduced and thiocarbonyldiimidazole (TCDI) was utilized for preparation of ionic liquid tagged benzmidazole linked benzoxazole **45**. High yields of diverse, *S*-alkylated conjugates **46** were obtained by the reaction of **45** with different alkyl bromides in the presence of diisopropylethylamine. The [*d*]oxazol-5-yl-*1H*-benzo[*d*]imidazoles **47** were cleaved from the ionic liquid-support using sodium methoxide in methanol under microwave conditions. The support was easily separated by precipitation with ether. The crude products were further purified by column chromatography. The reaction could be directly monitored by NMR spectroscopy. The short duration and operational ease made this method highly suitable for the synthesis of a wide range of analogs that have numerous applications in the field of drug development. Further, they have developed an efficient methodology for the preparation of dihydroquinazolines **51** and tetrahydroquinazolines **49** under microwave irradiation by the reaction of ionic liquid-bounded *ortho*-phenylenediamine **42** with isothiocyanates and aldehydes, respectively in acetonitrile followed by methanolysis (**Scheme 1.8**).

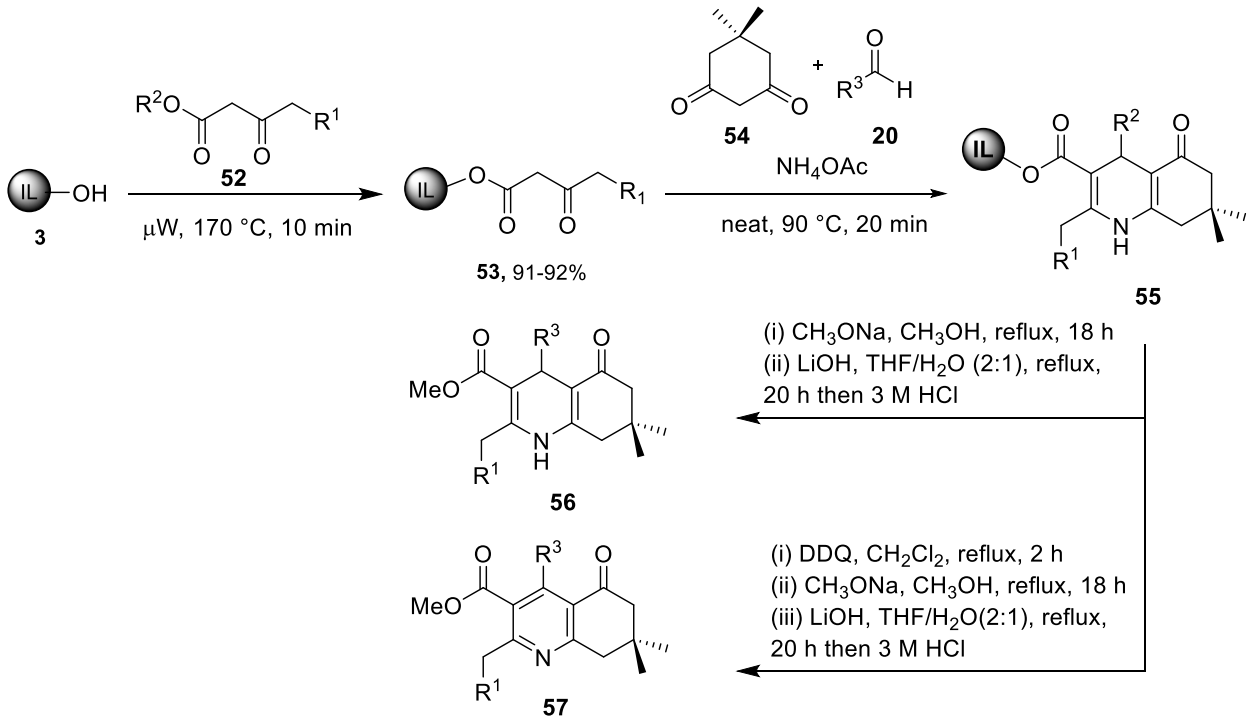


Scheme 1.8: Synthesis of benzo[*d*]oxazol-5-yl-*1H*-benzo[d]imidazole, dihydroquinazolines and tetrahydroquinazolines using **42**

1.7 Synthesis of polyhydroquinolines

Bazureau and co-workers have developed a novel method for three-component syntheses of polyhydroquinolines **56** and **57** using 1,3-diketo functionalized ionic liquid **53** (**Scheme 1.9**).[30] Synthesis of 1,3-diketo functionalized ionic liquid **53** was achieved by the reaction of **3** with 3-keto ester/3-keto acid (**52**) under microwave irradiation. Reaction of **53** with dimedone (**54**), aldehyde (**20**) and ammonium acetate resulted in the synthesis of ionic liquid supported polyhydroquinolines **55**. Cleaving ionic liquid support by treating **55** with sodium methoxide in refluxed MeOH resulted in the formation of **56** whereas oxidizing ionic liquid grafted **55** with

DDQ followed by removal of ionic liquid support my methanolysis led to preparation of **57**. No catalyst was required and easy monitoring was done by proton NMR spectroscopy. A library of polyhydroquinoline was created using aromatic aldehydes with electron-withdrawing or donating groups.

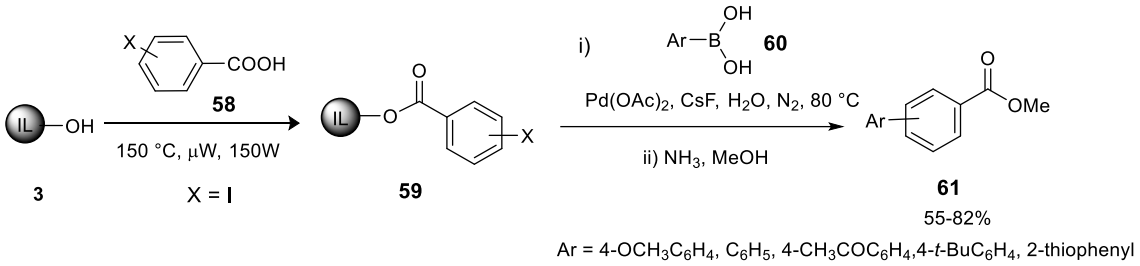


Scheme1.9: Ionic liquid phase synthesis of polyhydroquinoline **56** and **57** using **53**

1.8 Coupling reaction on ionic liquid-supported iodobenzene

Chan and Miao established the use of ionic liquid supported synthesis (ILSS) in Suzuki coupling reactions by drawing a comparison between the reactions taking place in almost identical conditions using conventional solution phase synthesis and ILSS.[31] Initally, ionic liquid supported aryl halide was prepared by the reaction of **3** with 3-iodobenzoic acid (**58**) to give 3-iodobenzoyloxyethyl(1-methylimidazolium) tetraflouroborate (**59**, X = I). Reaction of **59** with various aryl boronic acid **60** was performed using $Pd(OAc)_2$ in aqueous medium in the presence of CsF (**Scheme 1.10**). The product obtained was insoluble in ether and thus after washing it was cleaved from ionic liquid phase by reaction with ammonia/methanol. The desired Suzuki product **61** was obtained in good to excellent yield. A study of the same reaction with various aryl boronic acids (**60**) proved that in every case, the ILSS gave equal or higher yields as compared to

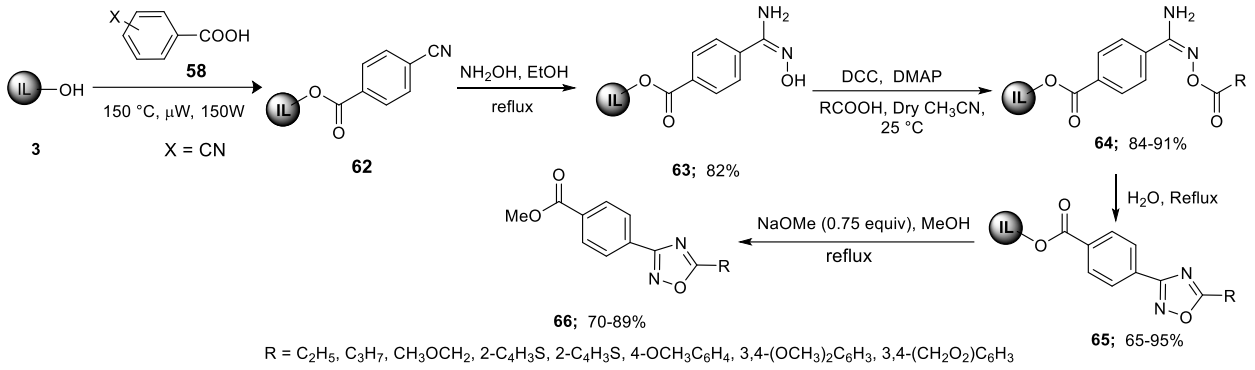
conventional solution phase synthesis. Purification was easy even when excess reagents were used and did not require chromatographic techniques.



Scheme 1.10: Suzuki coupling reaction on ionic liquid-supported iodobenzene **59**

1.9 Synthesis of 3,5-disubstituted 1,2,4-oxadiazoles

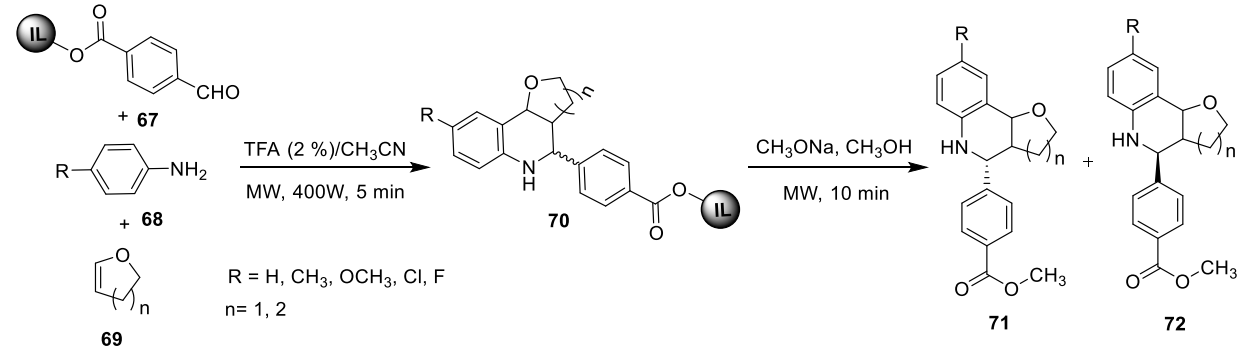
Bazureau group successfully implemented ionic liquid phase synthesis strategy for the preparation of bioactive 3,5-disubstituted 1,2,4-oxadiazoles **66** (**Scheme 1.11**).[32] For the synthesis of target compound initially, 4-cyanobenzoic acid (**58**) was anchored on ionic liquid support **3** was to give corresponding ionic liquid supported 4-cyanobenzoic acid (**62**, X = 4-CN). Reaction of **62** with KOH and hydroxylamine resulted in ionic liquid supported amidoxime **63**. Subsequently, **63** was washed with cold deionized water/diethyl ether and after purification; the dilute solution of the **63** was treated with different aliphatic, aromatic, heteroaromatic and heterocyclic acids in the presence of DCC and catalytic amount of DMAP in CH_3CN to afford ionic liquid supported *O*-acylamidoxime **64** in good yield. The reaction gave best results when acetonitrile was used with DCC and a little amount of 4-dimethylaminopyridine (DMAP). O-acyl amidoxime **64** was purified and cyclodehydration was carried out in deionized water to give ionic liquid bound 3,5-disubstituted 1,2,4-oxadiazoles **65**. Transesterification of **65** with methanol in the presence of sodium methoxide resulted in good to excellent yield of 3,5-disubstituted 1,2,4-oxadiazoles **66** in high purity. The ionic liquid support **3** obtained from transesterification cleavage was eluted by methanol and could be reused.



Scheme 1.11: Ionic liquid phase synthesis of 3,5-disubstituted 1,2,4-oxadiazoles

1.10 Synthesis of tetrahydropyranoquinolines and tetrahydrofuranoquinolines

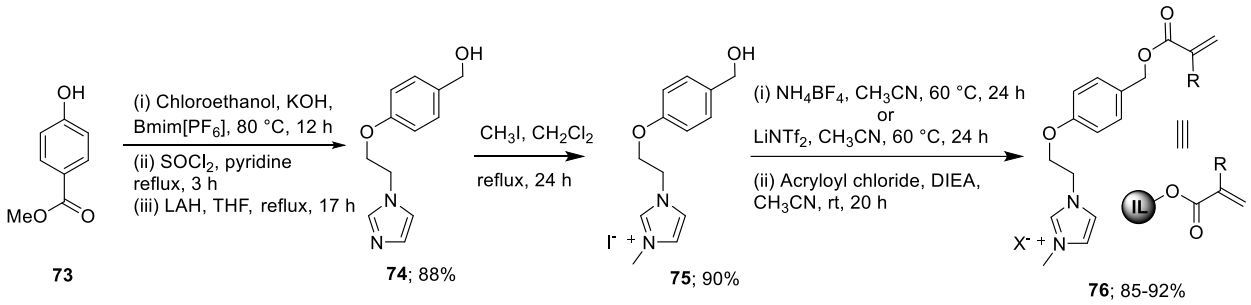
Li group reported the synthesis and use of an aldehyde functionalized ionic liquid **67** for the synthesis of tetrahydropyranoquinolines and tetrahydrofuranoquinolines (**Scheme 1.12**).[33] The use of **67** was examined in one-pot aza-Diels-Alder reaction under microwave irradiation. The synthesized ionic liquid-supported compound **70** was separated by the evaporation of CH_3CN and then filtered by deionized water. The ionic liquid support was cleaved by the treatment with sodium methoxide in methanol reflux under microwave irradiation to obtain the final product. The product was extracted with CH_2Cl_2 to obtain *cis* and *trans* isomers of tetrahydroqiunolines (**71** and **72**) with high diastereoselectivity which were further separated by column chromatography. It was found that for aryl amines having similar steric hindrance groups, aryl amines with electron-withdrawing groups increased the formation of the *trans*-isomer. The synthetic strategy has been used for the synthesis of library of tetrahydropyrano- and tetrahydrofuranquinolines.



Scheme 1.12: Ionic liquid phase synthesis of tetrahydropyrano- and tetrahydrofurano-quinolines

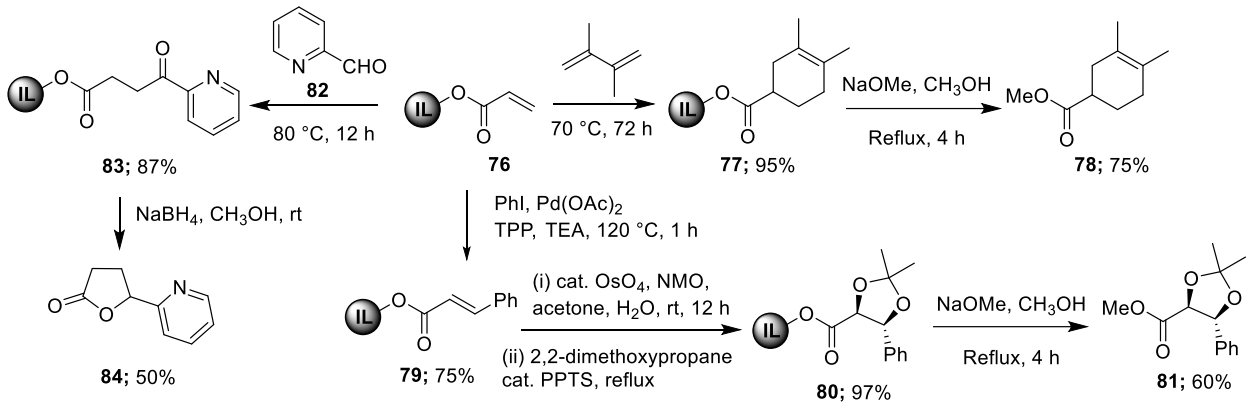
1.11 Synthesis of ionic liquid tagged acrylic ester and application in small molecule synthesis

Two new functionalized ionic liquids were prepared by Anjaiah *et al.* by attaching a Wang type linker to an imidazolium core (**Scheme 1.13**).[34] Reaction of methyl 4-hydroxybenzoate (**73**) with chloroethanol followed by reaction with sulfonyl chloride, alkylation of the imidazole, reduction of ester group with lithium aluminium hydride (LAH) gave (4-(2-(1*H*-imidazol-1-yl)ethoxy)phenyl)methanol (**74**). Further, *N*-methylation of **74** with methyl iodide led to formation of ionic liquid supported Wang type linker (**75**). Finally, esterification of **75** with the corresponding acid chloride in the presence of Hunig's Base and ion exchange resulted in corresponding ionic liquid tagged acrylic ester.



Scheme 1.13: Synthesis of ionic liquid tagged acrylic ester **76**

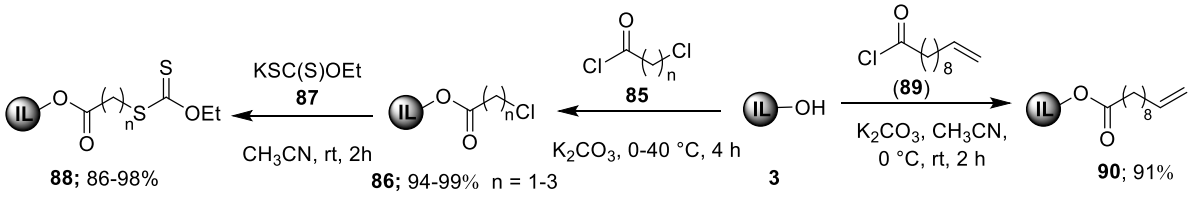
The Diels-Alder cycloaddition reactions of ionic liquid tagged acrylic ester **76** were carried out successfully giving ionic liquid tagged cyclohexene derivatives **77** after removal of excess reagents and washing with ether. Transesterification of **77** gave cyclohexene derivatives **76** in good to excellent yield and high purity. The study was further extended to the Pd-catalyzed Heck reaction. The ionic liquid tagged acrylic ester **76** was coupled with phenyl iodide effortlessly to give the ionic liquid tagged cinnamic ester **79** which on dihydroxylation with OsO_4 followed by protection with acetone gave **80**. The ionic liquid support from **80** was removed by transesterification to give 1,3-dioxolane-4-carboxylate derivative **81** in 60% yield. Lastly, the Stetter reaction was examined **76**, where pyridine-2-carboxaldehyde (**82**) was reacted to give ionic liquid tagged 1,4-diketo compound **83**. Reduction of **83** with $NaBH_4$ followed by intramolecular cyclization gave a lactone **84** in 50% yield.

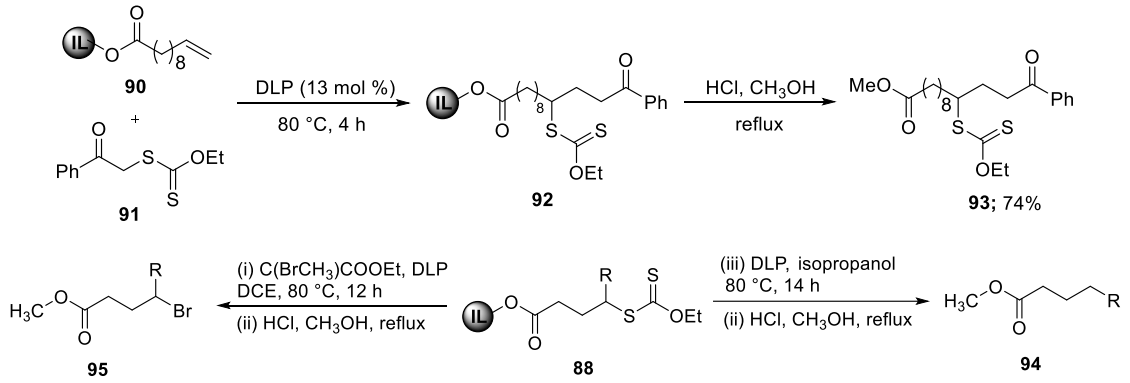


Scheme 1.14: Application of ionic liquid tagged acrylic ester **76** in synthesis of small molecules

1.12 Synthesis of ionic liquid supported olefins and xanthates

The use of ionic liquid supported olefins and xanthates also known as task specific onium salt have been prepared and studied for radical addition by Verron group.[35] Firstly, the radical addition of methoxycarbonylmethylxanthate to allylphthalimide with DLP as an initiator was carried out in some ionic liquids. Adducts were formed with four different ionic liquids based on cations in good yields. Higher amounts of DLP were required to overcome the recombination of radicals due to greater viscosity of ionic liquids which prevented the radicals from escaping out of the solvent cages. Next, xanthate and olefin supported salts (**88** & **90**) were prepared from **3** as depicted in scheme 1.15. Ionic liquid supported olefin **90** was reacted with excess of xanthate **91** for intermolecular radical addition to give ionic liquid supported xanthate **92**. After conversion, the **92** was separated from the xanthate **90** and washed with ether. The **92** was cleaved by transesterification to give xanthate **93** in 74% yield and the original support was isolated by ether extraction and could be reused. This reaction had increased efficiency as compared to that on a Wang resin. Ionic liquid supported xanthates **88** could also be used for functional group exchange. Heating **88** with DLP and a bromine source resulted in bromo derivative **95** and treating **88** with DLP in isopropanol resulted in removal of xanthate group to give **94**. These reactions could be easily monitored by NMR and show significant advantages over Wang resins and other supports.

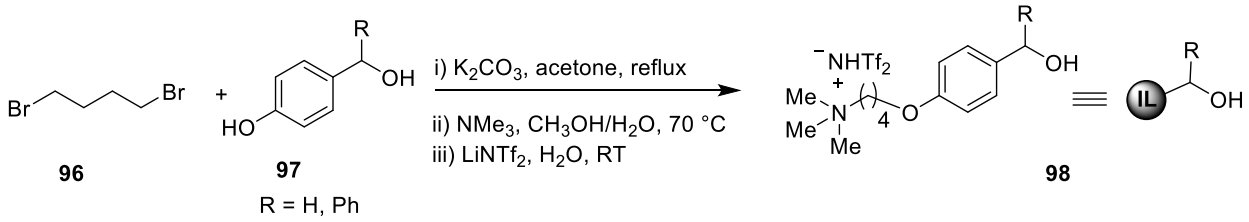




Scheme 1.15: Synthesis of ionic liquid supported olefins and xanthates and their application in radical addition reactions

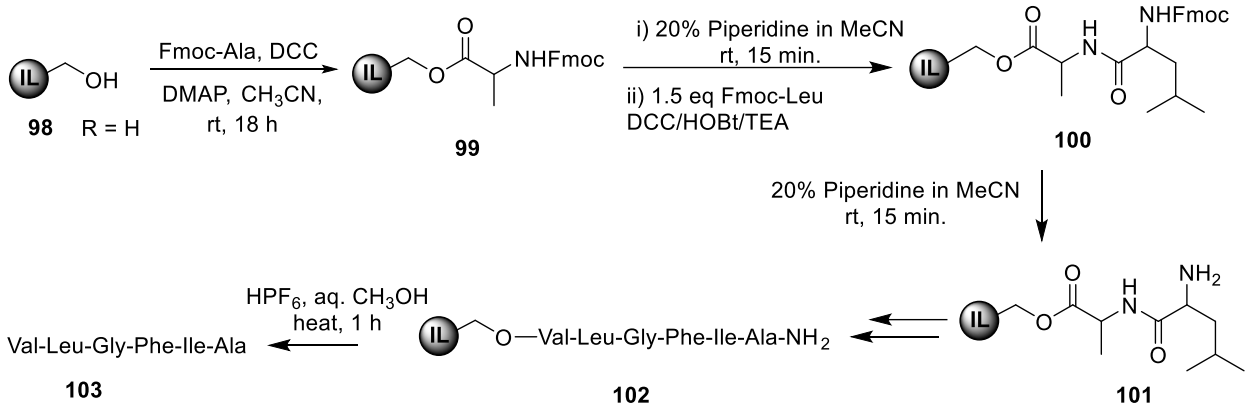
1.13 Synthesis of bio-oligomers

Roche and coworkers evaluated ionic liquids (onium salts) (**98**) as soluble supports in peptide synthesis.[36] For this purpose, various a novel ionic liquid tagged with Wang type linker was prepared from 4-(hydroxymethyl)phenol and benzhydril (**97**) (**Scheme 1.16**).



Scheme 1.16: Synthesis of novel ionic liquid tagged with Wang type linker

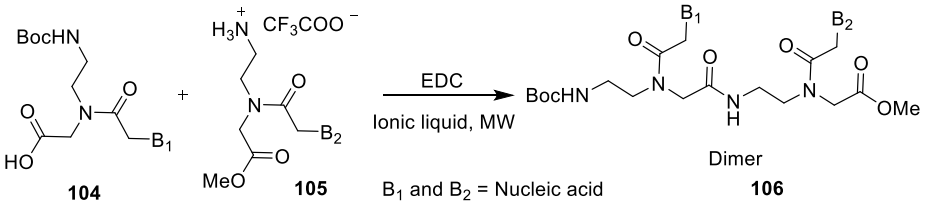
Ionic liquid **98** was then linked with Fmoc-Ala-OH using DCC as coupling agent in the presence of DMAP in acetonitrile to give ionic liquid supported Fmoc-protected alanine **99** (**Scheme 1.17**). Reaction of **99** with Fmoc protected leucine using DCC/HOBt as coupling agents led to formation of ionic liquid supported Fmoc-protected dipeptide **100.** Removal of Fmoc from **100** also resulted in formation of by-product diketopiperazine (DKP) which was removed by simple washing with ether leaving behind pure ionic liquid supported dipeptide **101**. Further elaboration of peptide chemistry on **101** using Fmoc protected amino acids and removal of soluble support using HPF_6 in aqueous methanol let to desired peptide **103**in good yield and high purity.



Scheme 1.17: Ionic liquid phase synthesis of peptides

The support could be recovered by reaction with thionyl chloride. Ionic liquid [bmim][PF_6] could be used as a solvent in *N*-protecting group cleavage reactions to reduce purification. NMR and racemization studies were carried out to show that almost no racemization occurred.

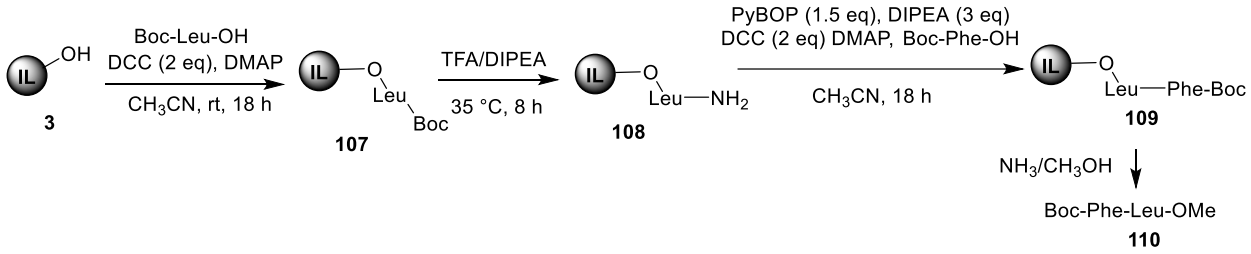
Giannini and Poletti explored the use of ionic liquids in the synthesis of peptide nucleic acids (PNA) oligomers **106** (Scheme **1.18**).[37] As a model reaction, the coupling of the carboxylic function of an *N*-Boc protected PNA monomer (**104**) was carried out with the amino function of another PNA monomer (**105**) using EDC and other coupling agent such as HBTU and COMU in ionic liquid to synthesize *aeg*PNA *N*-(2-aminoethyl)glycine dimer **106**. Three different solvents, [bmim][PF_6], [emim][BF_4] and [emim][OTf] were used as reaction media and the products were extracted by washing with isopropanol and the same coupling was carried out in DMF as a reference reaction. Among the three ionic liquids, [bmim][PF_6] and [emim][BF_4] were found to be more efficient than [emim][OTf]. Microwave irradiation proved helpful in accelerating the reaction and best results were obtained in [emim][BF_4] using HBTU under microwave. Ionic liquid was recovered and reused for four cycles without noticeable loss in activity.



Scheme 1.18: Synthesis of *aeg*PNA dimer **106** in ionic liquid.

Ionic liquid soluble support was also utilized in peptide synthesis by Chan-Miao Sun group.[38] They used imidazolium based ionic liquid **3** as soluble support and Boc peptide chemistry (**Scheme 1.19**). The coupling of amino acid was achieved by DCC/DMAP or PyOB/DIPEA and

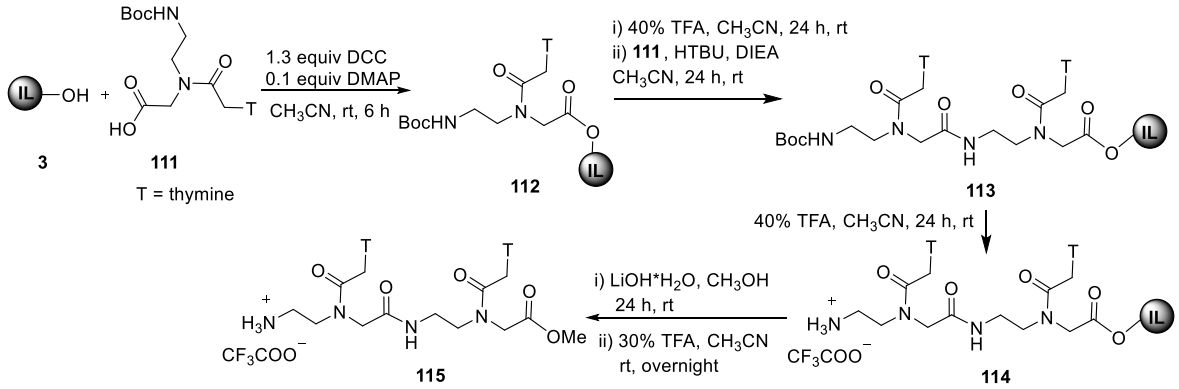
excess Boc-amino acid was removed by washing at each step. Deprotection of Boc group was most effective in tetrafluoroboric acid and tetrafluoroacetic acid. Preparation and HPLC analysis of a series of ionic liquid-supported dipeptides (**109**) and their subsequent cleavage in NH_3/CH_3OH showed that no racemization or epimerization occurred during ILSPS or cleavage steps.



Scheme 1.19: Ionic liquid phase synthesis of dipeptides

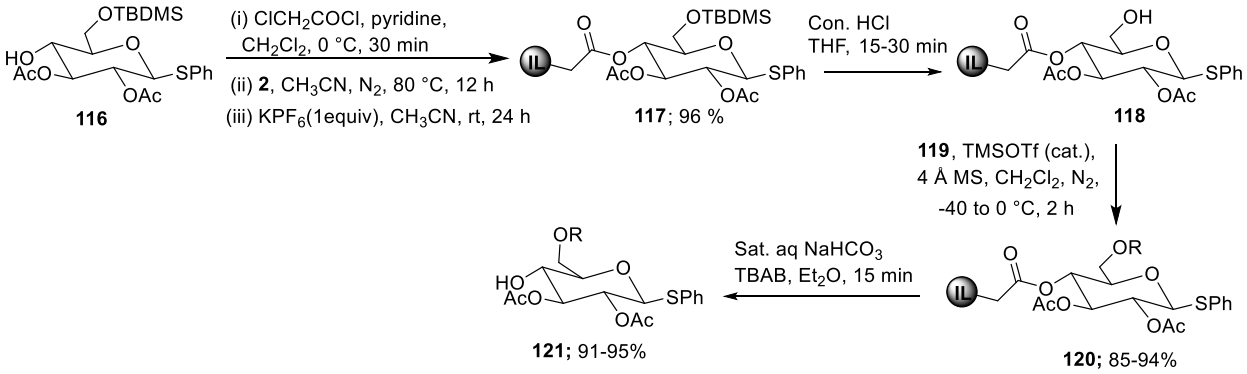
The intermediates in the protected and deprotected forms could be isolated by washing and were analyzed by NMR and mass analysis. The methodology was also applied for the synthesis of pentapetide Leu^5-enkephalin. The purity of the product obtained from ionic liquid soluble support was higher than obtained by any other SPPS before chromatographic purification. The method is cost-effective and highly apt for large scale synthesis but it remains to be seen as to whether longer peptides can change the solubility of ionic liquid.

To demonstrate the use of soluble ionic liquid phase (SILP), a PNA thymine monomer **111** was coupled to an ionic liquid support **3** using DCC and DMAP in acetonitrile (**Scheme 1.20**). The supported monomer was deprotected to give **112** and further coupling was carried out using thymine monomer **111** with HBTU. The reaction required a lesser amount of the monomer than usual and PNA dimer **115** was obtained by removal of Boc protecting group followed by cleavage from ionic liquid support.



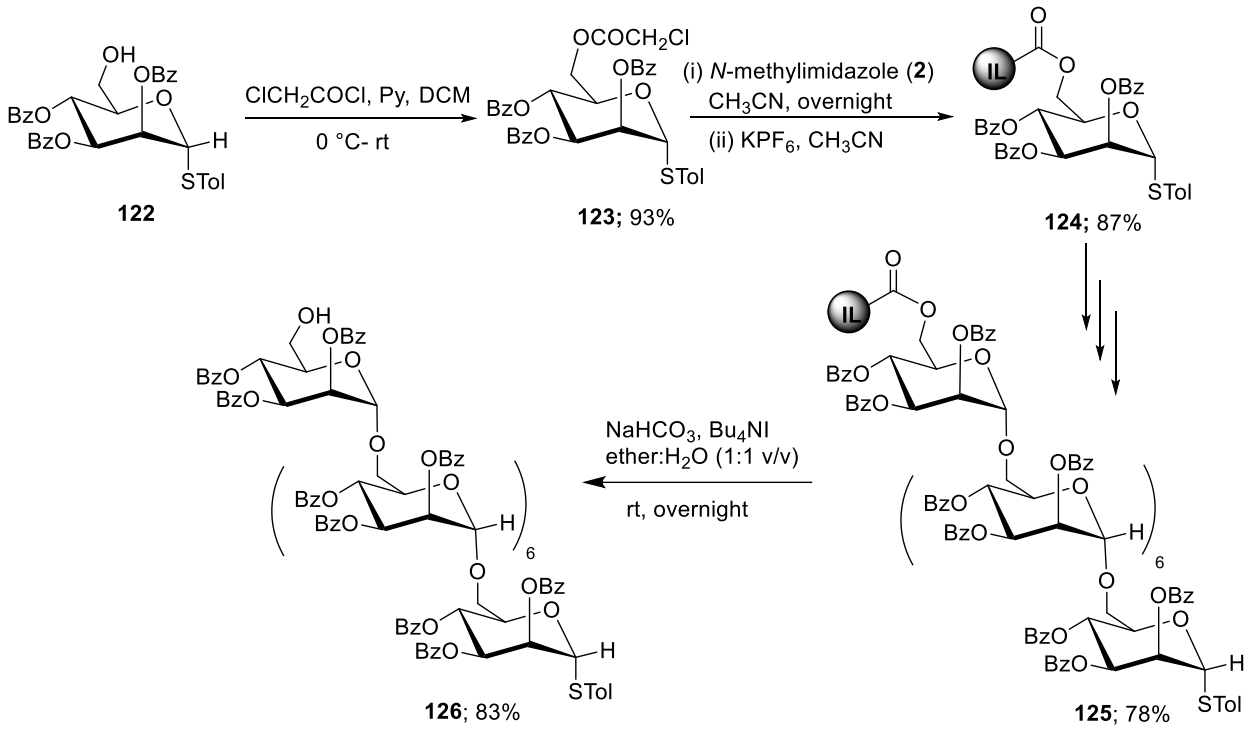
Scheme 1.20: Ionic liquid phase synthesis of PNA dimer **115**

In congruence with research in the field of supported synthesis of oligosaccharides Wang group reported the use of an ionic liquid supported glucoside (**118**) in the synthesis of a number of di- and tri-saccharides (**121**) (**Scheme 1.21**).[39] D-Glucose derivative (**116**) was converted to ionic liquid supported monosaccharide (**117**) by esterification with 2-chloroacetyl chloride in the presence of pyridine followed by reaction with *N*-methylimidazole (**2**) and anion metathesis. Deprotection of TBDMS group in the presence of hydrochloric acid led to formation of hydroxyl group free monosaccharide supported on ionic liquid (**118**). Further, coupling of **118** with various glycosyl donors (**119**) which had been activated by trichloroacetimidates gave ionic liquid supported di- and tri-saccharide (**120**). The di- and tri-saccharide (**121**) were liberated from ionic liquid support by cleavage of the ester link using a saturated aqueous $NaHCO_3$ solution with TBAB. Oligosaccharides of high yield and purity were obtained without the need for chromatography. Excess reagents and by-products could be removed at each stage by diethyl ether/EtOAc and were easily detected by ^1H & ^{13}C NMR and mass analysis.



Scheme 1.21: Ionic liquid-supported synthesis of oligosaccharides **121**

Pathak *et al* further explored the use of ionic liquid soluble support (ILSS) in larger saccharide chains by preparing octosaccharide (**126**) using ionic liquid-tagged *p*-tolylthiomannoside (**124**) (**Scheme 1.22**).[40] The ionic liquid-tagged thioglycoside was synthesized by the reaction of **123** with *N*-methylimidazole (**2**) at 80 °C for 12 h followed by anion metathesis. After a series of glycosylations, the ionic liquid-supported octasaccharide (**125**) was obtained and the ionic liquid was separated by washing with ether. NIS-TfOH and Cp_2HfCl_2-$AgClO_4$ were used as coupling reagents and this orthogonal block synthesis was highly efficient and ecofriendly.



Scheme 1.22: Ionic liquid phase synthesis of α(1→6)-linked octamannan

1.14 Conclusions

The progress in use of functionalized ionic liquids as soluble support in various organic transformations in the last decade is underpinning their importance and great potential in organic synthesis. Use of functionalized ionic liquids as soluble support has provided ways to address some of the disadvantages of solid-phase synthesis and fluorous phase synthesis. The advantages of high loading of the reagent, faster reaction rates in homogeneous environments, possibility of intermediate analysis and monitoring of progress of the reaction using modern techniques, and ready adaptability are making these soluble supports as viable support in organic synthesis. The is enormous possibility of developing novel soluble phase supports using range of combinations of anions and cations in ionic liquids. Application of functionalized ionic liquids (FILs) as soluble support is in the early stage of development. With increased availability of functionalized ionic liquids, they should find applications in the synthesis of complex molecules and biomolecules.

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Chapter II

Synthesis and Characterization of Ionic Liquid-supported Sulfonyl Hydrazine and its Applications in Organic Synthesis

Chapter II

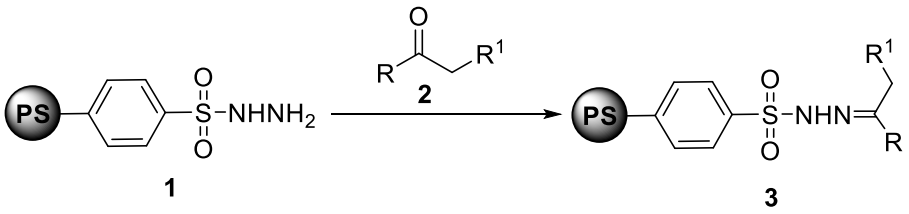
PART A

Ionic Liquid-supported Sulfonyl Hydrazine: Synthesis of 1,2,3-Thiadiazole and 1,2,3-Selenadiazole

2.1 Introduction

Sulfonyl hydrazine[1, 2] are stable solids, non odorous and readily accessible which can be used as a sulfenylating reagent in the sulfenylation of iodoles,[1] alkanes and ethers,[3] naphthols and naphthylamines,[4] as well as oxysulfenylation of alkenes[5] and as a scavengers for carbonyl compound. They have attracted great attraction of organic chemist due to their importance in the synthesis of a variety of heterocyclic compounds of biological importance such as anti-Alzheimer's agents, antimycobacterial, hepatitis C virus inhibition, antitumor, β-lactamase inhibitory properties against class A and C enzymes, anti-tuberculosis, and bacteriostatic activity.[6, 7]

Deleuze group[8, 9] have reported synthesis of polymer-bound phenylsulfonyl hydrazine (**1**) and used it as scavenger for aldehydes and ketones (Scheme 2.1). It is particularly useful in sequestering excess carbonyl containing components from sweat wine.



Scheme 2.1: Scavenging of carbonyl compounds using polymer supported-sulfonyl hydrazine

Solid-supported sulfonyl based reagents such as sulfonyl hydrazine, sulfonyl azides, sulfonyl amines etc. are versatile reagent with numerous applications in organic synthesis.[10-14] They have been used in solid supported synthesis of various heterocycles in a strategy known as "catch and release". However, slow rate of reaction and use of large excess of reagents to drive the reaction for completion are some of the main limitations associated with these solid-supported sulfonyl reagents along with the issue of reaction monitoring.

As described in chapter I, ionic liquid tathered with specific group also termed as functionalized ionic liquids are emerging as alternative to solid-supported reagents. These materials are promising and they overcome some of the disadvantages associated with solid-supported reagents. In this approach, the desired molecule is attached to an ionic liquid by an appropriate linker and multistep synthesis of the target molecule is carried out without detaching the ionic liquid for monitoring the reaction progress at every stage. Unreacted reagents and unwanted

compounds could be easily separated out from the ionic liquid by simple washing with appropriate solvents before the final cleavage. The main feature of ionic liquid-supported reagents resembles the polymer-supported reagents, but high loading efficiency, tunable solubility,[15] possibilities to monitor the reaction progress by different analytical techniques, and minimal use of solvents have made this method an attractive and favorable alternative to solid-phase synthesis.

Ionic liquids with a different type of linker and desired functional group or moiety (Figure 2.1) have been synthesized and used for several organic transformations.[16-20] Bazureau group[16] was the first to propose the use of ionic liquid as a soluble support for the synthesis of small organic molecules. Tao *et al.*[17] described the advantages of ionic liquid-supported synthesis over polymer-supported synthesis in combinatorial chemistry by synthesizing cis-*β*-lactam library. There are only a few reports on ionic liquid-supported synthesis of heterocycles,[19, 20] possibly because in most of the ionic liquid-supported synthesis the substrate should have a functionality to anchor on the ionic liquid support that leads to an extra or unwanted functional group upon cleavage.

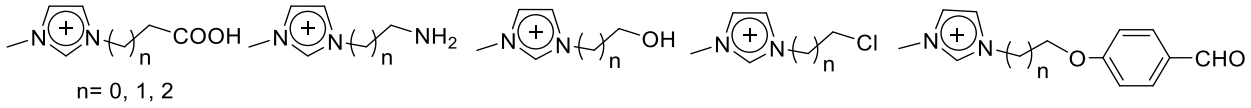


Figure 2.1: Some commonly used linkers in ionic liquid-supported synthesis.

In this chapter of thesis, we have discussed the synthesis of following two novel ionic liquid-supported sulfonyl reagents *viz* (a) Ionic liquid-supported sulfonic acid (b) Ionic liquid-supported sulfonyl hydrazine and they have been explored for the synthesis of selected heterocyclic compound. The details of this protocol are presented in three parts of this chapter.

2.2 Introduction

1,2,3-Thiadiazoles are important heterocycles[21] that possesses broad pharmacological properties such as anticancer, antibacterial, fungicidal, anti-hepatitis B virus,[22] and anti-HIV[23] activities. Figure 2.2 depicts chemical structures of selected bioactive 1,2,3-thiadiazoles. 1,2,3-Thiadiazoles are also useful intermediates in the synthesis of several organic compounds, such as 2-thioindole,[24] 2-alkoxybenzo[*b*]thiophenes,[24] β-hydroxy sulfides,[25] and thioamides.[26] 1,2,3-Selenadiazoles are bioisosteric heterocycles of 1,2,3-thiadiazoles and have attracted attention because of their diverse biological activities such as antibacterial,[27] antifungal,[28] anticancer,[29] and anti-HIV[30] activities. Furthermore, they have been utilized as intermediates for the synthesis of organic compounds such as dihydroselenophenes[31, 32] and 2,3-dihydro-1*H*-pyrroles.[33] Selenadiazoles are well-known source for strained alkynes and cycloalkynes.[34, 35]

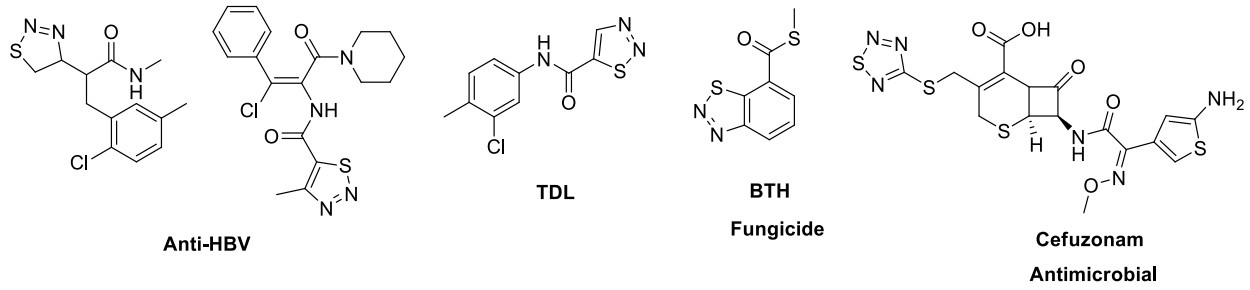
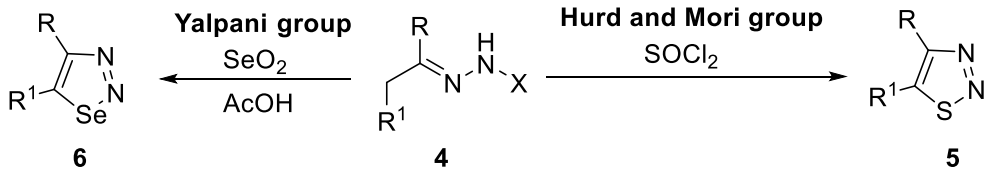


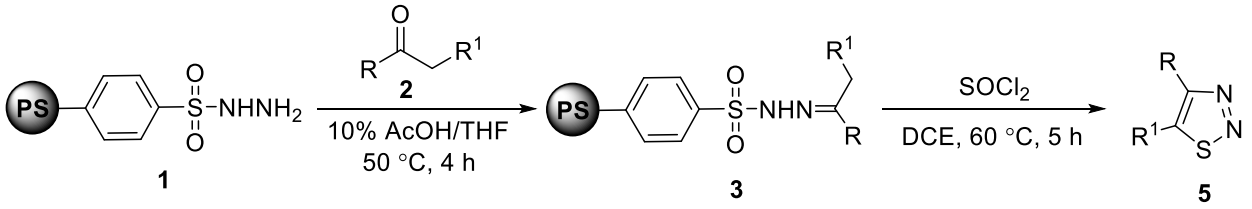
Figure 2.2: Some bioactive 1,2,3-thiadiazole containing compounds

Owing to their wide application, several synthetic routes have been developed for the synthesis of 1,2,3-thiadiazoles (**5**) and 1,2,3-selenadiazoles (**6**).[22, 36-40] Hurd and Mori reported synthesis of 1,2,3-thiadiazoles **5** by the cyclization of the corresponding tosyl hydrazone of α-methylene ketones **4** with thionyl chloride.[41] In analogy to the synthesis of 1,2,3-thiadiazoles, the Yalpani group described the synthesis of 1,2,3-selenadiazoles **6** by the oxidative cyclization of the tosyl hydrazone **4** with selenium dioxide (Scheme 2.2).[39, 42] The reaction of acetaldehyde semicarbazone with SeO_2 in glacial acetic acid gives unsubstituted 1,2,3-selenadiazole **3** in 25% yield.



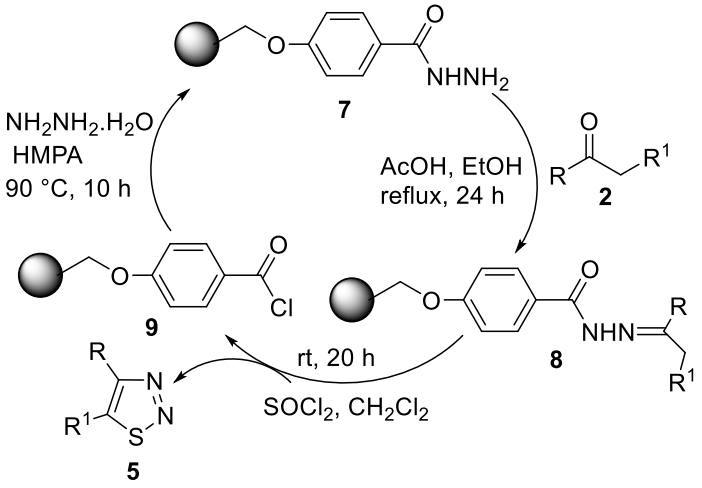
Scheme 2.2: Synthesis of 1,2,3-selenadiazoles and 1,2,3-thiadiazoles

Although the reported methods serve the synthetic requirements, yet they suffer from some disadvantages. For example, chromatographic separation is necessary to remove the sulfonyl chloride, which is tedious in multigram scale. To overcome these problems, Porco group[43] has described an efficient solid phase synthesis of 1,2,3-thiadiazoles **5** exploiting a "catch and release" strategy without employing chromatographic separation. In the first step, resin supported sulfonyl hydrazine (**1**) captured different ketones **2** to form resin-supported sulfonylhydrazone **3**, which was further cyclized and cleaved by thionyl chloride to afford 1,2,3-thiadiazoles **5** (Scheme 2.3).



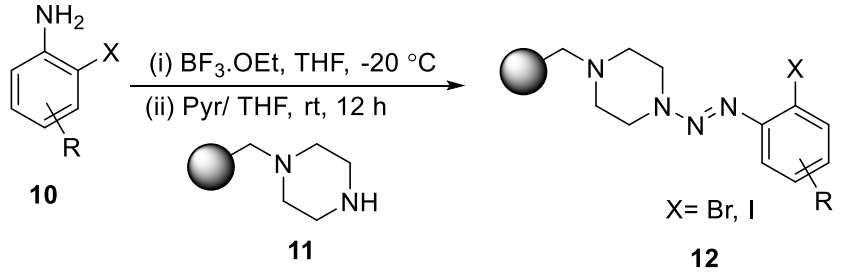
Scheme 2.3: Synthesis of 1,2,3-thiadiazoles using polystyrene-sulfonyl hydrazide resin

Liu group[44] employed solid phase synthesis for preparing 1,2,3-thiadiazoles **5** by effective cyclization of resin bound acyl hydrazones **8** followed by cleavage of resin using thionyl chloride and obtained 1,2,3-thiadiazoles **5** in good yield with high purities. The desired products were isolated by simple filtration of resin bound benzoyl chloride **9** which was further treated with hydrazine hydrate to recover and reuse resin bound acyl hydrazine **7** to complete the cycle (Scheme 2.4).

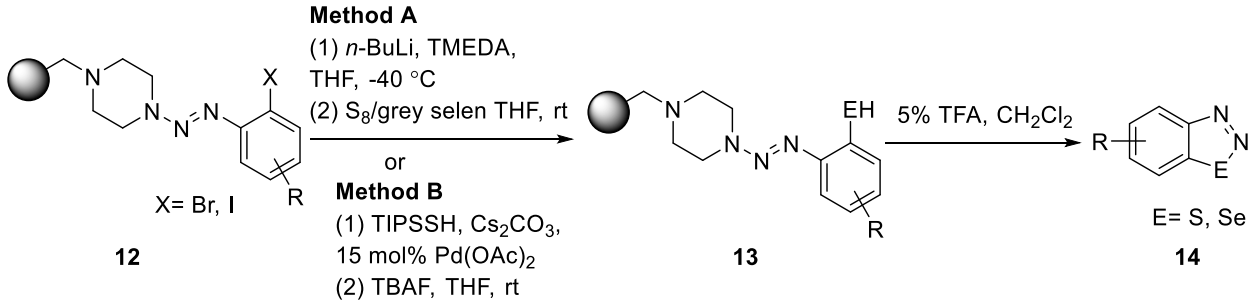


Scheme 2.4: Synthesis of 1,2,3-thiadiazoles from solid bound acyl hydrazones

Brase group[45] achieved solid phase synthesis of benzo[1,2,3]thiadiazoles and benzo[1,2,3]selenadiazoles (**14**) by the cyclization of resin-bound *ortho* bromo or iodo triazenes **12** by using method A or B followed by cleavage of resin using TFA in dichloromethane. The resin bound triazene linker **12** was prepared from easily available starting material *ortho*-halo anilines (**10)** as shown in scheme 2.5. Both electron rich, as well as electron poor halo anilines (**10**), resulted in good yields. By employing two synergetic methodologies A or B, Brase group were able to synthesize a wide range of substituted benzo[1,2,3]thiadiazoles and benzo[1,2,3]selenadiazoles **14**. While the advantages of the methodology A are the lower costs and eco-friendly conditions. The second methodology B performs better as regards to functional group tolerance and gives rise to a potential combinatorial approach towards benzo[1,2,3]thiadiazoles and benzo[1,2,3]selenadiazoles **14** (Scheme 2.6).



Scheme 2.5: Synthesis of resin bound *ortho*-halo triazene linker



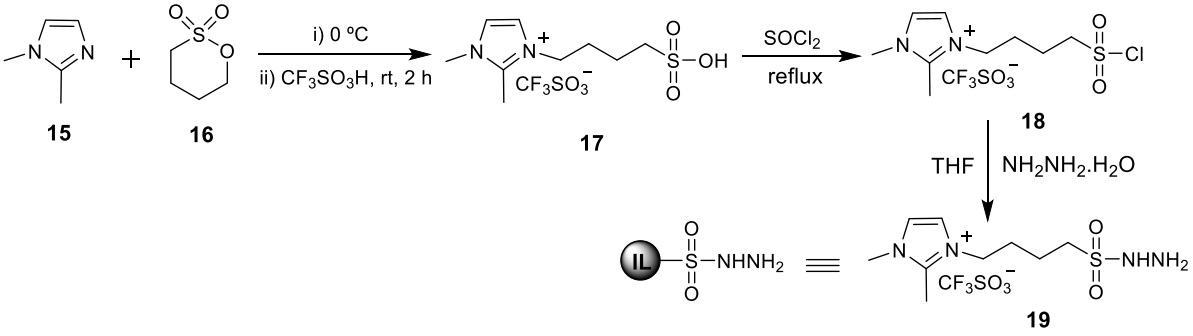
Scheme 2.6: Solid phase synthesis of benzo[1,2,3]thiadiazoles and benzo[1,2,3]selenadiazoles

However, these methods are also associated with limitations. The need of excess reagents, longer times to drive reactions to completion, and inability to use in pilot scale have made their applicability narrow.

In continuation of our efforts on the application of ionic liquids in organic synthesis,[46-48] we developed a new, simple, and convenient approach to the synthesis of 1,2,3-thiadiazoles and 1,2,3-selenadiazoles using soluble ionic liquid-supported sulfonyl hydrazine.

2.3 Results and Discussion

Ionic liquid-supported sulfonyl hydrazine (**19**) was synthesized by simple reaction sequences shown in scheme 2.7. Initially, the reaction of 1,2-dimethylimidazole (**15**) with 1,4-butane sultone (**16**) at 0 °C followed by reaction with a trifluoromethanesulfonic acid (TfOH) at room temperature for 2 h gave **17**. The reaction of **17** with thionyl chloride under reflux conditions gave ionic liquid-supported sulfonyl chloride (**18**), which on reaction with hydrazine hydrate afforded **19**. The structure of **19** was confirmed by IR, ^{1}H NMR and mass spectrometry. A singlet at δ 3.47 ppm corresponding to the *N*-methyl group, a triplet at δ 3.88 ppm for aliphatic methylene protons adjacent to the imidazole ring, and two doublets at 7.58 and 7.56 ppm for imidazole protons were observed in the ^{1}H NMR spectrum (Figure 2.4). In the ^{13}C NMR spectrum, three peaks at δ 144, 122, and 121 ppm for imidazole ring carbons along with other aliphatic carbons were observed (Figure 2.4). A peak at *m/z* 247.1208 $[M-CF_3SO_3]^+$ was observed in ESI-TOF MS spectra, that confirmed the structure of **19**.



Scheme 2.7: Synthesis of ionic liquid-supported sulfonyl hydrazine (**19**)

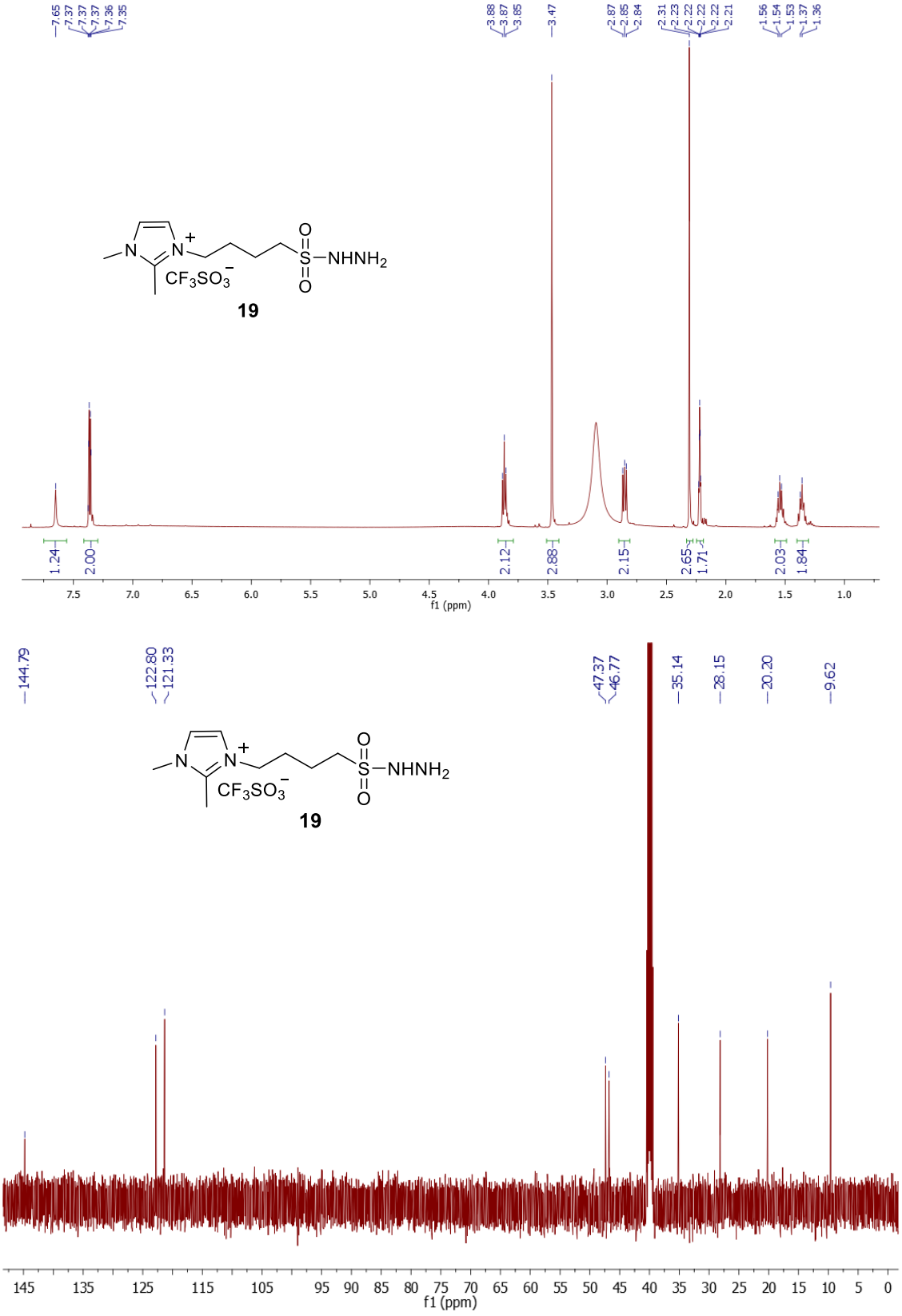


Figure 2.3: ^{1}H and ^{13}C NMR spectrum of **19**

The thermal stability of **19** was investigated by the differential scanning calorimetric (DSC) analysis and thermal gravimetric analysis (TGA) (Fig. 2.4). DSC analysis displayed a melting point peak at 111 °C with initiation temperature at 100 °C and ending temperature at 117.7 °C. The decomposition temperature was observed between 162.5 to 196 °C. TGA analysis was also in agreement with DSC analysis and showed that **19** is stable without any significant loss in weight up to 162.8 °C and afterwards gradual decrease in weight was observed, suggesting it can be used till 160 °C effectively. It is worth mentioning that **19** do not show any decomposition and loss of reactivity even after storing for 1 year at room temperature.

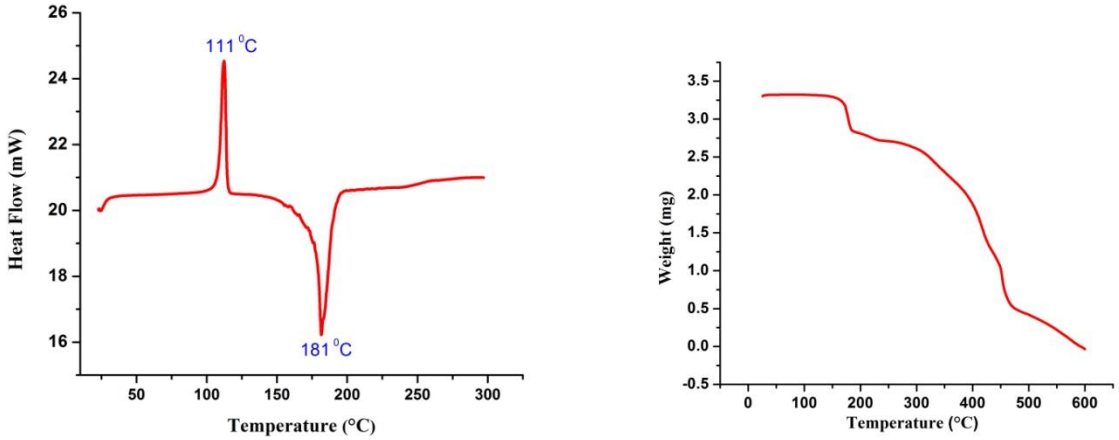
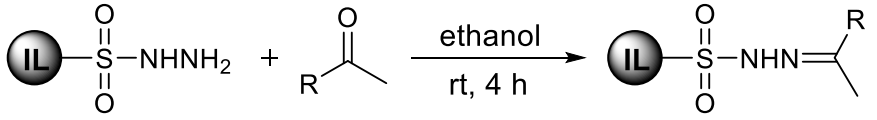


Figure 2.4: The DSC and TGA scan of **19** performed at a rate of 10 °C min^{-1}

We explored reaction of **19** with different carbonyl compounds to afford corresponding ionic liquid-supported sulfonyl hydrazone derivatives **22a–k** in good to excellent yields (Table 2.1) at room temperature. The structures of **22** were confirmed by ^{1}H NMR, ^{13}C NMR, and mass analysis. A characteristic peak in the range of δ 10.2–10.7 ppm was observed in the ^{1}H NMR spectra for the NH proton along with other protons, and a peak in the range of 150.2–156.5 ppm appeared for the C=NH carbon along with other carbons in the ^{13}C NMR spectra . In ESI-TOF MS, a peak appeared corresponding to the $[M-CF_3SO_3]^+$ ion. Figure 2.5 shows a representative ^{1}H NMR and ^{13}C NMR spectra of ionic liquid-supported hydrazone (**22a**).

Table 2.1: Synthesis of ionic liquid-supported sulfonyl hydrazone



20 **21** **22**

Entry	R	Compound No.	Yield[a] (%)
1	C_6H_5	**22a**	86
2	4-$OCH_3C_6H_4$	**22b**	81
3	4-$CH_3C_6H_4$	**22c**	82
4	1-Naphthyl	**22d**	88
5	2-Naphthyl	**22e**	86
6	4-FC_6H_4	**22f**	90
7	4-ClC_6H_4	**22g**	88
8	4-BrC_6H_4	**22h**	88
9	4-$NO_2C_6H_4$	**22i**	86
10	C_5H_4N	**22j**	92
11	C_4H_3S	**22k**	94

[a]Isolated yield

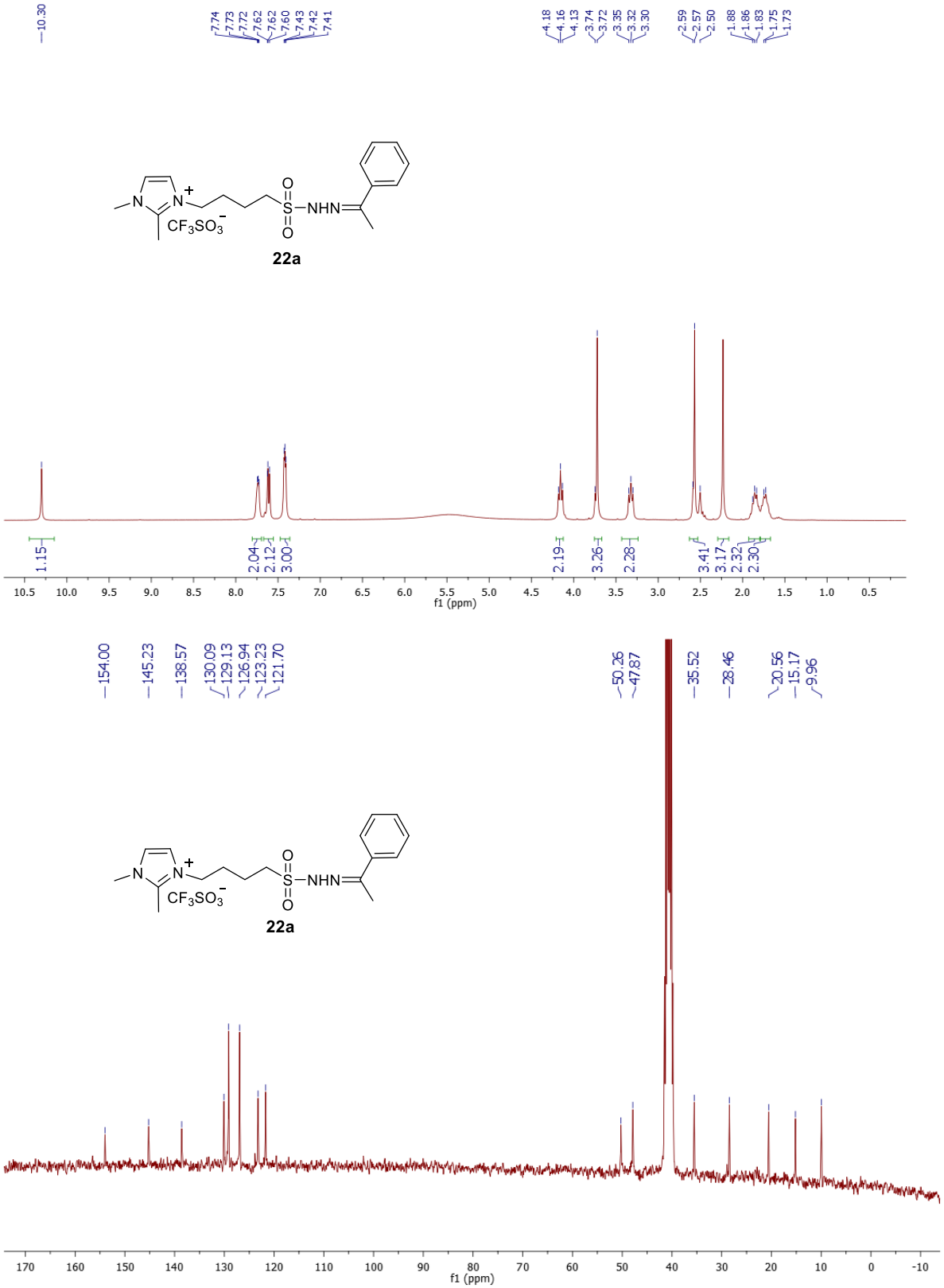
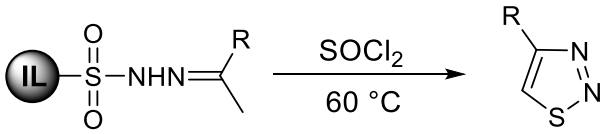


Figure 2.5: ^{1}H and ^{13}C NMR spectrum of ionic liquid-supported sulfonyl hydrazone (**22a**)

To optimize reaction conditions for the synthesis of 1,2,3-thiadiazoles, **22a** (1.0 equiv) was first reacted with $SOCl_2$ (5.0 equiv) in dichloroethane (DCE) at room temperature. The reaction was very sluggish and took 10 h to complete. However, when the reaction was heated at 60 °C, it took only 4 h for completion of the reaction. Next, we attempted the reaction without solvent, and it was found that there was not much difference in the yield of **5a** as well as in the time of reaction in the absence of a solvent. In fact, ionic liquid-supported hydrazone **22a** was readily reacted under solvent-free conditions with thionyl chloride producing **5** in excellent yield at 60 °C (Scheme 2.8, Table 2.2). The reaction mixture was neutralized with sodium bicarbonate solution, and the compound was removed from ionic liquid layer by extracting in ethyl acetate/hexane layer. The compound was pure enough and the chromatographic purification was not required. The formation of the thiadiazole **5a** was confirmed by spectroscopic analysis. A characteristic singlet peak in the range of 8.65 ppm was observed in the ^1H NMR spectra for the C_5-proton of the 1,2,3-thiadiazole ring, and the corresponding carbon was observed in the range of 130.3−136.4 ppm in the ^{13}C NMR spectra (Figure 2.6). To investigate the generality of the method, a library of 1,2,3-thiadiazoles were synthesized from the corresponding ionic liquid supported sulfonyl hydrazones **22a−k** and thionyl chloride (Table 2.2). Both electron-withdrawing and electron releasing aromatic ketones were found to be excellent substrates for this protocol to give corresponding 1,2,3-thiadiazoles.



22a-k **5**

Scheme 2.8: Synthesis of 1,2,3-thiadiazoles from ionic liquid-supported hydrazone (**22**)

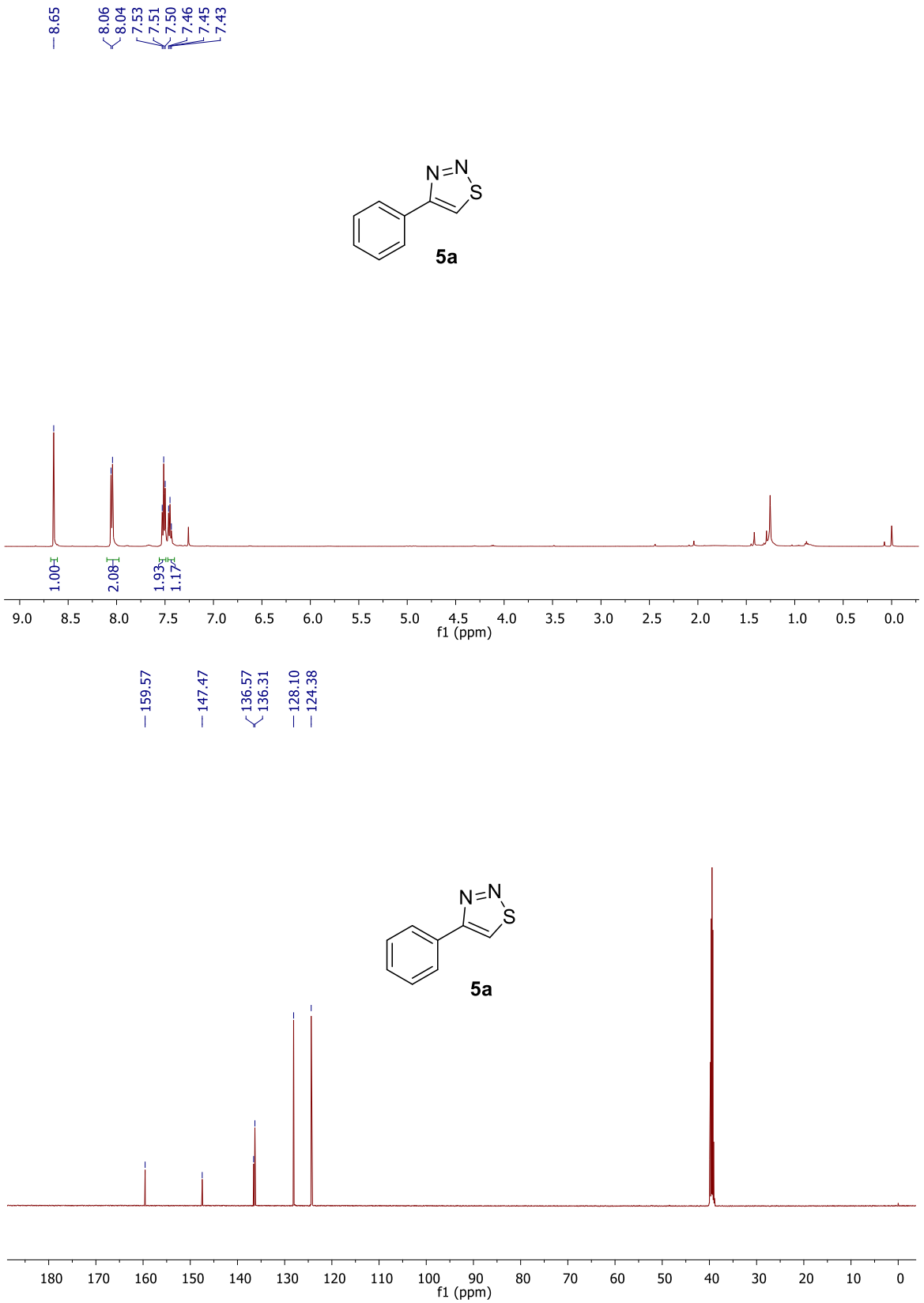
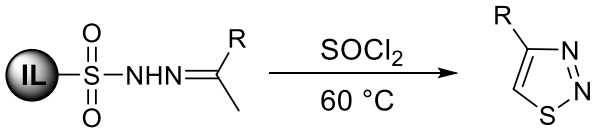
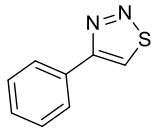
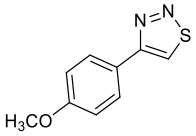
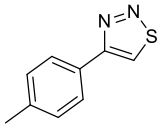
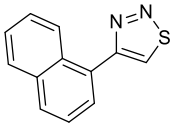
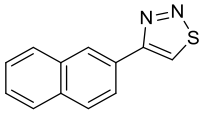
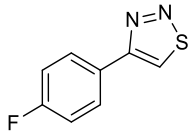
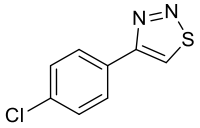
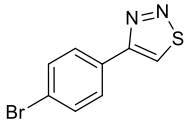
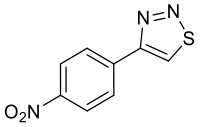


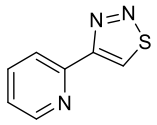
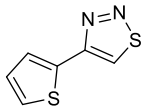
Figure 2.6: ^{1}H and ^{13}C NMR spectrum of **5a**

Table 2.2: Synthesis of 1,2,3-thiadiazoles[a] .



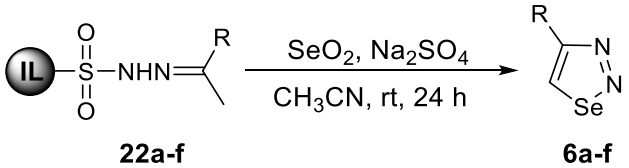
22a-k **5a-k**

Entry	Compound	R	Product		Yield[b] (%)
1	**22a**	C_6H_5		**5a**	91
2	**22b**	4-$OCH_3C_6H_4$		**5b**	86
3	**22c**	4-$CH_3C_6H_4$		**5c**	87
4	**22d**	1-Naphthyl		**5d**	84
5	**22e**	2-Naphthyl		**5e**	88
6	**22f**	4-FC_6H_4		**5f**	89
7	**22g**	4-ClC_6H_4		**5g**	88
8	**22h**	4-BrC_6H_4		**5h**	90
9	**22i**	4-$NO_2C_6H_4$		**5i**	83

10	**22j**	C_5H_4N		**5j**	80
11	**22k**	C_4H_3S		**5k**	88

[a]Reaction conditions: Ionic liquid-supported sulfonyl hydrazone **22** (1 mmol), thionyl chloride (5 mmol), 60 °C, 4 h. [b]Isolated yield.

Considering our success with 1,2,3-thiadiazoles, we employed a similar strategy for the synthesis of 1,2,3-selenadiazoles (Scheme 2.9). The reaction of ionic liquid-supported sulfonyl hydrazones **22** with selenium dioxide for the synthesis of 1,2,3-selenadiazoles **6a−f** was challenging. Initially, the reaction of **22a** with selenium dioxide in the presence of acetic acid with the expectation of 4-phenyl-1,2,3-selenadiazole (**6a**) did not result in the formation of the desired heterocycle; instead, it was hydrolyzed to generate the starting acetophenone **21a**. Thus, the reaction was carried out under different reaction conditions and in different solvents. Using selenium dioxide in acetonitrile without acetic acid led to the conversion of **22a** into **6a** in modest yield and high purity. There was a slight increase in the yield after using dry sodium sulfate as it absorbs the water released in the reaction. We then applied this methodology to different ionic liquid-supported hydrazones **22** to generate the corresponding selenadiazoles **6b−f** in moderate yield (Table 2.3). The yield was comparable with the reported solution phase yield of 1,2,3-selenadiazoles and purity were over 90% as analyzed by HPLC analysis. The chemical structures of 1,2,3-selenadiazoles **6** were confirmed by ^{1}H and ^{13}C NMR and mass spectroscopy. In ^{1}H NMR, C_5 proton gives a sharp singlet around at δ 9.00-9.50 ppm along with other protons, while the C_5 carbon appeared in the range of 135.0-146.0 ppm along with other carbons in ^{13}C NMR spectra. Figure 2.7 shows a representative ^{1}H and ^{13}C NMR for 1,2,3-selenadiazoles(**6a**).



22a-f **6a-f**

Scheme 2.9: Synthesis of 1,2,3-selenadiazole (**6**) from ionic liquid-supported hydrazone (**22**)

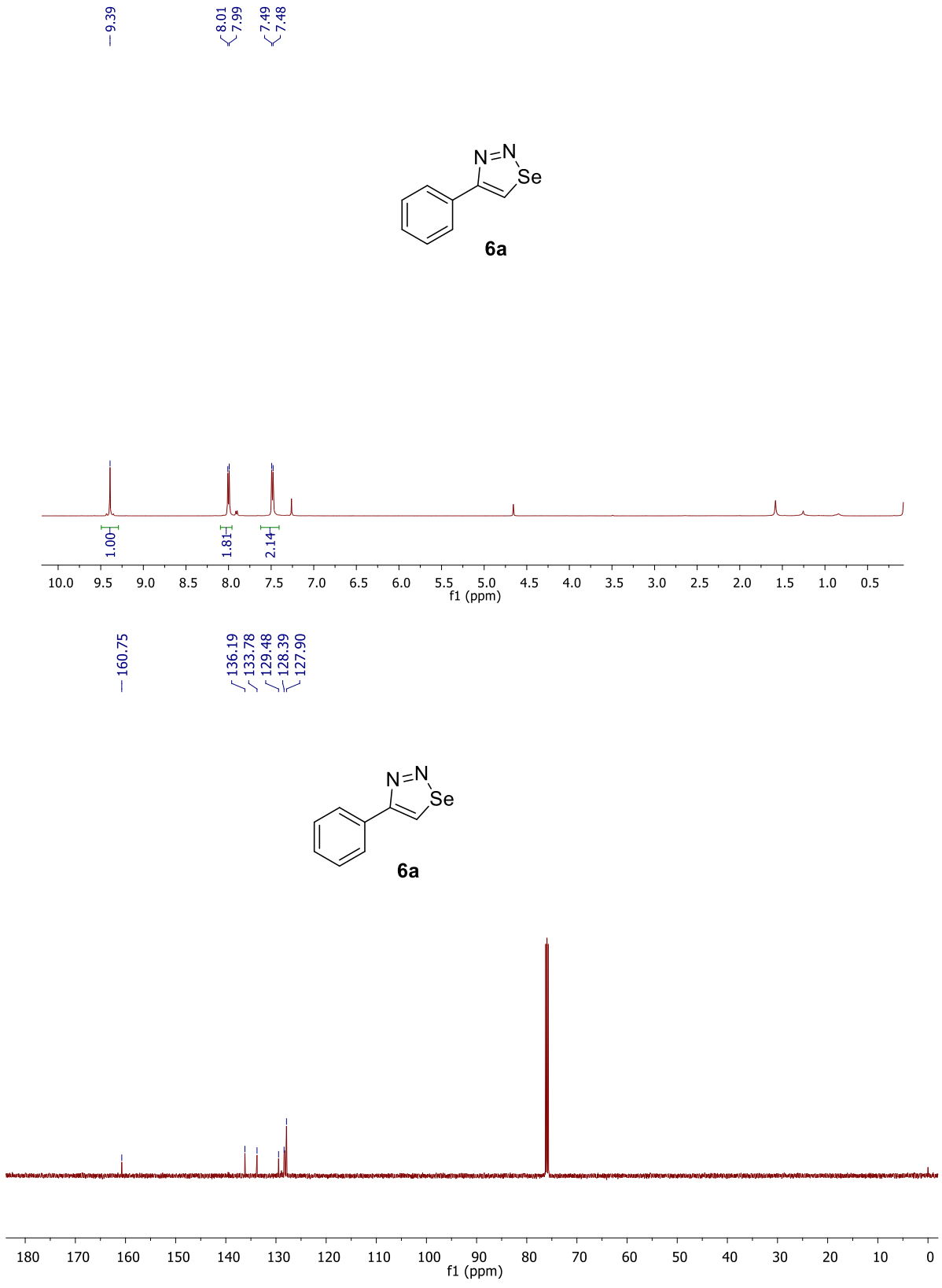
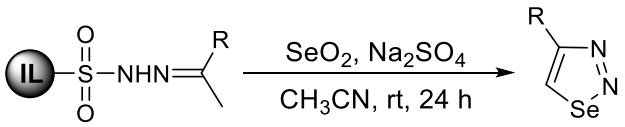
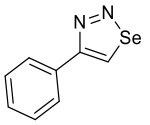
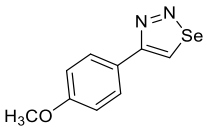
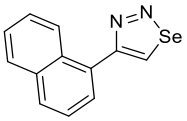
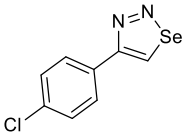
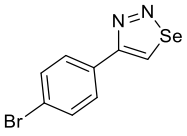
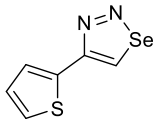


Figure 2.7: ^{1}H and ^{13}C NMR spectrum of **6a**

Table 2.3: Synthesis of 1,2,3-selenadiazoles[a]



22a-f **6a-f**

Entry	Compound	R	Product		Yield[b] (%)
1	**22a**	C_6H_5		**6a**	30
2	**22b**	4-$OCH_3C_6H_4$		**6b**	22
3	**22c**	1-Naphthyl		**6c**	25
4	**22d**	4-ClC_6H_4		**6d**	30
5	**22e**	4-BrC_6H_4		**6e**	40
6	**22f**	C_4H_3S		**6f**	32

[a]Reaction conditions: **22** (1 mmol), Selenium dioxide (1.05 mmol), sodium sulfate (1.5 mmol), acetonitrile (6 mL), 24 h. [b]Isolated yield

2.4 Conclusion

In summary, we have demonstrated a simple and convenient approach for ionic liquid-supported synthesis of 1,2,3-thiadiazoles and 1,2,3-selenadiazoles. The advantages of this methodology are the ease of workup, simple reaction conditions, and high purity. Indeed, 1,2,3-thiadiazoles were obtained in high purity by neutralization with sodium hydrogen carbonate and extraction in organic solvents. Thus, this methodology provides access toward the synthesis of diverse 1,2,3-thiadiazole and 1,2,3-selenadiazole derivatives under simple reaction conditions. This study also

provides insights into using ionic liquid-supported reagents for the synthesis of other heterocyclic compounds

2.5 Experimental

NMR spectra were recorded an 300 MHz, 400 MHz and 500 MHz spectrometers using $CDCl_3$ and DMSO-d_6 as solvents. The chemical shifts were expressed in ppm. Reactions were monitored by thin-layer chromatography (TLC) carried out on silica-coated aluminum plates (60F-254) using UV light as a visualizing agent. Melting points were determined in an open capillary tube on automated melting point apparatus and are uncorrected. All the chemicals and reagents were purchased at the highest commercial quality and were used without further purification unless otherwise stated.

Procedure for synthesis of ionic liquid-supported sulfonic acid 17

1,4-Butanesultone **16** (5g, 1 equiv) was added drop-wise to 1,2-dimethylimidazole **15** (3.3g, 1 equiv) at 30 °C. The resulting solution was stirred until a solid was obtained at room temperature. After completion of the reaction, the product was washed with toluene (3 × 15 mL) and finally with diethyl ether (3 × 15 mL) to remove unreacted starting materials. The compound was dried under reduced pressure to obtain the zwitterionic form. Trifluoromethanesulfonic acid (5.52 mL, 1.1 mmol) was added dropwise to the zwitter ion at 0 °C. After completion of the addition, the solution was stirred at 40 °C until a thick liquid was obtained. The resulting liquid was washed with diethyl ether to remove excess triflic acid. The compound was dried under reduced pressure to give a pale yellow thick liquid sulfonic acid (7 g, 98%).

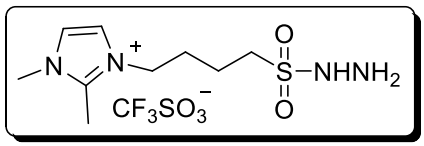
Synthesis of ionic liquid-supported sulfonyl chloride (18)

Thionyl chloride (3.84 mL, 3 equiv) was added dropwise by an additional funnel to the ionic-liquid sulfonic acid **17** (6.71g, 1 equiv) at 0 °C. The resulting mixture was stirred at room temperature for 8 h and finally heated to 80 °C for 2 h. Excess thionyl chloride was removed on a rotatory evaporator under reduced pressure to obtain a yellow, thick ionic liquid-supported sulfonyl chloride (7.08 g, 96%).

Synthesis of ionic liquid-supported sulfonyl hydrazide (19)

Hydrazine hydrate (1.70 mL, 2 equiv) was added slowly to **18** (7.0g, 1 equiv) at 0 °C in THF. After completion of addition, the reaction mixture was slowly heated up to 40 °C for 4 h. After completion of the reaction, THF was evaporated under reduced pressure. The resulting mixture was washed with ethyl acetate (3 × 15 mL) to remove hydrazine in order to get pure product.

Ionic liquid-supported sulfonyl hydrazide (19)

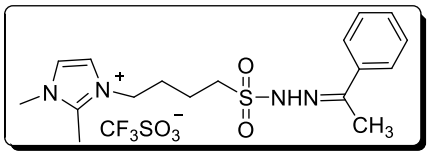


Yield 96%; white solid; mp 94−97 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.90 (s, 1H), 7.65 (d, J = 9.0 Hz, 2H), 7.19 (bs, 2H), 4.15 (t, J = 7.3 Hz, 2H), 3.75 (s, 3H), 3.13 (t, J = 7.7 Hz, 2H), 2.59 (S, 3H), 1.85-1.80 (m, 2H), 1.65-1.61 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 144.8, 122.8, 121.3, 47.4, 46.7, 35.2, 28.1, 20.2, 9.7; HRMS (ESI-TOF) (*m/z*): calcd for $C_9H_{19}N_4O_2S^+$ 247.1229, found 247.1208 $[M-CF_3SO_3]^+$.

General procedure for synthesis of ionic liquid-supported hydrazones (22a-k)

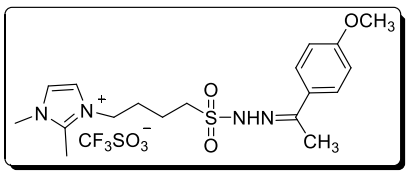
Acetophenone derivative (**21**, 1.05 equiv) and ionic liquid-supported sulfonyl hydrazide (**19**, 1equiv) were taken in ethanol (10 mL) and vigorously stirred at room temperature until the solid precipitated out. The reaction mixture was filtered and washed with cold ethanol (2 × 5 mL) and dried under reduced pressure to get the pure product.

3-(4-((2-(1-Phenylethylidene)hydrazinyl)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (22a)



Yield 96%; white solid; mp 145−150 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.34 (s, 1H), 7.73-7.71 (m, 2H), 7.63 (d, J = 2.0 Hz, 1H), 7.60 (d, J = 2.0 Hz, 1H), 4.15 (t, J = 7.0 Hz, 2H), 3.71 (s, 3H), 3.36-3.27 (m, 2H), 2.56 (s, 3H), 2.23 (s, 3H), 1.86-1.82 (m, 2H), 1.75-1.69 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 153.7, 144.8, 138.0, 129.8, 128.8, 126.6, 122.7, 121.3, 49.7, 47.3, 35.1, 28.1, 20.1, 15.0, 9.6; HRMS (ESI-TOF) (*m/z*) calcd for $C_{17}H_{25}N_4O_2S^+$ 349.1698, found 349.1719 $[M - CF_3SO_3]^+$.

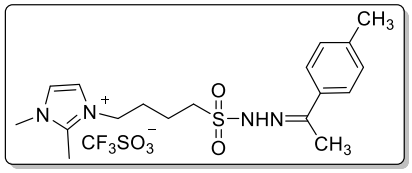
3-(4-((2-(1-(4-Methoxyphenyl)ethylidene)hydrazinyl)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (22b)



Yield 81%; light yellow solid; mp 126−130 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.21 (s, 1H), 7.75 (d, J = 9 Hz, 2H), 7.69

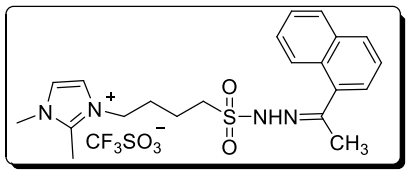
(d, *J* = 2.0 Hz, 1H), 7.66 (d, *J* = 2.0 Hz, 1H), 7.02 (d, *J* = 9 Hz, 2H), 4.22 (t, *J* = 7.0 Hz, 2H), 3.85 (s, 3H), 3.79 (s, 3H), 3.41-3.33 (m, 2H), 2.63 (s, 3H), 2.26 (s, 3H), 1.97-1.89 (m, 2H), 1.82-1.77 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.7, 153.7, 144.8, 130.4, 128.1, 122.7, 121.3, 114.1, 55.7, 49.3, 47.3, 35.1, 28.1, 20.1, 14.8, 9.6; HRMS (ESI-TOF) (*m/z*) calcd for $C_{18}H_{27}N_4O_3S^+$ 379.1804, found 379.1779 $[M - CF_3SO_3]^+$.

1,2-Dimethyl-3-(4-((2-(1-(*p*-tolyl)ethylidene)hydrazinyl)sulfonyl)butyl)-1*H*-imidazol-3-ium trifluoromethanesulfonate (22c)



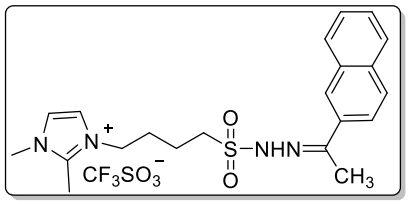
Yield 82%; light yellow solid; mp 139−142 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.22 (s, 1H), 7.63-7.59 (m, 4H), 7.21 (d, *J* = 7.7 Hz, 2H), 4.15 (t, *J* = 7.0 Hz, 2H), 3.72 (s, 3H), 3.45-3.09 (m, 2H), 2.56 (s, 3H), 2.32 (s, 3H), 2.20 (s, 3H), 1.91-1.79 (m, 2H), 1.79-1.61 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 153.7, 144.8, 139.5, 135.2, 129.4, 126.5, 122.7, 121.3, 49.4, 47.3, 35.1, 28.1, 21.3, 20.1, 14.9, 9.6; HRMS (ESI-TOF) (*m/z*) calcd for$C_{18}H_{27}N_4O_2S^+$ 363.1855, found 363.1874 $[M - CF_3SO_3]^+$.

1,2-Dimethyl-3-(4-((2-(1-(naphthalen-1-yl)ethylidene)hydrazinyl)sulfonyl)butyl)-1*H*-imidazol-3-ium trifluoromethanesulfonate (22d)



Yield 88%; white solid; mp 126−132 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.44 (s, 1H), 8.11-8.05 (m, 1H), 7.96 (d, *J* = 7.8 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.57-7.48 (m, 4H), 4.14 (t, *J* = 6.9 Hz, 2H), 3.71 (s, 3H), 3.30-3.23 (m, 2H), 2.54 (s, 3H), 2.39 (d, *J* = 17.9 Hz, 3H), 1.89-1.80 (m, 2H), 1.79-1.70 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 156.1, 144.8, 137.4, 133.8, 130.4, 129.4, 128.9, 127.1, 126.5, 126.3, 125.7, 125.6, 122.8, 121.3, 49.5, 47.3, 35.1, 28.2, 20.1, 19.8, 9.6; HRMS (ESI-TOF) (*m/z*): calcd for $C_{21}H_{27}N_4O_2S^+$ 399.1855, found 399.1830 $[M - CF_3SO_3]^+$.

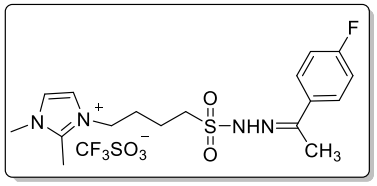
1,2-Dimethyl-3-(4-((2-(1-(naphthalen-2-yl)ethylidene)hydrazinyl)sulfonyl)butyl)-1*H*-imidazol-3-ium trifluoromethanesulfonate (22e)



Yield 86%; light yellow solid; mp 146−150 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.40 (s, 1H), 8.24 (s, 1H), 7.99 (d, *J* = 7.6 Hz, 2H), 7.91 (d, *J* = 7.1 Hz, 2H), 7.66-7.48 (m, 4H), 4.17 (t, *J* = 7.2 Hz, 2H), 3.70 (s, 3H), 3.38 (t, *J* = 7.2 Hz, 2H), 2.56 (s, 3H), 2.35 (s, 3H), 1.94-1.81 (m, 2H), 1.80-1.66 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ

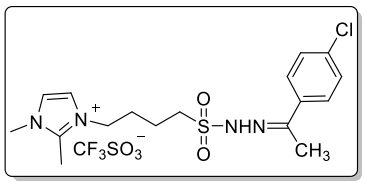
153.2, 144.8, 135.3, 133.7, 133.1, 129.0, 128.2, 128.0, 127.4, 127.0, 126.6, 123.8, 122.8, 121.3, 49.6, 47.3, 35.1, 28.1, 20.1, 14.7, 9.6; HRMS (ESI-TOF) (*m/z*) calcd for $C_{21}H_{27}N_4O_2S^+$ 399.1855, found 399.1844 $[M - CF_3SO_3]^+$.

3-(4-((2-(1-(4-Fluorophenyl)ethylidene)hydrazinyl)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (22f)



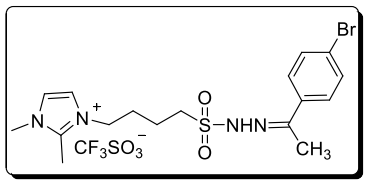
Yield 91%; white solid; mp 138−142 °C; ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 10.33 (s, 1H), 7.78 (dd, *J* = 8.5, 4.8 Hz, 2H), 7.62 (d, *J* = 3.0 Hz, 1H), 7.60 (d, *J* = 3.0 Hz, 1H), 7.24 (td, *J* = 9.0, 2.5 Hz, 2H), 4.15 (t, *J* = 7.5 Hz, 2H), 3.72 (s, 3H), 3.35-3.26 (m, 2H), 2.57 (s, 3H), 2.22 (s, 3H), 1.88-1.82 (m, 2H), 1.75-1.69 (m, 2H); ^{13}C NMR (125 MHz, DMSO-*d*$_6$) δ 152.6, 144.8, 134.5, 134.4, 128.8, 122.7, 121.3, 115.8, 49.5, 47.3, 35.1, 28.1, 20.1, 15.0, 9.6; HRMS (ESI-TOF) (*m/z*) calcd for $C_{17}H_{24}FN_4O_2S^+$ 367.1604, found 367.1635 $[M - CF_3SO_3]^+$.

3-(4-((2-(1-(4-Chlorophenyl)ethylidene)hydrazinyl)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (22g)



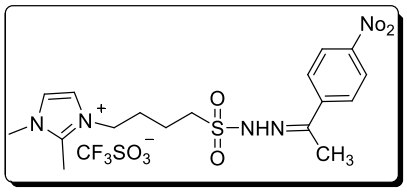
Yield 88%; white solid; mp 155−157 °C; ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 10.47 (s, 1H), 7.76 (d, *J* = 8.0 Hz, 2H), 7.65 (brs, 1H), 7.62 (brs, 1H), 7.46 (d, *J* = 9.0 Hz, 2H), 4.16 (t, *J* = 7.0 Hz, 2H), 3.74 (s, 3H), 3.36-3.29 (m, 2H), 2.58 (s, 3H), 2.23 (s, 3H), 1.92-1.84 (m, 2H), 1.80-1.70 (m, 2H); ^{13}C NMR (125 MHz, DMSO-*d*$_6$) δ 152.5, 144.8, 136.8, 134.5, 128.8, 128.4, 122.7, 121.3, 49.5, 47.3, 35.1, 28.1, 20.0, 14.9, 9.6; HRMS (ESI-TOF) (*m/z*) calcd for $C_{17}H_{24}ClN_4O_2S^+$ 383.1308, found 383.1332 $[M - CF_3SO_3]^+$.

3-(4-((2-(1-(4-Bromophenyl)ethylidene)hydrazinyl)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (22h)



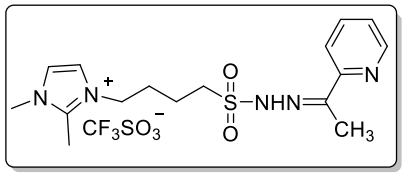
Yield 88%; white solid; mp 159−163 °C; ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 10.44 (s, 1H), 7.74-7.51 (m, 6H), 4.15 (t, *J* = 7.0 Hz, 2H), 3.72 (s, 3H), 3.37-3.22 (m, 2H), 2.57 (s, 3H), 2.22 (s, 3H), 1.90-1.78 (m, 2H), 1.78-1.65 (m, 2H); ^{13}C NMR (125 MHz, DMSO-*d*$_6$) δ 152.4, 144.8, 137.2, 131.8, 128.6, 123.3, 122.6, 121.3, 49.5, 47.3, 35.1, 28.1, 20.1, 14.8, 9.6; HRMS (ESI-TOF) (*m/z*) calcd for $C_{17}H_{24}BrN_4O_2S^+$ 427.0803, found 427.0800 $[M - CF_3SO_3]^+$.

3-(4-((2-(1-(4-Nitrophenyl)ethylidene)hydrazinyl)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (22i)



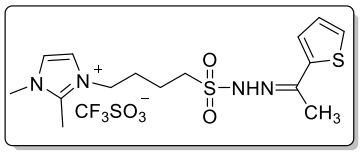
Yield 86%; white solid; mp 167−171 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.73 (s, 1H), 8.26 (d, J = 8.5 Hz, 2H), 8.02 (d, J = 8.5 Hz, 2H), 7.64 (d, J = 1.6 Hz, 1H), 7.62 (d, J = 1.7 Hz, 1H), 4.19 (t, J = 6.9 Hz, 2H), 3.76 (s, 3H), 3.44-3.32 (m, 2H), 2.60 (s, 2H), 2.31 (s, 3H), 1.94-1.83 (m, 2H), 1.82-1.75 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 150.8, 148.0, 144.8, 144.0, 127.7, 124.0, 122.7, 121.3, 49.8, 47.3, 35.1, 28.1, 20.1, 14.8, 9.6; HRMS (ESI-TOF) (*m/z*) calcd for $C_{17}H_{24}N_5O_4S^+$ 394.1549, found 394.1528 $[M - CF_3SO_3]^+$.

1,2-Dimethyl-3-(4-((2-(1-(pyridin-2-yl)ethylidene)hydrazinyl)sulfonyl)butyl)-1*H*-imidazol-3-ium trifluoromethanesulfonate (22j)



Yield 92%; black solid; mp 105−111 °C; ^{1}H NMR (500 MHz DMSO-d_6) δ 10.66 (s, 1H), 8.63 (d, J = 4.5 Hz, 1H), 8.00 (d, J = 9.0 Hz, 1H), 7.90 (td, J = 9, 2.5 Hz, 1H), 7.64 (d, J = 2.0 Hz, 1H), 7.61 (d, J = 2.0 Hz, 1H), 7.47 (dd, J = 7.0, 5.0 Hz, 1H), 4.17 (t, J = 7.1 Hz, 2H), 3.74 (s, 3H), 3.51-3.30 (m, 2H), 2.58 (s, 3H), 2.33 (s, 3H), 1.96-1.83 (m, 2H), 1.78-1.73 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.5, 153.0, 148.7, 144.8, 137.8, 124.8, 122.7, 121.3, 120.9, 49.8, 47.3, 35.1, 28.1, 20.1, 13.3, 9.6; HRMS (ESI-TOF) (*m/z*) calcd for $C_{16}H_{24}N_5O_2S^+$ 350.1651, found 350.1637 $[M - CF_3SO_3]^+$.

1,2-Dimethyl-3-(4-((2-(1-(thiophen-2-yl)ethylidene)hydrazinyl)sulfonyl)butyl)-1*H*-imidazol-3-ium trifluoromethanesulfonate (22k)



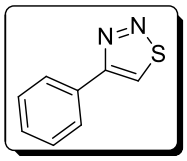
Yield 94%; yellow color solid; mp 121−134 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.33 (s, 1H), 7.62 (d, J = 2.0 Hz, 1H), 7.59 (d, J = 2.0 Hz, 1H), 7.55 (dd, J = 5.0, 1.0 Hz, 1H), 7.46-7.42 (m, 1H), 7.08-7.04 (m, 1H), 4.14 (t, J = 7.5 Hz, 2H), 3.71 (s, 3H), 3.26 (td, J = 7.5, 2.1 Hz, 2H), 2.56 (s, 3H), 2.25 (s, 3H), 1.91-1.79 (m, 2H), 1.79-1.66 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 150.3, 144.8, 142.8, 129.1, 128.3, 128.1, 122.8, 121.3, 49.6, 47.3, 35.1, 28.2, 20.1, 15.2, 9.6; HRMS (ESI-TOF) (*m/z*) calcd for $C_{15}H_{23}N_4O_2S_2^+$ 355.1262, found 355.1251 $[M - CF_3SO_3]^+$.

General procedure for synthesis of 1,2,3-thiadiazoles (5a-k)

To a 25ml round bottom flask containing ionic liquid-supported hydrazone (**22**, 1 mmol) added thionyl chloride (5 mmol) dropwise at room temperature and the reaction mixture was heated slowly to 60 °C for 4 h. Progress of the reaction was monitored by thin-layer chromatography

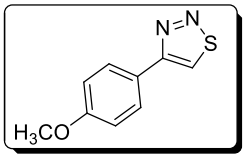
(TLC). After completion of the reaction, the reaction mixture was neutralized by sodium bicarbonate solution. The product was extracted using ethyl acetate/hexane (3: 2 v/v, 3 × 5 mL), dried over sodium sulfate, and evaporated under reduced pressure to obtain pure compound (**5**).

4-Phenyl-1,2,3-thiadiazole (5a)



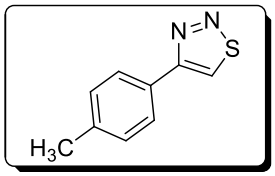
Yield 91%; white solid; mp 77−78 °C (lit[49] 75–77 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.05 (d, J = 7.8 Hz, 2H), 7.51 (t, J = 7.7 Hz, 2H), 7.45 (t, J = 7.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 147.5, 136.6, 136.3, 128.1, 124.4; HRMS (ESI-TOF) (*m/z*) calcd for $C_8H_7N_2S^+$ 163.0330, found 163.0321 $[M + H]^+$.

4-(4-Methoxyphenyl)-1,2,3-thiadiazole (5b)



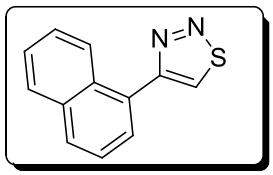
Yield 86%; white solid; mp 87−91°C (lit[49] 91–93.5 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.99 (d, J = 7.9 Hz, 2H), 7.04 (d, J = 8.8 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.7, 160.5, 128.8, 128.4, 123.6, 114.6, 55.5; HRMS (ESI-TOF) (*m/z*) calcd for $C_9H_9N_2OS^+$ 193.0436, found 193.0423 [M + H].

4-*p*-Tolyl-1, 2, 3-thiadiazole (5c)



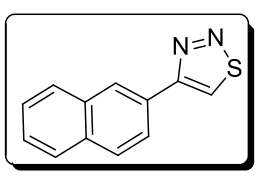
Yield 87%; white solid; mp 73−76 °C (lit[49] 74–76 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.94 (d, J = 7.7 Hz, 2H), 7.32 (d, J = 7.8 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0, 139.5, 129.8, 129.2, 128.0, 127.3, 21.3; HRMS (ESI-TOF) (*m/z*) calcd for $C_9H_9N_2S^+$ 177.0486, found 177.0458 $[M + H]^+$.

4-(Naphthalen-1-yl)–1, 2, 3-thiadiazole (5d)



Yield 87%; white solid; mp 197−201 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.09 (d, J = 7.8 Hz, 1H), 7.99 (d, J = 8.2 Hz, 1H), 7.95 (d, J = 7.4 Hz, 1H), 7.77 (dd, J = 7.1, 1.0 Hz, 1H), 7.63−7.49 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9, 133.2, 133.1, 132.8, 130.4, 129.0, 127.5, 127.4, 126.0, 125.2, 124.2, 124.1; HRMS (ESI-TOF) (*m/z*) calcd for $C_{12}H_9N_2S^+$ 213.0486, found 213.0474 $[M + H]^+$.

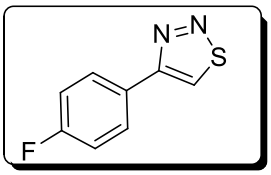
4-(Naphthalen-2-yl)–1, 2, 3-thiadiazole (5e)



Yield 88%; white solid; mp 203−207 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.61 (s, 1H), 8.11 (dd, J = 8.4, 1.3 Hz, 1H), 8.01-7.93 (m,

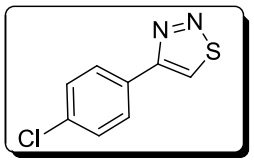
2H), 7.91-7.88 (m, 1H), 7.67-7.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9, 133.7, 133.5, 130.1, 130.0, 129.0, 128.5, 128.1, 127.8, 126.9, 126.9, 124.7; HRMS (ESI-TOF) (*m/z*) calcd for $C_{12}H_9N_2S^+$ 213.0486, found 213.0455 $[M + H]^+$.

4-(4-Fluorophenyl)-1,2,3-thiadiazole (5f)



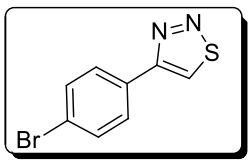
Yield 89%; white solid; mp 185−189 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.11-7.97 (m, 2H), 7.26-7.17 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4, 162.4, 129.7, 129.3, 127.0, 116.4; HRMS (ESI-TOF) (*m/z*) calcd for $C_8H_6FN_2S^+$ 181.0236, found 181.0220 $[M + H]^+$.

4-(4-Chlorophenyl)-1,2,3-thiadiazole (5g)



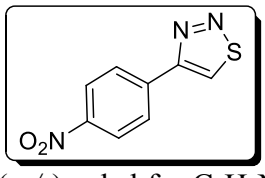
Yield 88%; white solid; mp 138−140 °C (lit[49] 136–137.5 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.99 (d, J = 7.8 Hz, 2H), 7.48 (d, J = 7.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.7, 135.4, 130.2, 129.4, 129.37, 128.6; HRMS (ESI-TOF) (*m/z*) calcd for $C_8H_6ClN_2S^+$ 196.9935, found 196.9905 $[M + H]^+$.

4-(4-Bromophenyl)-1,2,3-thiadiazole (5h)



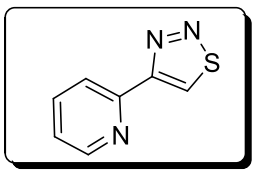
Yield 90%; white solid; mp 150−154 °C (lit[44] 150–152 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.40 (s, 1H), 7.93 (d, J = 8.5 Hz, 2H), 7.64 (d, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0, 133.9, 131.4, 130.0, 128.6, 125.1; HRMS (ESI-TOF) (*m/z*) calcd for $C_8H_6BrN_2S^+$ 240.9435, found 240.9434 $[M + H]^+$ and 242.9587 $[M + H + 2]^+$.

4-(4-Nitrophenyl)-1,2,3-thiadiazole (5i)



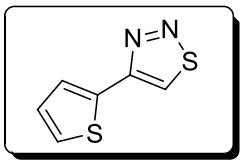
Yield 83%; white solid; mp 207−211 °C (lit[49] 183 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.53-8.25 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.6, 147.5, 136.6, 136.3, 128.1, 124.4; HRMS (ESI-TOF) (*m/z*) calcd for $C_8H_6N_3O_2S^+$ 208.0181, found 208.0166 $[M + H]^+$.

(4-Pyridin-2-yl)-1,2,3-thiadiazole (5j)



Yield 80%; white solid; mp 158−161 °C (lit[50] 163 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.69 (d, J = 4.7 Hz, 1H), 8.48 (d, J = 7.9 Hz, 1H), 7.92-7.85 (m, 1H), 7.35 (t, J = 6.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3, 149.9, 149.8, 137.4, 133.9, 123.9, 122.4; HRMS (ESI-TOF) (*m/z*) calcd for $C_7H_6N_3S^+$ 164.0282, found 164.0269 $[M + H]^+$.

(4-Thiophen-2-yl)-1,2,3-thiadiazole (5k)

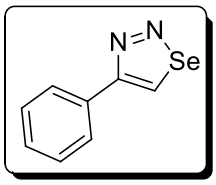


Yield 88%; white solid; mp 72−74 °C (lit[51] 70–71 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.64 (dd, J = 3.6, 1.2 Hz, 1H), 7.43 (m, 2H), 7.14 (dd, J = 4.8, 1.4 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.2, 139.0, 135.8, 128.6, 127.5, 126.8, HRMS (ESI-TOF) (m/z) calcd for $C_6H_5N_2S_2^+$ 168.9889, found 168.9875 $[M + H]^+$.

General procedure for synthesis of selenadiazoles (6a-f)

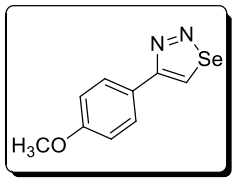
Ionic liquid-supported hydrazone (**22**, 1 mmol), selenium dioxide (1.05 mmol), and sodium sulfate (1.50 mmol) were mixed in acetonitrile (6 mL) and vigorously stirred at room temperature for 24 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the residue was purified using toluene as a mobile phase to obtain pure product **6a-f**.

4-Phenyl-1,2,3-selenadiazole (6a)



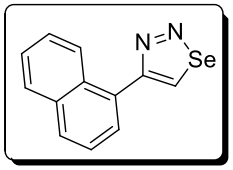
Yield 30%; yellow solid; mp 70−71 °C (lit[39] 76 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.06 (d, J = 7.8 Hz, 2H), 7.51 (t, J = 7.6 Hz, 2H), 7.43 (t, J = 7.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9, 137.0, 132.1, 129.1, 127.7; HRMS (ESI-TOF) (m/z) calcd for $C_8H_7N_2Se^+$ 210.9774, found 210.9753 $[M + H]^+$.

4-(4-Methoxyphenyl)-1,2,3- selenadiazole (6b)



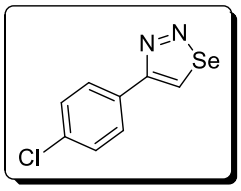
Yield 22%; yellow solid; mp 85−89 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.00 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.8, 160.1, 135.1, 129.1, 124.9, 114.6, 55.3; HRMS (ESI-TOF) (m/z) calcd for $C_9H_9N_2OSe^+$ 240.9875, found 240.9843 $[M + H]^+$.

4-(Naphthalen-1-yl)-1,2,3-selenadiazole (6c)



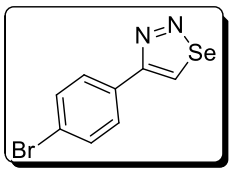
Yield 25%; black solid; mp 134−136 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.52 (s, 1H), 8.63 (s, 1H), 8.11 (d, J = 8.5 Hz, 1H), 8.02−7.94 (m, 2H), 7.89 (d, J = 8.2 Hz, 1H), 7.58-7.48 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 137.1, 133.6, 133.4, 129.3, 128.94, 128.5, 127.8, 127.2, 126.8, 126.7, 125.1; HRMS (ESI-TOF) (m/z) calcd for $C_{12}H_9N_2Se^+$ 260.9931, found 260.9902 $[M + H]^+$.

4-(4-Chlorophenyl)-1,2,3- selenadiazole (6d)



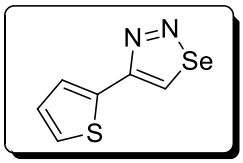
Yield 30%; black solid; mp 118−125 °C (lit[50] 154 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.39 (s, 1H), 8.00 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7, 136.2, 133.8, 129.5, 128.4, 127.9; HRMS (ESI-TOF) (*m/z*):Calcd for $C_8H_6ClN_2Se^+$ 244.9385, found 244.9386 $[M + H]^+$.

4-(4-Bromophenyl)-1,2,3-selenadiazole (6e)



Yield 40%; solid; mp 128−133 °C (lit[50] 177 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.40 (s, 1H), 7.93 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 137.3, 132.4, 131.0, 129.2, 123.0; HRMS (ESI-TOF) (*m/z*) calcd for $C_8H_6BrN_2Se^+$ 288.8880, found 288.8876 $[M + H]^+$ and 290.8872 $[M + H + 2]^+$.

(4-Thiophen-2-yl)-1,2,3-selenadiazole (6f)



Yield 32%; vicous liquid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.03 (s, 1H), 7.80-7.75 (m, 1H), 7.66 (dd, J = 5.1, 1.2 Hz, 1H), 7.20 (ddd, J = 5.2, 3.6, 1.6 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 138.9, 136.5, 134.8, 128.6, 127.5, 126.8; HRMS (ESI-TOF) (*m/z*) calcd for $C_6H_5N_2SSe^+$ 216.9333, found 216.9302 $[M + H]^+$.

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Chapter II

PART B

Ionic Liquid-supported Sulfonyl Hydrazine: Synthesis of Pyrazoles

2.7 Introduction

Pyrazole is a popular synthetic target for pharmaceutical, material and agrochemical industries.[1, 2] Pyrazole constitutes the basic framework of several drug molecules. Numerous compounds containing pyrazole moiety are known to exhibit versatile biological activities such as analgesic,[3] antimicrobial,[4] anti-convulsant,[5] antidepressant,[6] anti-inflammatory,[7, 8] anti-arthritics,[9] cannabinoid-1 (CB1) receptor antagonists,[10-12] Iκβ kinase β (IKKβ or IKK-2) inhibition[13] and HIV-1 reverse transcriptase inhibition.[14] Example of some important pyrazole-containing drugs includes Celecoxib (selective COX-2 inhibition, **a**), Zaleplon (insomnia, **b**), Zoniporide (selective human NHE-1 inhibition, **c**), Sildenafil (erectile dysfunction, **d**), and Acomplia (selective CB1 receptor blocker, **e**) are depicted in figure 2.8.

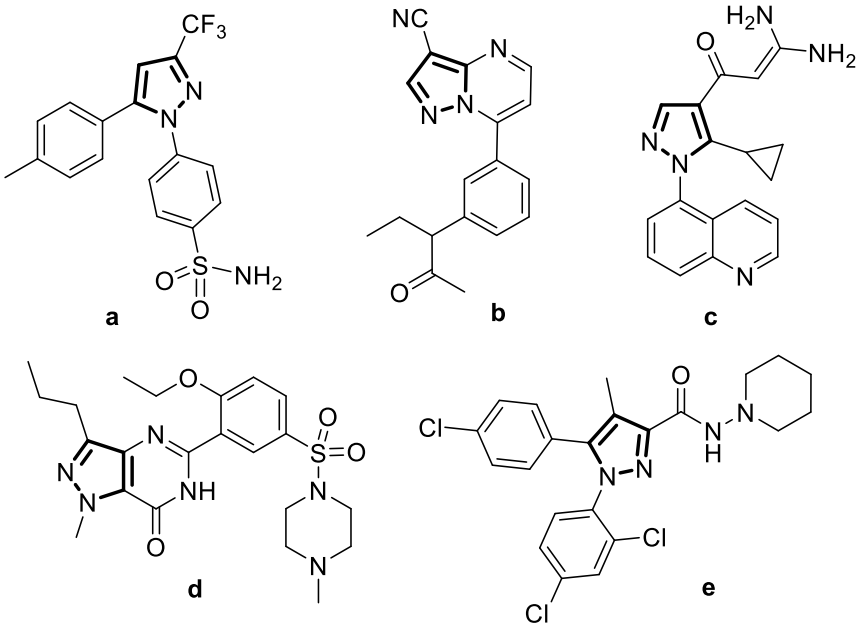
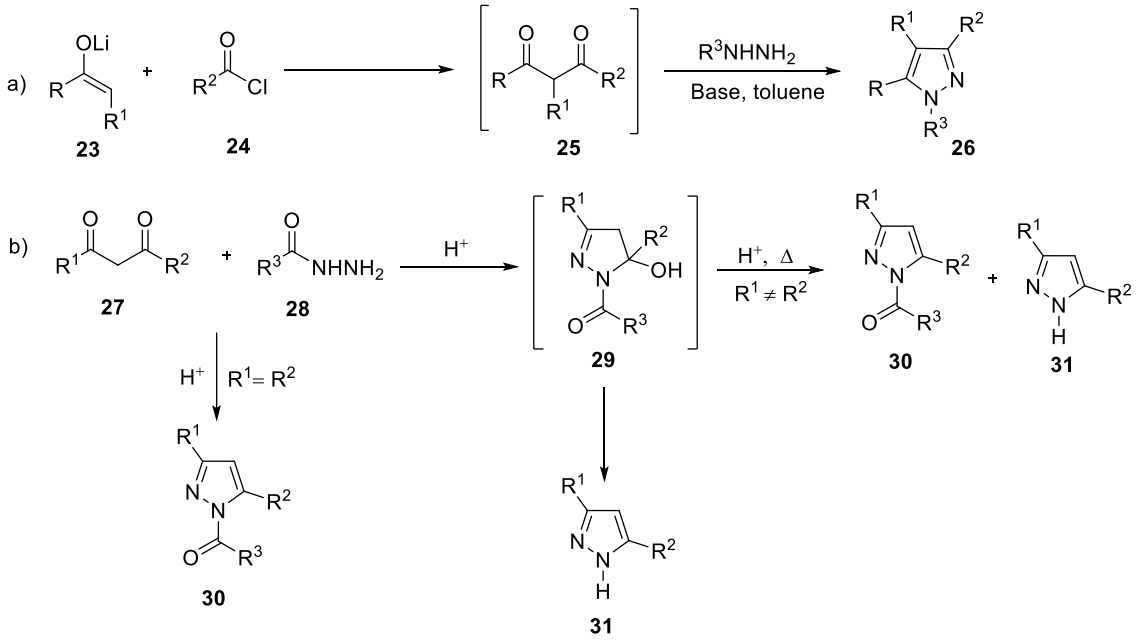


Figure 2.8: Structure of some drugs containing pyrazole ring

Owing to the attractive biological properties of pyrazoles, considerable attention has been focused on developing methods for the preparation of diversely substituted pyrazoles.[15-30]

Literature reports for synthesis of substituted pyrazoles

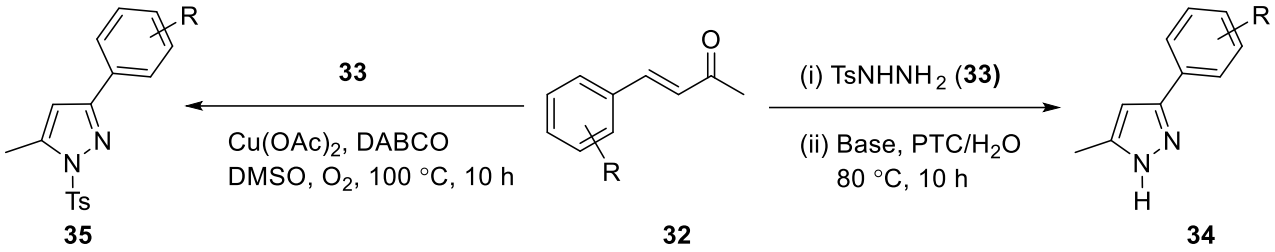
Heller and coworkers have developed synthesis of substituted pyrazoles (**26**) by the reaction of acid chloride (**24**) and lithium enolate (**23**) followed by cyclization using hydrazine in the presence of a base in toluene[31] (Scheme 2.10a). Wang group reported synthesis of pyrazole derivatives **30** and **31** by the condensation reaction of 1,3-dicarbonyl compound (**27**) and acyl hydrazide (**28**) at room temperature under solvent-free condition using H_2SO_4 as catalyst (Scheme 2.10b).[32] When an unsymmetrical diketone **27** was reacted with hydrazide in the presence of catalytic amount of H_2SO_4, the intermediate **29** could be dehydrated and deacylated to form pyrazoles **31** as a single product or a mixture with the *N*-acylated product (**30**). Formation of two mixture of **30** and **31** by the condensation of 1,3-diketones (**27**) with acyl hydrazide (**28**) or arylhydrazines was an inevitable drawback of this method.



Scheme 2.10: Synthesis of pyrazole (a) from acid chloride; (b) condensation of a 1,3-diketone and a hydrazide

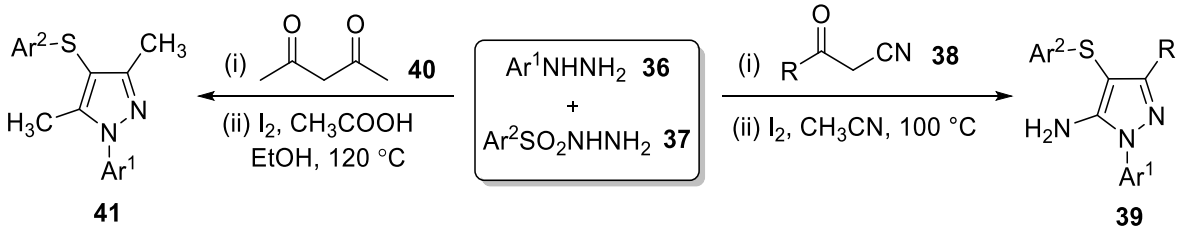
Yu group illustrated a simple, practical, ecofriendly and one-pot synthesis of **34** by the condensation reaction of *α,β*-unsaturated carbonyl compound (**32**) with tosyl hydrazine (**33**) in water as a reaction media (Scheme 2.11).[33] Aryl substitutes of *α,β*-unsaturated carbonyl compound **32** having different electron-withdrawing and electron-donating groups were well tolerated to yield corresponding pyrazoles **34** in good to excellent yields. When the same

reaction condition was applied on chalcone, the expected product was obtained in low yield. Another approach for the synthesis of pyrazole **35** have been reported by Jiang group.[34] In this method synthesis of pyrazoles was achieved by the reaction of tosyl hydrazine with *α,β*-unsaturated carbonyl compounds **32** under copper catalysis. The reaction involves direct aerobic oxidative C-H bond functionalized followed by C-N bond formation (Scheme 2.11).



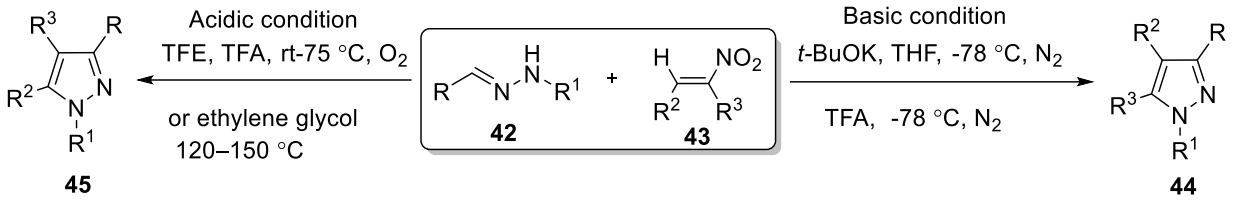
Scheme 2.11: One-pot synthesis of pyrazole from *α,β*-unsaturated carbonyl compound

Guo and colleagues[35] synthesized substituted pyrazole by using *β*-ketonitrile (**38**) or acetylacetone (**40**), arylhydrazines (**36**), and aryl sulfonyl hydrazides (**37**) by the [3+2] annulation in the presence of iodine as a catalyst as shown in scheme 2.12. This protocol afforded good yields of pyrazoles **39** and **41** through the formation of one C−S and two C−N bonds.



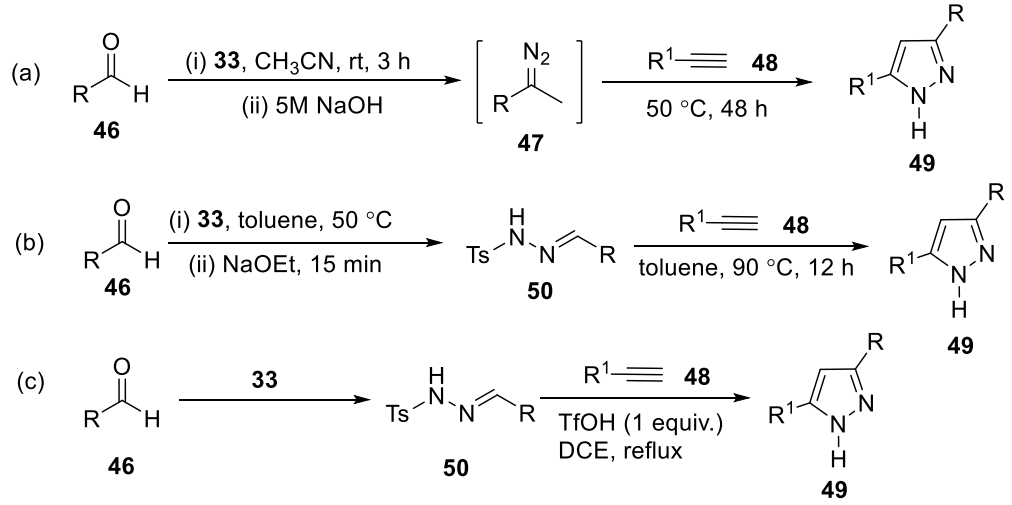
Scheme 2.12: I_2-catalyzed synthesis of substituted pyrazoles

Nitroolefins are known to be useful synthons for the synthesis of pyrazole and heterocyclic compounds. Deng group have demonstrated regioselective one-pot synthesis of substituted pyrazoles **44** and **45** in acidic and basic conditions (Scheme 2.13). In the case of acidic condition, the reaction of *N*-arylhydrazone (**42**) with nitroolefin (**43**) afforded pyrazole **45**, while in basic condition, the reverse regioselectively pyrazole **44** was formed. This protocol is useful to generate a diverse library of pyrazole products in 30-85% yields. [19-21]



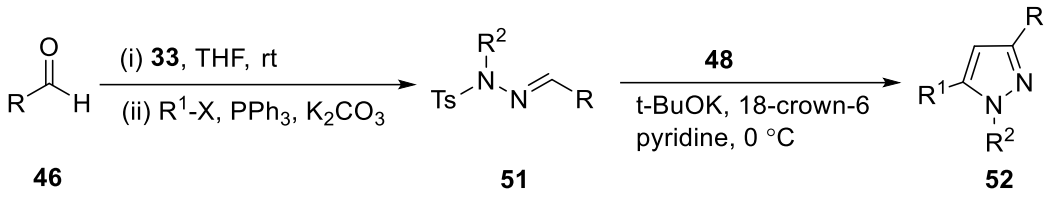
Scheme 2.13: Synthesis of 1,3,4,5-tetrasubstituted pyrazoles from nitroolefins

Handling of reactive 1,3-dipolar compounds limits the synthetic utility of the above method. With the aim to solve the handling problem in diazo compounds, Aggarwal *et al.* reported a one-pot method for the preparation of **49** by 1,3-dipolar cycloaddition of diazo compounds (**47**) generated *in-situ* from tosyl hydrazone of aldehydes (**46**) in the presence of base.[36] Diazo compounds (**47**) reacted regioselectively with monosubstituted alkynes **48** (Scheme 2.14a). In 2012, Wu *et al.*[37] also developed one pot three-component synthesis of 3,5-disubstituted pyrazoles (**49**) by the condensation reaction of aldehydes (**46**) with tosyl hydrazine **33** followed by cycloaddition with terminal alkynes **48** in toluene (Scheme 2.14b). In the same year, Lin group[38] have employed a complementary method for the synthesis of 3,5-disubstituted pyrazoles **32** by triflic acid mediated reaction of aldehydes **46** with tosylhydrazine **33** followed by **50** (Scheme 2.14c). The investigations of substitution effect on **48** have also been established for the reaction and it was found that the electron-rich groups on alkyne were not suitable, electron poor alkynes and alkyl substituted alkynes gave slightly low yields but carboxylate group on the alkyne failed to give target molecule.



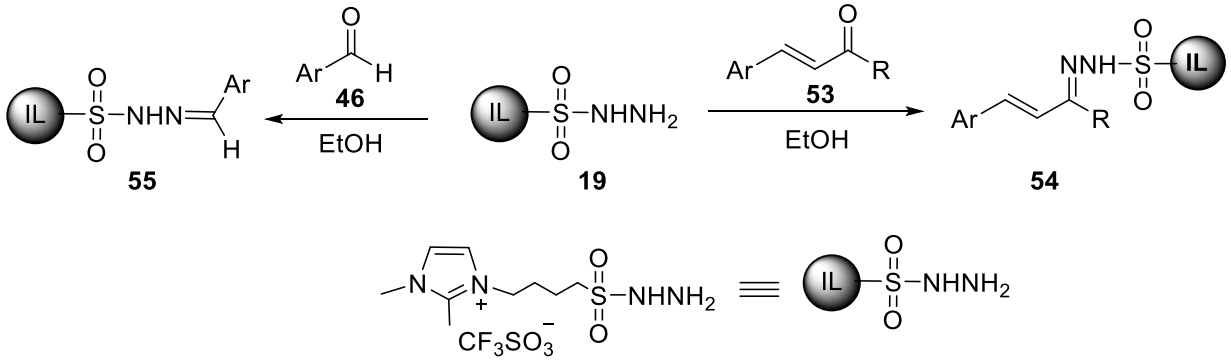
Scheme 2.14: Synthesis of 3,5-disubstituted pyrazole from alkynes

Tang group[39] applied this protocol for the synthesis of 1,3,5-trisubstituted-1*H*-pyrazoles (**34**) from *N*-alkylated tosyl hydrazones (**51**) to increase the range of substrates and demonstrated excellent tolerance to a variety of substituents, including both electron-donating and electron-withdrawing groups (Scheme 2.15). This approach solved some of the traditional problems inherent with the [3+2]-cycloaddition of diazo compounds with alkynes **48** for the synthesis of pyrazoles **52**. However, purification of pyrazoles from the co-product *p*-toluenesulfinic acid remains a challenge and requires extensive chromatographic separation.



Scheme 2.15: Regioselective synthesis of 1,3,5-trisubstituted pyrazoles

We envisioned that the use of ionic liquid-supported sulfonyl hydrazine (**19**) could solve the problem of separation in the synthesis of pyrazoles **32** and thus designed two routes to synthesize pyrazoles **32** using ionic liquid-supported sulfonyl hydrazine **24** as a soluble support (Scheme 2.16).The first one by the condensation of *α,β*-unsaturated carbonyl compounds (**35**) to **24** followed by cyclization in the presence of a base and the second one by the 1,3-dipolar cycloaddition of alkynes with **36** and **37**, that were obtained by reacting ionic liquid-supported sulfonyl hydrazine (**24**) with the corresponding aldehydes.



Scheme 2.16: Synthesis of ionic liquid-supported sulfonyl hydrazones (**54** and **55**)

2.8 Results and Discussion

Our investigations commenced with the synthesis of **54** and **55** by the reaction of ionic liquid-supported sulfonyl hydrazine (**19**) with *α,β*-unsaturated carbonyl compounds **53** and aryl aldehydes **46**, respectively (Scheme 2.16). The reaction procedure reported in part A was adopted for this reaction. For example, reaction of **19** with 1-phenylbut-2-en-1-one (**53a**) in ethanol for 5 h at 40 °C followed by evaporation of ethanol, washing of ionic liquid layer with ethyl acetate/hexane mixture (1:1 *v/v*) and drying under vacuum gave the **54a** in excellent yield (86%) with high purity. The structure and purity of ionic liquid-supported hydrazones **54a** were confirmed by ^{1}H and ^{13}C NMR data. In ^{1}H NMR of **54a** characteristic peak for CH_3-C=N proton appeared at δ 2.08 ppm as singlet and C=N carbon appeared at around δ 154.49 ppm in the ^{13}C NMR spectra (Figure 2.9). Similarly, ^{1}H and ^{13}C NMR of **54a and 55a** is given in figure 2.9.

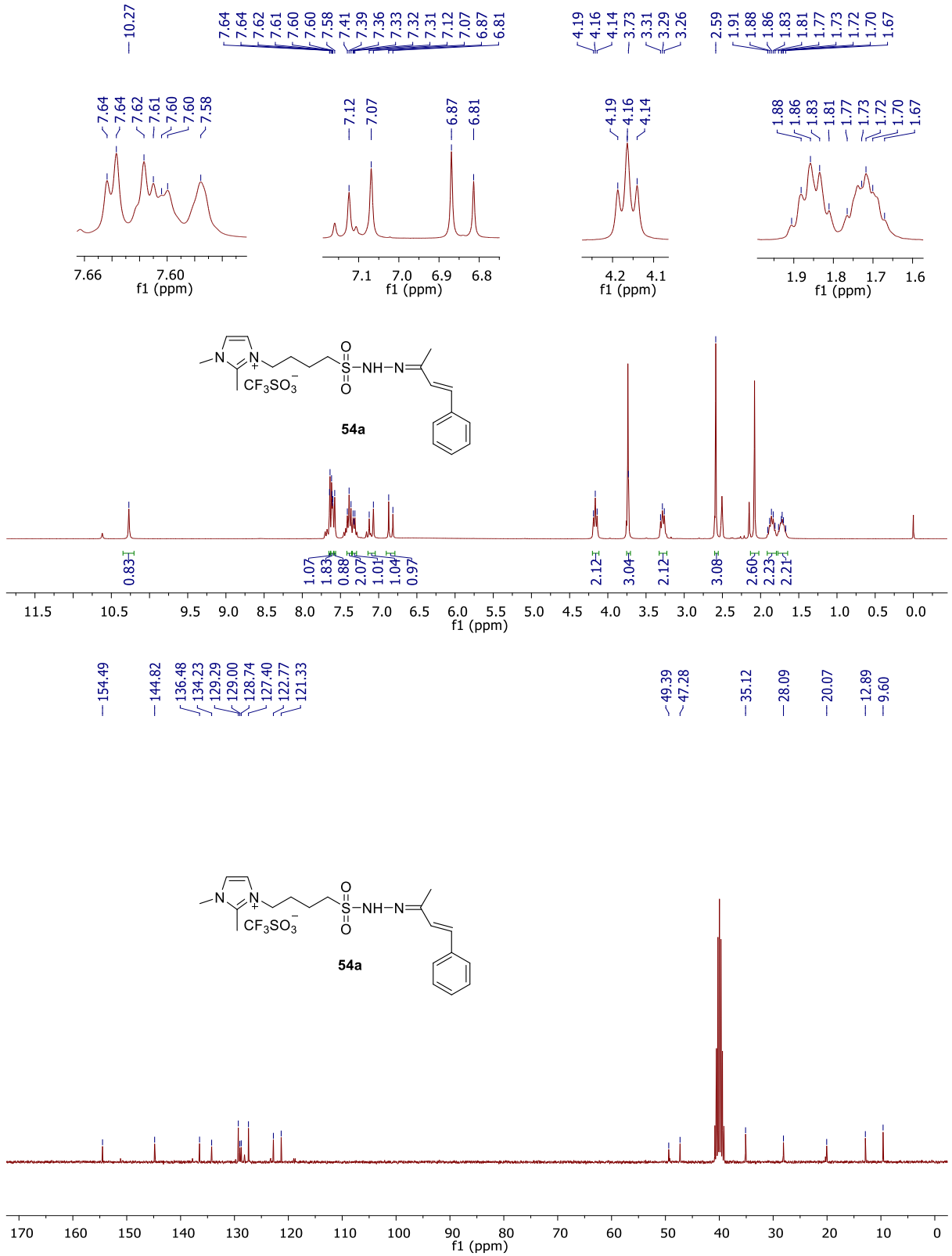


Figure 2.9: ^{1}H and ^{13}C NMR spectrum of **54a**

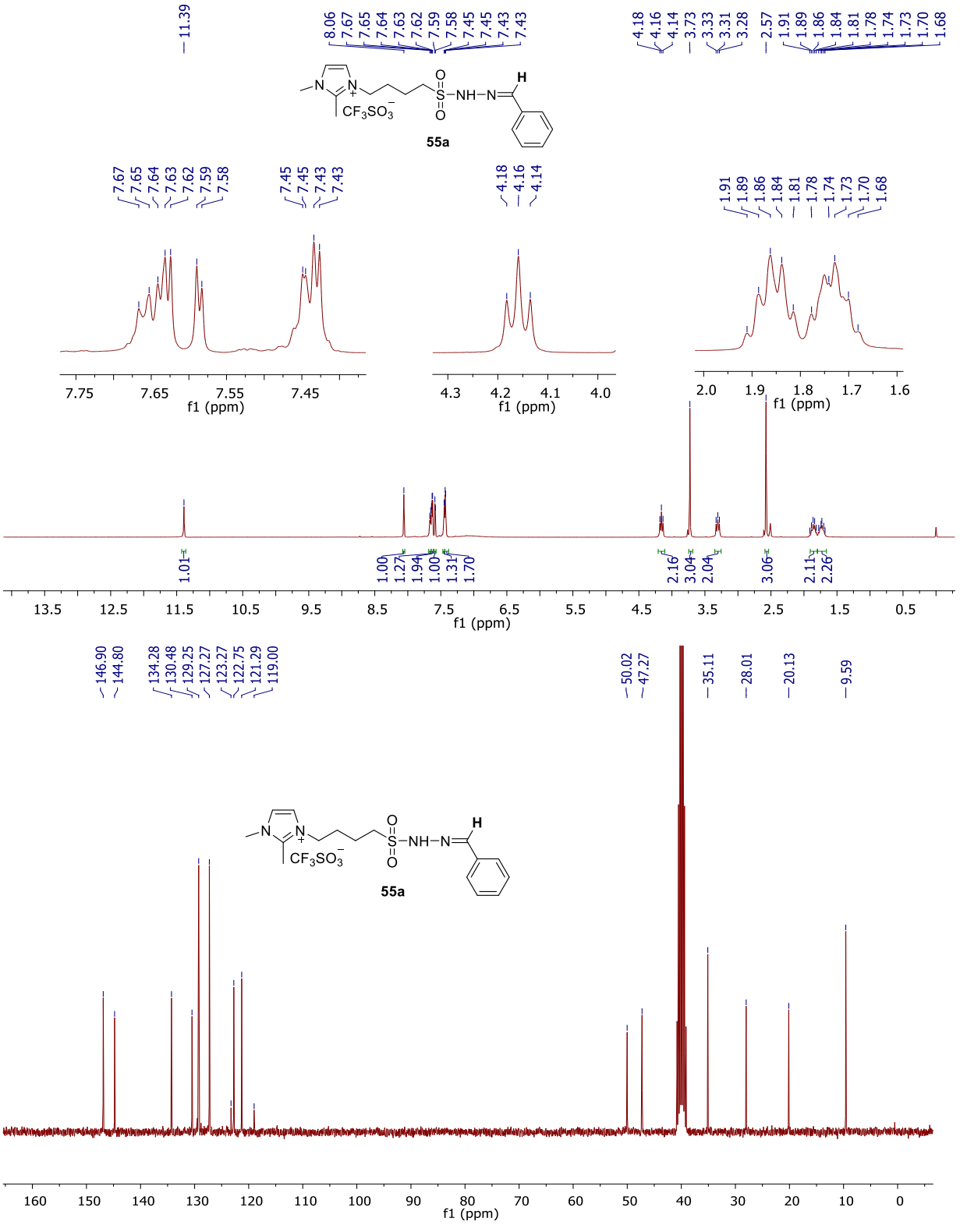
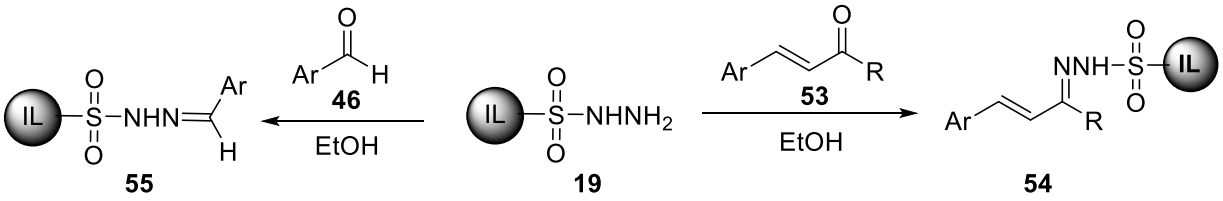


Figure 2.9: ^{1}H and ^{13}C NMR spectrum of **55a**

As can be seen from table 2.4, the reaction has wide substrate scope. The reaction of **19** with **46** or **54** bearing both electron-withdrawing and electron-donating substituents resulted in corresponding ionic liquid-supported sulfonyl hydrazones in good to excellent yields (54-92%). The ^{1}H and ^{13}C NMR spectra of all the ionic liquid-supported sulfonyl hydrazones (**54a-n** & **55a-g**) were in agreement with the structure.

Table 2.4: Preparation of ionic liquid-supported sulfonyl hydrazone **54** and **55**[a]



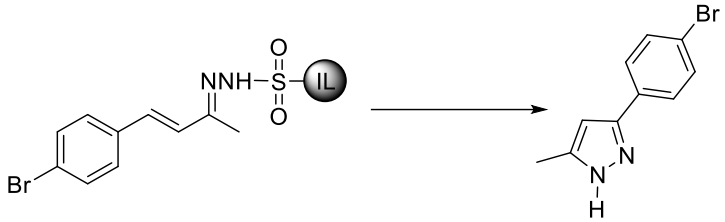
Entry	Ar	R	Product	Yield[b] (%)
1	C_6H_5	CH_3	**54a**	86
2	2-FC_6H_4	CH_3	**54b**	83
3	2-ClC_6H_4	CH_3	**54c**	81
4	3-ClC_6H_4	CH_3	**54d**	84
5	3-$NO_2C_6H_4$	CH_3	**54e**	79
6	4-ClC_6H_4	CH_3	**54f**	74
7	4-BrC_6H_4	CH_3	**54g**	87
8	2,6-$(Cl)_2C_6H_3$	CH_3	**54h**	80
9	3-$OCH_3C_6H_4$	CH_3	**54i**	54
10	4-$CH_3C_6H_4$	CH_3	**54j**	67
11	4-$OCH_3C_6H_4$	CH_3	**54k**	92
12	3,4-$(OCH_3)_2C_6H_3$	CH_3	**54l**	71
13	C_4H_3S	CH_3	**54m**	89
14	C_4H_3O	CH_3	**54n**	88
15	C_6H_5	H	**54o**	59
16	C_6H_5	-	**55a**	88
17	3-ClC_6H_4	-	**55b**	76
18	4-ClC_6H_4	-	**55c**	72
19	4-BrC_6H_4	-	**55d**	79

20	2,6-$(Cl)_2C_6H_3$	-	**55e**	77
21	4-$CH_3C_6H_4$	-	**55f**	89
22	C_4H_3S	-	**55g**	88

[a]Reaction conditions: **19** (1 mmol), **46** or **53** (1.1 mmol), EtOH (10 mL), 40 °C for 5 h
[b]Isolated yield

In an initial experiment for the synthesis of pyrazoles, we performed the cyclization of **54g** in the presence of K_2CO_3 at 100 °C in water. The reaction afforded **56g** in 72% yield after 24 h. After screening various bases including K_2CO_3, Cs_2CO_3 and NaOH, we found that the best yield of **56g** was achieved by employing 3N NaOH at 100 °C.

Table 2.5: Optimization of reaction conditions for the synthesis of **56g** from **54g**



54g **56g**

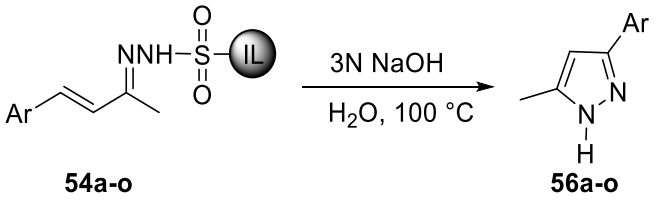
Entry	Base	Solvent	T (°C)	Yield[a](%)
1	NaOH (1 N)	Water	100 °C	71
2	NaOH (2 N)	Water	100 °C	76
3	KOH (2 N)	Water	100 °C	66
4	NaOH (3 N)	Water	30 °C	-[b]
5	**NaOH (3 N)**	**Water**	**100 °C**	**88**
6	NaOH (3 N)	DMSO	150 °C	47
7	NaOH (3 N)	DMF	150 °C	85
8	NaOH (3 N)	CH_3CN	80 °C	52
9	NaOH (3 N)	CH_3OH	60 °C	30
10	NaOH (5 N)	Water	100 °C	85
11	K_2CO_3 (1eq)	Water	100 °C	72
12	K_2CO_3 (2eq)	Water	100 °C	67
13	CS_2CO_3 (5eq)	Water	100 °C	87
14	CS_2CO_3 (3eq)	Water	100 °C	54

[a]Isolated yields. [b]No product isolated.

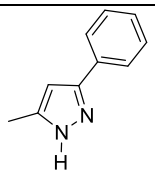
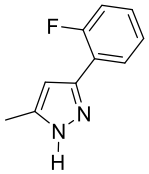
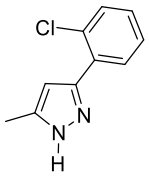
With the optimized conditions in hand, we next investigated the scope and generality of the cyclization, and the results are summarized in table 2.5. Various electron-withdrawing and electron-donating groups on aryl ring of ionic liquid-supported sulfonyl hydrazones **54** were well tolerated in this reaction. It was observed that compound **54** with electron-withdrawing groups

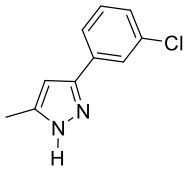
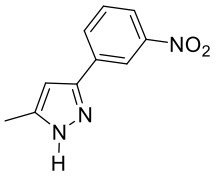
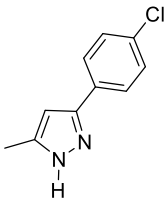
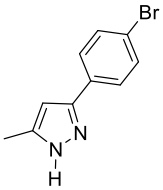
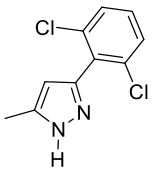
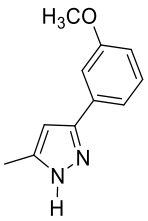
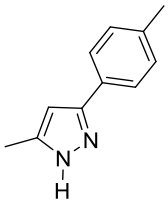
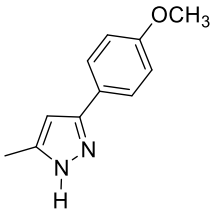
(Table 2.6, entries 1-4 and 6-8) furnished the target pyrazoles in slightly better yields compared to electron-donating groups (Table 2.6, entries 9-12). Remarkably, thiophene and furan-substituted pyrazoles **56m** & **56n** could also be obtained under given conditions in good to moderate yields (Table 2.6, entries 13, 14). Ionic liquid-supported sulfonyl hydrazone of cinnamaldehyde **54o** resulted corresponding pyrazole **56o** in moderate yield (Table 2.6, entry 15). In all cases the product was isolated by simple extraction with ethyl acetate/hexane mixture (1: 1 *v/v*). It is worthy to mention that the pyrazoles (**56**) were highly pure and no further chromatographic purification was required. The chemical structures of **56** were determined by ^{1}H and ^{13}C NMR (figure 2.10). In the ^{1}H NMR spectra of **56,** a characteristic singlet peak appeared around δ 6.3 ppm for C_4-protons of the pyrazole ring along with other protons and the corresponding C_4-carbon of the pyrazole ring appeared around δ 102 ppm in the ^{13}C NMR spectra. However, signals for quaternary C_3- and C_5-carbons of some 3,5-disubsituted pyrazoles could not be observed due to their longer relaxation time, that could be a consequence of the neighboring nitrogen atoms present in the highly conjugated pyrazole ring.

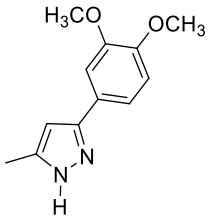
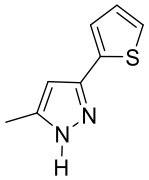
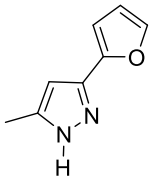
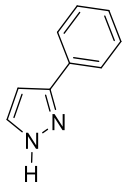
Table 2.6: Synthesis of 3,5-disubstituted pyrazoles **56** from **54**[a]



54a-o **56a-o**

Entry	Ar	R	Product		Yield[b] (%)
1	C_6H_5	CH_3		**56a**	70
2	2-FC_6H_4	CH_3		**56b**	77
3	2-ClC_6H_4	CH_3		**56c**	70

4	3-ClC_6H_4	CH_3		**56d**	76
5	3-$NO_2C_6H_4$	CH_3		**56e**	33
6	4-ClC_6H_4	CH_3		**56f**	83
7	4-BrC_6H_4	CH_3		**56g**	85
8	2,6-$(Cl)_2C_6H_3$	CH_3		**56h**	93
9	3-$OCH_3C_6H_4$	CH_3		**56i**	57
10	4-$CH_3C_6H_4$	CH_3		**56j**	62
11	4-$OCH_3C_6H_4$	CH_3		**56k**	60

12	3,4-$(OCH_3)_2C_6H_3$	CH_3		**56l**	27
13	C_4H_3S	CH_3		**56m**	80
14	C_4H_3O	CH_3		**56n**	57
15	C_6H_5	H		**56o**	65

[a]Reaction conditions: **54** (1 mmol), 3 N NaOH (2 mL), 100 °C for 24 h; [b]Isolated yield

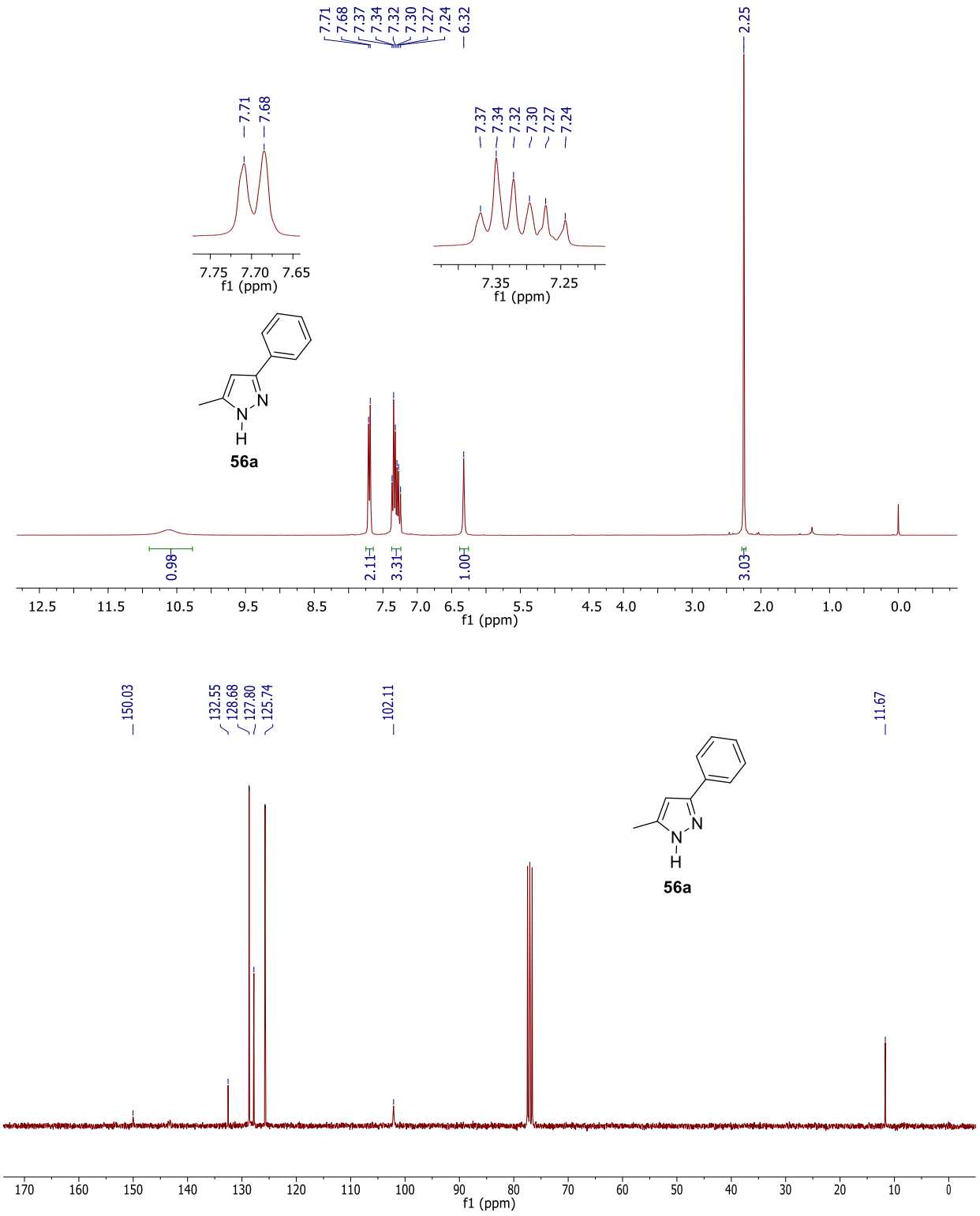
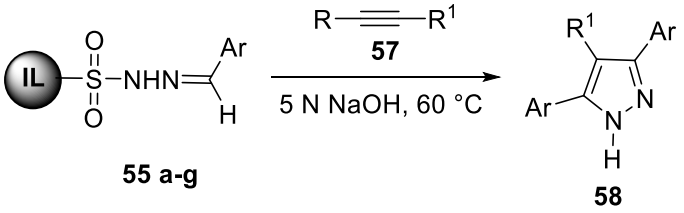


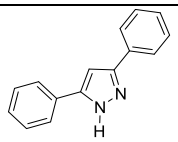
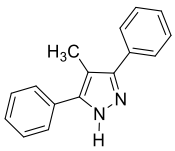
Figure 2.10: ^{1}H and ^{13}C NMR spectrum of **56a**

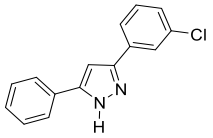
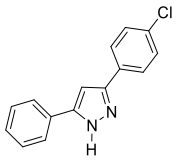
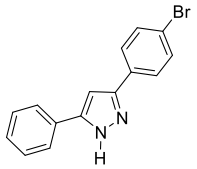
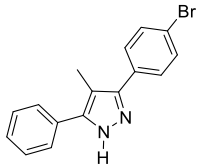
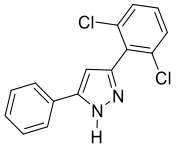
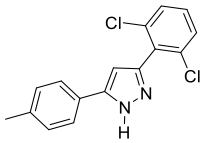
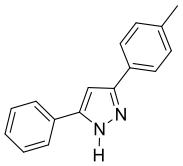
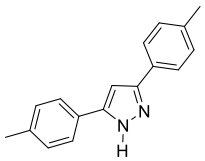
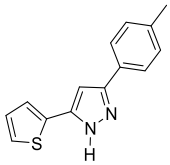
These results encouraged us to further explore an alternative protocol for the synthesis of 3,5-substituted pyrazoles by 1,3-dipolar cycloaddition of ionic liquid-supported tosyl hydrazone (**54**) to alkynes (**57**). To our delight the reaction of tosylhydrazone (**54d**) with phenylacetylene (**57a**) in the presence of 5N NaOH at 60 °C afforded 3-(4-bromophenyl)-5-phenyl-*1H*-pyrazole (**58da'**) in 85% yield. It is important to mention that the yield of **58da'** was low when 3N NaOH and other bases were used in this reaction.

The scope of the reaction was evaluated with regard to the structure of aldehydes and alkynes. As shown in table 2.7, various substituted aldehydes worked well with alkynes to provide the corresponding 3,5-disubstituted-*1H*-pyrazoles (**58**) with moderate to excellent yields. The reaction tolerated alkynes and aldehydes with various steric and electronic properties. In general, the electronic effect on the aldehydes had little influence on the reaction yield; both electron-withdrawing and electron-donating substituents gave good to excellent yields with simple phenylacetylene (**57a**) and 4'-methyl phenylacetylene (**57b**). We also found that the reaction could tolerate heteroaryl motifs (Table 2.7, entry 11). However, for the disubstituted alkynes the yields of the corresponding pyrazole were poor (Table 2.7, entries 2, 6). The chemical structures of the synthesized pyrazoles (**58**) were elucidated by ^{1}H and ^{13}C NMR data. A representative ^{1}H and ^{13}C NMR of pyrazole **58da** is given in figure 2.11.

Table 2.7: Synthesis of 3,5-disubstituted pyrazoles **58** formed by cyclization of **55**[a]



Entry	Ar	R	R^1	Product		Yield[b] (%)
1	C_6H_5	C_6H_5	H		**58aa**	90
2	C_6H_5	C_6H_5	CH_3		**58aa'**	15

3	3-ClC_6H_4	C_6H_5	H		**58ba**	87
4	4-ClC_6H_4	C_6H_5	H		**58ca**	87
5	4-BrC_6H_4	C_6H_5	H		**58da**	85
6	4-BrC_6H_4	C_6H_5	CH_3		**58da'**	14
7	2,6-$(Cl)_2C_6H_3$	C_6H_5	H		**58ea**	78
8	2,6-$(Cl)_2C_6H_3$	4-$CH_3C_6H_4$	H		**58eb**	74
9	4-$CH_3C_6H_4$	C_6H_5	H		**58fa**	80
10	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	H		**58fb**	83
11	C_4H_3S	C_6H_5	H		**58ga**	41

[a]Reaction conditions: **54** (1 mmol), **57** (1.5 mmol), 5 N NaOH (2 mL), 60 °C for 24 h; [b]Isolated yield

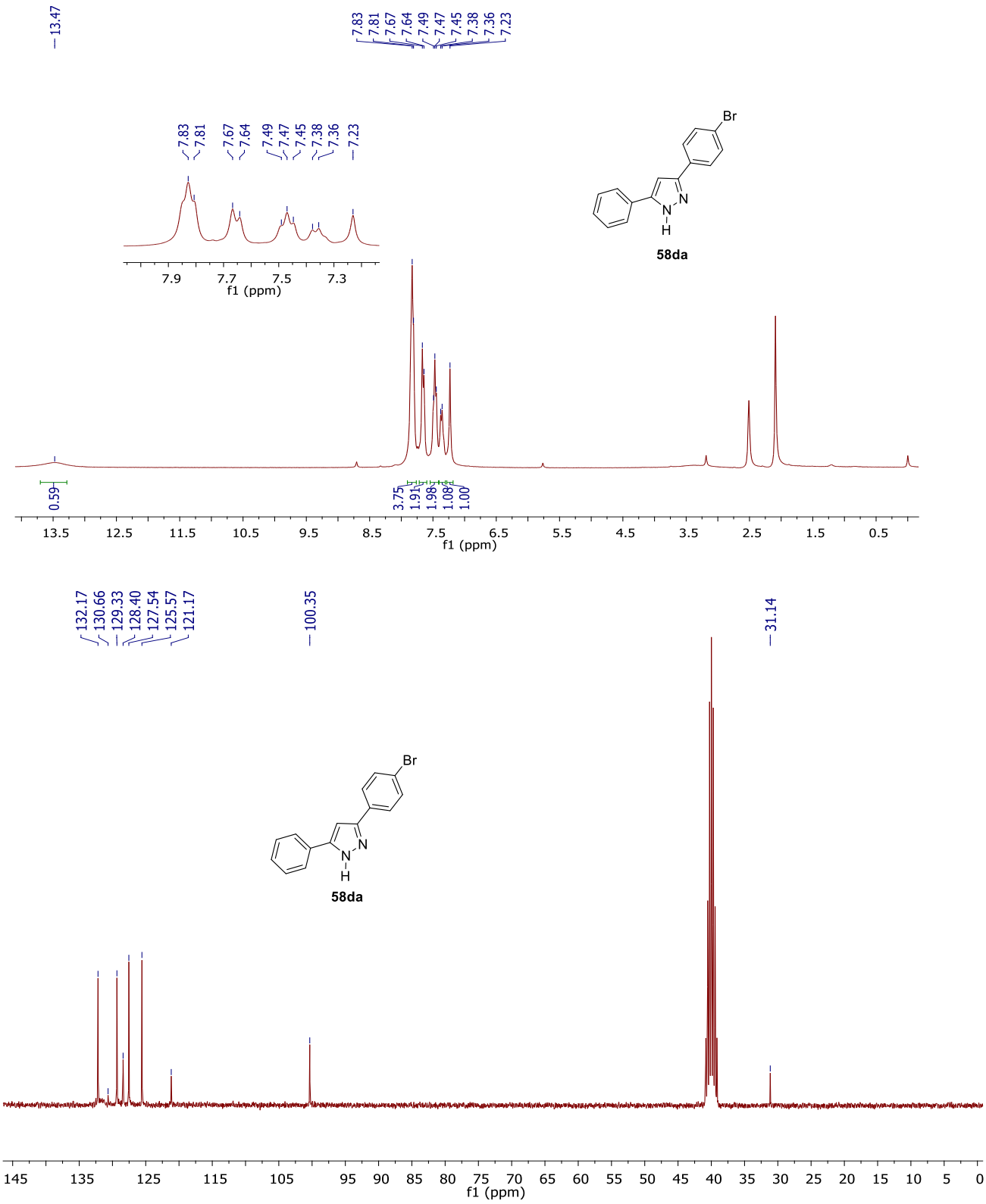


Figure 2.11: ^{1}H and ^{13}C NMR spectrum of **58da**

2.9 Conclusion

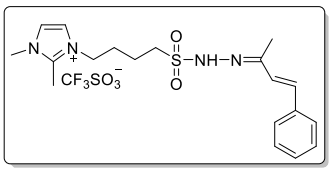
In summary, a facile and economical approach for the traceless synthesis of highly substituted pyrazole has been developed using ionic liquid-supported sulfonyl hydrazine. A key feature of the protocol is easy and convenient purification process that avoids chromatographic separation of products and thus makes the method ecofriendly and economical.

2.10 Experimental

General procedure for the synthesis of ionic liquid-supported sulfonyl hydrazones

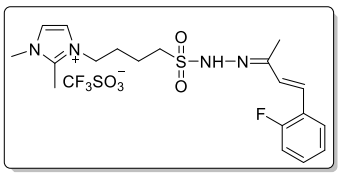
To the ionic liquid-supported sulfonyl hydrazine **19** (1 mmol) in ethanol *α,β*-unsaturated carbonyl compounds **53** (1.1 mmol) or aldehydes **46** (1.1 mmol) were added and the resulting solution was stirred at room temperature vigorously for 2-3 h. After completion of the reaction, ethanol was removed and the resulting mixture was washed with ethyl acetate/hexane mixture (1:1 *v/v*) and dried under reduced pressure to get the pure product.

3-(4-((2-((E)-4-Phenylbut-3-en-2-ylidene)hydrazinyl)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (54a)



Yield: 86%; white solid; mp: 150-151 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.27 (s, 1H), 7.64 (d, J = 2.0 Hz, 1H), 7.61 (dd, J = 3.5, 1.7 Hz, 2H), 7.58 (s, 1H), 7.39 (t, J = 7.2 Hz, 2H), 7.35-7.30 (m, 1H), 7.10 (d, J = 16.6 Hz, 1H), 6.84 (d, J = 16.6 Hz, 1H), 4.16 (t, J = 7.1 Hz, 2H), 3.73 (s, 3H), 3.33-3.24 (m, 2H), 2.59 (s, 3H), 2.08 (s, 3H), 1.90-1.81(m, 2H), 1.78-1.65 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 154.4, 144.8, 136.4, 134.2, 129.2, 129.0, 128.7, 127.4, 122.7, 121.3, 121.1 (q, $J_{C\text{-}F}$ = 320.25 Hz), 49.3, 47.2, 35.1, 28.0, 20.0, 12.8, 9.6; HRMS (*m/z*): Calcd. for $C_{19}H_{27}N_4O_2S^+$ 375.1849, found 375.1858 [M – $CF_3SO_3^-$]$^+$.

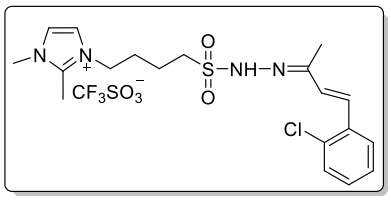
3-(4-((2-((E)-4-(2-Fluorophenyl)but-3-en-2-ylidene)hydrazinyl)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (54b)



Yield: 83%; Colourless solid; mp: 146-147 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.39 (s, 1H), 7.75 (t, J = 7.7 Hz, 1H), 7.64 (d, J = 6.2 Hz, 2H), 7.40-7.33 (m, 1H), 7.29-7.20 (m, 2H), 7.11 (d, J = 16.8 Hz, 1H), 6.93 (d, J = 16.7 Hz, 1H), 4.18 (t, J = 6.9 Hz, 2H), 3.75 (s, 3H), 3.35-3.24 (m, 2H), 2.60 (s, 3H), 2.09 (s, 3H), 1.92-1.81 (m, 2H), 1.80-1.66 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.3 (d, $J_{C\text{-}F}$ = 249.0 Hz), 154.1, 144.8, 131.5 (d, $J_{C\text{-}F}$ = 5.6 Hz), 130.7 (d, $J_{C\text{-}F}$ = 8.5 Hz), 128.6 (d, $J_{C\text{-}F}$ = 3.1 Hz), 126.0 (d, $J_{C\text{-}F}$ = 2.9 Hz), 125.3 (d, $J_{C\text{-}F}$ = 3.3 Hz),

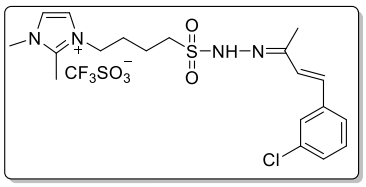
124.0 (d, J_{C-F} = 11.5 Hz), 121.1 (q, J_{C-F} = 320.25 Hz), 116.3 (d, J_{C-F} = 22.0 Hz), 49.4, 47.2, 35.1, 28.0, 20.0, 12.7, 9.5; HRMS (*m/z*): Calcd. for $C_{19}H_{26}FN_4O_2S^+$ 393.1755, found 393.1736 $[M - CF_3SO_3^-]^+$.

3-(4-((2-((E)-4-(2-Chlorophenyl)but-3-en-2-ylidene)hydrazinyl)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (54c)



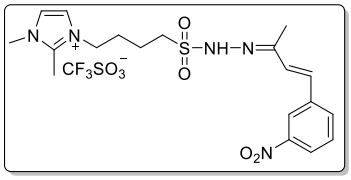
Yield: 81%; Colourless solid; mp: 129-131 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.44 (s, 1H), 7.86-7.79 (m, 1H), 7.64 (d, J = 3.2 Hz, 1H), 7.62 (d, J = 1.9 Hz, 1H), 7.53-7.48 (m, 1H), 7.40-7.33 (m, 2H), 7.26 (d, J = 16.4 Hz, 1H), 6.89 (d, J = 16.4 Hz, 1H), 4.17 (t, J = 7.1 Hz, 2H), 3.74 (s, 3H), 3.33-3.24 (m, 2H), 2.59 (s, 3H), 2.10 (s, 3H), 1.92-1.80 (m, 2H), 1.76-1.69 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 153.7, 144.8, 134.1, 132.9, 131.9, 130.4, 130.2, 129.0, 128.1, 127.7, 122.7, 121.3, 121.1 (q, J_{C-F} = 320.25 Hz), 49.5, 47.2, 35.1, 28.1, 20.0, 13.0, 9.6; HRMS (*m/z*): Calcd. for $C_{19}H_{26}ClN_4O_2S^+$ 409.1460, found 409.1443 $[M - CF_3SO_3^-]^+$.

3-(4-((2-((E)-4-(3-Chlorophenyl)but-3-en-2-ylidene)hydrazinyl)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (54d)



Yield: 84%; Yellow solid; mp: 150-153 °C ; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.31 (s, 1H), 7.67 (s, 1H), 7.63 (d, J = 2.0 Hz, 1H), 7.61 (d, J = 2.0 Hz, 1H), 7.57 (d, J = 7.3 Hz, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.40-7.36 (m, 1H), 7.09 (d, J = 16.6 Hz, 1H), 6.91 (d, J = 16.6 Hz, 1H), 4.16 (t, J = 7.1 Hz, 2H), 3.74 (s, 3H), 3.33-3.23 (m, 2H), 2.58 (s, 3H), 2.06 (s, 3H), 1.92-1.79 (m, 2H), 1.77-1.64 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 153.9, 144.8, 138.8, 134.0, 132.6, 131.0, 130.3, 128.5, 127.0, 125.9, 122.7, 121.3, 121.1 (q, J_{C-F} = 320.25 Hz), 49.4, 47.2, 35.1, 28.0, 20.0, 12.8, 9.5; HRMS (*m/z*): Calcd. for $C_{19}H_{26}ClN_4O_2S^+$ 409.1460, found 409.1451 $[M–CF_3SO_3^-]^+$.

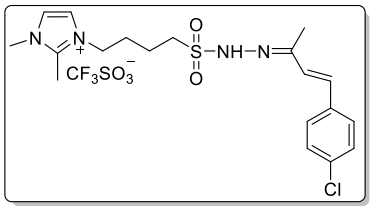
3-(4-((2-((E)-4-(3-Nitrophenyl)but-3-en-2-ylidene)hydrazinyl)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (54e)



Yield: 79%; white solid; mp: 153-155 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.37 (s, 1H), 8.40 (s, 1H), 8.15 (dd, J = 8.1, 1.7 Hz, 1H), 8.09 (d, J = 7.8 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 1.9 Hz, 1H), 7.61 (d, J = 2.0 Hz, 1H), 7.27 (d, J = 16.6 Hz, 1H), 7.03 (d, J = 16.6 Hz, 1H), 4.17 (t, J = 7.1 Hz, 2H), 3.74 (s, 3H), 3.35 – 3.25 (m, 2H), 2.59 (s, 3H), 2.09 (s, 3H), 1.92 – 1.80 (m, 2H), 1.78 – 1.67 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ

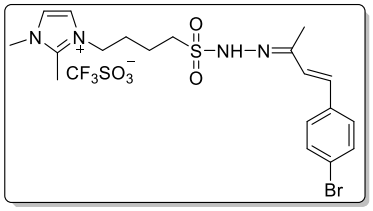
153.7, 148.7, 144.8, 138.4, 133.2, 131.9, 131.5, 130.7, 123.2, 122.7, 121.9, 121.3, 49.4, 47.2, 34.9, 28.0, 20.0, 12.8, 9.5; HRMS (*m/z*): Calcd. for $C_{19}H_{26}N_5O_4S^+$ 420.1700, found 420.1715 $[M–CF_3SO_3^-]^+$.

3-(4-((2-((E)-4-(4-Chlorophenyl)but-3-en-2-ylidene)hydrazinyl)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (54f)



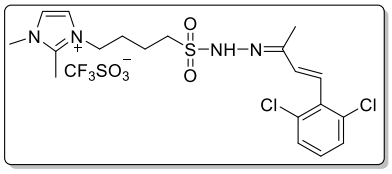
Yield: 74%; Pale yellow solid; mp: 155-157 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.31 (s, 1H), 7.68-7.58 (m, 4H), 7.43 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 16.6 Hz, 1H), 6.86 (d, J = 16.6 Hz, 1H), 4.17 (t, J = 7.0 Hz, 2H), 3.74 (s, 3H), 3.33-3.23 (m, 2H), 2.59 (s, 3H), 2.07 (s, 3H), 1.91-1.81 (m, 2H), 1.76-1.70 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 154.2, 144.8, 135.4, 133.3, 132.8, 129.5, 129.2, 129.0, 122.7, 121.3, 121.1 (q, J_{C-F} = 320.25 Hz), 49.4, 47.2, 35.1, 28.0, 20.0, 12.8, 9.6; HRMS (*m/z*): Calcd. for $C_{19}H_{26}ClN_4O_2S^+$ 409.1460, found 409.1452 $[M – CF_3SO_3^-]^+$.

3-(4-((2-((E)-4-(4-Bromophenyl)but-3-en-2-ylidene)hydrazinyl)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (54g)



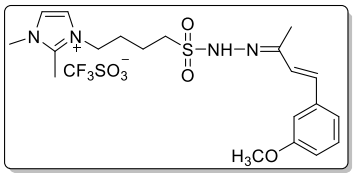
Yield: 87%; pale yellow solid; mp: 141-142 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.32 (s, 1H), 7.64 (d, J = 1.7 Hz, 2H), 7.62 (d, J = 1.9 Hz, 1H), 7.60-7.52 (m, 3H), 7.08 (d, J = 16.6 Hz, 1H), 6.87 (d, J = 16.6 Hz, 1H), 4.16 (t, J = 7.0 Hz, 2H), 3.74 (s, 3H), 3.33-3.23 (m, 2H), 2.59 (s, 3H), 2.07 (s, 3H), 1.90-1.81 (m, 2H), 1.76-1.68 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 154.2, 144.8, 135.8, 132.9, 132.1, 129.6, 129.3, 122.7, 121.9, 121.3, 121.1 (q, J_{C-F}=320.25 Hz), 49.4, 47.2, 35.1, 28.0, 20.0, 12.8, 9.6; HRMS (*m/z*): Calcd. for $C_{19}H_{26}BrN_4O_2S^+$ 453.0954, found 453.0927 $[M–CF_3SO_3^-]^+$ and 455.0918 $[M + 2 – CF_3SO_3^-]^+$.

3-(4-((2-((E)-4-(2,6-Dichlorophenyl)but-3-en-2-ylidene)hydrazinyl)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (54h)



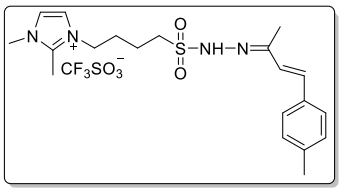
Yield: 80%; white solid; mp: 155-157 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.46 (s, 1H), 7.62 (d, J = 2.8 Hz, 2H), 7.55 (d, J = 8.1 Hz, 2H), 7.40-7.32 (m, 1H), 7.01 (d, J = 16.8 Hz, 1H), 6.71 (d, J = 16.8 Hz, 1H), 4.16 (m, 2H), 3.74 (s, 3H), 3.31-3.24 (m, 2H), 2.58 (s, 3H), 2.10 (s, 3H), 1.91-1.81 (m, 2H), 1.76-1.67 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 153.3, 144.8, 137.0, 133.9, 133.5, 130.3, 129.4, 127.7, 122.7, 121.3, 121.1 (q, J_{C-F} = 320.25 Hz), 49.5, 47.2, 35.1, 28.0, 20.0, 12.6, 9.5; HRMS (*m/z*): Calcd. for $C_{19}H_{25}C_{l2}N_4O_2S^+$ 443.1070, found 443.1043 $[M– CF_3SO_3^-]^+$.

3-(4-((2-((E)-4-(3-Methoxyphenyl)but-3-en-2-ylidene)hydrazinyl)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (54i)



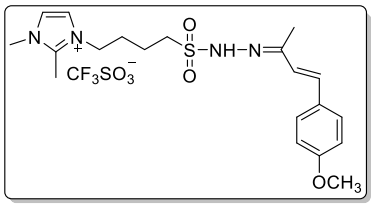
Yield: 54%; yellow solid; mp: 125-127 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.28 (s, 1H), 7.64 (d, J = 2.0 Hz, 1H), 7.62 (d, J = 2.0 Hz, 1H), 7.33-7.25 (m, 2H), 7.16 (d, J = 7.2 Hz, 2H), 7.07 (d, J = 16.6 Hz, 1H), 6.88 (dd, J = 12.7, 9.4 Hz, 2H), 4.16 (t, J = 7.1 Hz, 2H), 3.79 (s, 3H), 3.74 (s, 3H), 3.33-3.23 (m, 2H), 2.59 (s, 3H), 2.07 (s, 3H), 1.92-1.79 (m, 2H), 1.77-1.65 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.0, 154.4, 144.8, 137.9, 134.2, 130.2, 129.0, 122.7, 121.3, 121.1 (q, J_{C-F} = 320.25 Hz), 120.0, 115.1, 112.1, 55.5, 49.3, 47.2, 35.1, 28.1, 20.0, 12.8, 9.6; HRMS (*m/z*):Calcd. for $C_{19}H_{29}N_4O_3S^+$ 405.1955, found 405.1972 $[M–CF_3SO_3^-]^+$.

3-(4-((2-((E)-4-(p-Tolyl)but-3-en-2-ylidene)hydrazinyl)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (54j)



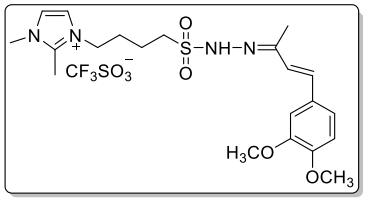
Yield: 67%; yellow solid; mp: 148-150 °C ; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.22 (s, 1H), 7.64 (d, J = 2.0 Hz, 1H), 7.61 (d, J = 2.0 Hz, 1H), 7.48 (d, J = 8.1 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 7.05 (d, J = 16.6 Hz, 1H), 6.78 (d, J = 16.6 Hz, 1H), 4.16 (t, J = 7.1 Hz, 2H), 3.74 (s, 3H), 3.32-3.22 (m, 2H), 2.59 (s, 3H), 2.31 (s, 3H), 2.06 (s, 3H), 1.92-1.78 (m, 2H), 1.76-1.68 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 154.6, 144.8, 138.5, 134.2, 133.7, 129.9, 127.7, 127.3, 122.7, 121.3, 121.1 (q, J_{C-F} = 320.25 Hz), 49.3, 47.2, 35.1, 28.1, 21.3, 20.0, 12.8, 9.5; HRMS (*m/z*): Calcd. for $C_{19}H_{29}N_4O_2S^+$ 389.2006, found 389.1987 $[M – CF_3SO_3^-]^+$.

3-(4-((2-((E)-4-(4-Methoxyphenyl)but-3-en-2-ylidene)hydrazinyl)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (54k)



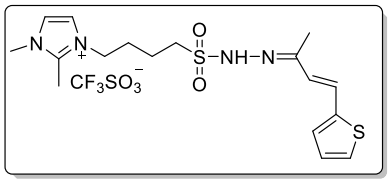
Yield: 92%; yellow solid; mp: 128-130 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.17 (s, 1H), 7.64 (d, J = 2.0 Hz, 1H), 7.62 (d, J = 2.0 Hz, 1H), 7.53 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 16.8 Hz, 1H), 6.96 (t, J = 7.0 Hz, 2H), 6.71 (d, J = 16.5 Hz, 1H), 4.16 (t, J = 7.1 Hz, 2H), 3.78 (s, 3H), 3.74 (s, 3H), 3.31-3.23 (m, 2H), 2.59 (s, 3H), 2.05 (s, 3H), 1.92-1.78 (m, 2H), 1.77-1.64 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.0, 154.9, 144.8, 134.0, 129.0, 128.8, 126.4, 122.7, 121.3, 121.1 (q, J_{C-F} = 320.25 Hz), 114.7, 55.6, 49.2, 47.2, 35.1, 28.1, 20.0, 12.8, 9.6; HRMS (*m/z*): Calcd. for $C_{19}H_{29}N_4O_3S^+$ 405.1955, found 405.1969 $[M – CF_3SO_3^-]^+$.

3-(4-((2-((E)-4-(3,4-Dimethoxyphenyl)but-3-en-2-ylidene)hydrazinyl)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (54l)



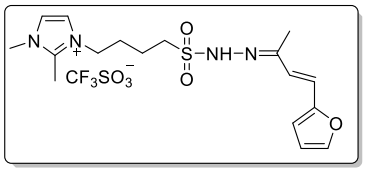
Yield: 71%; yellow solid; mp: 106-108 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.19 (s, 1H), 7.65 (d, J = 2.0 Hz, 1H), 7.62 (d, J = 2.0 Hz, 1H), 7.21 (d, J = 1.6 Hz, 1H), 7.13 – 7.04 (m, 1H), 6.97 (dd, J = 11.0, 5.7 Hz, 2H), 6.76 (d, J = 16.5 Hz, 1H), 4.17 (t, J = 7.1 Hz, 2H), 3.81 (s, 3H), 3.77 (s, 3H), 3.74 (s, 3H), 3.31 – 3.23 (m, 2H), 2.59 (s, 3H), 2.06 (s, 3H), 1.91-1.81 (m, 2H), 1.74-1.69 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 154.9, 149.8, 149.4, 144.8, 134.4, 129.3, 126.5, 122.7, 121.3, 121.2, 121.1 (q, J_{C-F} = 320.25 Hz), 112.1, 109.7, 55.9, 55.9, 49.2, 47.3, 35.1, 28.1, 20.0, 12.8, 9.6; HRMS (*m/z*): Calcd. for $C_{19}H_{31}N_4O_4S^+$ 435.2061, found 435.2096 [M – $CF_3SO_3^-$]$^+$.

3-(4-((2-((E)-4-(Thiophen-2-yl)but-3-en-2-ylidene)hydrazinyl)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (54m)



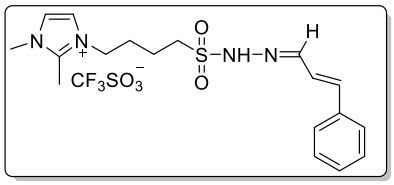
Yield 80%; white solid; mp 138-140 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.26 (s, 1H), 7.64 (d, J = 1.8 Hz, 1H), 7.61 (d, J = 2.1 Hz, 1H), 7.54 (d, J = 5.1 Hz, 1H), 7.29 (dd, J = 9.8, 6.4 Hz, 2H), 7.09 (dd, J = 5.1, 3.6 Hz, 1H), 6.54 (d, J = 16.3 Hz, 1H), 4.16 (t, J = 7.1 Hz, 2H), 3.74 (s, 3H), 3.32 – 3.23 (m, 2H), 2.59 (s, 3H), 2.03 (s, 3H), 1.88-1.81 (m, 2H), 1.75-1.69 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.2, 154.0, 144.8, 141.6, 128.8, 127.9, 127.5, 127.2, 122.8, 121.3, 121.1 (q, *JC-F* = 320.25 Hz), 49.3, 47.9, 35.1, 28.1, 20.1, 12.8, 9.6; HRMS (*m/z*): Calcd. for $C_{17}H_{25}N_4O_2S_2^+$ 381.1413 found 381.1437 [M – $CF_3SO_3^-$]$^+$.

3-(4-((2-((E)-4-(Furan-2-yl)but-3-en-2-ylidene)hydrazinyl)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (54n)



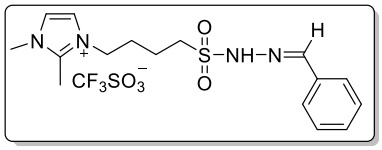
Yield: 88%; brown solid; mp: 145-146 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.30 (s, 1H), 7.73 (d, J = 0.9 Hz, 1H), 7.65 (d, J = 1.8 Hz, 1H), 7.63 (d, J = 1.9 Hz, 1H), 6.95 (d, J = 16.4 Hz, 1H), 6.67 (d, J = 3.3 Hz, 1H), 6.63 (s, 1H), 6.57 (d, J = 3.8 Hz, 1H), 4.17 (t, J = 6.9 Hz, 2H), 3.75 (s, 3H), 3.32 – 3.24 (m, 2H), 2.60 (s, 3H), 2.03 (s, 3H), 1.91-1.81 (m, 2H), 1.76-1.68 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 154.1, 152.2, 144.8, 144.3, 126.6, 122.7, 122.0, 121.3, 121.1 (q, J_{C-F} = 320.25 Hz), 112.7, 111.6, 49.3, 47.2, 35.1, 28.0, 20.0, 12.7, 9.6; HRMS (*m/z*): Calcd. for $C_{17}H_{25}N_4O_3S^+$ 365.1642, found 365.1671 [M – $CF_3SO_3^-$]$^+$.

3-(4-((2-((E)-3-Phenylallylidene)hydrazinyl)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (54o)



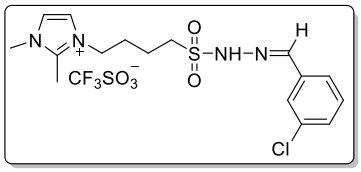
Yield: 59%; light Brown solid; mp: 129-131 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.35 (s, 1H), 7.87 (d, J = 8.7 Hz, 1H), 7.66 (d, J = 2.1 Hz, 1H), 7.63 (d, J = 2.1 Hz, 1H), 7.61 (d, J = 1.4 Hz, 1H), 7.58 (s, 1H), 7.43-7.31 (m, 3H), 7.02 (d, J = 16.1 Hz, 1H), 6.91 (dd, J = 16.1, 8.7 Hz, 1H), 4.16 (t, J = 7.1 Hz, 2H), 3.74 (s, 3H), 3.29-3.19 (m, 2H), 2.59 (s, 3H), 1.90-1.81 (m, 2H), 1.75-1.66 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 149.0, 144.8, 139.2, 136.2, 129.2, 127.4, 125.3, 123.2, 122.7, 121.3, 121.1 (q, $J_{C\text{-}F}$ = 320.25 Hz), 49.9, 47.2, 35.1, 28.0, 20.1, 9.6; HRMS (*m/z*): Calcd. for $C_{18}H_{25}N_4O_2S^+$ 361.1693, found 361.1706 [M – $CF_3SO_3^-$]$^+$.

3-(4-((2-Benzylidenehydrazinyl)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (55a)



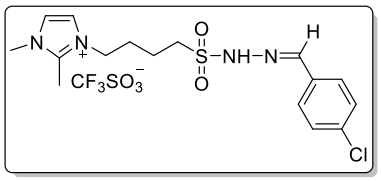
Yield: 88%; pale yellow solid; mp: 135-137 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.39 (s, 1H), 8.06 (s, 1H), 7.66 (d, J = 4.1 Hz, 1H), 7.65-7.61 (m, 2H), 7.59 (d, J = 2.0 Hz, 1H), 7.45 (d, J = 1.2 Hz, 1H), 7.43 (d, J = 2.2 Hz, 2H), 4.16 (t, J = 7.1 Hz, 2H), 3.73 (s, 3H), 3.35-3.25 (m, 2H), 2.57 (s, 3H), 1.91-1.81 (m, 2H), 1.79-1.66 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 146.9, 144.8, 134.2, 130.4, 129.2, 127.2, 122.7, 121.2, 121.1 (q, $J_{C\text{-}F}$ = 320.25 Hz), 50.0, 47.2, 35.1, 28.0, 20.1, 9.5; HRMS (*m/z*): Calcd for $C_{16}H_{23}N_4O_2S^+$ 335.1536, found 335.1523 [M–$CF_3SO_3^-$]$^+$.

3-(4-((2-(3-Chlorobenzylidene)hydrazinyl)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (55b)



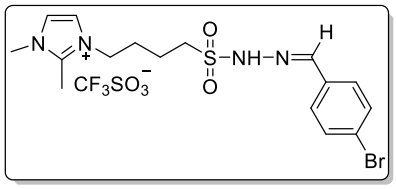
Yield: 76%; pale yellow solid; mp: 136-137 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.63 (s, 1H), 8.07 (s, 1H), 7.73 (s, 1H), 7.64 (d, J = 2.1 Hz, 1H), 7.60 (d, J = 1.9 Hz, 1H), 7.48 (dd, J = 3.7, 1.9 Hz, 1H), 4.17 (t, J = 7.1 Hz, 1H), 3.74 (s, 1H), 3.38-3.28 (m, 1H), 2.59 (s, 1H), 1.93-1.80 (m, 2H), 1.78-1.70 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 145.1, 144.8, 136.5, 134.0, 131.1, 130.0, 126.3, 126.1, 122.7, 121.2, 121.1 (q, $J_{C\text{-}F}$ = 320.25 Hz), 50.0, 47.2, 35.1, 27.9, 20.1, 9.6; HRMS (*m/z*): Calcd for $C_{16}H_{22}ClN_4O_2S^+$ 369.1147, found 369.1171 [M – $CF_3SO_3^-$]$^+$.

3-(4-((2-(4-Chlorobenzylidene)hydrazinyl)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (55c)



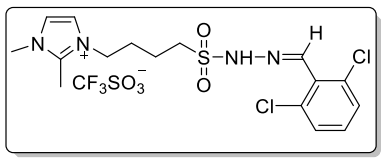
Yield: 72%; white solid; mp: 154-155 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.52 (s, 1H), 8.06 (s, 1H), 7.69 (d, J = 1.7 Hz, 1H), 7.66 (d, J = 3.5 Hz, 1H), 7.64 (d, J = 2.1 Hz, 1H), 7.60 (d, J = 2.0 Hz, 1H), 7.52 (s, 1H), 7.49 (d, J = 1.6 Hz, 1H), 4.16 (t, J = 7.1 Hz, 2H), 3.74 (s, 3H), 3.36-3.25 (m, 2H), 2.58 (s, 3H), 1.90-1.79 (m, 2H), 1.78-1.66 (m, 2H).; ^{13}C NMR (75 MHz, DMSO-d_6) δ 145.5, 144.8, 134.9, 133.2, 129.3, 128.9, 122.7, 121.3, 121.1 (q, $J_{C\text{-}F}$ = 320.25 Hz), 50.0, 47.2, 35.1, 28.0, 20.1, 9.6; HRMS (*m/z*): Calcd for $C_{16}H_{22}ClN_4O_2S$ + 369.1147, found 369.1165 $[M - CF_3SO_3^-]^+$.

3-(4-((2-(4-Bromobenzylidene)hydrazinyl)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (55d)



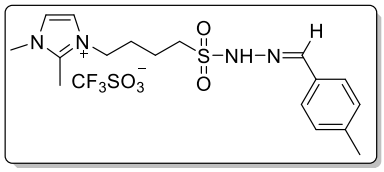
Yield: 79%; white solid; mp: 132-133 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.55 (s, 1H), 8.05 (s, 1H), 7.66 (d, J = 2.3 Hz, 1H), 7.64 (d, J = 2.3 Hz, 2H), 7.62-7.58 (m, 3H), 4.16 (t, J = 7.1 Hz, 2H), 3.74 (s, 3H), 3.34-3.26 (m, 2H), 2.58 (s, 3H), 1.90-1.79 (m, 2H), 1.78-1.66 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 145.6, 144.8, 133.5, 132.2, 129.1, 123.6, 122.7, 121.3, 121.1 (q, $J_{C\text{-}F}$ = 320.25 Hz), 50.0, 47.2, 35.1, 28.0, 20.1, 9.6; HRMS (*m/z*): Calcd for $C_{16}H_{22}BrN_4O_2S^+$ 413.0641, found 413.0659 $[M - CF_3SO_3^-]^+$ and 415.0643 $[M + 2 - CF_3SO_3^-]^+$.

3-(4-((2-(2,6-Dichlorobenzylidene)hydrazinyl)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (55e)



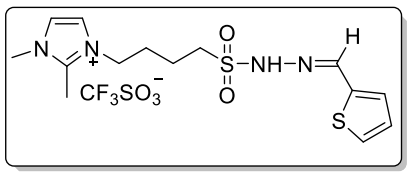
Yield: 77%; white solid; mp: 152-154 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.75 (s, 1H), 8.16 (s, 1H), 7.63 (d, J = 2.0 Hz, 1H), 7.61 (d, J = 2.0 Hz, 1H), 7.58 (d, J = 1.2 Hz, 1H), 7.55 (s, 1H), 7.45 (dd, J = 9.0, 7.0 Hz, 1H), 4.16 (t, J = 7.1 Hz, 2H), 3.75 (s, 3H), 3.36-3.27 (m, 2H), 2.59 (s, 3H), 1.91-1.82 (m, 2H), 1.80-1.67 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 144.8, 141.6, 134.2, 131.8, 130.4, 129.5, 122.8, 121.3, 121.1 (q, $J_{C\text{-}F}$ = 320.25 Hz), 50.4, 47.2, 35.1, 28.0, 20.1, 9.5; HRMS (*m/z*): Calcd for $C_{16}H_{21}Cl_2N_4O_2S^+$ 403.0757, found 403.0728 $[M - CF_3SO_3^-]^+$.

3-(4-((2-(4-Methylbenzylidene)hydrazinyl)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (55f)



Yield: 89%; white solid; mp: 131-132 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.02 (s, 1H), 7.63 (d, J = 2.1 Hz, 1H), 7.59 (d, J = 2.0 Hz, 1H), 7.54 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 4.16 (t, J = 7.1 Hz, 2H), 3.73 (s, 3H), 3.34 – 3.24 (m, 2H), 2.58 (s, 3H), 2.33 (s, 3H), 1.89 – 1.79 (m, 2H), 1.78 – 1.65 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 147.0, 144.7, 140.2, 131.5, 129.8, 127.2, 122.7, 121.2, 121.1 (q, $J_{C\text{-}F}$ = 320.25 Hz), 49.9, 47.2, 35.1, 28.0, 21.4, 20.1, 9.5; Calcd for $C_{17}H_{25}N_4O_2S^+$ 349.1693, found 349.1682 [M – $CF_3SO_3^-$]$^+$.

3-(4-((2-(Thiophen-2-ylmethylene)hydrazinyl)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (55g)

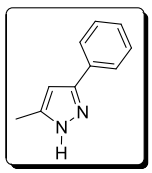


Yield: 88%; pale yellow solid; mp: 126-127 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.37 (s, 1H), 8.25 (s, 1H), 7.66 – 7.62 (m, 2H), 7.60 (d, J = 2.1 Hz, 1H), 7.42 (dd, J = 3.6, 0.9 Hz, 1H), 7.12 (dd, J = 5.0, 3.6 Hz, 1H), 4.16 (t, J = 7.1 Hz, 2H), 3.74 (s, 3H), 3.28 – 3.17 (m, 2H), 2.58 (s, 3H), 1.89 – 1.79 (m, 2H), 1.76 -1.67 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 144.8, 142.2, 138.8, 131.1, 129.0, 128.3, 122.7, 121.3, 121.1 (q, $J_{C\text{-}F}$ = 320.25 Hz), 50.0, 47.2, 35.1, 28.0, 20.1, 9.6; HRMS (*m/z*): Calcd for $C_{14}H_{21}N_4O_2S_2^+$ 341.1100, found 341.1092 [M – $CF_3SO_3^-$]$^+$.

General procedure for the synthesis of pyrazoles 56a-o from ionic liquid-supported sulfonyl hydrazones 54a-o:

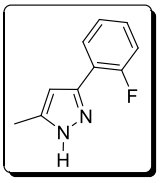
To the ionic liquid-supported hydrazones **54** (1 mmol) 2 mL of 3N NaOH was added, and the reaction mixture was heated at 100 °C for 24 h. The progress of the reaction was monitored by thin-layer chromatography. After completion of the reaction, the product was extracted in ethyl acetate (2 × 10 mL) and dried over sodium sulfate. The combined organic layers were evaporated under reduced pressure to get pure compound.

5-Methyl-3-phenyl-1*H*-pyrazole (56a)



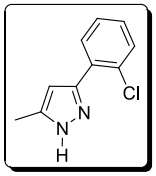
Yield 60%; light brown solid; mp 121-122 °C (lit.[40] 124-126 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.62 (s, 1H), 7.70 (d, J = 7.3 Hz, 2H), 7.31 (dt, J = 22.7, 7.7 Hz, 3H), 6.32 (s, 1H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 132.5, 128.7, 127.8, 125.7, 102.1, 11.7.

3-(2-Fluorophenyl)-5-methyl-1*H*-pyrazole (56b)



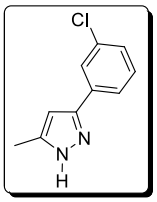
Yield 77%; colorless liquid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.77 (s, 1H), 7.91 (t, J = 7.7 Hz, 1H), 7.40 – 7.28 (m, 1H), 7.24 (dd, J = 8.9, 4.9 Hz, 2H), 6.40 (d, J = 3.8 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.5 (d, J = 247.3 Hz), 129.4 (d, J = 8.3 Hz), 128.3 (d, J = 3.9 Hz), 125.0 (d, J = 3.3 Hz), 116.5 (d, J = 22.0 Hz), 104.7 (d, J = 8.7 Hz), 11.5.

3-(2-Chlorophenyl)-5-methyl-1*H*-pyrazole (56c)



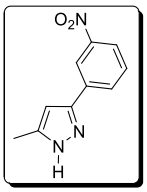
Yield 70%; light yellow liquid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.75 (s, 1H), 7.75 (s, 1H), 7.50 (d, J = 7.1 Hz, 1H), 7.42 – 7.27 (m, 2H), 6.48 (s, 1H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 131.3, 130.7, 130.6, 129.2, 127.6, 107.2, 105.2, 10.8.

3-(3-Chlorophenyl)-5-methyl-1*H*-pyrazole (56d)



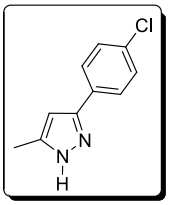
Yield 76%; white solid; mp 136-139 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.01 (brs, 1H), 7.69 (s, 1H), 7.56 (d, J = 6.4 Hz, 1H), 7.23 (d, J = 5.9 Hz, 2H), 6.29 (s, 1H), 2.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.4, 142.5, 134.7, 134.6, 129.9, 127.7, 125.8, 123.8, 102.3, 11.3.

3-(3-Nitrophenyl)-5-methyl-1*H*-pyrazole (56e)



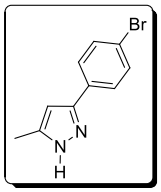
Yield 33%; white solid; mp 139-141 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.83 (s, 1H), 8.55 (s, 1H), 8.19 (d, J = 7.6 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.69 (t, J = 8.0 Hz, 1H), 6.64 (s, 1H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 148.7, 140.7, 136.2, 131.7, 130.7, 122.1, 119.4, 102.1, 10.9.

3-(4-Chlorophenyl)-5-methyl-1*H*-pyrazole (56f)



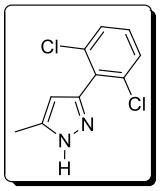
Yield 83%; brownish white solid; mp 136-139 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 6.32 (s, 1H), 2.32 (s, 3H; ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.5, 130.3, 129.2, 127.8, 126.8, 125.8, 101.0, 10.2.

3-(4-Bromophenyl)-5-methyl-1*H*-pyrazole (56g)



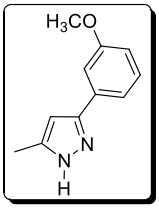
Yield 85%; white solid; mp 136-139 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, J = 8.5 Hz, 2H), 7.47 (d, J = 8.5 Hz, 2H), 6.31 (s, 1H), 2.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.7, 127.2, 121.7, 102.1, 11.4.

3-(2,6-Dichlorophenyl)-5-methyl-1*H*-pyrazole (56h)



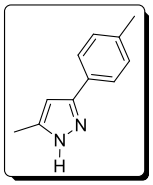
Yield 93%; colorless solid; mp 169-171 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.71 (s, 1H), 7.54 (d, J = 7.9 Hz, 2H), 7.46 – 7.38 (m, 1H), 6.06 (s, 1H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 135.6, 131.0, 128.7, 105.4, 11.3.

3-(3-Methoxyphenyl)-5-methyl-1*H*-pyrazole (56i)



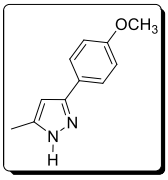
Yield 57%; white solid; mp 135-136 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, J = 5.2 Hz, 3H), 6.86 (dd, J = 7.9, 3.8 Hz, 1H), 6.34 (s, 1H), 3.82 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 133.9, 129.7, 118.2, 113.7, 110.8, 102.2, 55.2, 11.7.

5-Methyl-3-(*p*-tolyl)-1*H*-pyrazole (56j)



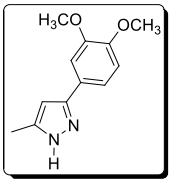
Yield 62%; white solid; mp 136-139 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 7.9 Hz, 2H), 6.31 (s, 1H), 2.36 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7, 129.4, 129.4, 128.0, 127.9, 125.5, 101.9, 21.2, 11.9.

3-(4-Methoxyphenyl)-5-methyl-1*H*-pyrazole (56k)



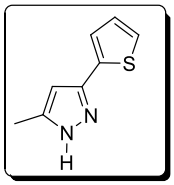
Yield 60%; brown solid; mp 136-139 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, J = 8.5 Hz, 2H), 6.90 (d, J = 8.5 Hz, 2H), 6.26 (s, 1H), 3.82 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 126.9, 114.1, 101.6, 55.3, 11.5

3-(3,4-Dimethoxyphenyl)-5-methyl-1*H*-pyrazole (56l)



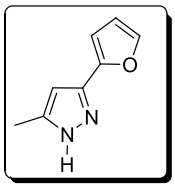
Yield 27%; white solid; mp 77-79 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (s, 1H), 7.15 (dd, J = 8.3, 1.4 Hz, 1H), 6.78 (d, J = 8.3 Hz, 1H), 6.20 (s, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 149.1, 148.9, 142.9, 125.6, 118.2, 111.2, 108.8, 101.6, 55.9, 55.8, 11.7.

5-Methyl-3-(thiophen-2-yl)-1*H*-pyrazole (56m)



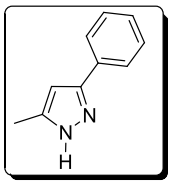
Yield 80%; white solid; mp 125-128 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.54 (s, 1H), 7.39 (d, J = 4.6 Hz, 1H), 7.31 (d, J = 2.9 Hz, 1H), 7.08 – 7.02 (m, 1H), 6.31 (s, 1H), 2.24 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 128.0, 124.7, 123.7, 101.5, 11.1.

3-(Furan-2-yl)-5-methyl-1*H*-pyrazole (56n)



Yield 57%; black solid; mp 85-87 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.67 (s, 1H), 7.65 (s, 1H), 6.64 (d, J = 2.9 Hz, 1H), 6.53 (s, 1H), 6.25 (s, 1H), 2.24 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 142.3, 111.9, 105.5, 101.3, 11.3.

3-Phenyl-1*H*-pyrazole (56o)

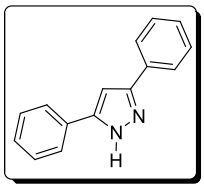


Yield 65%; brown viscous liquid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.88 (s, 1H), 7.81 (d, J = 7.1 Hz, 2H), 7.41 (t, J = 7.4 Hz, 3H), 7.35 – 7.23 (m, 1H), 6.71 (d, J = 1.8 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 129.1, 127.8, 125.6, 102.3.

General procedure for the synthesis of pyrazole 58 from ionic liquid-supported sulfonyl hydrazones 55

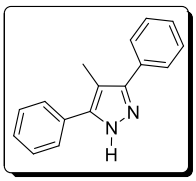
Alkyne (**57**, 1.5 mmol) and 2 mL of 5N NaOH were added to the ionic liquid-supported hydrazone (**55**) (1.0 mmol) at room temperature. The resulting solution was stirred for 24 h at 60 °C and the progress of the reaction was monitored by thin-layer chromatography. After completion of the reaction, the product was extracted in ethyl acetate (2 × 10 mL) and dried over sodium sulfate. The combined organic layers were evaporated under reduced pressure to get pure compound **58.**

3,5-Diphenyl-1*H*-pyrazole (58aa)



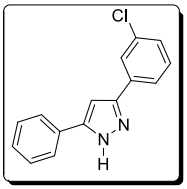
Yield 90%; yellow solid; mp 195-198 °C (lit.[25] 197-198.5 ºC); ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.38 (s, 1H), 7.85 (s, 4H), 7.46 (t, J = 6.8 Hz, 4H), 7.36 (d, J = 6.8 Hz, 2H), 7.19 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 129.3, 128.5, 128.2, 128.0, 125.6, 100.0.

4-Methyl-3,5-diphenyl-1*H*-pyrazole (58aa')



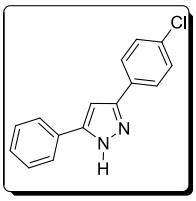
Yield 15%; yellow solid; mp 162-164 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.06 (s, 1H), 7.62 (s, 4H), 7.48 (d, J = 6.2 Hz, 4H), 7.39 (d, J = 6.3 Hz, 2H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.1, 129.1, 127.8, 109.9, 10.6.

3-(3-Chlorophenyl)-5-phenyl-1*H*-pyrazole (58ba)



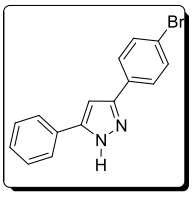
Yield 87%; white solid; mp 180-182 °C (lit.[37] 158-162 °C ; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.50 (s, 1H), 7.93 (s, 1H), 7.89 – 7.79 (m, 3H), 7.48 (d, J = 5.3 Hz, 3H), 7.39 (d, J = 6.5 Hz, 2H), 7.31 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 150.4, 144.1, 136.3, 134.0, 131.1, 129.5, 129.1, 128.7, 127.6, 125.6, 125.1, 124.1, 100.7.

3-(4-Chlorophenyl)-5-phenyl-1*H*-pyrazole (58ca)



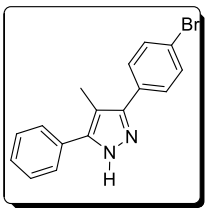
Yield 87%; white solid; mp 217-219 °C; (lit.[41] 214-215 ºC); ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.46 (s, 1H), 7.86 (d, J = 11.3 Hz, 4H), 7.50 (d, J = 6.1 Hz, 4H), 7.37 (s, 1H), 7.23 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 150.6, 144.0, 133.0, 132.4, 132.4, 129.4, 129.1, 128.6, 127.2, 125.6, 100.3.

3-(4-Bromophenyl)-5-phenyl-1*H*-pyrazole (58da)



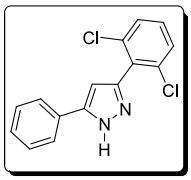
Yield 85%; white solid; mp 211-213 °C; (lit.[41] 212-214 ºC); ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.47 (s, 1H), 7.82 (d, J = 6.4 Hz, 4H), 7.65 (d, J = 7.7 Hz, 2H), 7.47 (t, J = 6.5 Hz, 2H), 7.37 (t, J = 6.7 Hz, 1H), 7.23 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.95, 132.2, 130.7, 129.3, 128.4, 127.5, 125.6, 121.2, 100.4, 31.1.

3-(4-Bromophenyl)-4-methyl-5-phenyl-1*H*-pyrazole (58da')



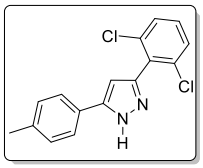
Yield 14%; white solid; mp 211-213 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.16 (s, 1H), 7.76 – 7.34 (m, 9H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 131.9, 129.7, 127.9, 10.5.

3-(2,6-Dichlorophenyl)-5-phenyl-1*H*-pyrazole (58ea)



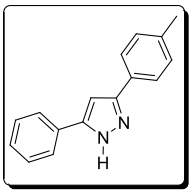
Yield 78%; off White solid; mp 150-154 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.43 (s, 1H), 7.85 (d, J = 7.4 Hz, 2H), 7.61 (d, J = 7.8 Hz, 2H), 7.47 (dd, J = 16.9, 8.8 Hz, 3H), 7.39 – 7.30 (m, 1H), 6.83 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 135.6, 131.5, 129.6, 129.3, 129.0, 128.8, 128.3, 126.0, 125.5, 104.0.

3-(2,6-Dichlorophenyl)-5-(*p*-tolyl)-1*H*-pyrazole (58eb)



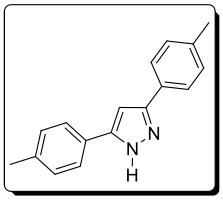
Yield 74%; off white solid; mp 138-143 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.72 (d, J = 2.2 Hz, 2H), 7.60 (d, J = 4.4 Hz, 2H), 7.49 (d, J = 5.6 Hz, 1H), 7.26 (d, J = 3.6 Hz, 2H), 6.77 (s, 1H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 135.6, 129.9, 128.8, 125.5, 103.6, 21.3.

5-Phenyl-3-(*p*-tolyl)-1*H*-pyrazole (58fa)



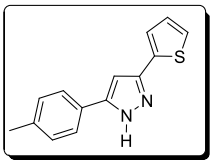
Yield 80%; off white solid; mp 174-175 °C; (lit.[41] 170-172 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.30 (s, 1H), 7.84 (d, J = 7.3 Hz, 2H), 7.73 (d, J = 8.1 Hz, 2H), 7.45 (t, J = 7.5 Hz, 2H), 7.33 (t, J = 7.3 Hz, 1H), 7.26 (d, J = 8.0 Hz, 2H), 7.13 (s, 1H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 137.6, 129.8, 129.2, 128.1, 125.5, 125.5, 99.7, 21.3.

3,5-Di-*p*-tolyl-1*H*-pyrazole (58fb)



Yield 83%; white solid; mp 174-175 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.22 (s, 1H), 7.73 (d, J = 7.0 Hz, 4H), 7.25 (d, J = 7.5 Hz, 4H), 7.07 (s, 1H), 2.33 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 129.89, 125.5, 99.4, 21.3.

5-Phenyl-3-(thiophen-2-yl)-1*H*-pyrazole (58ga)



Yield 41%; brown solid; mp 160-164 °C; (lit.[41] 187-188 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.33 (s, 1H), 7.81 (d, J = 6.7 Hz, 2H), 7.46 (d, J = 5.7 Hz, 4H), 7.36 (t, J = 6.6 Hz, 1H), 7.12 (s, 1H), 7.05 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 216.4, 207.0, 129.4, 128.9, 128.6, 128.1, 127.2, 127.0, 125.6, 125.2, 124.2, 100.1, 100.0.

2.11 References

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Chapter II

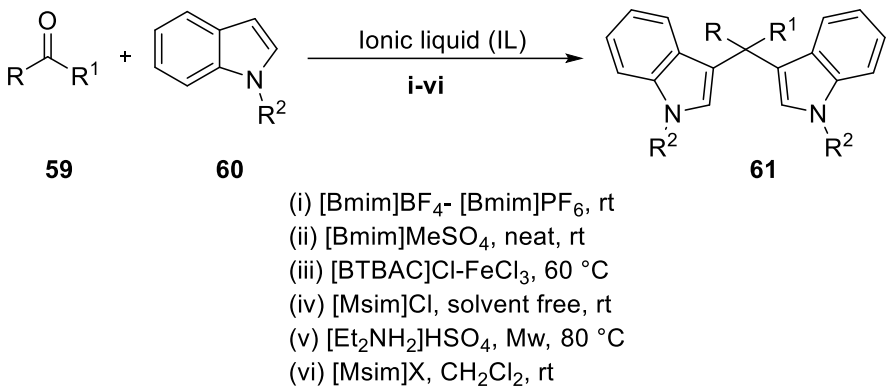
PART C

Ionic Liquid-supported Sulfonyl Hydrazine: Synthesis of Bisindolyl Methane

2.12 Introduction

Indole and their derivatives are important class of heterocyclic moiety possessing a wide range of biological activities such as antioxidant,[1] antibacterial, and insecticidal. Among various derivatives of indole, *bis*(indolyl)methane and their derivatives have found profuse applications in agrochemicals, pharmaceuticals and biologically active natural products.[2-6] Owing to their tremendous applications, various methodologies using different catalyst systems such as lanthanide triflates,[7] $InCl_3$,[8] $LiClO_4$,[9] Zn^{2+} ion-exchanged Y zeolite,[10] CuBr,[11] montmorillonite K10 clay,[12] FPS resins,[13] $NaHSO_4.SiO_2$/Amberlyst-15,[14] pyridinium-tribromide,[15] ammonium-niobium oxalate,[16] $RuCl_3 \cdot 3H_2O$,[17] $Zr(Cl_4)$,[18] $Zr(DS)_4$,[19] [Cu(3,4-tmtppa)]$(MeSO_4)_4$,[20] $H_3PW_{12}O_{40}$,[21] Zeokarb-225,[22] SBA-15-supported-poly(styrenesulfonyl-(perfluorobutylsulfonyl)imide),[23] and sulfamic acid[24] have been described for the synthesis of *bis*(indolyl)methanes. However, these methods suffer from certain disadvantages such as use of expensive or toxic catalyst, long reaction time, tedious workup procedures, difficulties in regeneration of catalyst and purification using column chromatography.

On the other hand, ionic liquids (ILs) have received significant interest as a greener media in organic synthesis owing to their distinctive properties such as negligible vapor pressure, thermal stability, high chemical stability, wide liquid range, and high electrical conductivity.[25] The most attractive aspect of ionic liquid is tunability of their properties depending upon reaction demands. By amending the structure of cation or anions, their chemical and physical properties could be altered to influence the outcomes of the reaction. In recent years functionalized ionic liquids have been explored as efficient and catalyst in the synthesis of *bis*(indolyl)methanes(Scheme 2.17).[26-31]



Scheme 2.17: Synthesis of substituted *bis*(indolyl)methane

Yadav group demonstrated simple, convenient and eco-friendly method for the synthesis of *bis*(indolyl)methanes (**61**) by the reaction of indoles (**60**) with carbonyl compounds (**59**) using [Bmim]BF_4 and [Bmim]PF_6 ionic liquids as a reaction media as well as reusable catalyst.[32] The electrophilic substitution reaction of indole (**60**) with different aldehydes (**59**) afforded the corresponding *bis*(indolyl)methanes (**61**) in good to excellent yields (80-95%) in ionic liquid. The ionic liquid can be recycled and reused without much loss of activity in the synthesis of *bis*(indolyl) methane. The advantage of this protocol is metal free, mild reaction conditions and shorter reaction time. Chakraborti group have reported catalytic application of room temperature ionic liquid [Bmim]$MeSO_4$, for the synthesis of *bis*(indolyl)methanes (**61**) *via* the electrophilic substitution reaction of indole with different aldehyde under solvent free condition.[33] Veisi group described the use of [BTBAC]Cl-$FeCl_3$ based ionic liquid as a solvent as well as catalyst in the synthesis of *bis*(indolyl)methanes (**61**) by the reation of indole (**60**) with carbonyl compounds at 60 °C.[34] Aromatic aldehydes bearing electron-withdrawing groups reacted faster than electron-donating group to afford corresponding *bis*(indolyl)methanes (**61**). A large number of diverse *bis*(indolyl)methanes (**61**) were synthesized in excellent yields using this protocol. Further, Zolfigol have introduced acidic ionic liquid, 3-methyl-1-sulfonic acid imidazolium chloride [Msim]Cl as a catalyst for the synthesis of *bis*(indolyl)methanes (**61**) by the condensation of indole (**60**) and aldehydes (**59**) under solvent free conditions at room temperature.[35] Das group reported synthesis of aryl/alkyl(2,2'-*bis*-3-methylindolyl)methanes and aryl(3,3'-*bis*(indolyl)methanes using secondary amine based ionic liquid under microwave conditions.[26] The main advantages of this methodology include simple reaction conditions, absence of strong acids and recyclability of catalyst. The combined use of ILs and microwave

makes this procedure more efficient and productive alternative over conventional acid catalysed reaction. Recently, Borah group have developed 3-methyl-1-sulfonic acid imidazolium transition metal chlorides [Msim]X where X = $[FeCl_4]^-$, $[ZnCl_3]^-$, $[CuCl_2]^-$ as a heterogeneous catalysts containing both Lewis and Bronsted acidic sites from the reaction of 3-methyl-1-sulfonic acid imidazolium chloride ILs with transition metal chlorides.[36] The efficiency of catalyst was evaluated in the synthesis of *bis*(indolyl)methanes (**61**) using ethylacetate as a solvent at ambient temperature. The noticeable advantages of this protocol are simple operation with easy work up, high thermal stability and recyclability of catalyst without significant loss in the catalytic activity.

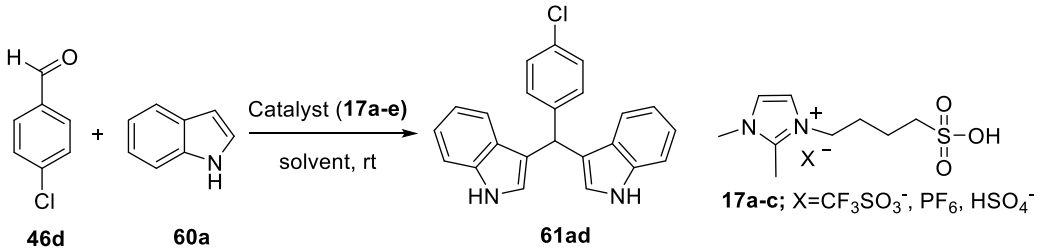
As mentioned above, use of ionic liquid based acidic catalysts have improved the synthesis of *bis*(indolyl)methanes, however, each of these methods required chromatographic separation to remove unreacted carbonyl compounds. In continuation of our efforts in synthesis and application of sulfonyl functionalized ionic liquids in organic transformation,[37-43] we envisaged their use in chromatography free synthesis of *bis*(indolyl)methanes (**61**). In this part of chapter we have described a facile and convenient synthesis of *bis*(indolyl)methanes using sulfonic acid functionalized ionic liquid.

2.13 Results and discussion

Initially, different acidic ionic liquids and bronsted acids (**17a-e**) were evaluated to find best yield of 3,3'-((4-chlorophenyl)methylene)*bis*(1*H*-indole) (**61aa**) by the reaction of 4-chlorobenzaldehyde (**46d**) and indole (**60a**). The results are described in table 2.8. Yield of **61ad** was highest (88%) when 10 mol % of $[IL\text{-}SO_3H][CF_3SO_3]$ (**17a**) was employed as catalyst in tetrahydrofuran (THF) as solvent. Use of other solvents such as acetonitrile, dichloromethane (DCM) and methanol gave lower yield of **61ad** under similar conditions. Decreasing loading of catalyst to 5 mol % decreased yield of **61ad**, while increasing it to 20 mol % did not affect yield of **61ad** significantly. We were delighted to note that 100% conversion of **60a** to **61ad** was observed when slight excess (1.2 equivalent) of **46d** was used for the model reaction using **17a** as catalyst in THF (Table 2.8, entry 12). Although, complete conversion of **60a** was achieved by increasing concentration of aldehyde but presence of unreacted aldehyde was observed in the reaction mixture by HPLC (Fig. 2.13, ii). It was decided that unreacted aldehyde **46d** from the

reaction mixture can be removed by the scavenging it with ionic liquid-supported sulfonyl hydrazine (**19**).

Table 2.8: Optimization of reaction condition for synthesis of **61ad**[a]



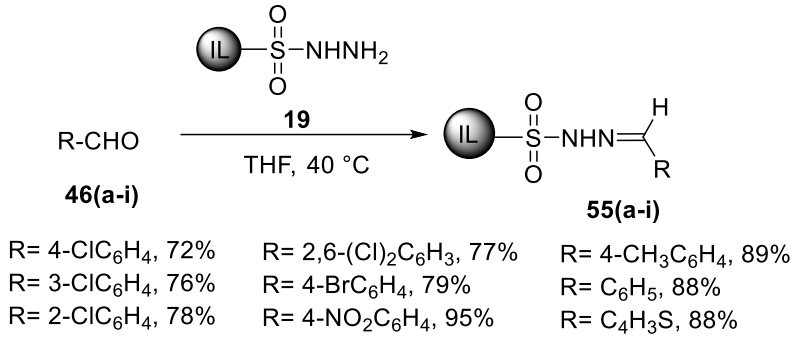
46d **60a** **61ad**

Entry	Catalyst		Equiv. of **46d**	Solvent	Time (min.)	Conversation[b] (%)	Yield[c] (%)
1	[IL-SO_3H][CF_3SO_3]	**17a**	1.0	THF	15	92	88
2	[IL-SO_3H][PF_6]	**17b**	1.0	THF	30	75	72
3	[IL-SO_3H][HSO_4]	**17c**	1.0	THF	30	84	80
4	*p*TSA	**17d**	1.0	THF	60	75	69
5	CF_3COOH	**17e**	1.0	THF	60	40	32
6	[IL-SO_3H][CF_3SO_3]	**17a**	1.0	DCM	15	60	52
7	[IL-SO_3H][CF_3SO_3]	**17a**	1.0	CH_3CN	15	93	87
8	[IL-SO_3H][CF_3SO_3]	**17a**	1.0	CH_3OH	15	70	64
9	[IL-SO_3H][CF_3SO_3]	**17a**	1.0	-	15	63	60
10	[IL-SO_3H][CF_3SO_3]	**17a**	1.0	THF	15	67	62[d]
11	[IL-SO_3H][CF_3SO_3]	**17a**	1.0	THF	15	94	90[e]
12	[IL-SO_3H][CF_3SO_3]	**17a**	1.2	THF	15	100	96
13	-		1.0	THF	15	0	-

[a]Reaction condition: **46d** (as per table 2.8), **60a** (1.0 mmol), catalyst (10 mol%, except entry 10 and 11), room temperature, time (as per table 2.8), [b]based on indole conversion by HPLC, [c]Isolated yield, [d]5 mol % catalyst used, [e]20 mol % catalyst used.

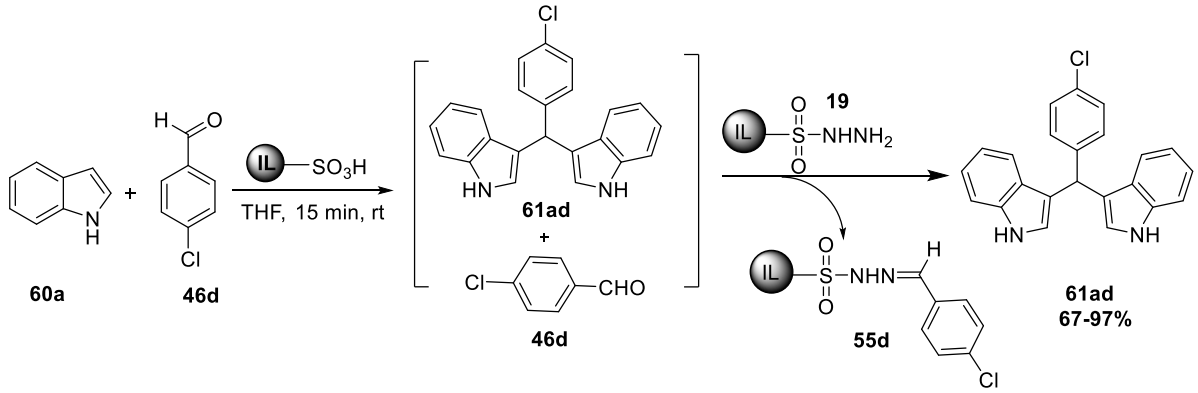
Synthesis of **19** was achieved as reported in chapter 2 part a (Scheme 2.7). Then, scavenging of different aldehydes was investigated using **19** (Scheme 2.17). Complete consumption of aryl aldehydes in relatively short reaction time was observed. Surprisingly, the reaction does not require any external acid catalyst probably due to the presence of the triflate anion in IL-sulfonyl

hydrazine making it slightly acidic in nature. To our delight, ionic liquid-supported sulfonyl hydrazone (**55**) formed was insoluble in THF leading to easy work up procedure.



Scheme 2.18: Reaction of **19** with different aldehyde

After establishing the condition for scavenging of aldehydes with **19**, we moved our attention towards development of a unique protocol for the synthesis of *bis*(indolyl)methanes (**61**) by employing IL-supported sulfonic acid and IL-supported sulfonyl hydrazine (Scheme 2.18). Initially, the reaction of indole (1.0 mmol, **60**) with aldehyde (0.6 mmol, **46d**) in the presence of catalytic amount of IL-sulfonic acid (10 mol %) was performed in THF at room temperature for 15 min. After completion of the reaction and separating the catalyst by decanting, IL-supported sulfonyl hydrazine **19** was added to the decanted organic phase and stirred for 1 h. Aqueous work-up followed by drying and evaporation of the organic solvent afforded pure *bis*(indolyl)methane (**61ad**) without any column chromatographic purification. Using an excess aldehyde allowed for the complete consumption of indole and the desired product was found to be more than 95% pure by HPLC and NMR analysis.

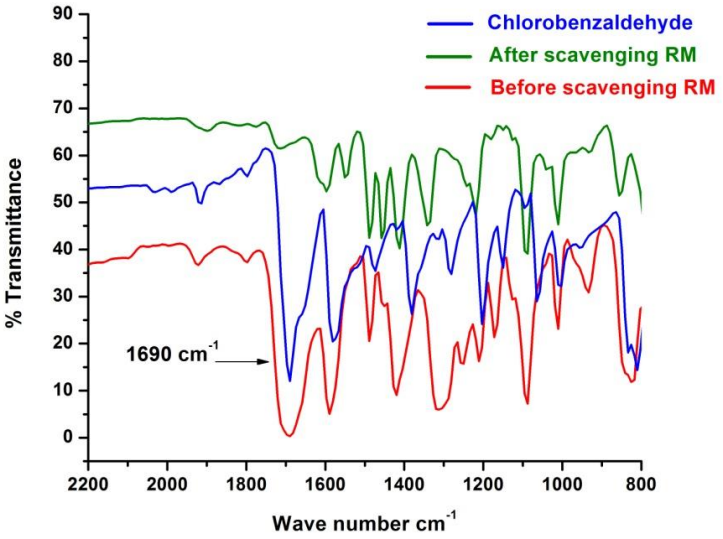


Scheme 2.19: Synthesis of *bis*(indolyl)methane from indole and 4-chlorobenzaldehyde

The aldehyde sequestration reaction was verified by IR, NMR and HPLC analysis (Fig. 2.13). Disappearance of the signal at 1690 cm^{-1} in the IR spectrum (Fig. 2.13, i), disappearance of a

peak at retention time of 4 min. corresponding to aldehyde **46d** in the HPLC analysis (Fig. 2.13, ii) and disappearance of peak at δ 9.98 in the ^{1}H NMR spectrum (Fig 2.13, iii) of **55d** obtained after treating with **19** confirmed that unreacted aldehyde was completely scavenged.

i)



ii) iii)

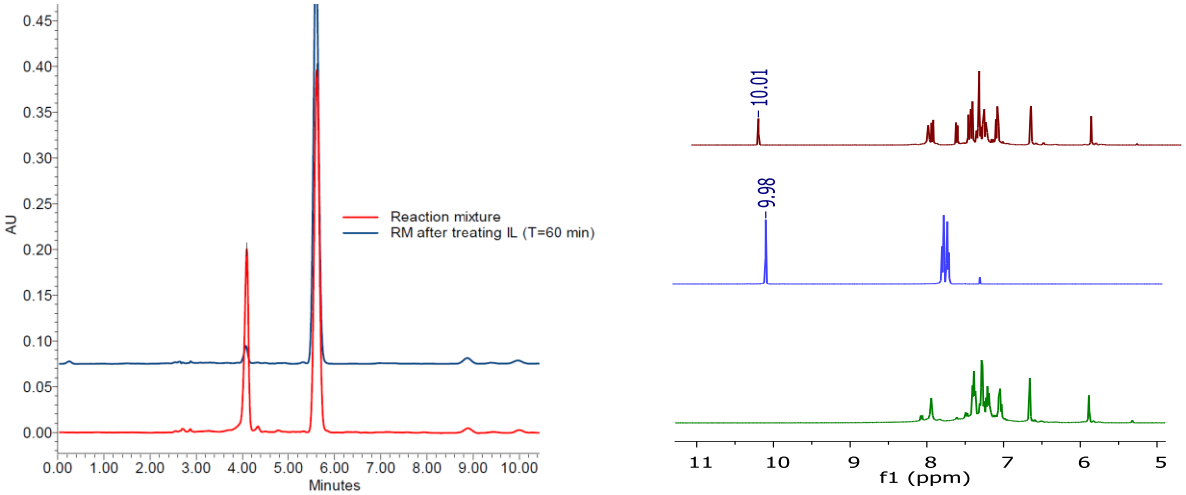


Figure 2.13: i) IR analysis, ii) HPLC analysis iii) ^{1}H NMR of a) reaction mixture, b) 4-chlorobenzaldehyde, c) reaction mixture after treating with **19**

After establishing the protocol for model reaction, the developed methodology was applied for the synthesis of different substituted *bis*(indolyl)methane (**61aa-ia**) by varying different aldehydes and indoles (Table 2.9). Structures of all the isolated *bis*(indolyl)methanes were

confirmed by comparing their melting point with literature melting point and NMR data. A representative ^{1}H NMR and ^{13}C NMR of **61ad** is given in figure 2.14.

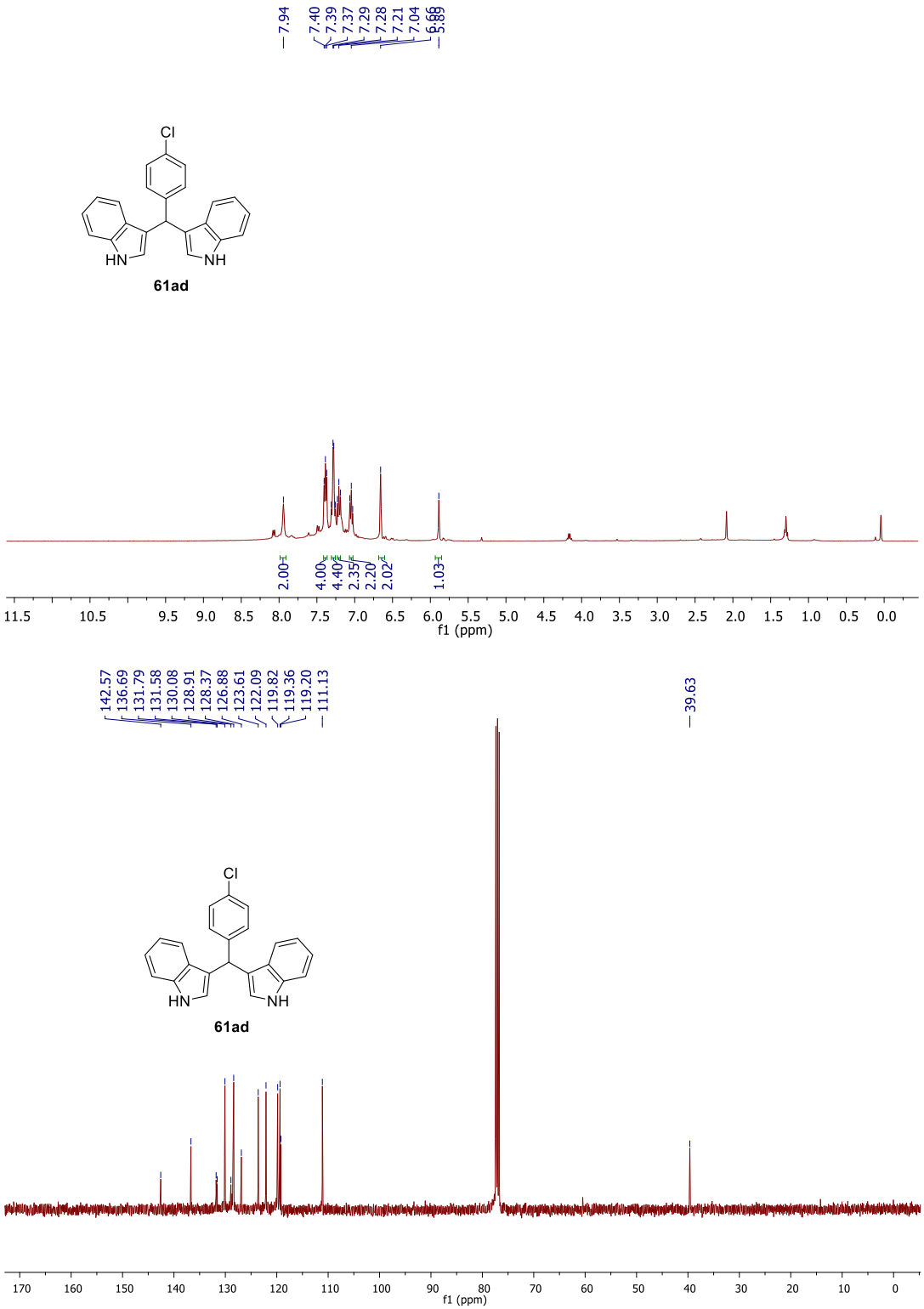


Figure 2.14: ^{1}H and ^{13}C NMR spectrum of **61ad**

Table 2.9: Synthesis of substituted *bis*(indolyl)methane by employing aldehyde scavenging method

Entry	R	R^1	Product	Time (min)	Yield (%)	M.P
1	H	C_6H_5	**61aa**	10	89	142-145 °C[44]
2	H	2-ClC_6H_4	**61ab**	15	87	71-73 °C[20, 44]
3	H	3-ClC_6H_4	**61ac**	15	91	64-68 °C[17]
4	Br	3-ClC_6H_4	**61bc**	20	89	165-168 °C
5	H	4-ClC_6H_4	**61ad**	15	93	80-82 °C[44]
6	Br	4-ClC_6H_4	**61bd**	10	82	210-212 °C[11]
7	H	4-BrC_6H_4	**61ae**	15	97	110-112 °C[24]
8	H	2,6-$(Cl)_2C_6H_3$	**61af**	30	85	114-118 °C[20]
9	H	4-$CH_3C_6H_4$	**61ag**	30	95	95-98 °C[17]
10	H	C_4H_3S	**61ah**	30	67	143-145 °C[20]
11	H	4-$NO_2C_6H_4$	**61ai**	240	70	218-220 °C[20,45]

[a]Reaction conditions: **60** (1.0 mmol), **46** (0.6 mmol), IL-SO_3H (10 mol %) and THF (2 ml) at room temperature.

Recyclability of the catalyst [IL-SO_3H][CF_3SO_3] (**17a**) was also evaluated. To recover the catalyst, aqueous layer was distilled under reduced pressure and the residue obtained was washed with ether. The recovered catalyst was reused for 5 cycles in the model reaction to give 96%, 94%, 92%, 92% and 90% isolated yield of **61ad** without much loss in reactivity (Fig 2.15).

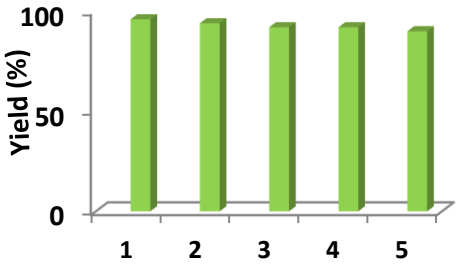
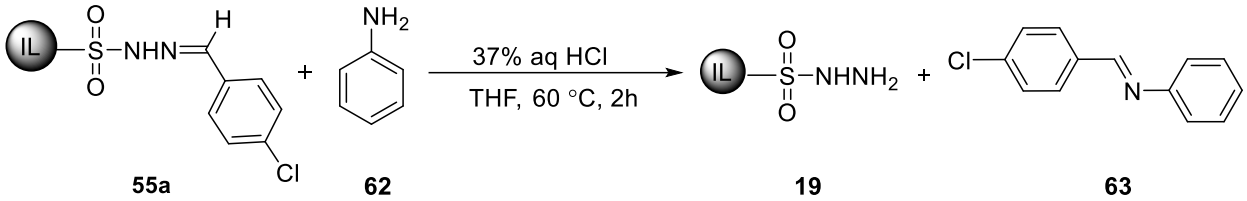


Figure 2.15: Reusability of **17a** in the synthesis of *bis*(indolyl)methane

It is also worth mentioning that recovered IL-supported sulfonyl hydrazone (**55**) can be easily converted to reagent **19** by reacting with aniline (**62**) in the presence of 37% HCl in THF at 60 °C for 2 h (Scheme 2.20). The recovered IL-supported sulfonyl hydrazine **19** could be reused at

least two times in scavenging experiments with purities similar to those obtained in the first run.[46]



Scheme 2.20: Regeneration of ionic liquid-supported sulfonyl hydrazine (**19**)

2.14 Conclusion

In conclusion, we have illustrated that the ionic liquid-supported sulfonic acid and sulfonyl hydrazine can be utilized as an efficient acid catalyst and scavenger in simple and efficient manner for the synthesis of *bis*(indolyl)methane. The *bis*(indolyl)methanes were obtained in good to excellent yield (67-97%) with high purity. There are several advantages associated with this approach, specifically, high loading capacity of catalyst/scavenger, low reaction time, short sequestration duration and reusability. The purification of products without column chromatography and ease of monitoring the progress reaction by IR, ^{1}H NMR, ^{13}C NMR and HPLC spectroscopy are some of the supplementary advantages of this protocol. The ionic liquid-supported sulfonic acid and ionic liquid-supported sulfonyl hydrazine has been regenerated and reused up to 5 to 2 times without significant loss of activity respectively.

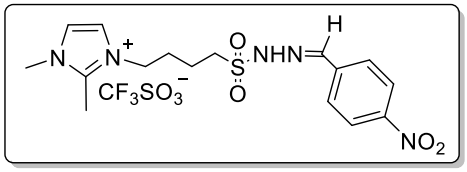
2.15 Experimental

NMR spectra were recorded on 400 MHz spectrometer using $CDCl_3$ and DMSO-d_6 as solvents. The chemical shifts were expressed in ppm. The IR spectra were recorded with KBr on ABB Bomem MB3000 FTIR spectrophotometer. Reactions were monitored by thin-layer chromatography (TLC) carried out on silica-coated aluminum plates using UV light as visualizing agent. All the chemicals and reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. DSC was recorded on Perkin Elmer DSC 4000 at a heating rate of 10 °C min^{-1} using nitrogen as the carrier gas in the range 0 °C to 300 °C and thermogravimetric analysis (TGA) was recorded using the Perkin Elmer TGA 4000 using nitrogen at a linear heating of 10 °C min^{-1}.

General procedure for the synthesis of ionic liquid-supported sulfonyl hydrazones

To the ionic liquid-supported sulfonyl hydrazide (**19**, 1 mmol) in ethanol aldehydes (**46**, 1.1 mmol) were added and the resulting solution was stirred at room temperature vigorously for 2-3 h. After completion of the reaction, ethanol was removed and the resulting mixture was washed with ethyl acetate/hexane mixture (1:1 *v/v*) and dried under reduced pressure to get the pure product. Then mention their spectral data for all the compounds expect **55i** are given in part B.

Compound 55i

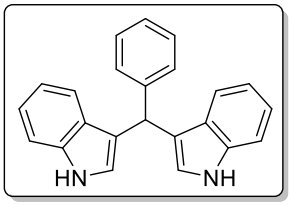


Yield: 95%; yellow solid; mp 155-158 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.74 (s, 1H), 8.29 (d, J = 8.8 Hz, 2H), 8.09 (s, 1H), 7.92 (d, J = 8.9 Hz, 2H), 7.61 (d, J = 2.0 Hz, 1H), 7.58 (d, J = 2.0 Hz, 1H), 4.15 (t, J = 7.2 Hz, 2H), 3.72 (s, 1H), 3.34 (d, J = 7.7 Hz, 4H), 2.57 (s, 1H), 1.90 – 1.79 (m, 1H), 1.72 (dt, J = 15.1, 7.5 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.3, 144.8, 144.0, 140.45, 128.2, 124.5, 122.8, 121.3, 119.5, 50.4, 47.2, 35.12, 27.9, 20.2, 9.6.

General procedure for the synthesis of *bis*(indolyl)methane

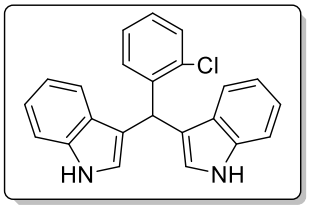
A mixture of indole (**60**) (1.0 mmol), aldehyde (**46**) (0.6 mmol) and ionic liquid-sulfonic acid **17a** (10 mol %) in THF (2 mL) was stirred at room temperature for 15 min. The reaction was monitored by TLC. After completion of the reaction, hexane-ethyl acetate (2 mL, 1: 1 *v/v*) was added and organic layer was removed by decantation from the reaction mixture. IL-sulfonyl hydrazine **19** (0.15 mmol) was added in the organic phase to scavenge the excess aldehyde. The reaction mixture was stirred at room temperature for 1h. On complete consumption of the aldehyde as indicated by TLC and DNP test, water (2 mL) was added to the reaction mixture and the organic layer was decanted leaving behind IL-sulfonyl hydrazine **19** and IL-sulfonyl hydrazone **55** in the aqueous phase. The aqueous phase was washed with ethyl acetate/hexane (1 × 2 mL, 1: 1, *v/v*) and the combined organic phase was evaporated using a rotatory evaporator to obtain pure *bis*(indolyl)methanes (**61**) without column chromatography.

3,3'-(Phenylmethylene)*bis*(1*H*-indole) (61aa)



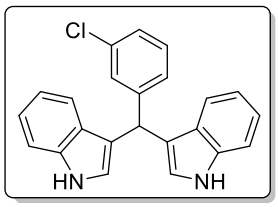
Yield: 89% (HPLC purity 95.9%); pink solid; mp 142-145 °C (lit. 151-152 °C [44]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (bs, 2H), 7.34 (m, 11H), 7.07 (d, J = 6.3 Hz, 2H), 6.59 (s, 2H), 5.93 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1, 136.6, 128.7, 128.3, 127.0, 126.2, 123.7, 121.9, 119.9, 119.6, 119.2, 111.1, 40.2.

3,3'-((2-Chlorophenyl)methylene)*bis*(1*H*-indole) (61ab)



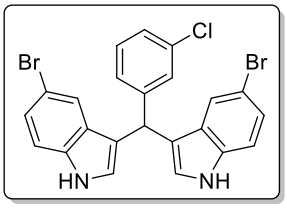
Yield: 87% (HPLC purity 97.2%); pink solid; mp 71-73 °C (lit. 74-76 °C [20, 44]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (bs, 2H), 7.44 (td, J = 8.3, 0.9 Hz, 3H), 7.38 (dt, J = 8.2, 0.8 Hz, 2H), 7.27-7.10 (m, 6H), 7.05 (ddd, J = 8.0, 7.1, 1.0 Hz, 2H), 6.64 (dd, J = 2.4, 0.9 Hz, 2H), 6.37 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 136.7, 133.9, 130.3, 129.5, 127.5, 127.0, 126.6, 123.8, 122.0, 119.8, 119.3, 118.3, 111.0, 36.6.

3,3'-((3-Chlorophenyl)methylene)*bis*(1*H*-indole) (61ac)



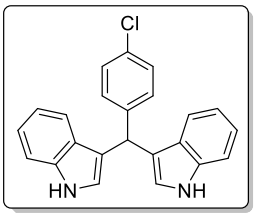
Yield: 91% (HPLC purity 96.5%); pink solid; mp 64-68 °C (lit. 64-68 °C [17]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 2H), 7.41 (dd, J = 8.2, 7.7 Hz, 3H), 7.37 (s, 2H), 7.27-7.19 (m, 5H), 7.09-7.03 (m, 2H), 6.64 (s, 2H), 5.89 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 136.6, 134.0, 129.5, 128.8, 126.9, 126.8, 126.4, 123.6, 122.1, 119.7, 119.3, 118.9, 111.1, 39.9.

3,3'-((3-Chlorophenyl)methylene)*bis*(5-bromo-1*H*-indole) (61bc)



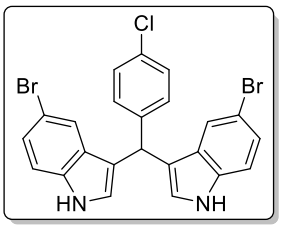
Yield: 89% (HPLC purity 98.3%); pink solid; mp 165-168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (bs, 1H), 7.49 (s, 1H), 7.33-7.23 (m, 4H), 6.64 (s, 1H), 5.75 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 135.3, 134.2, 129.7, 128.6, 128.4, 126.8, 126.7, 125.1, 124.8, 122.1, 118.2, 112.8, 112.7, 39.6.

3,3'-((4-Chlorophenyl)methylene)*bis*(1*H*-indole) (61ad)



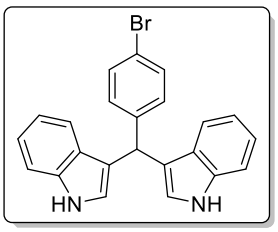
Yield: 96%; (HPLC purity 96.8%); pink solid; mp 80-82 °C (lit. 76-77 °C [44]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (bs, 2H), 7.43-7.36 (m, 5H), 7.28 (q, J = 8.9 Hz, 6H), 7.24-7.17 (m, 4H), 7.05 (t, J = 7.5 Hz, 3H), 6.66 (s, 2H), 5.89 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 136.6, 131.7, 131.5, 130.0, 128.9, 128.3, 126.8, 123.6, 122.0, 119.8, 119.3, 119.2, 111.1, 39.6.

3,3'-((4-Chlorophenyl)methylene)*bis*(5-bromo-1*H*-indole) (61bd)



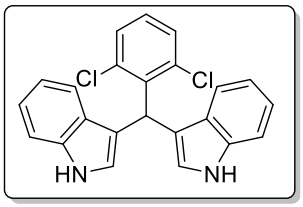
Yield: 82%; (HPLC purity 97.3%); pink solid; mp 210-212 °C (lit. 212-214 °C [11]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (bs, 2H), 7.48 (d, J = 0.9 Hz, 2H), 7.32-7.20 (m, 8H), 6.63 (s, 2H), 5.75 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 135.3, 132.2, 129.9, 128.6, 128.4, 125.1, 124.7, 122.1, 118.5, 112.8, 112.7, 39.3.

3,3'-((4-Bromophenyl)methylene)*bis*(1*H*-indole) (61ae)



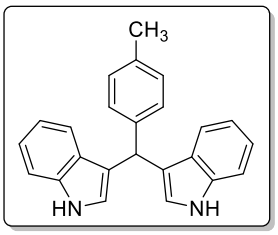
Yield: 97% (HPLC purity 99.05%); pink solid; mp 110-112 °C (lit. 112-113 °C [24]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (bs, 2H), 7.39 (m, 6H), 7.27-7.16 (m, 4H), 7.05 (t, J = 7.4 Hz, 2H), 6.62 (s, 2H), 5.87 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 136.6, 131.3, 130.5, 126.8, 123.6, 122.1, 119.9, 119.8, 119.3, 119.0, 111.2, 39.6.

3,3'-((2,6-Dichlorophenyl)methylene)*bis*(1*H*-indole) (61af)



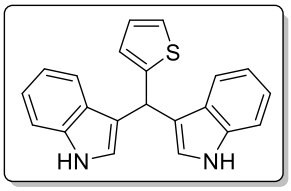
Yield: 85% (HPLC purity 98.6%); pink solid; mp 124-128 °C (lit. 108 °C [20]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (bs, 1H), 7.40 (dd, J = 7.5, 5.0 Hz, 5H), 7.18 (m, J = 15.9, 7.6 Hz, 2H), 7.06 (t, J = 7.4 Hz, 1H), 6.89 (s, 1H), 6.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 136.3, 128.1, 127.1, 124.4, 121.8, 119.6, 119.3, 115.2, 111.1, 37.1.

3,3'-(*p*-Tolylmethylene)*bis*(1*H*-indole) (61ag)



Yield: 95% (HPLC purity 95.4%); pink solid; mp 95-98 °C (lit. 93-95 °C [17]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (bs, 1H), 7.44 (d, J = 7.9 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.29-7.23 (m, 2H), 7.20 (t, J = 7.6 Hz, 1H), 7.12 (d, J = 7.8 Hz, 1H), 7.04 (t, J = 7.5 Hz, 1H), 6.65 (s, 1H), 5.88 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 136.6, 135.5, 128.9, 128.5, 127.1, 123.6, 121.8, 119.9, 119.8, 119.1, 111.0, 39.7, 21.1.

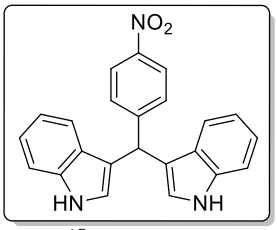
3,3'-(Thiophen-2-ylmethylene)*bis*(1*H*-indole) (61ah)



Yield: 67% (HPLC purity 98.5%); off white solid; mp 143-145 °C (lit. 147-149 °C [20]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (bs, 2H), 7.51 (d, J = 7.9 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H), 7.25-7.17 (m, 3H), 7.08 (m, 2H), 6.95 (dt, J = 5.2, 2.8 Hz, 2H), 6.82 (s, 2H), 6.20 (s, 1H); ^{13}C NMR (100

MHz, $CDCl_3$) δ 148.6, 136.5, 126.7, 126.4, 125.1, 123.6, 123.2, 122.0, 119.8, 119.6, 119.3, 111.1, 35.3.

3,3'-((4-Nitrophenyl)methylene)*bis*(1*H*-indole) (61ai)



Yield: 70% (HPLC purity 99.6%); yellow solid; mp 218-220 °C (lit. 217-219 °C [20, 45]) ; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.94 (bs, 2H), 8.16 (d, J = 8.7 Hz, 2H), 7.61 (d, J = 8.7 Hz, 2H), 7.37 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 7.9 Hz, 2H), 7.06 (t, J = 7.3 Hz, 2H), 6.93-6.84 (m, 4H), 6.03 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.6, 146.2, 137.0, 129.9, 126.8, 124.3, 123.9, 121.5, 119.3, 118.8, 117.1, 112.0, 39.8.

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Chapter III

Synthesis of Ionic Liquid-supported Hypervalent Iodine Reagent and their Applications in Organic Synthesis

Chapter III

PART A

Ionic Liquid-supported Hypervalent Iodine Reagent: Synthesis of α-Substituted Acetophenones

3.1 Introduction

A hypervalent state is defined as when an atom expands its valence shell beyond the limits of the Lewis octet rule. Iodine is the largest, more electropositive and most polarizable element in the halogen family of the periodic table, due to this it can form multivalent compounds. In 1886, the German chemist Conrad Willgerodt reported first hypervalent iodine compound dichloro iodobenzene ($PhICl_2$) which was synthesized from iodobenzene and chlorine gas.[1, 2] Iodine forms two type of hypervalent compound with oxidation state +III and +V. According to IUPAC rules, iodine(III) and iodine(V) compounds are called λ^3 and λ^5-iodanes, respectively. The most common type of λ^3-iodanes are $ArIL_2$ (where Ar = aryl group and L = hetero-ligand) which shows a pseudo-trigonal bipyramidal (T-shape) geometry with an aryl moiety and two free electron pairs in equatorial positions whereas the two hetero ligands (L) are in apical positions[3, 4] (Figure 3.1). The chemistry of hypervalent iodine compounds have been extensively studied and reported in several books[3, 5] and reviews[6-8] published.

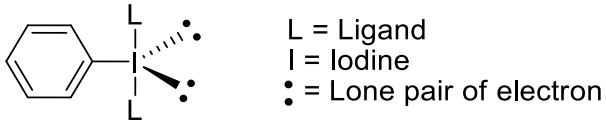


Figure 3.1: Geometry of hypervalent iodine (III)

Iodine(III) compounds can be further classified into two types: a) **two** heteroatom ligand bound to iodine this class includes iodosylbenzene, [hydroxy(tosyloxy)iodo]benzene (HTIB, Koser's reagent) and (diacetoxyiodo)benzene reagents (Figure 3.2) and they can be employed in oxidation of alcohols and alkenes, synthesis of quinones, in rearrangements and also in α-acetoxylation of carbonyl compounds,[6] b) two carbon ligands bound to iodine such as diaryliodonium salts which are not very good oxidizing agents but owing to their highly electron deficient nature and excellent leaving group ability, they are used as an arylating agent with different nucleophiles. In recent years, hypervalent iodine compounds have received great interest in organic synthesis due to their environmentally friendly, easy handling, mild oxidant and nontoxic nature. Morever, highly selective electrophilic reagents under either metal-free or in presence of metal have also gained significant traction.[9-14]

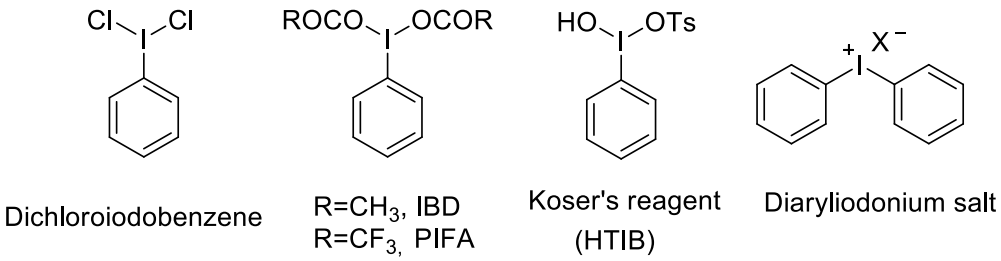


Figure 3.2: Important hypervalent iodine(III) compounds

Iodine(III) compounds with two heteroatom ligands are believed to retain T-shape in solution, whereas the diaryliodonium salt structure in solution has been debated and could depend on the anion X^- as well as the solvent. The IUPAC nomenclature for this class of compound is "diaryl-λ^3-iodanes", although the old term diaryliodonium salt is still in use. Reactions of iodine(III) compounds with various nucleophiles (Nu^-) initially construct Nu-I bond with the release of one of the ligand which take place by ligand exchange, either by an associative or dissociative mechanism.[3] In the associative mechanism, ArILNu is formed through square planar iodate intermediate $ArIL_2Nu$ with subsequent release of a ligand (L) and further reductive elimination (also called ligand coupling) gives the product Nu-L and releases ArI as byproducts. The mechanism of the second step depends on the nucleophile, the nature of the ligand and the reaction conditions (Figure 3.3).[5]

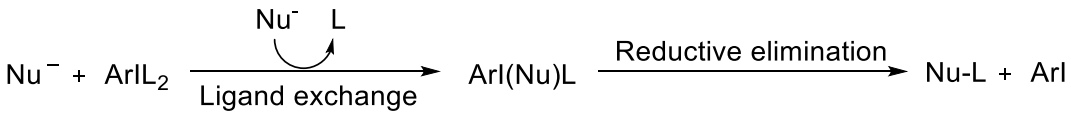


Figure 3.3: Reactivity of diaryliodonium salt

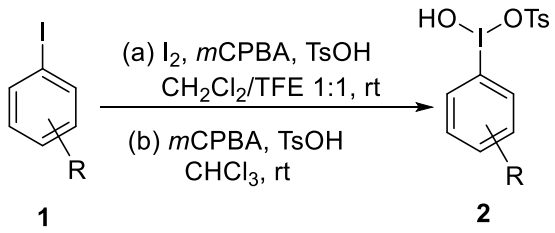
Among different iodine(III) reagents, HTIB and diaryliodonium salts have received special attention in organic synthesis in recent years as reagents. A brief overview of these reagents in given below

3.1.1 [Hydroxy(tosyloxy)iodo]benzene (HTIB):

In 1970, Neiland and Karele first time reported [hydroxy(tosyloxy)iodo]benzene (HTIB) which was readily prepared from (diacetoxyiodo)benzene and *p*-TsOH•H_2O in organic solvents and was recrystallized from acetonitrile.[15] It is a stable, nonhygroscopic crystalline solid which does not require any special precautions under atmospheric conditions. HTIB have been employed in oxidation of olefins, ring contractions and expansions, dearomatization of phenols, synthesis of

iodonium salts and α-oxidation of carbonyl compounds.[16-18] It is an efficient reagent for the α-tosyloxylation of ketones which are the precursors for the formation of alkynyl phenyl iodonium tosylate and for construction of heterocyclic compounds such as imidazoles, pyrazoles, thiazoles, oxazoles, selenazoles, benzofurans, lactones, enediynes and natural products.[7, 19-21] Recently, synthesis of chiral HTIBs and its catalytic application have also been reported.[22-24]

Olofsson group have synthesized a wide range of electron-deficient and electron-rich HTIBs **2** from iodoarenes **1** by oxidative addition of TsOH in the presence of *m*-chloroperbenzoic acid (*m*-CPBA) and TFE as co-solvent along with dichloromethane (1:1). [25] Togo and co-workers have also reported a one-pot synthesis of HTIBs **2** from iodoarenes **1**.[26] They treated iodoarenes with *m*-CPBA at room temperature in chloroform to give HTIBs **2** in high yields (Scheme 3.1).



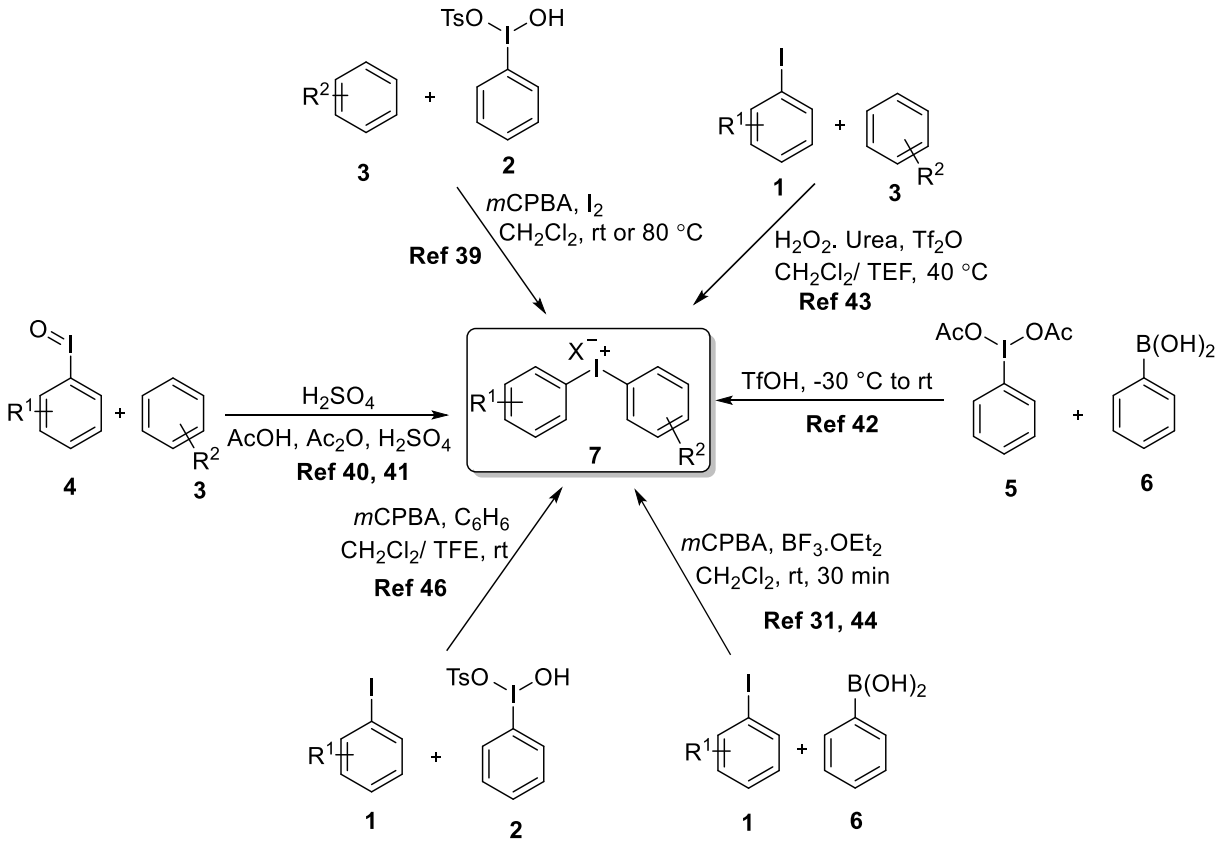
1 **2**

Scheme 3.1: Synthesis of HTIB using iodoarene **2**

3.1.2 Diaryliodonium salt:

Diaryliodonium salts also referred to as diaryl-λ^3-iodane (III) compounds consist of an iodine atom, two aryl moieties, and an anion. In 1894, Hartmann and Meyer prepared the first known diaryliodonium salt (4-iodophenyl)phenyl iodonium bisulfate by reacting iodosylbenzene with sulfuric acid (H_2SO_4).[27] Diaryliodonium salts are useful versatile arylating reagents for various nucleophiles. They have emerged as a source of aryl cation in the *O*-arylation of phenols, carboxylic acids, alcohols, vicinal diols, and *N*-hydroxyphthalimide.[28] They have received renewed interest in organic synthesis as a more reactive version of iodoarenes for various C–C, C–O, C–N, and C–S cross-coupling reactions.[29] Usually, diaryliodonium salts are prepared by two to three reaction steps, commonly followed by an anion exchange.[30-32] Although the shorter routes are available, it requires the use of toxic chromium regents or inorganic iodine (III) reagents which need to be prepared in advance.[33-35] These salts are air and moisture-stable whose solubility and reactivity are strongly affected by the nature of the anionic part of the molecule.[36, 37] The salts with anions such as tosylate, triflate and tetrafluoroborate have better solubility in many organic solvents than the halide anions, therefore, these non-nucleophilic

anions are easily applicable in organic synthesis. Diaryliodonium salts can be classified in two types: a) Symmetrical diaryliodonium salts where both aryl groups are identical and these salts are generally preferable over unsymmetrical salt to avoid chemoselectivity issues of the reactions. b) Unsymmetrical diaryliodonium salts where both aryl groups are differentiated electronically or sterically from each other. Unsymmetrical salts are desirable when the starting materials are expensive, as one aryl moiety can be selectively transferred over the other aryl moiety behaving as a "dummy ligand" and this type of selectivity will be referred to as the chemoselectivity of the reaction.[13, 38] The general trend is that the more electron-deficient aryl moiety is transferred in enolate and heteroatom arylations whereas the more electron-rich aryl group is transferred in cross-coupling reactions. Scheme 3.3 shows various methods for the one pot synthesis of diaryliodonium.[13, 31, 39-46]



Scheme 3.3: One-pot synthesis of diaryliodonium salts (**7**)

Finding novel and more expedient techniques that will facilitate the rapid production and purification of desired molecules is an area of continued creativity for organic chemists. Although solid-phase "catch and release" methods enable the efficient generation of many

pharmacological important compounds, difficulties in analyzing the intermediates, non-linear kinetics and heterogeneous reaction conditions are major concerns in these methods.

It is very challenging to improve the efficiency of the reaction and make the purification process simple and straightforward. Solid-phase organic synthesis (SPOS)[47-51] is a widely employed tool in a combinatorial synthesis that has facilitated the synthesis of many pharmacologically important compounds and made the purification process more facile. Development of new linkers for tethering organic compounds to the supports is an area of active investigation in supported synthesis.[52-54] Choice of the linker is a key consideration in planning a supported synthesis since the cleavage conditions often lead to extra or unwanted functional groups in the molecule and moreover, the liability of the linker limits the chemistry which may be carried out on it. In this context, "catch and release" strategy has been very useful and they has been explored in combinatorial chemistry for rapid production of a library of organic compounds with adequate purity.

This has driven the re-evaluation of supported reagents and scavengers in combinatorial synthesis with the combined advantages of solid- and solution-phase chemistry. The synthesis of polymer, polyethylene glycol (PEG) and silica-supported reagents is tricky, and it is difficult to determine the amount of reagent that has been grafted on these supports. On the other hand, fluorous-supported reagents are expensive and need specialized solvents to carry out the reactions. In recent years, ionic liquid-supported reagents[55-63] have gained considerable interest as a promising alternative of supported reagents due to their high loading capacity, tunable solubility, homogeneity and easy monitoring of the reaction by various analytical techniques such as NMR, IR and mass spectrometry. Several ionic liquid-supported reagents including hypervalent iodine reagents have been synthesized and used for different organic transformations (Figure 3.4).[59, 61-66]

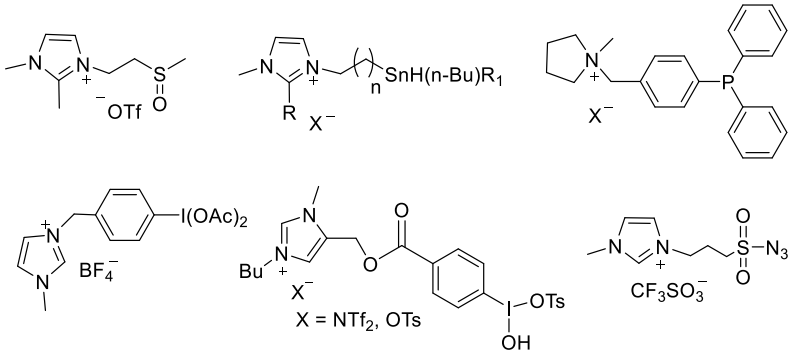


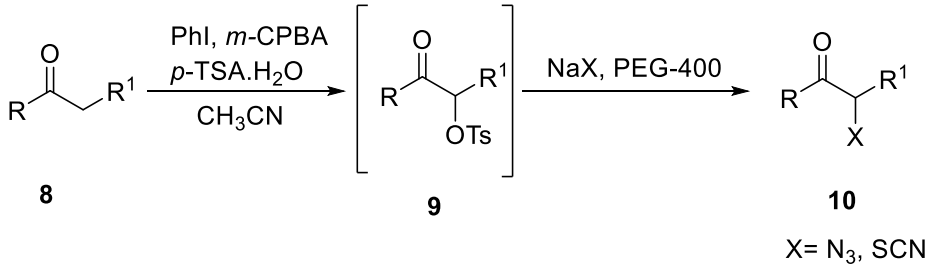
Figure 3.4: Structure of some ionic liquid-supported reagents

This chapter of thesis deals with synthsis of novel ionic liquid-supported iodine reagents and exploration of this application in selected organic transformation. The chapter is divided in three parts. In part A, a novel ionic liquid-supported iodine reagent is synthesized and used for the synthesis of α-substituted ketones. In part B of this chapter, 2-aminothiazole and imidazo[1,2-*a*]pyridine have been synthesized using ionic liquid-supported reagent. In part C of this chapter, different ionic liquid-supported iodonium reagents have been synthesized and explored for arylation of phenols and carboxylic acids.

3.2 Introduction

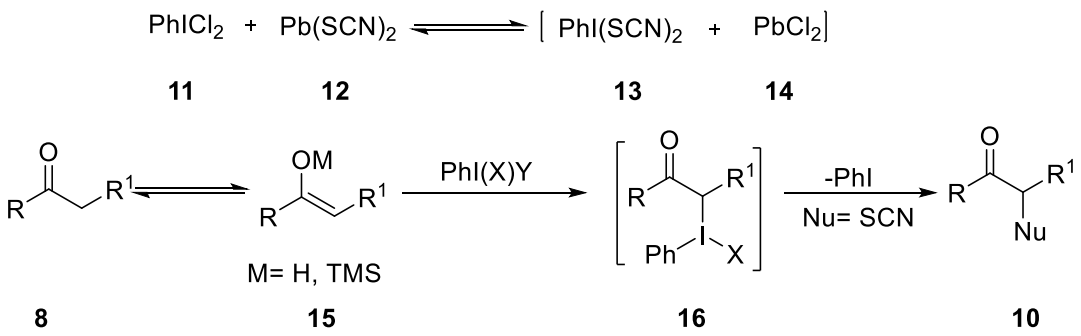
α-Functionalized carbonyl compounds are important precursors for the construction of wide variety of heterocyclic compounds such as imidazoles, thiazoles and oxazoles.[67] Thus, there has been a great interest of organic chemists towards synthesis of *α*-functionalized ketones. Several methods have been developed for the synthesis of different *α*-functionalized ketones such as *α*-azidoketones, *α*-iodoketo and *α*-thiocyanatoketo.[57, 68-77] A brief overview of some recent methods for synthesis of *α*-substituted ketones is given below.

Chen *et al.* have demonstrated one pot synthesis of *α*-thiocyanatoketo and *α*-azidoketone by the reaction of aryl ketone **8** with *in situ* generated HTIB followed by a nucleophilic substitution reaction of *α*-tosyloxy ketone **9** by sodium thiocyanate and an azide, respectively at room temperature.[78] The salient features of this methodology are mild reaction conditions, less reaction time and high yields. Various Aryl substituents bearing different electron-withdrawing and electron-donating groups were well tolerated to give corresponding α-substituted ketone **10** in good to excellent yields (75-86%) (Scheme 3.6).



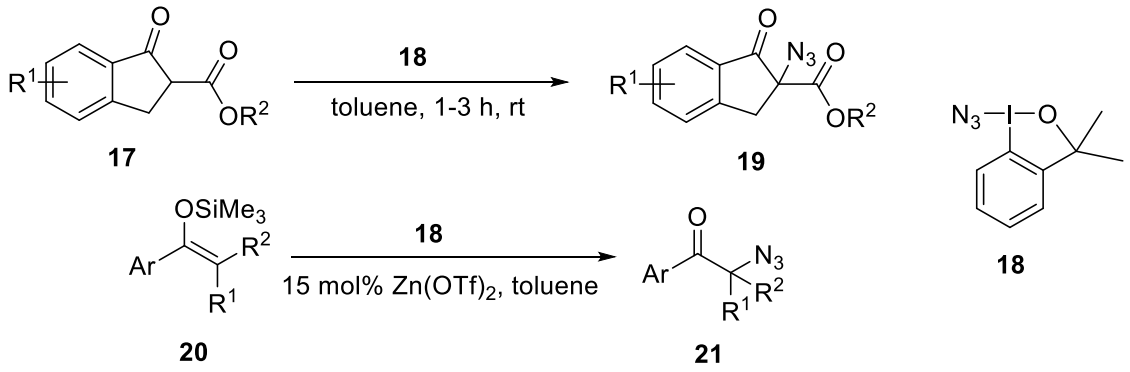
Scheme 3.6: Synthesis of *α*-azidoketone and *α*-thiocyanatoketones

Moriarty group has demonstrated very effective *α*-thiocyanation of carbonyl and *β*-carbonyl compounds **8** using $PhICl_2$ + $Pb(SCN)_2$ in dry DCM at 0 °C (Scheme 3.7).[79] The reaction of a carbonyl compound with hypervalent iodine reagent **13** provided tricoordinate iodine intermediate **16**. This intermediate **16** further reacts with a nucleophile to produce the *α*-substituted carbonyl compound **10** and iodobenzene. The reaction did not take place in case of *p*-nitro acetophenone.



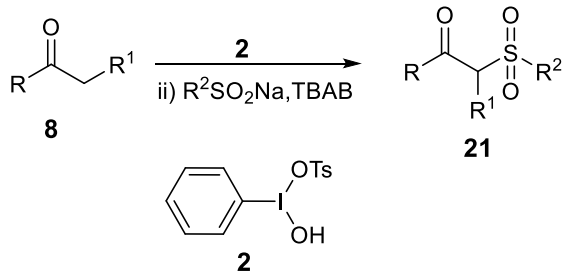
Scheme 3.7: α-Thiocyanation of carbonyl compound using **13**

Waser group reported azidation of cyclic *β*-ketoester **17** and silyl enol ethers **20** using azidobenziodoxole reagent **18** in the absence of any catalyst in toluene (Scheme 3.8).[80] In the case of less reactive acyclic *β*-ketoester and silyl enol ethers, the presence of Lewis acid $Zn(OTf)_2$ along with **18** complete the conversion through nucleophilic activation by the formation of zinc enolate or by electrophilic activation of reagent.



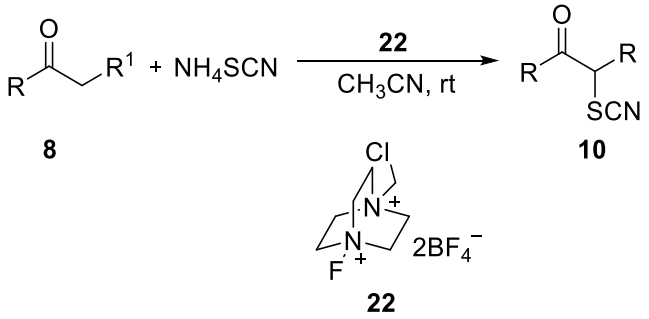
Scheme 3.8: Azidation of silyl enol ethers and *β*-ketoesters using **18**

Kumar *et al* have devised an efficient solvent free one pot synthesis of *β*-ketosulfones **25** from readily available ketones **24** in the presence of TBAB (scheme 3.9).[81] The *α*-tosyloxy ketone produced *in-situ* was further reacted with $ArSO_2N(^tBu)_4$ which was generated from TBAB and sodium arenesulfinate at room temperature to obtain desired product **25** in high yields (80-92%) in short reaction time. Same group applied similar synthetic methodology for the synthesis of *α*-azidoketone from the reaction of ketone **24** with sodium azide using **32**.[82]



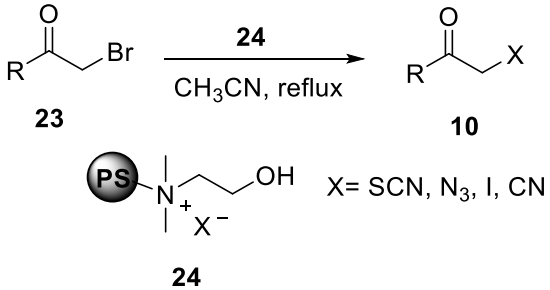
Scheme 3.9: Synthesis of *β*-ketosulfone using **2**

Wu group have achieved the synthesis of *α*-ketothiocyanate **10** by the reaction of a ketone with ammonium thiocyanate using selectflour **22** under mild and neutral condition (Scheme 3.10).[83] The reaction proceeds *via* the electrophilic substitution of ketones by *in situ* generated thiocyanogen which was amalgamated from ammonium thiocyanate and selectflour **22**. A large number of various *α*-thiocyanoketones **10** were synthesized in good to excellent yield (80-94%).



Scheme 3.10: *α*-Thiocyanation of ketones using **22**

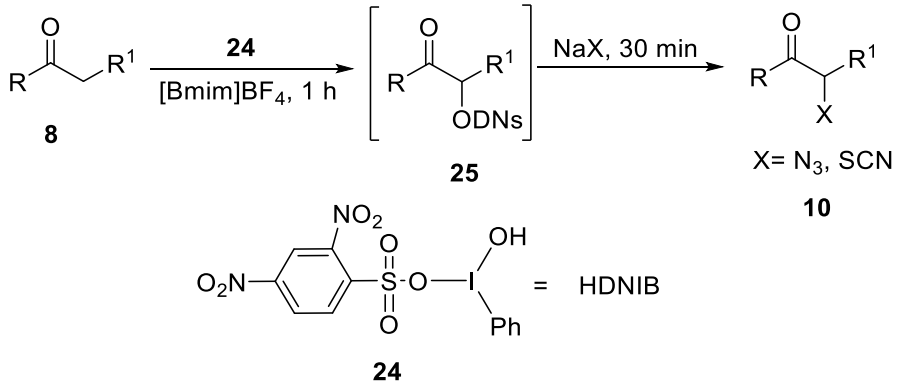
Kiasat group prepared different *α*-substituted ketones using polymer supported reagent **28** with different counter ions (Scheme 3.11).[84] The polymer supported reagent does not suffer from any decomposition and can be recycled without any loss of efficiency.



Scheme 3.11: Synthesis of *α*-substituted ketone using **24**

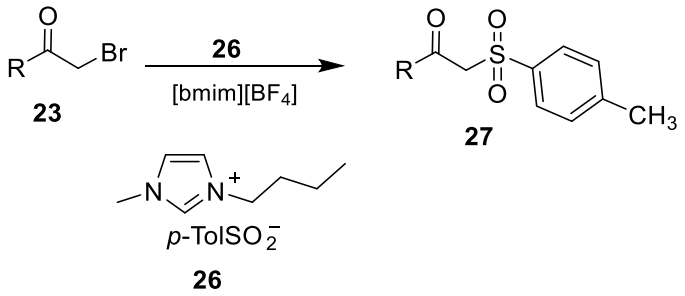
Lee group [15, 85] have reported the synthesis of *α*-azidoketone and *α*-thiocyanatoketones **10** by the reaction of aryl ketone **8** with HDNIB **24** in ionic liquid [bmim]BF_4 (Scheme 3.12).[78,79] The

reaction of ketone **8** with **24** gave an intermediate α-[(2,4-dinitrobenzene)sulfonyl]oxy ketone **25** and further nucleophilic attack on intermediate **25** gave a corresponding product α-azidoketone and α-thiocyanatoketones **10** in high yield (80-90%).



Scheme 3.12: Synthesis of α-azidoketone and α-thiocyanatoketones from aryl ketone in [bmim]BF_4

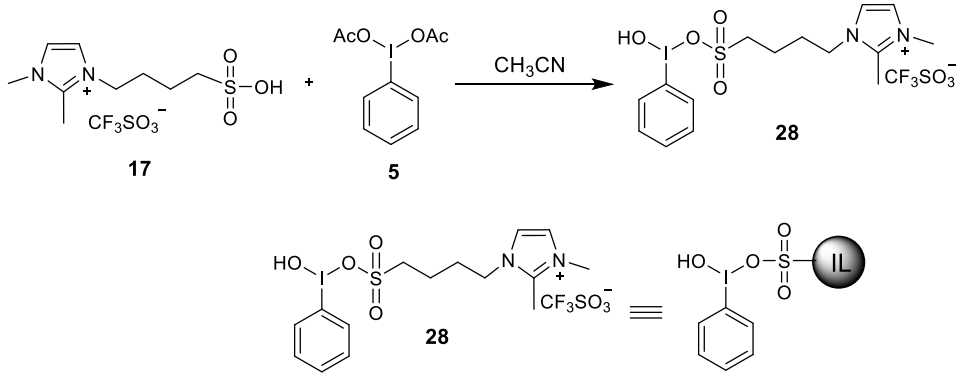
Kumar *et al*[86] have illustrated the synthesis of novel task specific ionic liquid [bmim]*p*-TolSO_2 **26** and used as a nucleophile for the synthesis of β-ketosulfone **27** from phenacyl bromide **23** respectively in ionic liquid [bmim]BF_4 as a reaction media (Scheme 3.13). All products were obtained in good to excellent yields (80-93%). Ionic liquid [bmim]BF_4 was best solvent for this reaction.



Scheme 3.13: Synthesis of β-ketosulfones using **26**

Continuing our interest in functionalized ionic liquids, we envisaged a new synthetic approach where ionic liquid supported reagents can be employed in a "catch and release (CAR)" strategy for the synthesis of α-functionalized ketones. The strategy is a hybrid of scavenging and liquid phase synthesis, where the ionic liquid-supported reagent captures the required substrate and releases the desired product by subsequent reactions.

3.3 Results and discussion



Scheme 3.14: Synthesis of ionic liquid-supported hypervalent iodine

The synthesis of **17** was achieved as reported in chapter 2a. The homogeneous solution of **17** in CH_3CN was added to a hot solution of iodobenzene diacetate (**5**), and the reaction mixture was kept at room temperature for one week to obtain **28**. Several attempts were made by varying the reaction conditions to reduce the reaction time with no success and the best yield of **28** was obtained in a week. The structure of **28** was unambiguously established by ^{1}H, ^{13}C NMR data and high-resolution mass spectrometry (HRMS). The ^{1}H NMR spectrum of **28** showed doublets at δ 7.63 and 7.59 for imidazole protons, along with other aromatic and aliphatic protons (Figure 3.5). In the ^{13}C NMR spectrum, the C_1 carbon of the phenyl ring attached to iodine resonated at *δ* 94.93 and the CF_3 carbon of $CF_3SO_3^-$ resonated at δ 121.02 as a quartet, in addition to the other six aliphatic and seven aromatic carbons of the molecule (Figure 3.5). The molecular ion peak at *m/z* 453.0345 $[M–CF_3SO_3]^+$ in the HRMS provided clear evidence towards the structure of **28**.

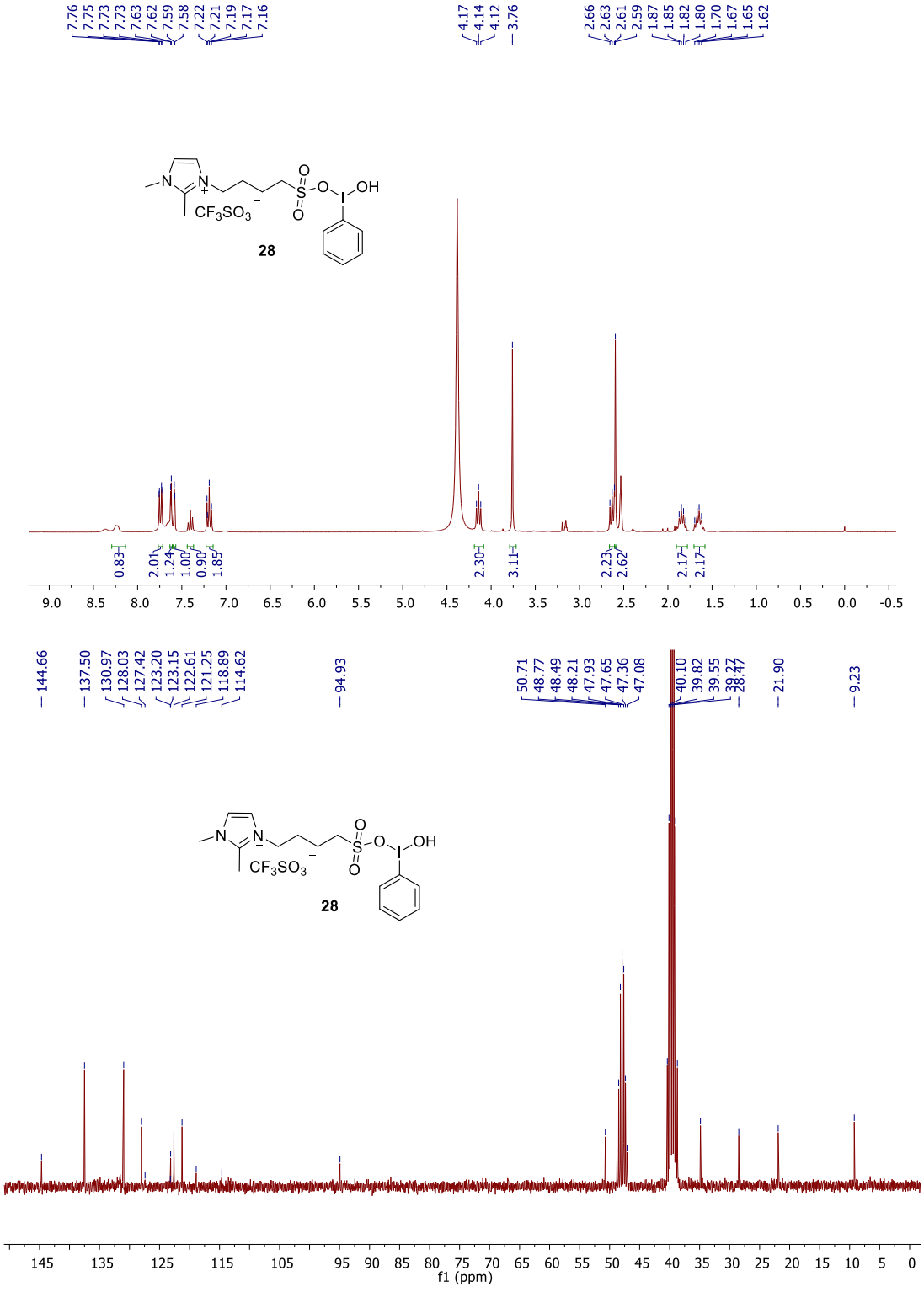
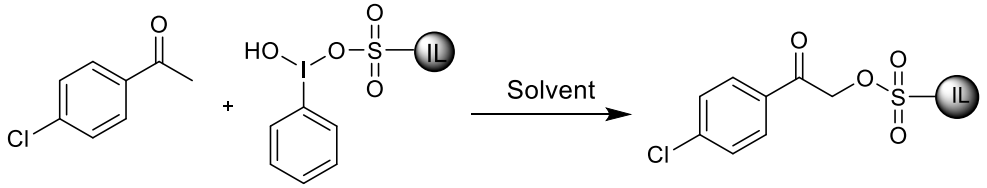


Figure 3.5: ^{1}H and ^{13}C NMR spectrum of **28**

After successful synthesis of **28,** we explored its application as α-sulfonating agent to capture ketones. To optimize the reaction conditions, 4-chloroacetophenone (**29a**) was selected as model substrate and reaction of **29a** with **28** was examined under different reaction conditions as outlined in table 3.1. It was found that **29a** was completely captured in CH_3CN (Table 3.1, entry 10) using 2 equiv of **28** at 80 °C after 12 h. Use of other solvents such as THF, $CHCl_3$ and [bmim][BF_4] did not result in efficient capturing of **29a**. Although capturing efficiency was observed more in solvent-free conditions (Table 3.1, entry 2), the formation of unidentified impurity was major drawback under this condition. To purify the product **30a**, acetonitrile was evaporated and the reaction mixture was run through a short plug of silica using dichloromethane: methanol mixture (95: 5 *v/v*) as eluent. The obtained pure product was analyzed by NMR and mass spectrometric data. The appearance of a peak at δ 5.70 for methylene protons attached to ionic liquid-supported sulfonate group along with other six aromatic and fourteen aliphatic protons in ^{1}H NMR spectrum, peak at δ 191.27 for carbonyl group along with other carbons in ^{13}C NMR spectrum (Figure 3.6) showed that **29a** was 'captured' on ionic liquid. Finally, a peak at *m/z* 385.098 corresponding to molecular formula $C_{17}H_{22}ClN_2O_4S^+$ $[M\text{-}CF_3SO_3]^+$ in HRMS confirmed the structure of **30a.**

Table 3.1: Optimization of the reaction condition to capture **29a** using **33**[a]



29a **28** **30a**

Entry	Solvent	**28** (mmol)	Temp (°C)	Time (h)	Conversion[b] (%)
1	-c	1	30	12	10
2	-c	1	80	12	70[d]
3	THF	1	Reflux	18	Traces
4	THF	2	Reflux	16	22
5	[bmim][BF_4]	1	80	16	17
6	[bmim][BF_4]	2	80	12	32
7	$CHCl_3$	2	Reflux	14	50

8	CH_3CN	1	80	12	51
9	CH_3CN	2	30	12	27
10	CH_3CN	2	80	12	100

[a]Reaction conditions: **29a** (1 mmol), **28** (as indicated in table), solvent (5 mL), Na_2SO_4 (0.5 mmol).
[b]Determined based on recovered **29a,** [c]No solvent, [d] Unidentified impurity was formed along with **30a.**

To explore the generality of the reaction, acetophenones with both electron-withdrawing and releasing groups were reacted with **28** to get **30**. Most of the substituted acetophenones reacted with **28** smoothly under given conditions (Table 3.2), however in the case of 4-methoxy and 4-nitroacetophenones small amount of corresponding benzoic acid (10-12 %) was formed along with **30** which was removed by simple washing with diethyl ether.

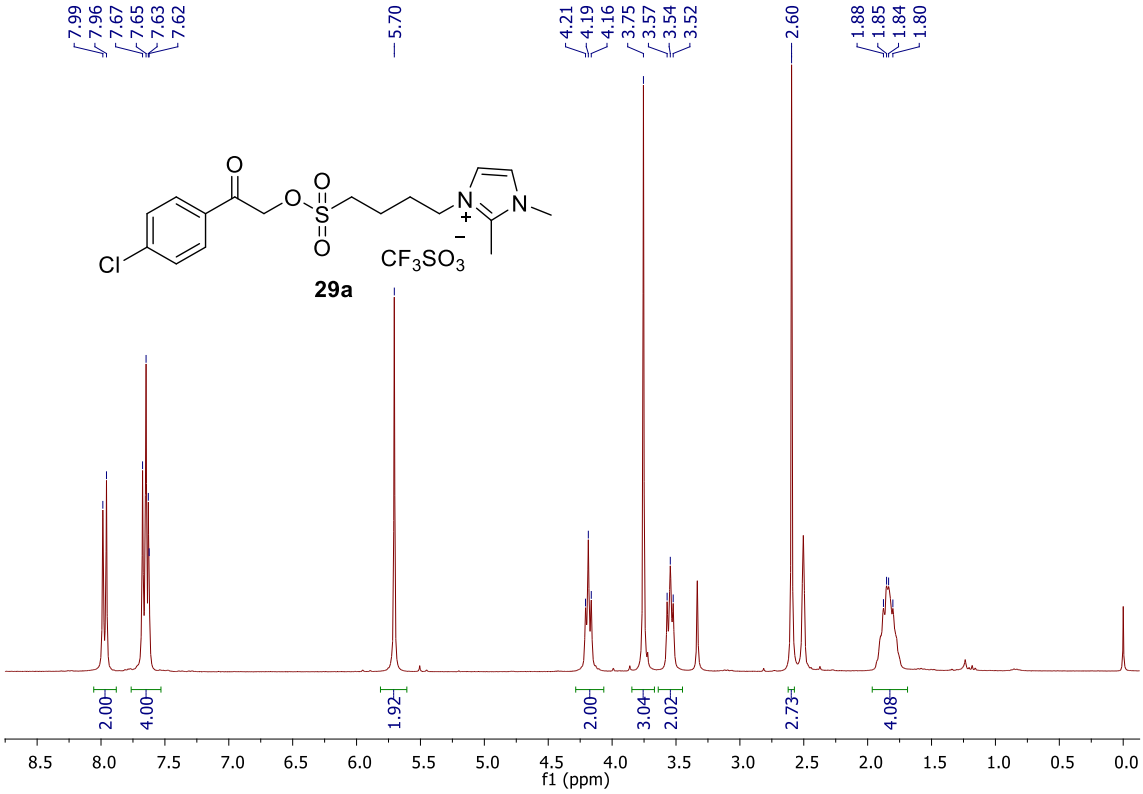


Figure 3.6: ^{1}H NMR spectra of ionic liquid-supported sulfonates **29a**

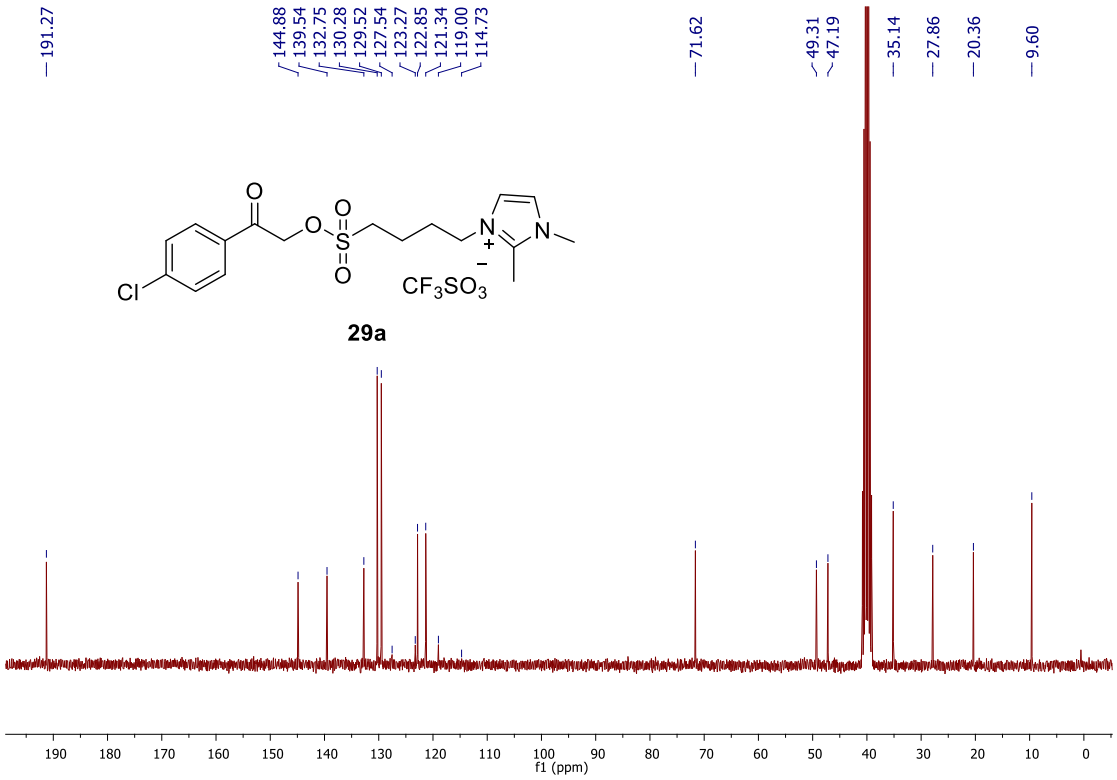
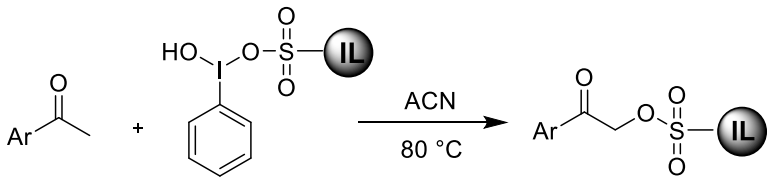


Figure 3.6: ^{13}C NMR spectra of ionic liquid-supported sulfonates **29a**

Table 3.2: Synthesis of ionic liquid-supported sulfonates **30** using **28**[a]



29(a-h) **28** **30(a-h)**

Entry	Ar	Conversion[b](%)	Entry	Ar	Conversion[b](%)
a	4-ClC_6H_4	100	e	4-$CH_3OC_6H_4$	80[c]
b	3-ClC_6H_4	100	f	$C_{10}H_7$	100
c	4-BrC_6H_4	90	g	4-$NO_2C_6H_4$	80[c]
d	4-$CH_3C_6H_4$	90	h	C_4H_4S	100

[a]Reaction conditions: **34**(a–h) (1.0 mmol), **33** (2.0 mmol), Na_2SO_4 (0.5 mmol), CH_3CN (5.0 mL), 80 °C, 12 h. [b]Determined based on recovered acetophenone. [c]The corresponding benzoic acid was formed in 10–12% yield.

Next, we studied the 'release' of acetophenone from **30a** using thiocyanate as the anion to give α-thiocyanato-β-ketones (**31a**). When **30a** was treated with KSCN at room temperature for 4 h, the ionic liquid-supported substituted acetophenone was released cleanly with the thiocyanate ion without any side product. Simple extraction with hexane–ethyl acetate (7: 3 *v/v*), followed by washing with water, gave **31a** in 92% yield and high purity.

Encouraged with these systematic "catch and release" results for **29a**, we focused our attention on developing a simple and straightforward, chromatographic-free protocol for the synthesis of *α*-substituted acetophenones (**31-33**) from **29** (Table 3.3). Initially, **29a** was treated with **28** in dry CH_3CN at 80 °C for 12 h in the presence of anhydrous Na_2SO_4. After completion of the reaction, the reaction mixture was filtered and CH_3CN was evaporated under reduced pressure. The residue containing ionic liquid-supported 4-chloroacetophenone (**29a**) was washed with diethyl ether and subsequently treated with KSCN at room temperature for 4 h. On completion of the reaction, the product was extracted with hexane–ethyl acetate (7: 3 *v/v*), washed with water, dried with anhydrous Na_2SO_4 and concentrated to give **31a** in 92% yield. The purity of **31a** was over 98% as indicated by HPLC and NMR (Figure 3.7).

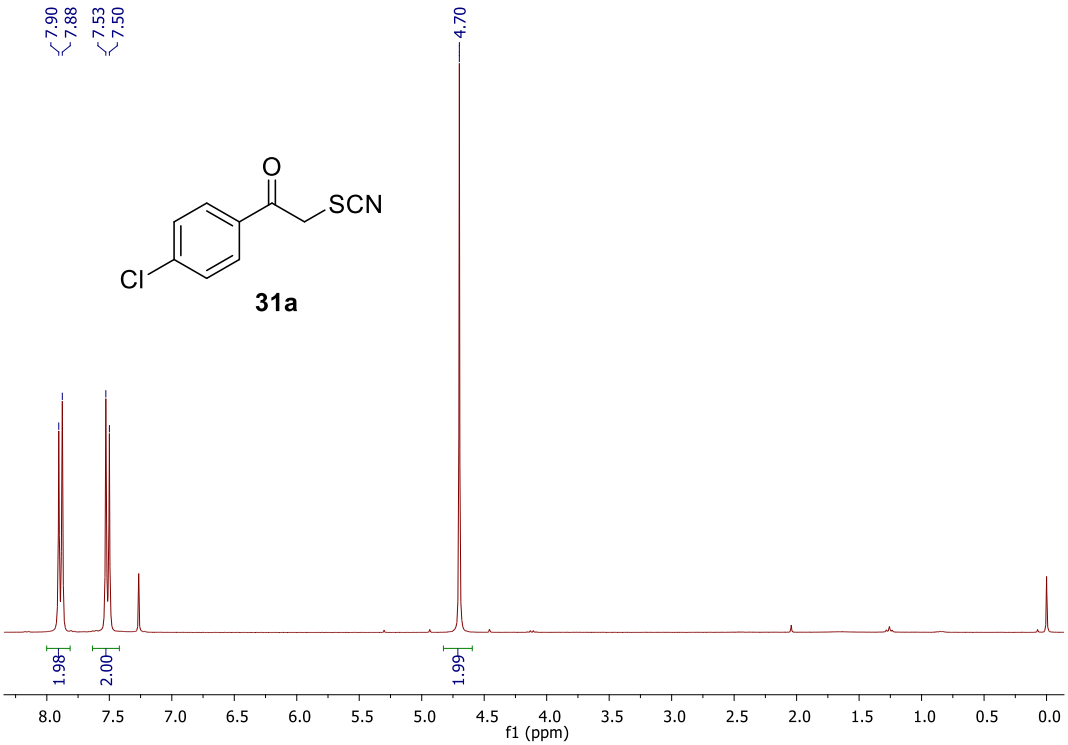


Figure 3.7: ^{1}H NMR spectra of *α*-substituted acetophenone

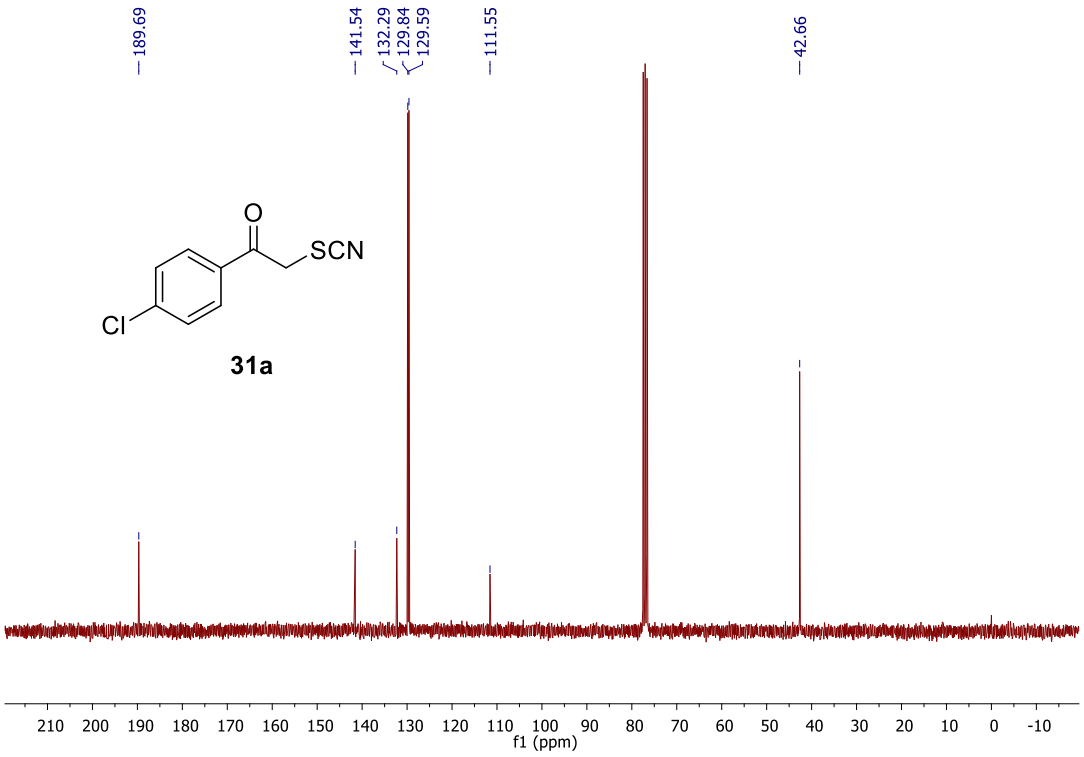
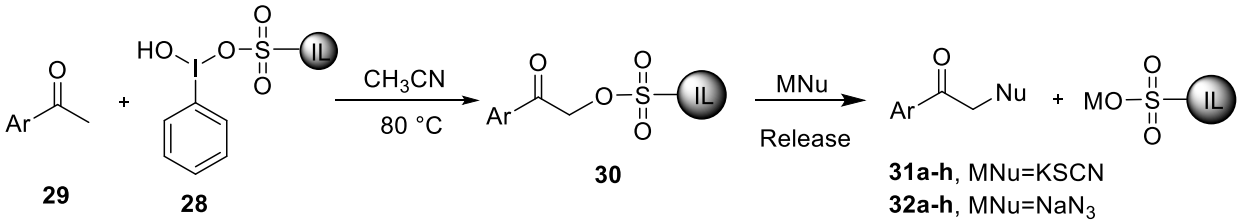
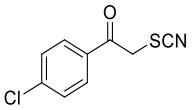
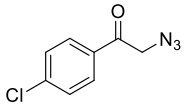
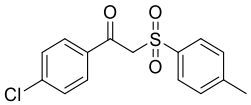
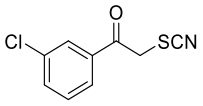
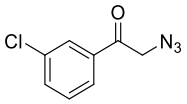
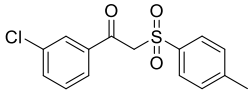
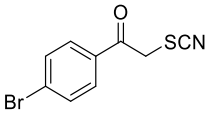
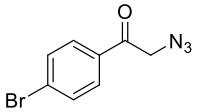
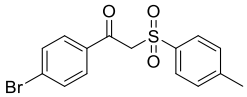
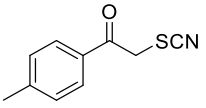


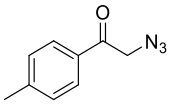
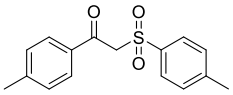
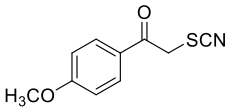
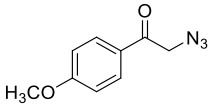
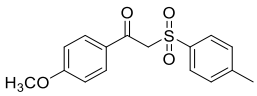
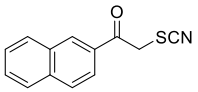
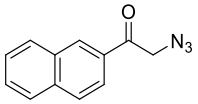
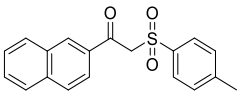
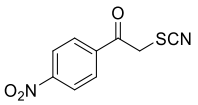
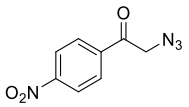
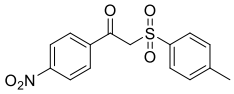
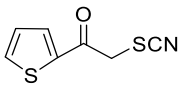
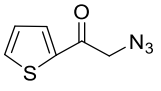
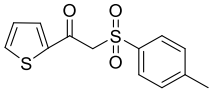
Figure 3.7: ^{13}C NMR spectra of α-substituted acetophenone

On establishing a simple and chromatographic-free method for the synthesis of **31a**, we utilized different acetophenones (**29a–h**) with three nucleophiles, -SCN, $-N_3$ and $CH_3C_6H_4SO_2^-$ to obtain the corresponding β-substituted acetophenones **31, 32** and **33** respectively (Table 3.3). As indicated in table 3.3, acetophenone with both electron-releasing and electron-withdrawing groups reacted smoothly. α-Thiocyanato-β-ketones (**31**) and α-azido-β-ketones (**32**) were obtained in good to excellent yield (62–92%) while β-ketosulfones (**33**) were obtained in moderate to good yield (46–68%). This may be attributed to their different nucleophilicity. It is worth mentioning that all the compounds were of high purity and no chromatographic separation was performed. The yields of the products (**31–33**) are based on the acetophenones after two steps. The purification method is simple and involves extraction with hexane–ethyl acetate (7: 3 *v/v*) followed by washing with water and drying with anhydrous sodium sulfate.

Table 3.3: Synthesis of α-substituted acetophenones (**31-33**) using **28**[a]



Entry	Ar	MNu	Product		Yield[b] (%)
		KSCN		**31a**	92
1	4-ClC_6H_4	NaN_3		**32a**	90
		$CH_3C_6H_4SO_2Na$		**33a**	68
		KSCN		**31b**	70
2	3-ClC_6H_4	NaN_3		**32b**	84
		$CH_3C_6H_4SO_2Na$		**33b**	58
		KSCN		**31c**	80
3	4-BrC_6H_4	NaN_3		**32c**	67
		$CH_3C_6H_4SO_2Na$		**33c**	46
4	4-$CH_3C_6H_4$	KSCN		**31d**	76

		NaN_3		**32d**	62
		$CH_3C_6H_4SO_2Na$		**33d**	52
		KSCN		**31e**	65
5	4-$CH_3OC_6H_4$	NaN_3		**32e**	78
		$CH_3C_6H_4SO_2Na$		**33e**	50
		KSCN		**31f**	90
6	$C_{10}H_7$	NaN_3		**32f**	92
		$CH_3C_6H_4SO_2Na$		**33f**	68
		KSCN		**31g**	65
7	4-$NO_2C_6H_4$	NaN_3		**32g**	70
		$CH_3C_6H_4SO_2Na$		**33g**	51
		KSCN		**31g**	75
8	C_4H_4S	NaN_3		**32g**	76
		$CH_3C_6H_4SO_2Na$		**33g**	55

[a]Reaction conditions: **29** (1.0 mmol), **28** (2.0 mmol), Na_2SO_4 (0.5 mmol) CH_3CN (5 mL), 80 °C, 12 h, followed by Nu (1.0 mmol), 30 °C, 4 h. [b]Isolated yields.

Compared to the polymer-bound iodine(III) reagent the loading capacity is higher for the ionic liquid-supported reagent, and the reaction can be monitored easily by different spectroscopic techniques. The present method does not require an excess amount of nucleophile to "release" the products as is the case with the polymer-bound reagent, and purification of the products does not require chromatographic separation.

3.4 Conclusion

In summary, we have successfully developed an efficient and simple protocol for the synthesis of an ionic liquid-supported hypervalent iodine reagent, and its use has been demonstrated in the generation of α-substituted acetophenones through a "catch and release" strategy. The two-step protocol for the conversion of substituted acetophenones to α-substituted acetophenones involves no chromatographic separation and gives the product in good to excellent yield and high purity. The scope and utility of the developed ionic liquid-supported reagent are general and can be used for the synthesis of various substituted ketones.

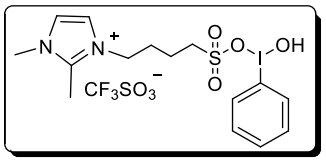
3.5 Experimental

The NMR spectra were recorded on 300 MHz, 400 MHz and 500 MHz spectrometers using $CDCl_3$ and DMSO-d_6 as solvents. The chemical shifts were expressed in ppm. Reactions were monitored by thin-layer chromatography (TLC) carried out on silica-coated aluminum plates (60F-254) using UV light as a visualizing agent. Melting points were determined on an open capillary tube on automated melting point apparatus and are uncorrected. All the chemicals and reagents were purchased at the highest commercial quality and were used without further purification unless otherwise stated.

Synthesis of ionic liquid-supported hypervalent iodine 28

Ionic liquid-supported sulfonic acid **17** (3gm, 13 mmol) and IBD **5** (1.26gm, 13 mmol) were dissolved in the minimum amount of CH_3CN in two different conical flasks and heated on a hot plate. The warm ionic liquid-supported sulfonic acid solution was added to the flask containing IBD under hot conditions. The reaction mixture was kept aside for one week. Acetonitrile was removed on a rotary evaporator under reduced pressure, and the resulting mixture was washed

with dry DCM (3 × 30 mL) to remove unreacted starting materials to obtain a thick yellow liquid (5.55 g, 96%)

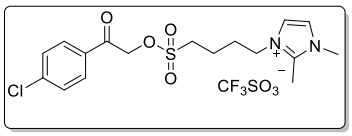


Yield 90%; yellow thick liquid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.22 (s, 1H), 7.76 (d, J = 1.1 Hz, 1H), 7.73 (d, J = 1.1 Hz, 1H), 7.62 (d, J = 2.1 Hz, 1H), 7.58 (d, J = 2.0 Hz, 1H), 7.44-7.37 (m, 1H), 7.23-7.15 (m, 2H), 4.14 (t, J = 7.3 Hz, 2H), 3.76 (s, 3H), 2.64 (d, J = 7.5 Hz, 2H), 2.59 (s, 3H), 1.91-1.78 (m, 2H), 1.71-1.58 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 144.6, 137.5, 130.9, 128.0, 123.1, 122.6, 121.2, 121.0 (q, $J_{C\text{-}F}$ = 320.25 Hz, OTf), 94.9, 50.7, 34.8, 28.4, 21.9, 9.2; HRMS (ESI-TOF) (*m/z*) calculated for $C_{15}H_{22}IN_2O_4S^+$: 453.0339, found: 453.0356 $[M–CF_3SO_3]^+$.

Synthesis of ionic liquid-supported sulfonates (30):

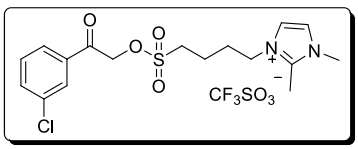
Substituted acetophenones **29** (1 mmole), ionic-liquid supported HTIB **28** (2 mmole) and dry Na_2SO_4 (0.5 equiv) were taken in dry acetonitrile (5 mL) and heated at reflux until acetophenone was completely consumed. The reaction mixture was filtered and CH_3CN was removed under reduced pressure and resulting reaction mixture was purified by silica-gel column chromatography (dichloromethane-methanol 75: 25 as an eluent) to give the desired compound (**30a-h**).

3-(4-((2-(4-Chlorophenyl)-2-oxoethoxy)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (30a)



Yield 51%; off-white solid; mp: 90-96 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.97 (d, J = 8.6 Hz, 2H), 7.70-7.60 (m, 4H), 5.70 (s, 2H), 4.19 (t, J = 6.7 Hz, 2H), 3.75 (s, 3H), 3.55 (t, J = 7.1 Hz, 2H), 2.60 (s, 3H), 1.94-1.70 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 191.2, 144.8, 139.5, 132.7, 130.2, 129.5, 122.8, 121.3, 121.1 (q, $J_{C\text{-}F}$ = 320.25 Hz, OTf), 71.6, 49.3, 47.1, 35.1, 27.8, 20.3, 9.6; HRMS (ESI-TOF) (*m/z*) calculated for $C_{17}H_{22}ClN_2O_4S^+$: 385.0983, found: 385.0975 $[M–CF_3SO_3]^+$.

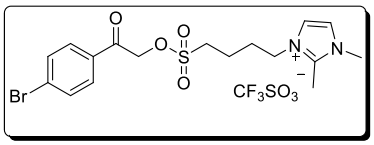
3-(4-((2-(3-Chlorophenyl)-2-oxoethoxy)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (30b)



Yield 50%; yellow liquid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01-7.97 (m, 1H), 7.92 (d, J = 7.9 Hz, 1H), 7.80 (dd, J = 8.0, 1.1 Hz, 1H), 7.67-7.62 (m, 3H), 5.74 (s, 2H), 4.19 (t, J = 6.9 Hz, 2H), 3.76 (s, 3H), 3.59-3.52 (m, 2H), 2.60 (s, 3H), 1.94-1.76 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 189.1, 142.7, 142.5, 133.7, 132.2, 129.3, 126.0, 124.8, 120.7, 119.2, 119.0 (q, $J_{C\text{-}F}$ = 320.25 Hz,

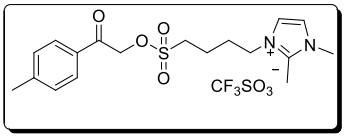
OTf), 69.6, 47.1, 45.1, 33.0, 25.7, 18.2, 7.5; HRMS (ESI-TOF) (*m/z*) calculated for $C_{17}H_{22}N_2ClO_4S^+$ 385.0989, found 385.0805 $[M\text{-}CF_3SO_3]^+$.

3-(4-((2-(4-Bromophenyl)-2-oxoethoxy)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (30c)



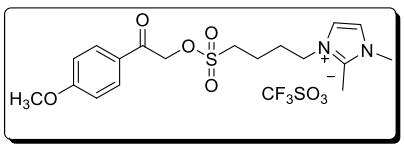
Yield: 45%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.92-7.86 (m, 2H), 7.83-7.77 (m, 2H), 7.65 (d, J = 2.1 Hz, 1H), 7.62 (d, J = 2.1 Hz, 1H). 5.70 (s, 2H), 4.19 (t, J = 6.8 Hz, 2H), 3.75 (s, J = 6.4 Hz, 2H), 3.60-3.49 (m, 2H), 2.60 (s, 3H), 1.95-1.72 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 191.4, 144.8, 133.0, 132.4, 130.3, 128.7, 122.8, 121.3, 121.1 (q, $J_{C\text{-}F}$ = 320.25 Hz, OTf), 71.6, 49.2, 47.1, 35.1, 27.8, 20.3, 9.5; HRMS (ESI-TOF) (*m/z*) calculated for $C_{17}H_{22}BrN_2O_4S^+$ 429.0478, found: 429.0512 $[M - CF_3SO_3]^+$ and 431.0489 $[M + 2 - CF_3SO_3]^+$.

3-(4-((2-(4-Methylphenyl)-2-oxoethoxy)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (30d)



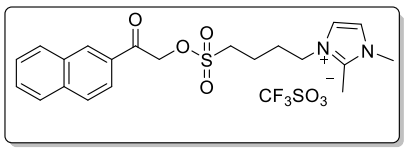
Yield 45%; yellow solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.86 (d, J = 8.2 Hz, 2H), 7.64 (dd, J = 8.9, 2.1 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 5.68 (s, 2H), 4.19 (t, J = 6.8 Hz, 2H), 3.76 (s, 3H), 3.63-3.48 (m, 2H), 2.60 (s, 3H), 2.40 (s, 3H), 1.96-1.78 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 191.5, 145.2, 144.8, 131.5, 129.9, 128.4, 122.8, 121.3, 121.1 (q, $J_{C\text{-}F}$ = 320.25 Hz, OTf), 71.6, 49.3, 47.1, 35.1, 27.8, 21.6, 20.3, 9.5; HRMS (ESI-TOF) (*m/z*)calculated for $C_{18}H_{25}N_2O_4S^+$ 365.1530, found: 365.1555 $[M - CF_3SO_3]^+$.

3-(4-((2-(4-Methoxyphenyl)-2-oxoethoxy)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (30e)



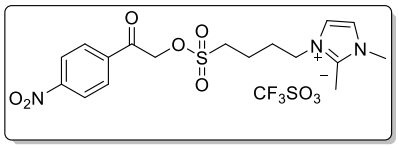
Yield 40%; light brown thick liquid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.94 (d, J = 9.0 Hz, 2H), 7.63 (dd, J = 8.9, 2.1 Hz, 2H), 7.12-7.06 (m, 2H), 5.64 (s, 2H), 4.21-4.11 (m, 2H), 3.86 (s, 3H), 3.75 (s, 3H), 3.56-3.47 (m, 2H), 2.59 (s, 3H), 1.95-1.78 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 190.3, 164.3, 144.8, 130.7, 126.8, 122.8, 121.3, 121.0 (q, $J_{C\text{-}F}$ = 320.25 Hz, OTf), 114.6, 71.4, 63.2, 56.1, 49.3, 47.1, 35.1, 27.8, 20.3, 9.5; HRMS (ESI-TOF) (*m/z*) calculated for $C_{18}H_{25}N_2O_5S^+$: 381.1479, found: 381.1504 $[M - CF_3SO_3]^+$.

3-(4-((2-(Naphthalen-2-yl)-2-oxoethoxy)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (30f)



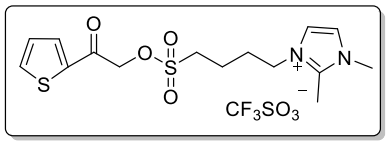
Yield 68%; brown liquid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.70 (s, 1H), 8.16-7.95 (m, 4H), 7.76-7.62 (m, 4H), 5.88 (s, 2H), 4.21 (t, J = 6.7 Hz, 2H), 3.77 (s, 3H), 3.60 (t, J = 7.1 Hz, 2H), 2.61 (s, 3H), 2.02-1.70 (m, 4H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 191.9, 144.8, 135.8, 132.4, 131.3, 130.5, 130.0, 129.6, 129.0, 128.2, 127.7, 123.5, 122.8, 121.3, 121.2 (q, $J_{C\text{-}F}$ = 320.25 Hz, OTf), 71.7, 49.3, 47.2, 35.1, 27.8, 20.4, 9.5; HRMS (ESI-TOF) (*m/z*) calculated for $C_{21}H_{25}N_2O_4S^+$: 401.1530, found: 401.1524 $[M - CF_3SO_3]^+$.

3-(4-((2-(4-Nitrophenyl)-2-oxoethoxy)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (30g)



Yield 40%; brown solid; mp: 85-90 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.39 d, J = 8.7 Hz, 2H), 8.19 (d, J = 8.8 Hz, 2H), 7.64 (dd, J = 7.5, 1.8 Hz, 2H), 5.78 (s, 2H), 4.19 (t, J = 6.7 Hz, 2H), 3.76 (s, 3H), 3.56 (t, J = 7.0 Hz, 2H), 2.60 (s, 3H), 1.98-1.73 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 191.5, 150.8, 144.8, 138.7, 129.8, 124.4, 122.8, 121.3, 121.2 (q, $J_{C\text{-}F}$ = 320.25 Hz, OTf), 71.8, 49.2, 47.1, 35.1, 27.8, 20.3, 9.5; HRMS (ESI-TOF) (*m/z*) calculated for $C_{17}H_{21}N_3O_6S^+$: 395.1240, found: 395.1252 $[M-CF_3SO_3]^+$.

3-(4-((2-Oxo-2-(Thiophen-2-yl)ethoxy)sulfonyl)butyl)-1,2-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (30h)



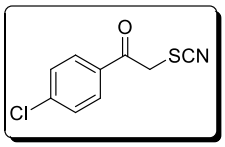
Yield 50%; light brown thick liquid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.14 (dd, J = 4.9, 0.7 Hz, 1H), 8.08-8.01 (m, 1H), 7.64 (dd, J = 8.2, 2.0 Hz, 2H), 7.32 (dd, J = 4.7, 4.0 Hz, 1H), 5.60 (s, 2H), 4.19 (t, J = 6.7 Hz, 2H), 3.75 (s, 3H), 3.60-3.47 (m, 2H), 2.59 (s, 3H), 1.95-1.71 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 185.4, 144.8, 139.9, 136.4, 134.5, 129.5, 122.8, 121.3, 121.1 (q, $J_{C\text{-}F}$ = 320.25 Hz, OTf), 70.8, 49.3, 47.1, 35.1, 27.8, 20.3, 9.5; HRMS (ESI-TOF) (*m/z*) calculated for $C_{15}H_{21}N_2O_4S_2^+$: 357.0937, found: 357.0949 $[M-CF_3SO_3]^+$.

General procedure for the synthesis of *α*-substituted acetophenones

To a solution of substituted acetophenone **29** (100mg, 1.0 mmol) and **28** (1.2gm, 2.0 mmol) in CH_3CN, anhydrous Na_2SO_4 (0.5 mmol) was added and the resulting mixture was heated until the acetophenone was completely consumed (monitored by TLC). After completion of the reaction, the reaction mixture was filtered and CH_3CN was evaporated under reduced pressure. The

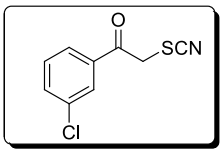
residue was washed with ether (3-10 mL), and the viscous ionic liquid-supported sulfonate obtained (**30**) was treated with KSCN/NaN_3/$CH_3C_6H_4SO_2Na$ (1.0 mmol) and stirred vigorously at room temperature under solvent-free conditions. After completion of the reaction, the product was extracted with hexane–ethyl acetate (3-10 mL, 7: 3 v/v), leaving behind the ionic liquid **17** which is insoluble in this solvent mixture. Thus, the product was extracted in hexane–ethyl acetate and washed with water. The organic layers were dried over anhydrous sodium sulfate and concentrated to obtain the pure product (**31–33**) without chromatographic purification.

1-(4-Chlorophenyl)-2-thiocyanatoethanone (31a)



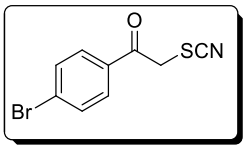
Yield 90%; yellow solid; mp: 132-137 °C (lit.[87] 133–135 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 8.6 Hz, 2H), 7.51 (d, J = 8.5 Hz, 2H), 4.70 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.6, 141.54, 132.2, 129.8, 129.5, 111.5, 42.6; HRMS (ESI-TOF) (*m/z*) calculated for $C_9H_6NClOS^+$ 210.9859, found 211.9889 $[M + H]^+$.

1-(3-Chlorophenyl)-2-thiocyanatoethanone (31b)



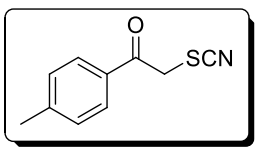
Yield 70%; yellow soild; mp: 84-86 °C (lit.[87] 68–70 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.65 (d, J = 7.7 Hz, 1H), 7.49 (t, J = 7.8 Hz, 1H), 4.69 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.7, 135.6, 135.4, 134.7, 130.5, 128.5, 126.5, 111.4, 42.6; HRMS (ESI-TOF) (*m/z*) calculated for $C_9H_6NClOS^+$ 210.9859, found 211.9892 $[M + H]^+$.

1-(4-Bromophenyl)-2-thiocyanatoethanone (31c)



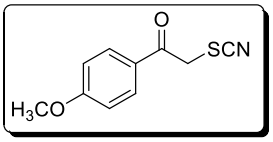
Yield 80%; off- white solid; mp: 143-144 °C (lit.[73] 140–143 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.95 (d, J = 8.6 Hz, 2H), 7.80 (d, J = 8.6 Hz, 2H), 5.08 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 192.1, 133.8, 132.4, 130.9, 128.9, 113.1, 42.0; HRMS (ESI-TOF) (*m/z*) calculated for C_9H_7BrNOS: 255.9426, found: 255.9442 $[M + H]^+$ and 257.9436 $[M + H + 2]^+$.

2-Thiocyanato-1-tolylethanone (31d)



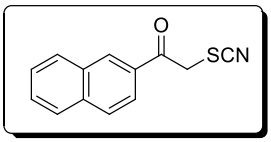
Yield 76%; white color solid; mp: 99-101 °C (lit.[87] 104–107 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J = 7.1 Hz, 2H), 7.32 (d, J = 6.8 Hz, 2H), 4.72 (s, 2H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.4, 146.0, 131.5, 129.8, 128.5, 112.0, 43.0, 21.8; HRMS (ESI-TOF) (*m/z*) calculated for $C_{10}H_9NOS^+$ 191.0405, found 192.0503 $[M + H]^+$.

1-(4-Methoxyphenyl)-2-thiocyanatoethanone (31e)



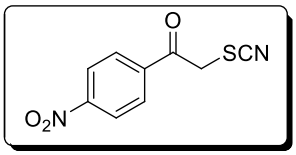
Yield 60%; off-white solid; mp: 121-123 °C (lit.[87] 120–122 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, J = 8.6 Hz, 2H), 6.98 (d, J = 8.6 Hz, 2H), 4.71 (s, 2H), 3.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.2, 164.8, 130.9, 126.9, 114.3, 112.1, 55.6, 42.9; HRMS (ESI-TOF) (*m/z*) calculated for $C_{10}H_9NO_2S^+$ 208.0427, found 208.0423 $[M + H]^+$.

1-(Naphthalene-2-yl)-2-thiocyanatoethanone (31f)



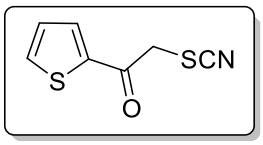
Yield 90%; yellow color solid; mp: 104-109 °C (lit.[58] 102–104 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.09-7.80 (m, 4H), 7.73-7.48 (m, 2H), 4.83 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.7, 136.1, 132.2, 131.2, 130.8, 129.7, 129.5, 129.1, 127.9, 127.4, 123.3, 112.0, 43.1; HRMS (ESI-TOF) (*m/z*) calculated for $C_{13}H_9NOS^+$ 228.0478, found 228.0463 $[M + H]^+$.

1-(4-Nitrophenyl)-2-thiocyanatoethanone (31g)



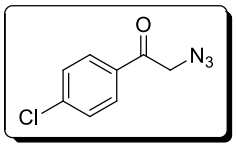
Yield 65%; off-white **c**olor solid; mp: 117-118 °C (lit.[87] 118–120 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.27 (d, J = 8.3 Hz, 2H), 8.03 (d, J = 8.3 Hz, 2H), 4.63 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 184.8, 146.4, 133.5, 124.9, 119.6, 106.2, 37.67; HRMS (ESI-TOF) (*m/z*) calculated for $C_9H_6N_2O_3S^+$ 223.0172, found 223.0184 $[M + H]^+$.

2-Thiocyanato-1-(thiophen-2-yl)ethanone (31h)



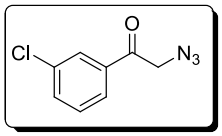
Yield 75%; yellow color solid; mp: 91-94 °C (lit.[79] 89–91 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (dd, J = 4.3, 1.5 Hz, 2H), 7.24-7.19 (m, 1H), 4.57 (s, 2H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.3, 140.4, 136.1, 133.8, 128.7, 111.5, 41.6; HRMS (ESI-TOF) (*m/z*) calculated for $C_7H_5NOS_2^+$ 183.9985, found 183.9978 $[M + H]^+$.

2-Azido-1-(4-chlorophenyl)ethanone (32a)



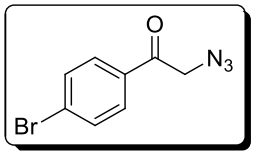
Yield 90%; colorless solid; mp 66–69 °C (lit.[72] 65–67 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 8.1 Hz, 2H), 7.49 (d, J = 8.1 Hz, 2H), 4.53 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.2, 140.8, 131.7, 129.3, 129.0, 65.4. HRMS (ESI-TOF) (*m/z*) calculated for $C_8H_7ClN_3O^+$ 196.0272, found: 196.0258 $[M + H]^+$.

2-Azido-1-(3-chlorophenyl)ethanone (32b)



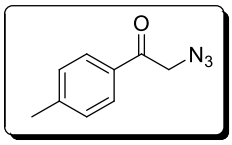
Yield 84%; brown solid; m.p. 64–67 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.78 (d, J = 7.7 Hz, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.45 (t, J = 7.9 Hz, 1H), 4.54 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.1, 135.8, 135.4, 134.0, 130.3, 128.0, 125.9, 54.9; HRMS (ESI-TOF) (*m/z*) calculated for $C_8H_7ClN_3O^+$ 196.0272, found: 196.0284 $[M + H]^+$.

2-Azido-1-(4-bromophenyl)ethanone (32c)



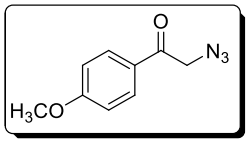
Yield 67%; yellow solid; m.p. 74–76 °C (lit.[88] 79.5–81 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 4.53 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.3, 133.0, 132.3, 129.4, 129.4, 54.8; HRMS HRMS (ESI-TOF) (*m/z*) calculated for $C_8H_7BrN_3O^+$ 239.9767, found: 239.9756 $[M + H]^+$ and 241.9687 $[M + H + 2]^+$.

2-Azido-1-*p*-tolyl ethanone (32d)



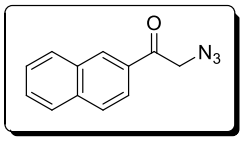
Yield 62%; off-white solid; m.p. 57–59 °C (lit.[72] 56–57 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 7.9 Hz, 2H), 4.46 (s, 2H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.7, 145.1, 131.9, 129.6, 128.0, 54.7, 21.7; HRMS HRMS (ESI-TOF) (*m/z*) calculated for $C_9H_{10}N_3O^+$ 176.0818, found 176.0834 $[M + H]^+$.

2-Azido-1-(4-methoxyphenyl)ethanone (32e)



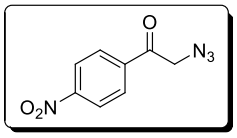
Yield 78%; yellow solid; m.p. 65–67 °C (lit.[72] 67–68 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 4.43 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.6, 163.2, 129.2, 126.3, 113.1, 54.5, 53.5; HRMS HRMS (ESI-TOF) (*m/z*) calculated for $C_9H_{10}N_3O_2$ 192.0768, found: 192.0779 $[M + H]^+$.

2-Azido-1-(naphthalene-2-yl)ethanone (32f)



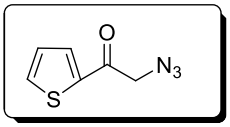
Yield 92%; yellow solid; m.p. 64–66 °C (lit.[89] 66–67 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.01-7.87 (m, 4H), 7.61 (m, 2H), 4.70 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.1, 135.9, 132.3, 131.7, 129.8, 129.6, 129.0, 129.0, 127.9, 127.1, 123.3, 54.9; HRMS HRMS (ESI-TOF) (*m/z*) calculated for $C_{12}H_{10}N_3O^+$ 212.0818, found: 212.0788 $[M + H]^+$.

2-Azido-1-(4-nitrophenyl)ethanone (32g)



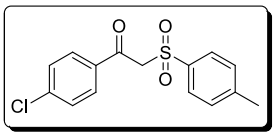
Yield 70%; brown solid; m.p. 91–93 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, J = 1.9 Hz, 1H), 8.35 (d, J = 1.9 Hz, 1H), 8.11 (d, J = 2.0 Hz, 1H), 8.09 (d, J = 1.8 Hz, 1H), 4.63 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.05, 150.86, 138.71, 129.13, 124.20, 55.26; HRMS (ESI-TOF) (*m/z*) calculated for $C_8H_7N_4O_3^+$ 207.0513, found: 207.0496 $[M + H]^+$.

2-Azido-1-(thiophen-2-yl)ethanone (32h)



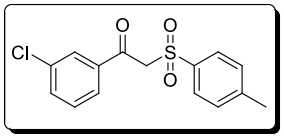
Yield 76%; colorless solid; m.p. 67–69 °C (lit.[90] 62–64 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.04 (d, J = 37.0 Hz, 2H), 7.29 (m, 1H), 4.81 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 188.0, 140.8, 136.1, 134.4, 129.3, 54.7; HRMS (ESI-TOF) (*m/z*) calculated for $C_6H_6N_3OS^+$ 168.0226, found: 168.0247 $[M + H]^+$.

1-(4-Chlorophenyl)-2-tosylethanone (33a)



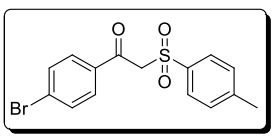
Yield 68%; yellow solid; m.p. 139–140 °C (lit.[81] 136–138 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.91 (dd, J = 6.7, 2.0 Hz, 2H), 7.71 (d, J = 8.3 Hz, 2H), 7.55 (dd, J = 6.7, 2.0 Hz, 2H), 7.40 (d, J = 8.5 Hz, 2H), 5.20 (s, 2H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 188.6, 145.3, 145.2, 134.7, 131.3, 130.1, 129.3, 129.3, 128.4, 62.8, 21.4; HRMS (ESI-TOF) (*m/z*) calculated for $C_{15}H_{14}ClO_3S^+$ 309.0347, found: 309.0338 $[M + H]^+$.

1-(3-Chlorophenyl)-2-tosylethanone (33b)



Yield 58%; pale yellow solid; m.p. 120–124 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.83 (d, J = 7.9 Hz, 1H), 7.75 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 7.9 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.34 (d, J ¼ 7.9 Hz, 2H), 4.69 (s, 2H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.08, 145.6, 137.2, 135.5, 135.2, 134.2, 130.1, 129.9, 129.1, 128.5, 127.5, 63.6, 21.7; HRMS (ESI-TOF) (*m/z*) calculated for $C_{15}H_{14}ClO_3S^+$ 309.0347, found 309.0337 $[M + H]^+$.

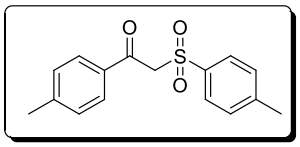
1-(4-Bromophenyl)-2-tosylethanone (33c)



Yield 46%; pale yellow solid; m.p. 135–140 °C (lit.[91] 144–146 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 8.6 Hz, 2H), 7.74 (d, J = 8.2 Hz, 2H), 7.62 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 4.68 (s, 2H), 2.44

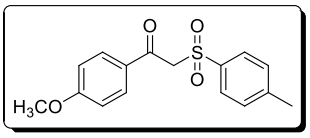
(s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.2, 145.5, 135.5, 134.5, 132.2, 132.0, 130.8, 129.9, 128.5, 63.6, 21.7; HRMS (ESI-TOF) (*m/z*) calculated for $C_{15}H_{14}BrO_3S^+$ 352.9842, found: 352.9864 $[M + H]^+$ and 354.9834 $[M + H + 2]^+$.

1-*p*-Tolyl-2-tosylethanone (33d)



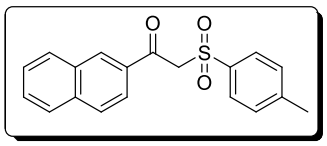
Yield 52%; light yellow solid; m.p. 98–101 °C (lit.[92] 100–102 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.67 (d, *J* = 7.6 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 7.7 Hz, 2H), 4.61 (s, 2H), 2.36 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.6, 145.5, 145.3, 135.8, 133.3, 129.8, 129.5, 129.5, 128.6, 63.5, 21.8, 21.7; HRMS (ESI-TOF) (*m/z*) calculated for $C_{16}H_{17}O_3S^+$ 289.0893, found 289.0914 $[M + H]^+$.

1-(4-Methoxyphenyl)-2-tosylethanone (33e)



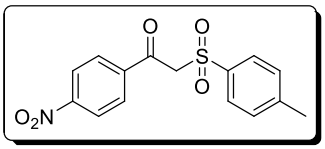
Yield 50%; off-white solid; m.p. 120–121 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 8.7, 1.6 Hz, 2H), 7.75 (d, *J* = 6.9 Hz, 2H), 7.33 (d, *J* = 7.8 Hz, 2H), 6.95 (dd, *J* = 8.7, 1.5 Hz, 2H), 4.66 (s, 2H), 3.89 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.3, 164.5, 145.2, 135.8, 131.9, 129.8, 128.9, 128.5, 114.0, 63.5, 55.6, 21.7; HRMS (ESI-TOF) (*m/z*) calculated for $C_{16}H_{17}O_4S^+$ 305.0842, found 305.0858 $[M + H]^+$.

1-(Naphthalene-2-yl)-2-tosylethanone (33f)



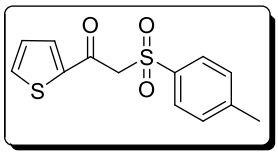
Yield 68%; sticky yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.95 (d, *J* = 8.3 Hz, 2H), 7.90-7.84 (m, 2H), 7.80-7.75 (m, 2H), 7.68-7.55 (m, 2H), 7.34-7.28 (m, 2H), 4.86 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.5, 145.2, 135.8, 134.6, 133.9, 133.4, 130.8, 130.3, 129.8, 129.1, 128.7, 128.6, 126.8, 125.5, 124.2, 66.3, 21.7; HRMS (ESI-TOF) (*m/z*) calculated for $C_{19}H_{17}O_3S^+$ 325.0893, found: 325.0915 $[M + H]^+$.

1-(4-Nitrophenyl)-2-tosylethanone (33g)



Yield 51%; pale yellow solid; m.p. 139–144 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.8 Hz, 2H), 8.15 (d, *J* = 8.8 Hz, 2H), 7.75 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 4.77 (s, 2H), 2.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.0, 150.8, 145.9, 139.9, 135.3, 130.5, 130.0, 128.5, 123.9, 64.0, 21.7; HRMS (ESI-TOF) (*m/z*) calculated for $C_{15}H_{14}NO_5S^+$ 320.0587, found: 320.0593 $[M + H]^+$.

1-(Thiophenyl-2-yl)-2-tosylethanone (33h)



Yield 55%; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 3.5 Hz, 1H), 7.69 (d, J = 7.8 Hz, 3H), 7.27 (d, J = 8.0 Hz, 2H), 7.09 (t, J = 4.3 Hz, 1H), 4.54 (s, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.3, 145.5, 143.2, 136.4, 135.5, 135.3, 129.9, 128.7, 128.6, 64.7, 21.7; HRMS (ESI-TOF) (*m/z*) calculated for $C_{13}H_{13}O_3S_2^+$ 281.0301, found: 281.0288 $[M + H]^+$

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Chapter III

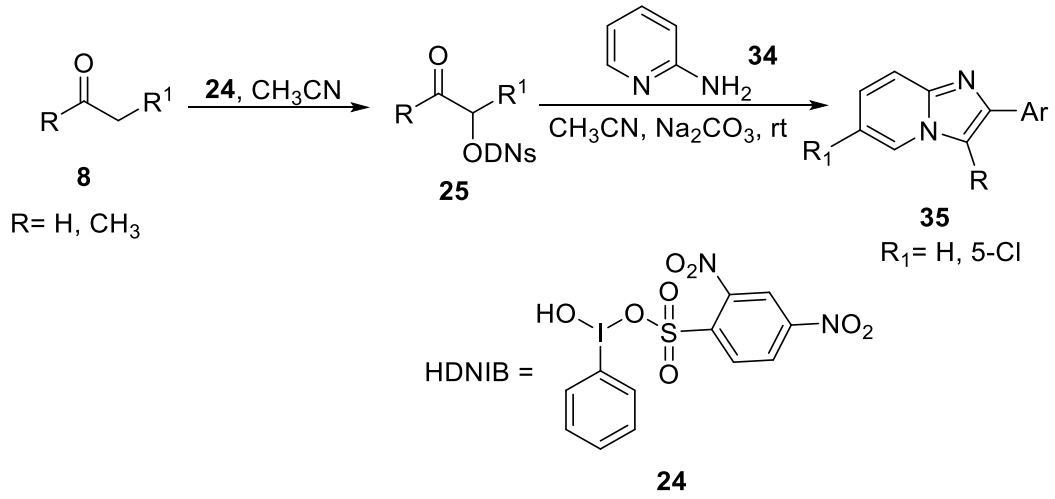
PART B

Ionic Liquid-supported Hypervalent Iodine Reagent: Synthesis of 2-Aminothiazoles and Imidazo[1,2-*a*]pyridines

3.7 Introduction

Nitrogen-containing heterocyclic compounds for instance 2-aminothiazoles and imidazo[1,2-*a*]pyridines play significant role in the pharmaceutical and agrochemical industries.[1-3] Several synthetic methodologies have been developed for the synthesis of thiazoles and imidazo[1,2-*a*]pyridines.[4-7]

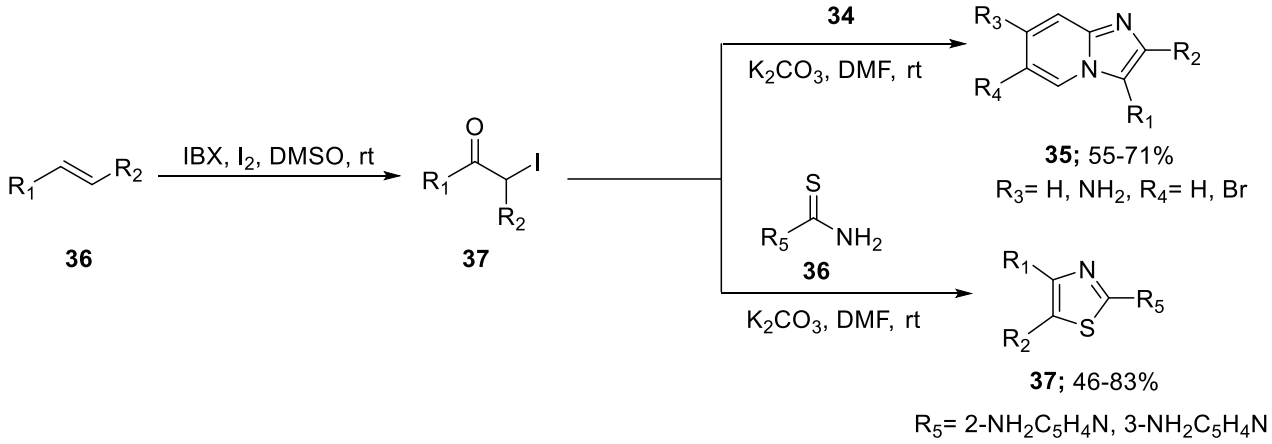
Chen group have developed highly efficient, low toxic and easy handling method for the synthesis of imidazo[1,2-*a*]pyridine **35** (Scheme 3.17).[8] The reaction of a ketone with hydroxy-2,4-dinitrophenylsulfonyliodobenzen (HDNIB) **24** provided (2, 4-dinitrobenzene)sulfonyloxy ketones **25**, which reacted with 2-aminopyridine **34** in the presence of Na_2CO_3 to yield **35**. Aryl ketone **8** having different electron-withdrawing and electron-donating groups in the aryl ring were well tolerated to give corresponding imidazo[1,2-*a*]pyridine **35** in good to excellent yields (75-87%). When the same reaction was performed with HTIB it requires longer reaction time to complete the reaction, which clearly indicate that –ODNs group have a good leaving ability compared to –OTs in nucleophilic substitution reaction



Scheme 3.17: Synthesis of imidazo[1,2-*a*]pyridine (**35**) by using **24**

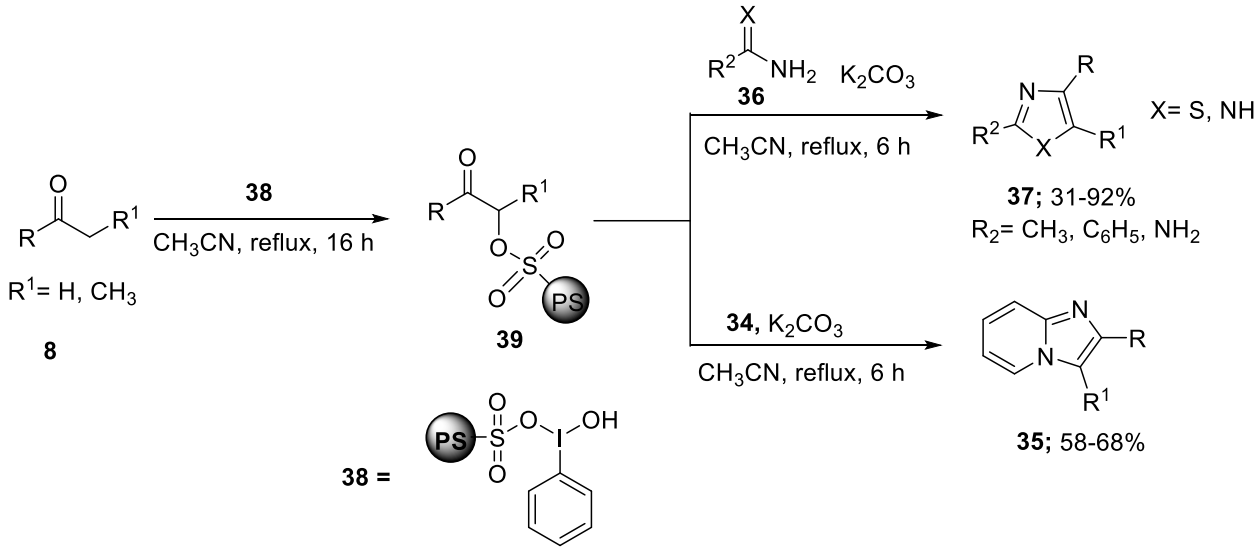
Donohoe *et al* have demonstrated the synthesis of thiazoles (**35**) and imidazo[1,2-*a*]pyridines (**37)** from the corresponding alkene (**36)** by the iodination, Kornblum oxidation followed by cyclization.[9] A range of solvents such as DMF, dioxane, THF, H_2O, DMSO and DCM were tried but intermediate α-iodoketone (**37**) was not generated under these conditions expect in DMSO. Alkene was converted into α-iodoketone (**37**) in the presence of IBX, I_2 and DMSO.

Finally, iodoketone underwent cyclization to produced single isomer of the heteroarenes *via* nucleophilic attack of thiourea, thioamide, amidine and aminopyridine (Scheme 3.18).



Scheme 3.18: Synthesis of imidazo[1,2-*a*]pyridines and thiazoles from alkenes using I_2/IBX

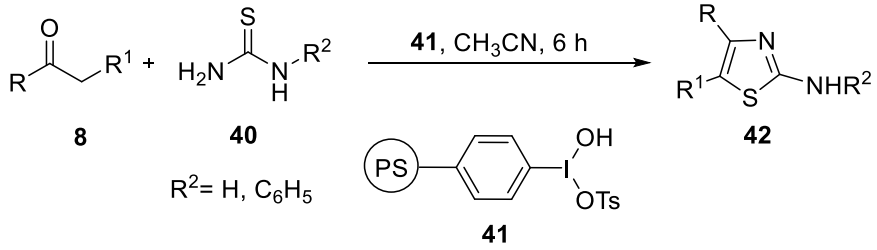
Togo group have reported synthesis of polymer-supported α-sulfonyloxy acetophenone (**39)** from different ketones using polymer supported HTIB.[10, 11] Polymer-supported α-sulfonyloxy ketone (**39)** was treated with benzamidine, thioamides and 2-aminopyridine in the presence of K_2CO_3 in acetonitrile to obtain corresponding imidazole, thiazoles and imidazo[1,2-*a*]pyridine (**35**) by simple filtration of the reaction mixture (Scheme 3.19).



Scheme 3.19: Synthesis of imidazo[1,2-*a*]pyridines and thiazoles from ketones using polymer-suppported HTIB

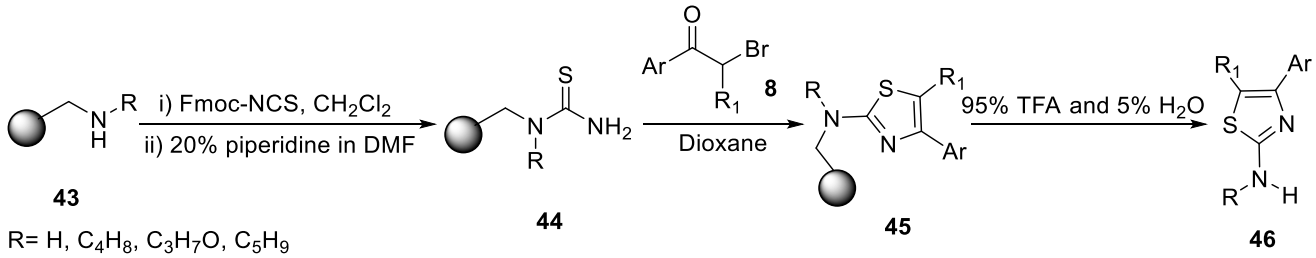
Zhang group have reported polymer supported [4-hydroxy(tosyloxy)iodo]styrene (**41)**, which was used in the synthesis of 2-amino-4-arylthiazoles (**42)**.[12] The main advantage of this reagent

is that it avoided the use of highly lachrymatory compound such as α-haloketones for the synthesis of the heterocycles. The product **42** was isolated in pure form by simple resin filtration in good to excellent yields (50-72%). The reagent **41** was regenerated by the reaction of poly(iodososstyrene) with peracetic acid and *p*-toluenesulfonic acid (Scheme 3.20).



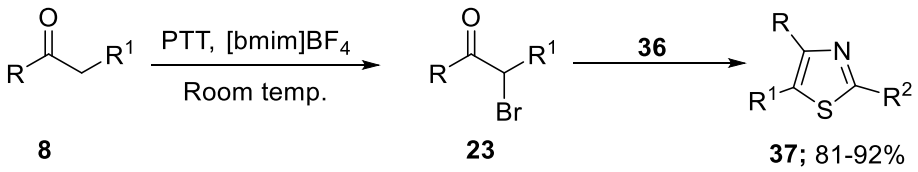
Scheme 3.20: Synthesis of 2-amino-4-arylthiazoles using **41**

Flygare *et al.* have reported synthesis of 2-aminothiazoles from immobilized 2-aminothiourea (**44**) with the reaction of different α-bromoketones (**8**) (Scheme 3.21).[13] The resin supported 2-aminothiourea was synthesized by the reaction of Fmoc-NCS with resin bound amino acid (**45**). The cleavage of immobilized resin from 2-aminothiazole was carried out by 95% TFA and 5% H_2O. The different types of thiazole (**46**) were synthesized in good to excellent yields using this methodology.



Scheme 3.21: Synthesis of 2-aminothiazole using solid supported 2-aminothiourea

Kumar *et al* have developed novel, highly efficient and environmentally benign ecofriendly one-pot method for the synthesis of thiazoles (**37)** using PTT as a brominating agent followed by the cyclization in ionic liquid [bmim]BF_4.[14] The main advantage of this method is to avoid the hazardous organic solvent, toxic catalyst and lachrymetric compounds.

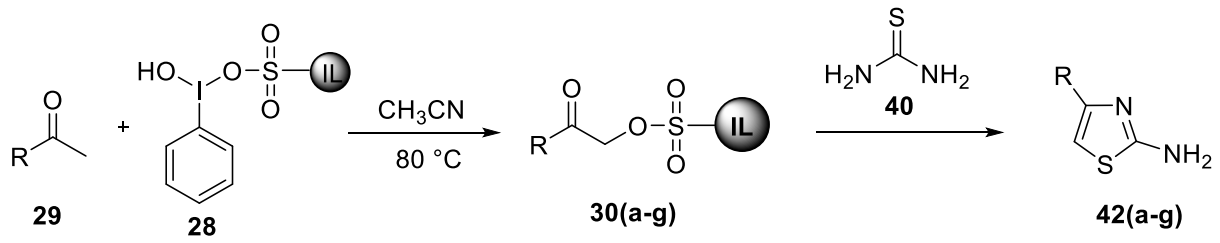


Scheme 3.22: Synthesis of substituted thiazoles in [bmim]BF_4

Several other methods have been reported in the literature on the synthesis of imidazo[1,2-*a*]pyridine using ionic liquids $BPyBF_4$[15], [emim]OTs[16], [bmim]br_3[17] and [Hbim]BF_4[18] etc. The most widely and practically used method for the synthesis of these aza-heterocycles is coupling reaction of α-tosyloxycarbonyls/α-halocarbonyls with thiourea and 2-aminopyridine. However, this method requires isolation and purification of the intermediates and/or use of lachrymatory α-halocarbonyls and thus a novel method is desired which can address these issues for the synthesis of aza-heterocycles. Adding to our continuous interest and our ongoing research program on functionalized ionic liquids, we have developed the ionic liquid phase synthesis of 2-aminothiazoles and imidazo[1,2-a]pyridines *via* catch and release strategy using ionic liquid-supported hypervalent iodine reagent.

3.8 Results and discussion

The synthetic procedure for 2-aminothiazoles **42** was started by the reaction of **29a** with **28** in dry CH_3CN at 80 °C for 12 h in the presence of anhydrous Na_2SO_4 followed by reaction with thiourea as shown in Scheme 3.23. After complete 'capture' of **29a** by **28**, the reaction mixture was filtered to remove Na_2SO_4 and CH_3CN was evaporated under reduced pressure and the residue containing **30a** was washed with diethyl ether to remove excess iodobenzene. Next, **30a** was allowed to react with thiourea under solvent-free conditions at 40 °C for 4 h to 'release' **42a**. Use of the ionic liquid-linked reagent facilitated easy product isolation by simple phase separation. After completion of the reaction, the product **42a** was isolated by extracting with hexane-ethyl acetate (2: 8 *v/v)* mixture.



Scheme 3.23: Synthesis of 2-aminothiazoles using ionic liquid-supported iodine reagent (**28**)

The ^{1}H NMR spectrum of **42a** showed a characteristic primary amine proton as singlet at δ = 5.18 ppm along with other protons. In the ^{13}C NMR spectrum, the appearance of carbon (C=N) peak at δ = 167 ppm support the confirmation of structure **42a** (Figure 3.8).

It is worth to mention that lower yields of 2-aminothiazoles were obtained with the traditional method under similar conditions. For example when, thiourea was reacted with α-tosyloxy-4-chloroacetophenone and α-tosyloxy-4-methylacetophenone corresponding 2-aminothiazole were obtained in 63% and 58% yield as compared to 83% and 71% yield respectively, using our method (Table 3.4, entry 2,4). In order to ascertain the scope of the reagent **28** in combinatorial synthesis, a library of 2-aminothiazoles **42(a-g)** was prepared from acetophenones bearing both electron-donating and electron-withdrawing substituents. The yield of all the 2-aminothiazoles **42(a-g)** is given in table 3.4. It is worthy to mention that the 2-aminothiazoles were of high purity and no further purification was required.

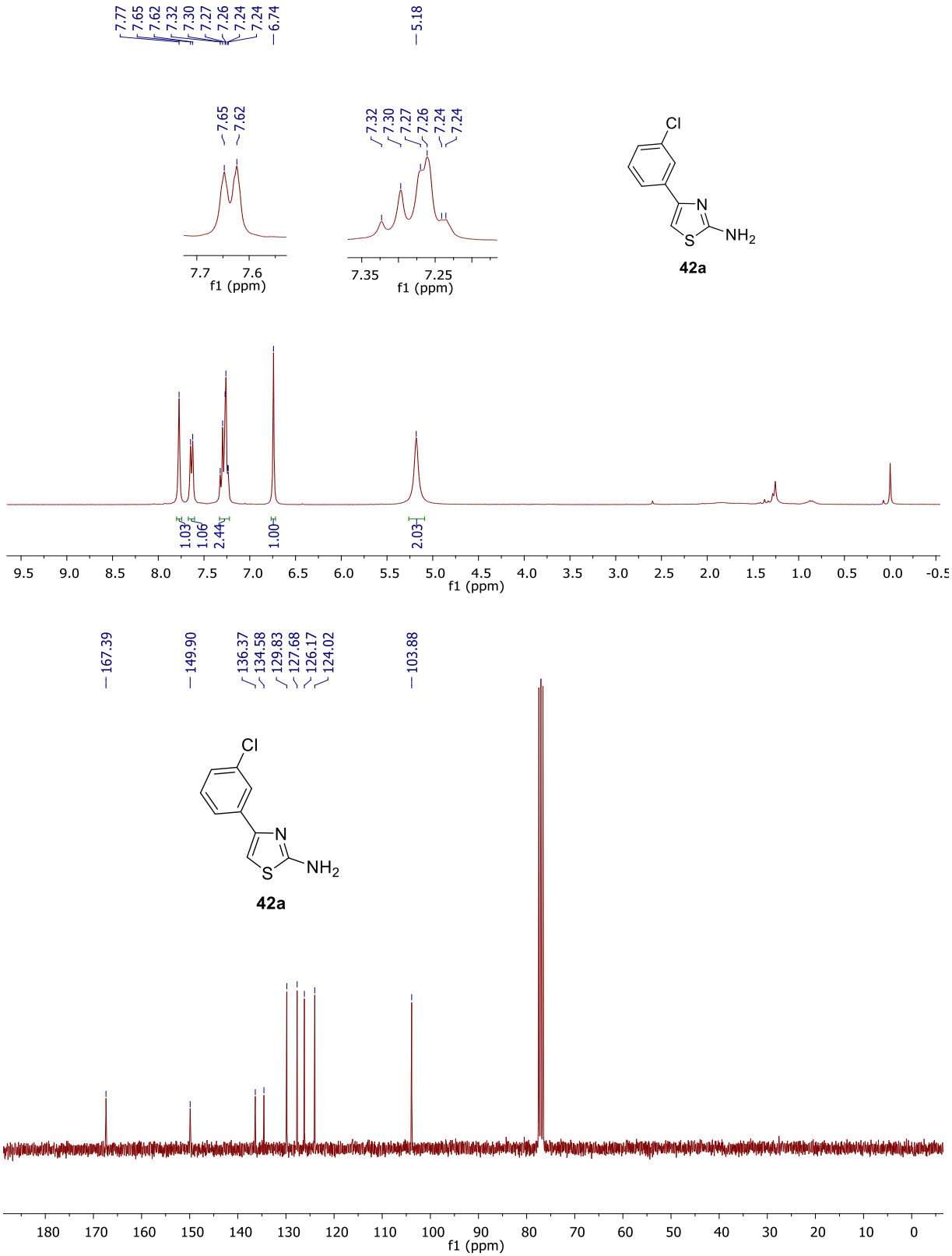
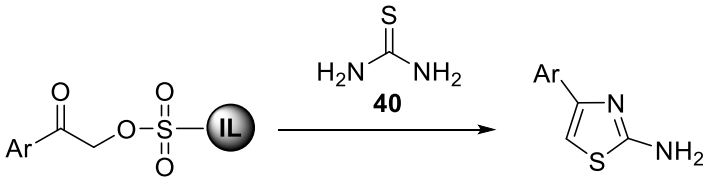
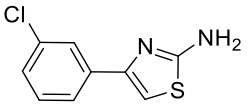
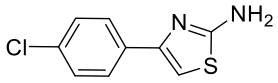
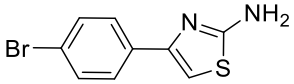
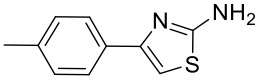
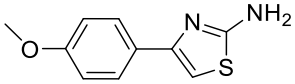
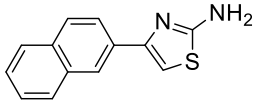
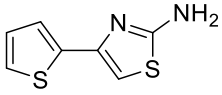


Figure 3.8: ^{1}H and ^{13}C NMR spectrum of **42a**

Table 3.4: Synthesis of 2-aminothiazoles **(42)** using **28**[a]

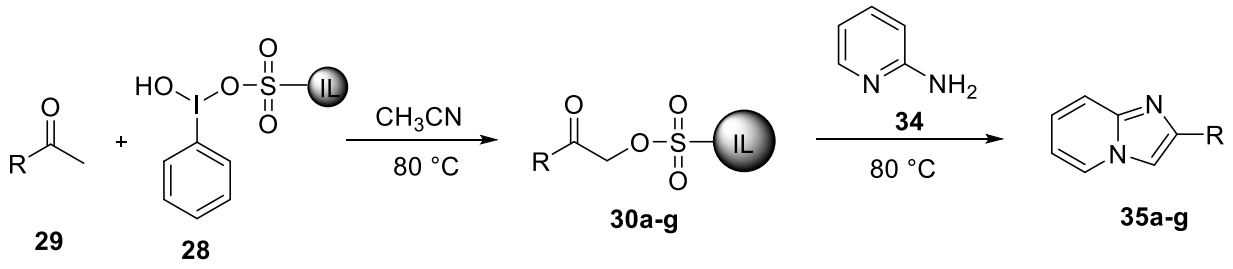


29(a-g) 42(a-g)

Entry	Ar	Product		Yield (%)[b]	Purity[c]
1	3-ClC_6H_4		**42a**	84	>98
2	4-ClC_6H_4		**42b**	83[63][d]	>99
3	4-BrC_6H_4		**42c**	80	99
4	4-$CH_3C_6H_4$		**42d**	71[58][d]	99
5	4-$OCH_3C_6H_4$		**42e**	71	97
6	$C_{10}H_7$		**42f**	81	89
7	C_4H_3S		**42g**	77	94

[a]Reaction conditions: **29** (0.5 mmol), **28** (1 mmol), Na_2SO_4 (0.25 mmol), CH_3CN (3 mL) , 80 °C, 12 h, followed by **40**, 40 °C, 4 h. [b]Isolated yields. [c]Purity determined by HPLC. [d]Isolated yields of **42b** and **42d** when α-tosyloxycarbonyls were used in acetonitrile.

With our interest in the synthesis of imidazo[1,2-*a*]pyridines we further extended this "catch and release" method for the synthesis of imidazo[1,2-*a*]pyridine ring systems (Scheme 3.24). Initial attempt showed that the capture of **29a** with **28**, followed by reaction with 2-aminopyridine did not give desired imidazo[1,2-*a*]pyridines **35a** at 40 °C. Heating the reaction mixture at elevated temperature (80 °C) was fruitful and the desired imidazo[1,2-*a*]pyridine **35a** was obtained in 84% yield.



Scheme 3.24: Synthesis of imidazo[1,2-*a*]pyridines **35a-g** using IL-supported iodine reagent **28**

The structure of **35a** was accelerated by NMR and mass data. Presence of singlet at δ = 8.11 for C-3 protons along with all other expected protons in ^{1}H NMR and peak at 145.7 for C-7 carbon along with other carbons was in well agreement with the structure of **35a**. ^{1}H NMR and ^{13}C NMR of **35a** is shown in figure 3.9.

It is worth to mention that lower yields of imidazo[1,2-*a*]pyridines were obtained with the traditional method under similar conditions. For example when, 2-aminopyridine was reacted with *α*-tosyloxy-4-chloroacetophenone and *α*-tosyloxy-4-methylacetophenone corresponding imidazo[1,2-*a*]pyridines were obtained in 68% and 57% yield as compared to 83% and 71% yield respectively, using our method (Table 3.5, entry 2,4). Under the optimized reaction conditions, various acetophenones were found to be suitable substrates to provide the desired imidazo[1,2-*a*]pyridines (Table 3.5). The results demonstrated that both electron-donating and electron releasing groups on the aryl group of acetophenones were well tolerated to give corresponding imidazo[1,2-*a*]pyridines in moderate to good yields. Moreover, heteroaryl substituted imidazo[1,2-*a*]pyridines (Table 3.5, **35g**) can also be synthesized using this method. All the compounds were well characterized by analysis.

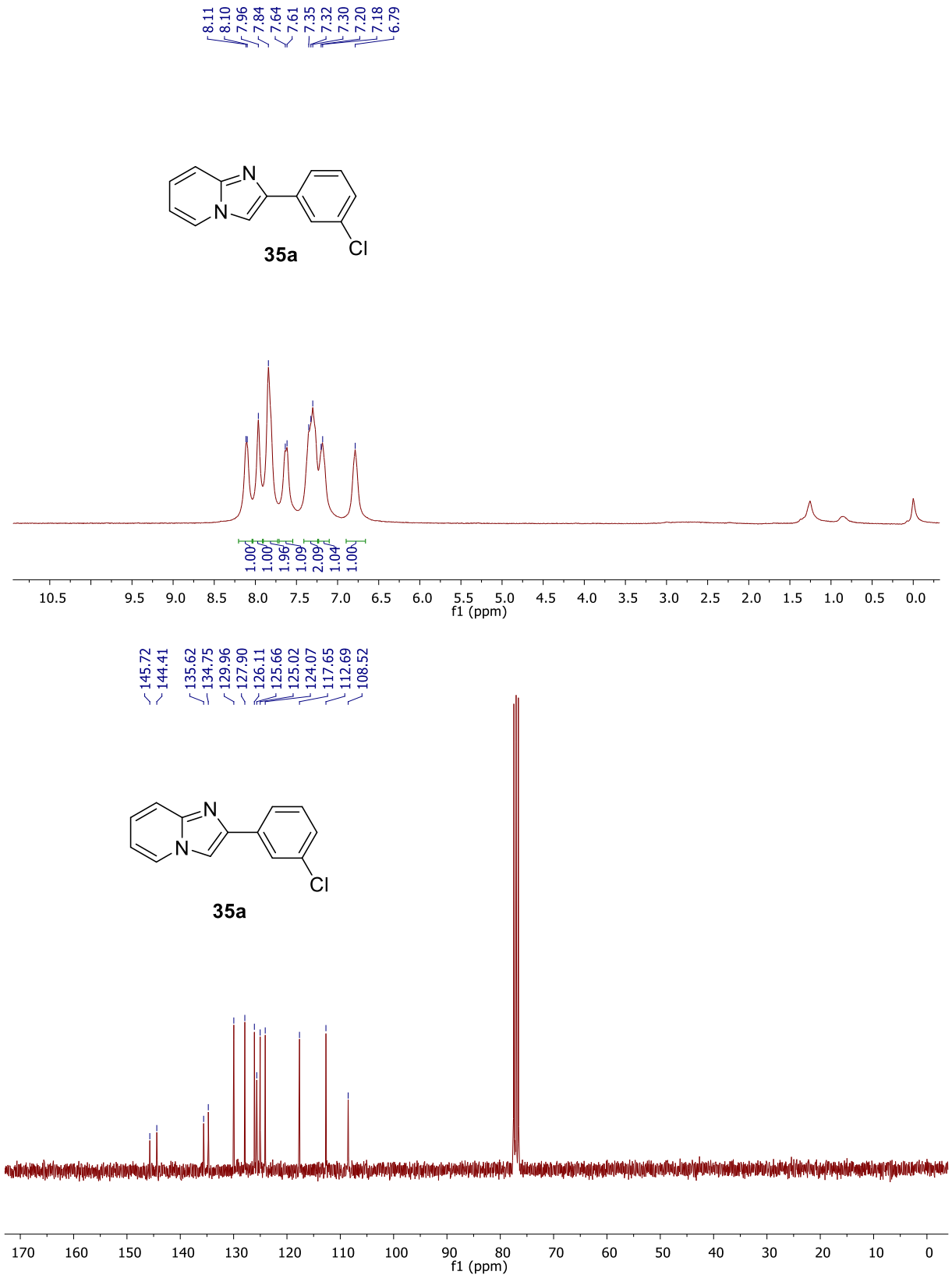
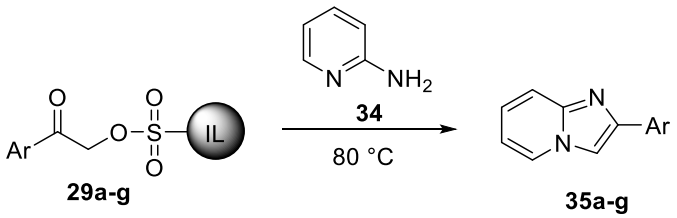
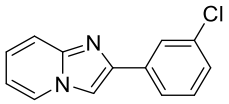
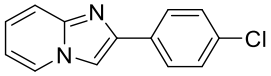
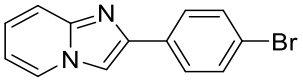
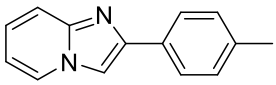
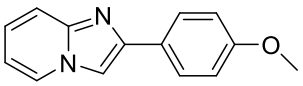
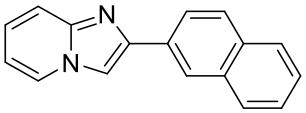
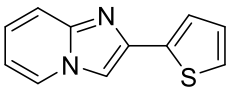


Figure 3.9: ^{1}H and ^{13}C NMR spectrum of **35a**

Table 3.5: Synthesis of imidazo[1,2-*a*]pyridines (**35a-g**) using **28**[a]



Entry	Ar	Product		Yield (%)[b]	Purity[c]
1	3-ClC_6H_4		**35a**	84	82
2	4-ClC_6H_4		**35b**	83[68][d]	>98
3	4-BrC_6H_4		**35c**	80	>99
4	4-$CH_3C_6H_4$		**35d**	71[57][d]	>99
5	4-$OCH_3C_6H_4$		**35e**	58	99
6	$C_{10}H_7$		**35f**	63	99
7	C_4H_3S		**35g**	66	>99

[a]Reaction conditions: **29**(0.5 mmol), **28** (1 mmol), Na_2SO_4 (0.25 mmol), CH_3CN (3 mL), 80 °C, 12 h, followed by **34** (0.5 mmol), 80 °C, 5 h. [b]Isolated yields. [c]Purity determined by HPLC. [d]Isolated yields of **35b** and **35d** when *α*-tosyloxycarbonyls were used in acetonitrile

3.9 Conclusions

In summary, a new approach have been developed for the synthesis of 2-aminothiazoles and imidazo[1,2-*a*]pyridines by the combination of ionic liquid phase synthesis and 'catch-and-release' strategy. The method developed for the synthesis of aza-heterocycles using ionic liquid-supported hypervalent iodine reagent provided good to excellent yield of aza-heterocycles,

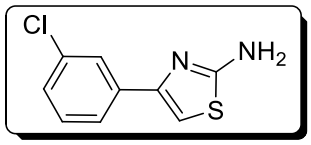
avoids chromatographic purification and allows easy monitoring of the reaction progress. This combinatorial approach could be a good alternative for the synthesis of 2-aminothiazoles and imidazo[1,2-*a*]pyridines and can also be extended to other heterocyclic compounds.

3.10 Experimental Section

General procedure for synthesis of 2-aminothiazoles

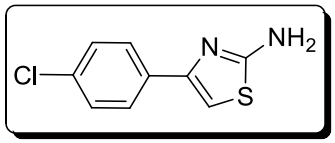
Substituted acetophenone derivative (**29**) (0.5 mmol), Na_2SO_4 (0.25 mmol) and **28** (1 mmol) were added to the round bottom flask containing CH_3CN (5 mL) and the resulting reaction mixture was heated until the acetophenone is completely consumed (TLC). After completion of the reaction, Na_2SO_4 was separated by filtration and the CH_3CN was evaporated under reduced pressure. The residue was washed with ether (3 × 10 mL) and ionic liquid-supported sulfonate (**30**) obtained was treated with thiourea (0.5 mmol) under vigorous stirring at room temperature under solvent free conditions. Progress of the reaction was monitored by TLC. After completion of the reaction, the product was extracted with hexane/ethyl acetate mixture (3 × 10 mL, 2: 8 *v/v*). The combined organic layers were washed with water, dried with anhydrous sodium sulfate, and evaporated under reduced pressure to give the pure 2-aminothiazoles (**42**).

4-(3-Chlorophenyl)-1,3-thiazol-2-amine (42a)



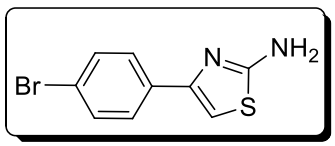
Yield 84%; off white solid; mp 132-133 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.64 (d, J = 7.2 Hz, 2H), 7.36-7.19 (m, 2H), 6.74 (s, 1H), 5.18 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 149.9, 136.4, 134.9, 129.8, 127.7, 126.2, 124.0, 103.9.

4-(4-Chlorophenyl)-1,3-thiazol-2-amine (42b)



Yield 83%; Colorless solid; mp 163-165 °C (lit.[19] 163-164 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (s, 2H), 7.36 (d, J = 6.8 Hz, 2H), 6.73 (s, 1H), 5.10 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 135.4, 133.5, 133.1, 128.8, 127.3, 103.2.

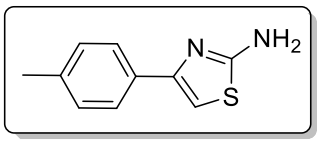
4-(4-Bromophenyl)-1,3-thiazol-2-amine (42c)



Yield 80%; yellow solid; mp 178-180 °C; ^{1}H NMR (300 MHz, DMSO- d_6) δ 7.75 (d, J = 8.0 Hz, 2H), 7.55 (d, J = 8.2 Hz, 2H), 7.10 (s, 2H), 7.08 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.8, 149.1,

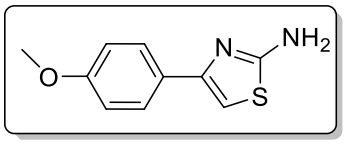
134.5, 131.8, 128.0, 120.5, 102.8.

4-(4-Methylphenyl)-1, 3-thiazol-2-amine (42d)



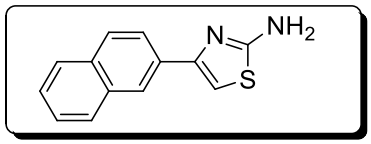
Yield 71%; off white solid; mp 130-131 °C (lit.[19] 125-126 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, J = 6.4 Hz, 2H), 7.18 (d, J = 6.1 Hz, 2H), 6.65 (s, 1H), 5.26 (s, 2H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 151.4, 137.5, 132.0, 129.3, 125.9, 102.0, 21.2.

4-(4-Methoxyphenyl)-1, 3-thiazol-2-amine (42e)



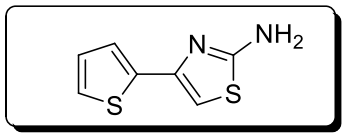
Yield 71%; off white solid; mp 200-203 °C (lit.[20] 204-207 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 7.5 Hz, 2H), 6.91 (d, J = 7.5 Hz, 2H), 6.58 (s, 1H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 159.3, 150.4, 127.4, 127.2, 113.9, 100.5, 55.2.

4-(Naphthalen-6-yl) thiazol-2-amine (42f)



Yield 81%; solid; mp152-154 °C (lit.[20] 152-153 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.30 (s, 1H), 7.89 (dd, J = 37.4, 4.3 Hz, 4H), 7.47 (s, 2H), 7.15 (s, 1H), 7.09 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.7, 150.2, 133.6, 132.8, 132.7, 128.5, 128.3, 128.0, 126.8, 126.2, 124.5, 124.4, 102.8.

4-Thiophen-2-yl-thiazol-2-ylamine (42g)



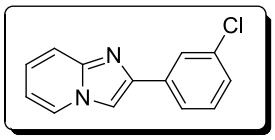
Yield 77%; off white solid; mp 135-136 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.42-7.36 (m, 2H), 7.14 (s, 2H), 7.04 (dd, J = 5.0, 3.7 Hz, 1H), 6.84 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.7, 144.9, 139.7, 128.2, 125.1, 123.2, 100.2.

General procedure for synthesis of imidazo[1,2-*a*]pyridine

To a stirred solution of substituted acetophenone derivatives **29** (0.5 mmol) and sodium sulphate (0.25 mmol) in CH_3CN (3 mL), **28** (1 mmol) was added and the resulting reaction mixture was heated until the acetophenone is completely consumed. After completion of the reaction (as indicated by TLC), reaction mixture was filtered and the CH_3CN was evaporated under reduced pressure. The resulting residue was washed with ether (3 × 10 mL) and subsequently treated with 2-aminopyridine (0.5 mmol) and stirred vigorously at 80 °C temperature under solvent-free conditions. After completion of the reaction, the product was extracted with hexane/ethyl acetate mixture (3 × 10 mL, 2: 8 *v/v*) and washed with water. The combined organic layers were dried

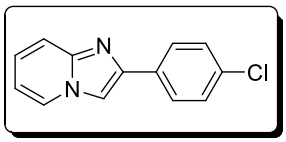
with anhydrous sodium sulfate, and evaporated under reduced pressure to give the desired products in pure form (**35**).

4-(3-Chlorophenyl)*H*-imidazo[1,2-*a*]pyridine (35a)



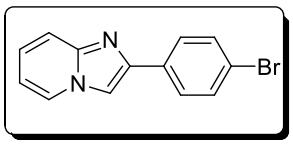
Yield 84%; Yellow solid; mp 105-107 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, J = 4.7 Hz, 1H), 7.96 (s, 1H), 7.84 (s, 2H), 7.63 (d, J = 6.4 Hz, 1H), 7.42-7.23 (m, 2H), 7.19 (d, J = 5.6 Hz, 1H), 6.79 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.7, 144.4, 135.6, 134.7, 130.0, 127.9, 126.1, 125.7, 125.0, 124.1, 117.6, 112.7, 108.5.

4-(4-Chlorophenyl)*H*-imidazo[1,2-*a*]pyridine (35b)



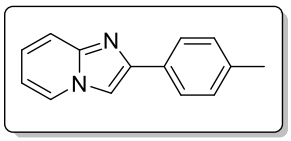
Yield 83%; Yellow solid; mp 199-201°C (lit.[17] 201-202 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 6.8 Hz, 1H), 7.79 (d, J = 8.5 Hz, 2H), 7.72 (s, 1H), 7.53 (d, J = 9.1 Hz, 1H), 7.31 (d, J = 8.5 Hz, 2H), 7.09 (dd, J = 11.4, 4.4 Hz, 1H), 6.69 (t, J = 6.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 143.6, 132.6, 131.3, 127.9, 126.2, 124.6, 123.9, 116.5, 111.6, 107.2.

4-(4-Bromophenyl)*H*-imidazo[1,2-*a*]pyridine (35c)



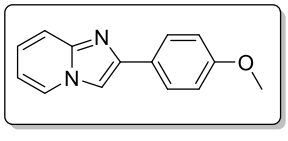
Yield 80%; Yellow solid; mp 196-198 °C (lit.[21] 201-203 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.83 (s, 3H), 7.59 (d, J = 16.6 Hz, 3H), 7.19 (s, 1H), 6.79 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.7, 144.6, 132.7, 131.8, 127.6, 125.6, 125.1, 121.9, 117.5, 112.7, 108.3.

4-(4-Methylphenyl)*H*-imidazo[1,2-*a*]pyridine (35d)



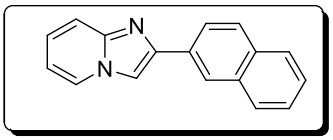
Yield 71%; Off white solid; mp 142-144 °C (lit.[22] 144-145 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 6.0 Hz, 1H), 7.84 (d, J = 7.5 Hz, 2H), 7.79 (s, 1H), 7.61 (d, J = 8.7 Hz, 1H), 7.24 (d, J = 7.5 Hz, 2H), 7.18-7.06 (m, 1H), 6.79-6.67 (m, 1H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.9, 145.6, 137.8, 130.9, 129.4, 126., 125.5, 124.5, 117.4, 112.3, 107.7, 21.3.

4-(4-Methoxyphenyl)*H*-imidazo[1,2-*a*]pyridine (35e)



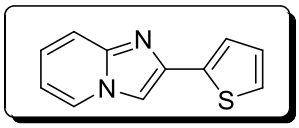
Yield 58%; Colorless solid; mp 142-144 °C (lit.[22] 137-138 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 6.7 Hz, 1H), 7.89 (d, J = 8.8 Hz, 2H), 7.76 (s, 1H), 7.60 (d, J = 9.1 Hz, 1H), 7.14 (ddd, J = 9.0, 6.8, 1.1 Hz, 1H), 6.97 (d, J = 8.8 Hz, 2H), 6.74 (t, J = 6.7 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 145.7, 145.6, 127.3, 126.5, 125.4, 124.4, 117.3, 114.3, 112.2, 107.2, 55.3.

2-(Naphthalen-1-yl)imidazo[1,2-*a*]pyridine (35f)



Yield 63%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.11 (d, J = 6.0 Hz, 1H), 8.06-7.78 (m, 5H), 7.67 (d, J = 8.6 Hz, 1H), 7.47 (s, 2H), 7.20 (dd, J = 19.1, 12.1 Hz, 1H), 6.77 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8, 145.8, 133.8, 133.2, 131.1, 128.4, 128.3, 127.7, 126.3, 126.0, 125.6, 124.8, 124.8, 124.2, 117.6, 112.5, 108.6.

2-(Thiophen-2-yl)*H* -imidazo[1,2-*a*]pyridine (35g)



Yield 66%; off white solid; mp: 134-137 °C (lit.[21] 137-139 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 6.7 Hz, 1H), 7.73 (s, 1H), 7.59 (d, J = 9.1 Hz, 1H), 7.49-7.42 (m, 1H), 7.29 (dd, J = 4.9, 0.9 Hz, 1H), 7.16-7.10 (m, 1H), 7.08 (dd, J = 4.9, 3.6 Hz, 1H), 6.74 (dd, J = 9.7, 3.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.4, 140.8, 137.5, 127.7, 125.4, 125.0, 124.8, 123.7, 117.3, 112.5, 107.4.

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Chapter III

PART C

Synthesis of Ionic Liquid-supported Diaryliodonium Salts

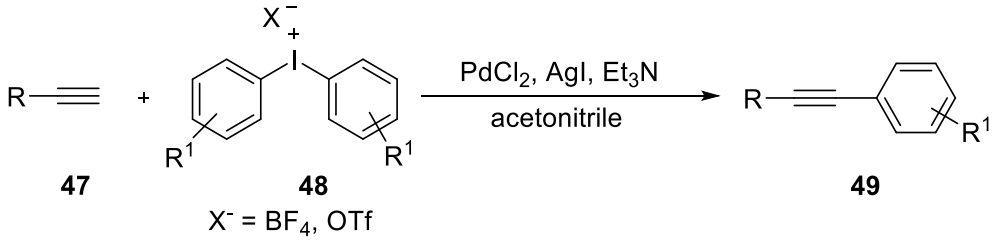
3.12 Introduction

Diaryliodonium salts[1-8] serve as an efficient and powerful electrophilic arylating agents for carbon–carbon and carbon–heteroatom bond-forming reactions under both metal-free and metal-catalyzed conditions, due to their high electron-deficiency and their ability to act as hyper leaving groups. Recently, diaryliodonium salts have also been used in multicomponent cascade annulations for the synthesis of diverse heterocyclic compounds.[9, 10] These salts have been used as aryl sources in the enantioselective generation of "α-carbonyl benzylic stereocentres" in the presence of chiral catalysts. Symmetrical diaryliodonium salts are generally preferred over unsymmetrical salts to avoid chemoselectivity problems, however electron-rich and electron-poor symmetrical diaryliodonium salts are not synthesized in a straightforward.

Diaryliodonium salts have been extensively used for the arylation of different nucleophiles such as C-arylation of malonates,[11, 12] acetanilide,[13] oxindoles,[14] nitroalkanes,[15] ketoximes,[16] indole[17-19] and *N*-arylation of indolines,[20] amide,[21] carbazoles,[22] *O*-arylation of phenol,[23] carboxylic acids,[24, 25] 4-phenyl-6-methyl-pyrimidine-2(*1H*)-ones,[26] *S*-arylation[27] and *P*-arylation.[28] Few representative examples of these reactions are given below-

3.12.1 C-Arylation using diaryliodonium salts-

Zhu group reported synthesis of aryl alkynes **49** by Pd/Ag-catalyzed Sonogashira coupling reaction of terminal alkynes **47** with hypervalent iodonium salts **48** as shown in scheme 3.25.[29] Here, alkyne acts as a nucleophile for the formation of aryl alkynes **49** in good yields in a short time. When aliphatic alkyne was used, the reaction required longer time for the coupling because of the weaker acidity of the acetylenic proton.

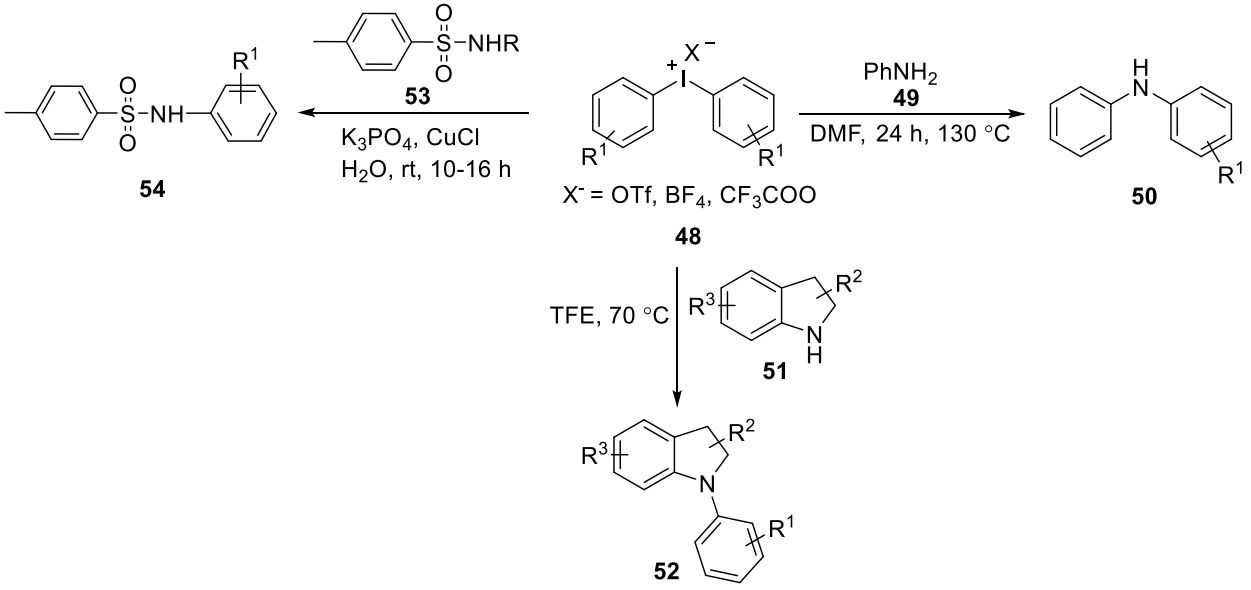


Scheme 3.25: Sonogashira reaction of alkynes with iodonium salts **48**

3.12.2 *N*-Arylation using diaryliodonium salts-

Carroll group described a new synthetic approach for the formation of diarylamines **50** by the reaction of anilines **49** with diaryliodonium salts **48** having trifluoroacetate as a counter ions.[30] Wang group have demonstrated the simple and an efficient synthesis of *N,N*-diarylsulfonamide

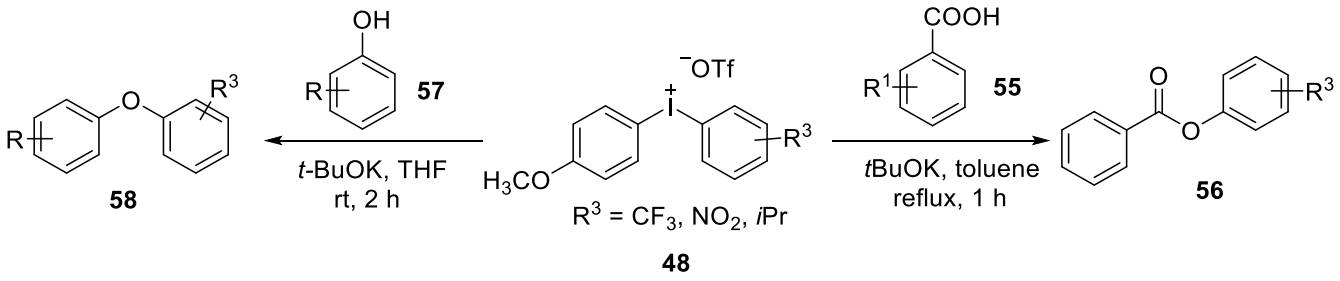
(**72)** using diverse symmetrical or unsymmetrical diaryliodonium salts **48** in water through copper catalyzed direct *N*-arylation of *N*-arylsulfonamides **53**.[31] In the case of unsymmetrical salt (2,4,6-trimethylphenyl)(phenyl)iodonium triflate and 4-methoxy-4′-nitrodiphenyliodonium tosylate, phenyl group and 4-nitrophenyl group were selectively transferred to the *N*-phenylsulfonamide, respectively. Nachtsheim group have also used diaryliodonium salt **48** as electrophilic arylating reagent under metal free condition to get *N*-arylation of indolines **51** in good to excellent yield (Scheme 3.26).[20]



Scheme 3.26: *N*-Arylation of aniline, sulfonamide and amides using iodonium salts **48**

3.12.3 *O*-Arylation using diaryliodonium salts-

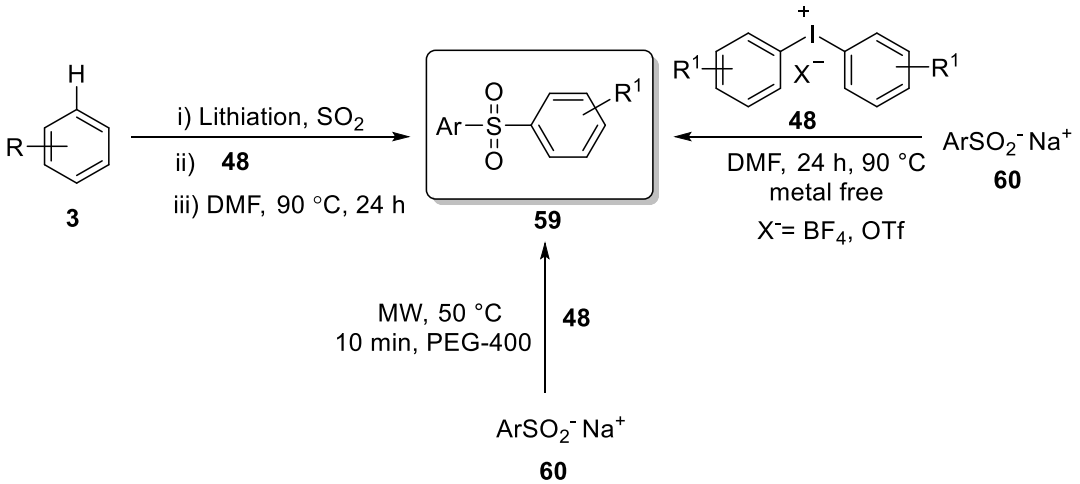
Olofsson developed an efficient, metal-free methodology for the synthesis of diaryl ethers **58** and aryl ester **56** by the reaction of phenols (**57**) and carboxylic acids **55** with diaryliodonium salt **48** in the presence of basic conditions respectively (Scheme 3.27).[23-25] By-product of the reaction iodoarene was recovered and employed to regenerate the diaryliodonium salt **48**. When unsymmetrical diaryliodonium salt was used, the electron poor aryl groups were transferred easily over electron rich aryl groups and *ortho*-substituted aryl groups were more preferred to other aryl groups in metal-free reactions.



Scheme 3.27: *O*-Arylation of carboxylic acids and phenols using **48**

3.12.4 *S*-Arylation using diaryliodonium salts-

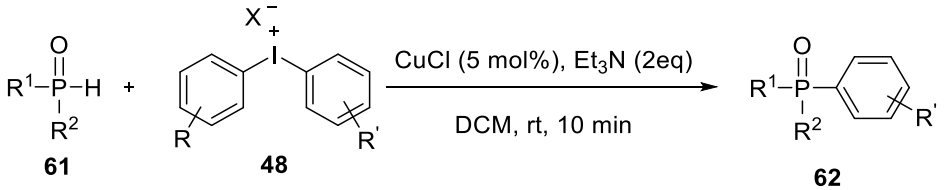
Sulfones are important synthetic intermediates in organic synthesis, which are widely utilized in organic transformations and in medicinal chemistry.[32, 33] Manolikakes group have described an efficient, metal-free, convenient synthesis of aryl sulfones **59** *via* coupling of diaryliodonium salts **48** and arenesulfinates (sodium, magnesium, lithium and zinc salts of sulfinic acid) in DMF at 90 °C (Scheme 3.28).[34] The scope of method was further extended by employing one-pot synthesis of aryl sulfones from organometallic reagents and diaryliodonium salt **48**. The reaction conditions were mild and do not require any additive and excess of reagents. The scope of this reaction was quite broad and includes the synthesis of halogen-substituted or sterically hindered diarylsulfones. Same synthetic procedure has been employed by Kumar group to develope a metal-free, microwave assisted green and facile protocol for the synthesis of diaryl sulfones **59** *via* the reaction of diaryliodonium salts **48** with sodium salt of arenesulfinic acid **60**.[27] Chemo selective arylation of arenesulfinate with and without metal has been performed and different selectivity was observed. This method affords various diaryl sulfones **59** in high yields and shorter reaction time.



Scheme 3.28: Synthesis of diaryl sulfones using **48**

3.12.5 *P*-Arylation using diaryliodonium salts-

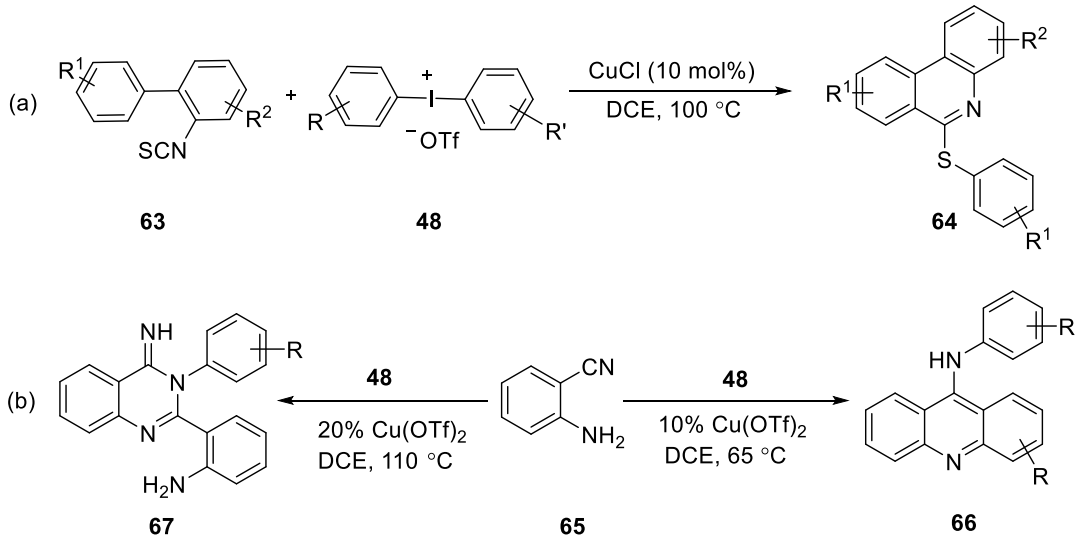
Zhao group achieved synthesis of diaryl, dialkyloxy, diallyloxy and dibenzyloxy phosphine oxides **86** through the reaction of phosphorus nucleophiles **62** with symmetrical and unsymmetrical diaryliodonium salt **48** catalyzed by copper (I) chloride at room temperature (Scheme 3.29).[28] In case of unsymmetrical iodonium salts preferentially nucleophilic substitution occurs, on the sterically hindered aromatic ring or the more electron deficient ring compare to less hindered aromatic ring or electron rich ring.



Scheme 3.29: Copper catalyzed *P*-arylation of diarylphosphine oxide using **48**

3.12.6 Sequential arylation and cyclization using diaryliodonium salts

Chen group reported copper-catalyzed reaction of 2-biarylisothiocyanates (**63)** with diaryliodonium salt (**48)** for the synthesis of 6-(arylthio)-phenanthridines (**64)** through sequential arylation and cyclization under mild reaction conditions (Scheme 3.30a).[35] Diaryliodonium salts with triflate and hexafluorophosphate ion gave good yields whereas low yields were obtained from tetrafluoroborate anion and case of chloride ion. The reaction conditions are mild and desired products were obtained moderate to excellent yields (75–92%). Same group have further reported nitrogen containing heterocyclic compound quinazolinimine **67** and acridine **66** scaffolds by assembling *O*-cyanoaniline **65** and diaryliodonium salt **48** with copper catalyst *via* tandem cyclization pathway (Scheme 3.30b).[36]



Scheme 3.30: (a) Synthesis of substituted phenanthridine and (b) Synthesis of quinazolinimines and acridines using diaryliodonium salts

In arylation methods using diaryliodonium salt, an expensive aryl iodide moiety is generated as waste that renders this approach less attractive. In contrast, it is easier to synthesize unsymmetrical salts than the corresponding symmetrical salts, however controlling the chemoselectivity of the reactions of these unsymmetrical salts, and purification of the reaction products are major concerns. Moreover, every now and then the possibility arises that the aryl iodide by-product interferes with the desired reaction products, which causes severe purification problems. Furthermore, some aryl iodides are very hard to recover and reuse. An alternative approach using polymer-supported diaryliodonium reagents[37-39] also suffers from low loading capacity, long reaction times, multi-step synthesis, the inability to monitor the reaction by various analytical techniques, and a paucity of literature reports. Thus there is a need to develop ionic-liquid-supported diaryliodonium salts to deal with the purification, isolation, and loading problems associated with diaryliodonium salts. With our interest in ionic-liquid-supported reagents,[40-42] along with the synthetic utility of diaryliodonium salts prompted us to pursue a project devoted to the synthesis of ionic liquid-supported diaryliodonium salts. This part of thesis describes synthesis of ionic liquid-supported diaryliodonium salts and the application in *O*-arylation with different counter ions (Figure 3.10).

3.13 Results and discussion

Initally, three different types of ionic liquid-supported iodobenzenes (Figure 3.10) were prepared for the synthesis of ionic liquid-supported diaryliodonium salts but unfortunately, these ionic

liquid-supported iodobenzenes did not work under Olofsson[43-45] conditions to synthesize corresponding ionic liquid-supported diaryliodonium salts.

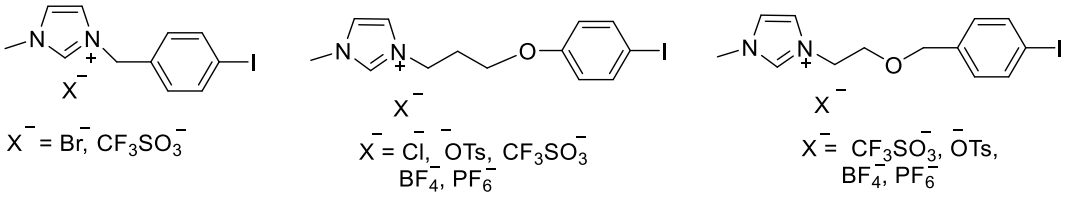
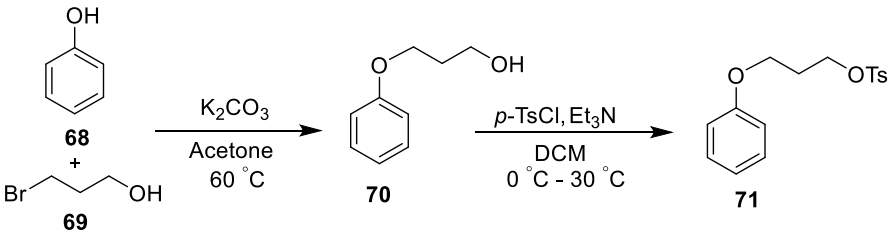


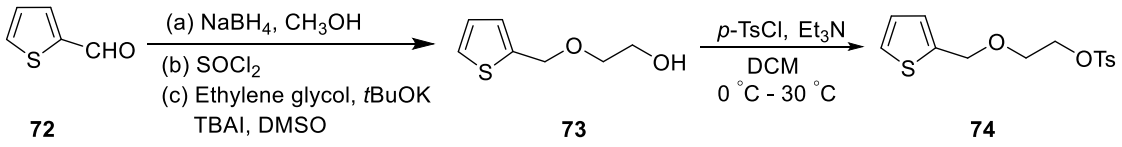
Figure 3.10: Various ionic liquid-supported iodobenzenes

Considering earlier literature reports,[46, 47] we intended to take (diacetoxyiodo)arenes or [hydroxy(tosyloxy)iodo]arenes (HTIA) as aryl iodide source and thus planned to synthesized ionic liquid-supported aryls (**75** and **76**). To achieve synthesis of **75** and **76** required to synthesis **71** and **74** were prepared as mentioned in scheme 3.31. Alkylation of phenol **68** with 1- bromo-3-propanol **69** in the presence of K_2CO_3 and anhydrous acetone afforded **70**. Subsequent reaction of **70** with *p*-toluenesulfonyl chloride in the presence of triethylamine gave **71** (Scheme 3.31A). For the synthesis of **74**, reduction of 2-formylthiophene followed by reaction will $SOCl_2$ and ethylene glycol gave **73** which on subsequent reaction with *p*-TsCl resulted in formation of **74** in 62% yield.

(A) Synthetic scheme for the synthesis of ionic liquid-supported benzene



(B) Synthesis of ionic liquid-supported thiophene



Scheme 3.31: Synthesis of various ionic liquid-supported aryls

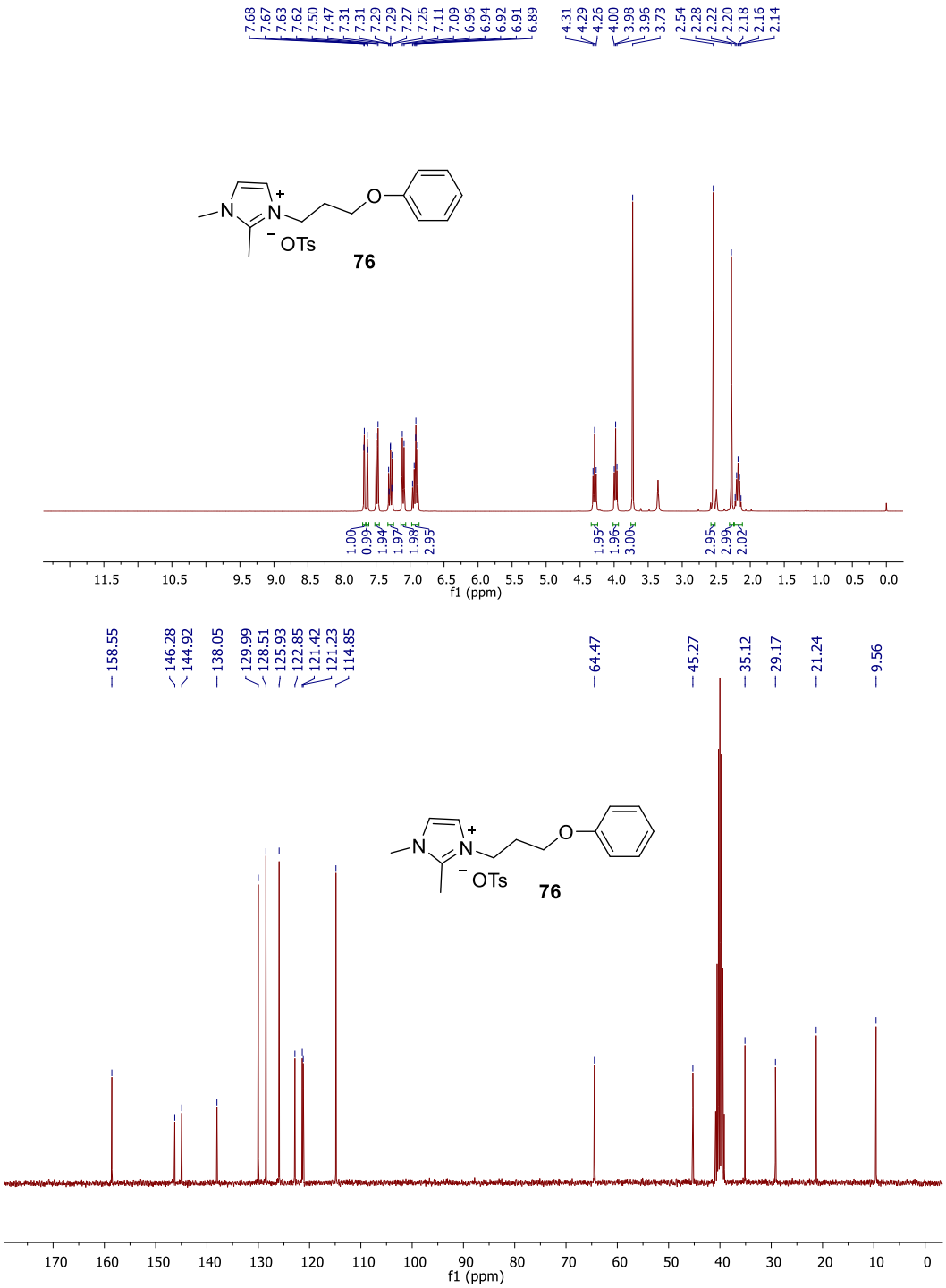


Figure 3.11: ^{1}H and ^{13}C NMR spectrum of **76**

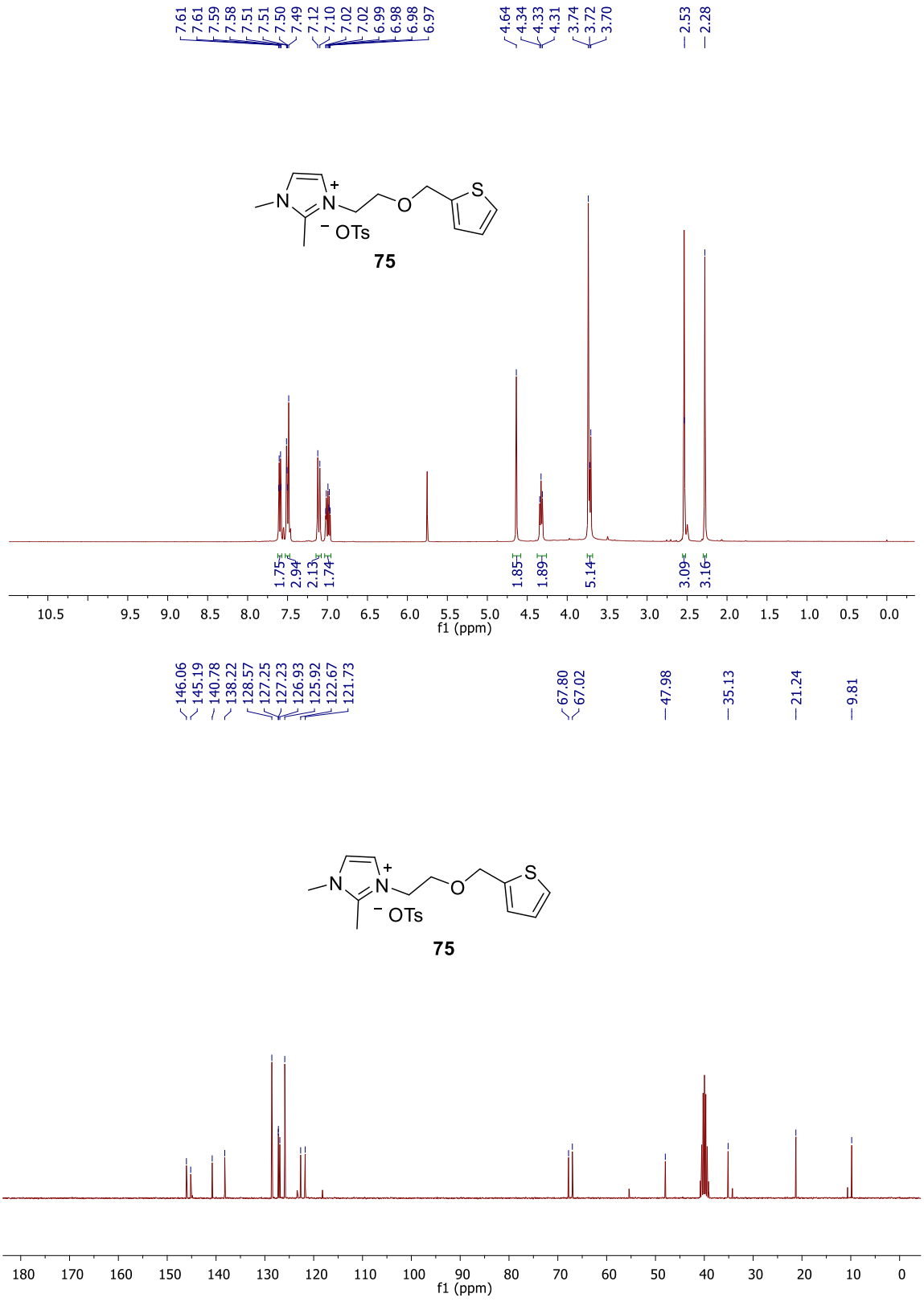
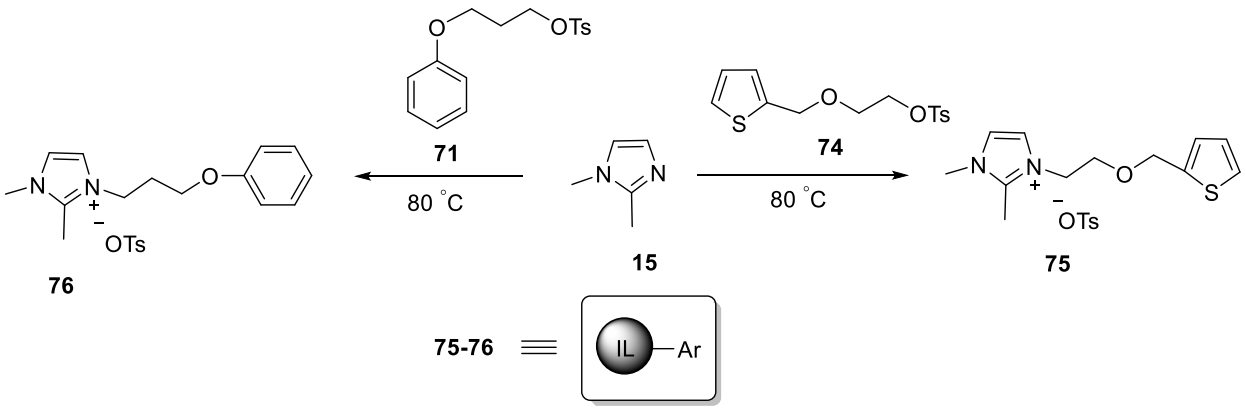


Figure 3.11: ^{1}H and ^{13}C NMR spectrum of **75**

Reaction of **71** and **74** with 1,2-dimethylimidazole (**15**) at 80 °C gave corresponding imidazolium supported aryls (**75-76**) in excellent yields (95-96%). Simple washings of the ionic liquid layer with an ethyl acetate/hexane mixture (1:1 *v/v*) followed by drying under vacuum gave the pure products in good to excellent yield with high purity. The ^{1}H NMR, ^{13}C NMR and mass data of the synthesized ionic liquids were in agreement with the structure of **75** and **76** (Figure 3.11).



Scheme 3.32: Synthesis of various ionic liquid-supported aryls

Based on Pike's[46] and Kita's[47] work on the synthesis of unsymmetrical iodonium salts, we anticipated that the reaction of imidazolium-supported aryls (**75-76**) with [hydroxy(tosyloxy) iodo]arenes (HTIA) or (diacetoxyiodo)arenes would lead to the corresponding ionic liquid-supported diaryliodonium salts. Initial attempts to synthesize ionic-liquid supported diaryliodonium salts by the reaction of **76** with HTIB (**78a**) in $CHCl_3$ at room temperature, did not result in the expected product (**81a**). However, when the same reaction mixture was heated to reflux temperature, the desired product (**81a**) was formed in good yield. Decanting the solvent, followed by washing with tetrahydrofuran gave the product in a quite pure form, without the need of any chromatographic purification. It is worth to mention here that for unsupported diaryliodonium salts, column chromatography is obligatory for purification.[45]

The structure of **81a** was confirmed by ^{1}H and ^{13}C NMR spectroscopy (Figure 3.12). The ^{1}H NMR spectrum of **81a** showed a characteristic multiplet at δ = 8.15 ppm due to the *ortho*-protons adjacent to the iodonium ion, and a singlet peak at δ =3.71 ppm due to the *N*-methyl group along with other protons. In the ^{13}C NMR spectrum, a peak at δ = 106 ppm due to the C–I carbon provides clear evidence for the structure of iodonium salt **81a**.

Having established the reaction conditions for the synthesis of ionic liquid-supported iodonium salts, we went on to examine the possibility of accessing unsymmetrical ionic liquid-supported iodonium salts by the reaction of **75** and **76** with various functionalized HTIAs **79(a–f)**. Gratifyingly, both electron-releasing (**79b**) and electron-withdrawing **79(c–f)** groups were tolerated quite well on the HTIAs to give the desired products (i.e., **81a–81f** and **80a–80f**) in good to excellent yields (Table 3.6).

Ionic liquid-supported diaryliodonium salts (**80** & **81**) can also be synthesized by the reaction of **75** and **76** with (diacetoxyiodo)arenes (**79g-j**) and *p*-toluenesulfonic acid by generating corresponding HTIAs *in situ*. Generally, this approach is more useful for electron-rich iodoaryls for which synthesis of corresponding HTIAs was difficult due to their instability. Thus, (diacetoxyiodo)arenes **79(g-j)** were reacted with **75** and **76** to get corresponding products **80(g-i)** and **81(g-j)** in good to excellent yields (Table 3.6, entries 7-9, 15-18).

Different unsymmetrical ionic liquid-supported diaryliodonium salts bearing functional groups such as bromo, acetoxy, nitro, methyl and methoxy were synthesized in overall good to excellent yield (67-87%). In all cases, the products were purified by simply washing with THF (no chromatographic purification was required). The synthesized ionic-liquid-supported diaryliodonium salts were characterized by NMR spectroscopy and mass spectrometry. The good yields of the diaryliodonium salts were obtained from **76** compared to **75,** which uses thiophene as the aryl source. The stability of these salts was particularly noteworthy. The synthesized ionic liquid-supported diaryliodonium salts (i.e. **80** and **81**) did not show any sign of decomposition or loss of reactivity, even after storage for one month at 5 °C.

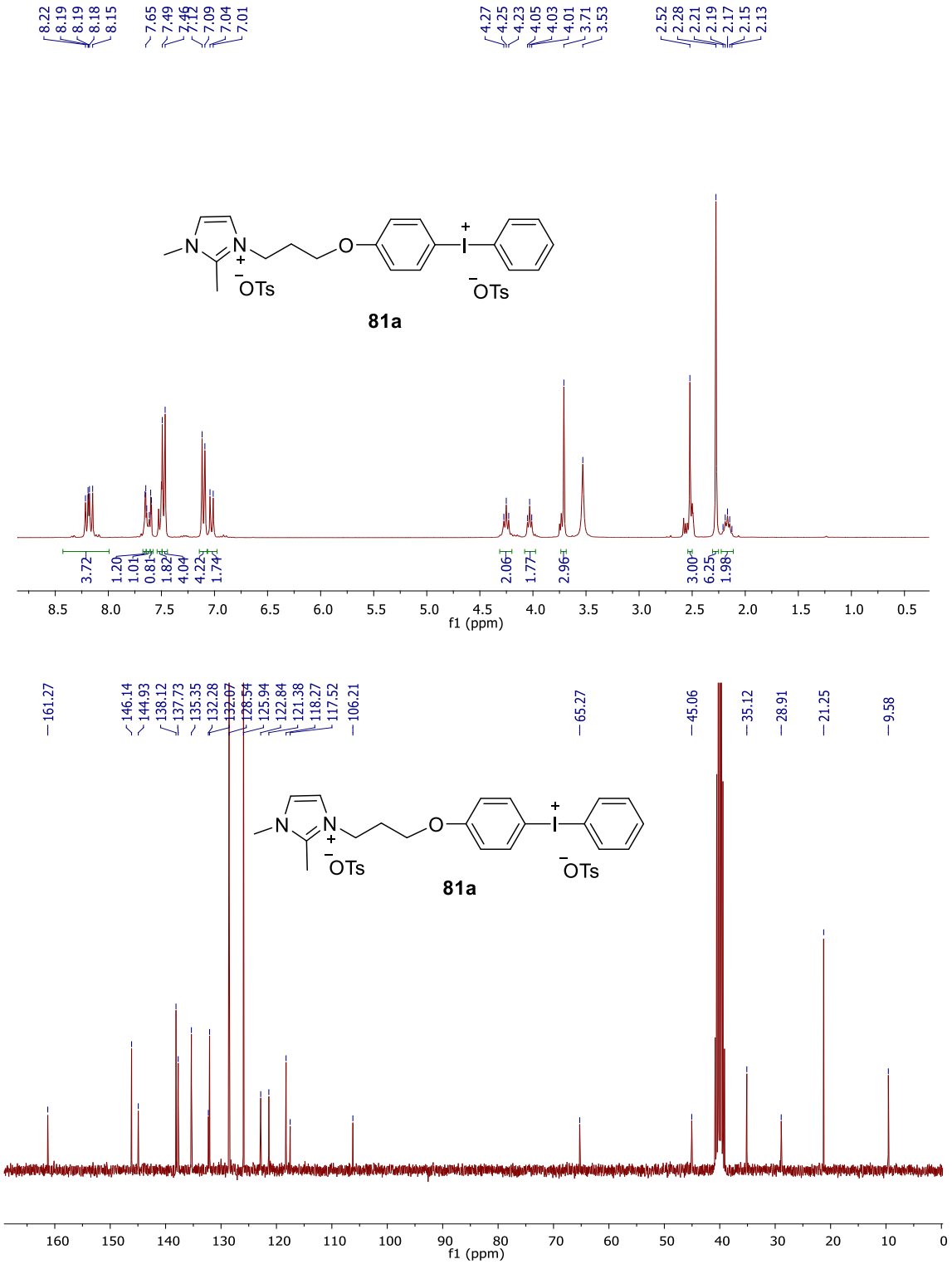
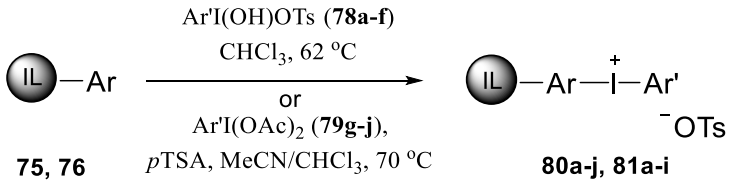


Figure 3.12: ^{1}H and ^{13}C NMR spectrum of **81a**

Table 3.6: Preparation of ionic liquid-supported diaryliodonium salts from **75** and **76**[a/b]



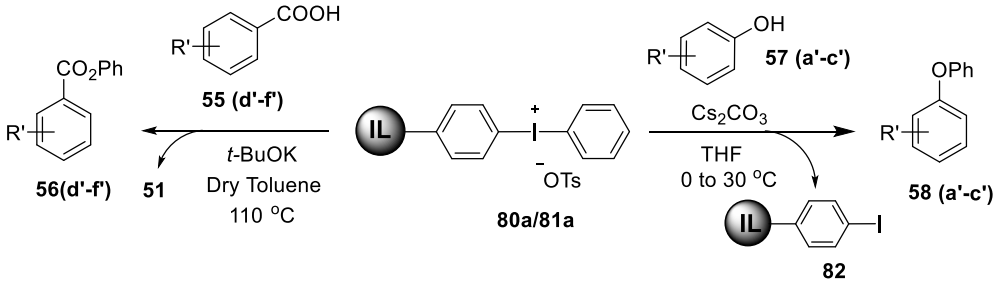
75, 76 **80a-j, 81a-i**

Entry	Ar	Ar′	Product	Yield (%)
1	C_6H_5	C_6H_5	**81a**	80[a]
2	C_6H_5	2,4,6-$(CH_3)_3C_6H_2$	**81b**	72[a]
3	C_6H_5	4-BrC_6H_4	**81c**	80[a]
4	C_6H_5	4-$(OCOPh)C_6H_4$	**81d**	85[a]
5	C_6H_5	4-$(CO_2CH_3)C_6H_4$	**81e**	76[a]
6	C_6H_5	4-$NO_2C_6H_4$	**81f**	72[a]
7	C_6H_5	4-CH_3	**81g**	87[b]
8	C_6H_5	2-CH_3	**81h**	86[b]
9	C_6H_5	4-OCH_3	**81i**	75[b]
10	2-C_4H_3S	C_6H_5	**80a**	72[a]
11	2-C_4H_3S	4-BrC_6H_4	**80c**	70[a]
12	2-C_4H_3S	4-$(OCOPh)C_6H_4$	**80d**	76[a]
13	2-C_4H_3S	4-$(CO_2CH_3)C_6H_4$	**80e**	70[a]
14	2-C_4H_3S	4-$NO_2C_6H_4$	**80f**	68[a]
15	2-C_4H_3S	4-CH_3	**80g**	80[b]
16	2-C_4H_3S	2-CH_3	**80h**	77[b]

17	2-C_4H_3S	4-OCH_3	**80i**	70[b]
18	2-C_4H_3S	2-OCH_3	**80j**	67[b]

Reagents and reaction conditions: [a]Method A: **75** or **76**(1.0 mmol) and ArI(OH)(OTs) (1.0 mmol), $CHCl_3$ (10 mL) at 62 °C for 10 h. [b]Method B: **75** or **76** (1.0 mmol), $ArI(OAc)_2$ (1.0 mmol), *p*-TSA (1.0 mmol), $CH_3CN/CHCl_3$ (1: 2, 10 mL) at 70 °C, 12 h.

The direct electrophilic arylation of various nucleophiles is a synthetically useful reaction of diaryliodonium salts. To demonstrate the utility of the ionic liquid-supported diaryliodonium salts, we examined the *O*-arylation of substituted phenols and acids under metal-free conditions (Scheme 3.33). Initial attempts to optimize the reaction conditions for the *O*-arylation of phenols using **81a** were made using 4-bromophenol (**57b**) as a model substrate. When **57b** was treated with potassium *tert*-butoxide at 0 °C, followed by the addition of **81a** at room temperature, 1-bromo-4-phenoxybenzene (**58b′**) was formed in 70% yield. After further optimization of the reaction conditions for this transformation by varying solvents and bases, we found that the best yield was obtained by using THF as solvent and Cs_2CO_3 as base. Structure of **58b′** was accertained by ^1H NMR and ^{13}C NMR (Figure 3.13) and purity was check by HPLC analysis. It is worth to mention that **58b′** was obtained is more than 96% purity without column chromatography.



Scheme 3.33: *O*-Arylation of phenols and carboxylic acids using **80a/81a**

Having established standard reaction conditions, we set out to survey a range of phenols **57a′**–**57c′** and carboxylic acids **55d′**–**55f′** towards O-arylation (Table 3.7). Interestingly, both phenols and carboxylic acids reacted smoothly with **81a** to give the corresponding diaryl ethers (**58a′–58c′**) and aryl esters (**56d′–56f′**), respectively, in good to excellent yields (70–85 %). A significant advantage of this protocol is that the products were obtained in excellent purity without the need for chromatographic purification. After completion of the reaction, the solvent was evaporated and the product was extracted with a hexane/ethyl acetate mixture. This leaves

behind the by-product supported on the ionic liquid. *O*-Arylation of phenols using **80a** gave the desired products (**58a′**–**58c′**) in yields slightly lower than those obtained with **81a**. The recovered ionic-liquid-supported iodophenyl (**82**) can potentially be reused as a supported reagent in many other organic transformations[48-50] and can also serve as a starting material to synthesize ionic-liquid supported hypervalent iodine reagents.[51-54]

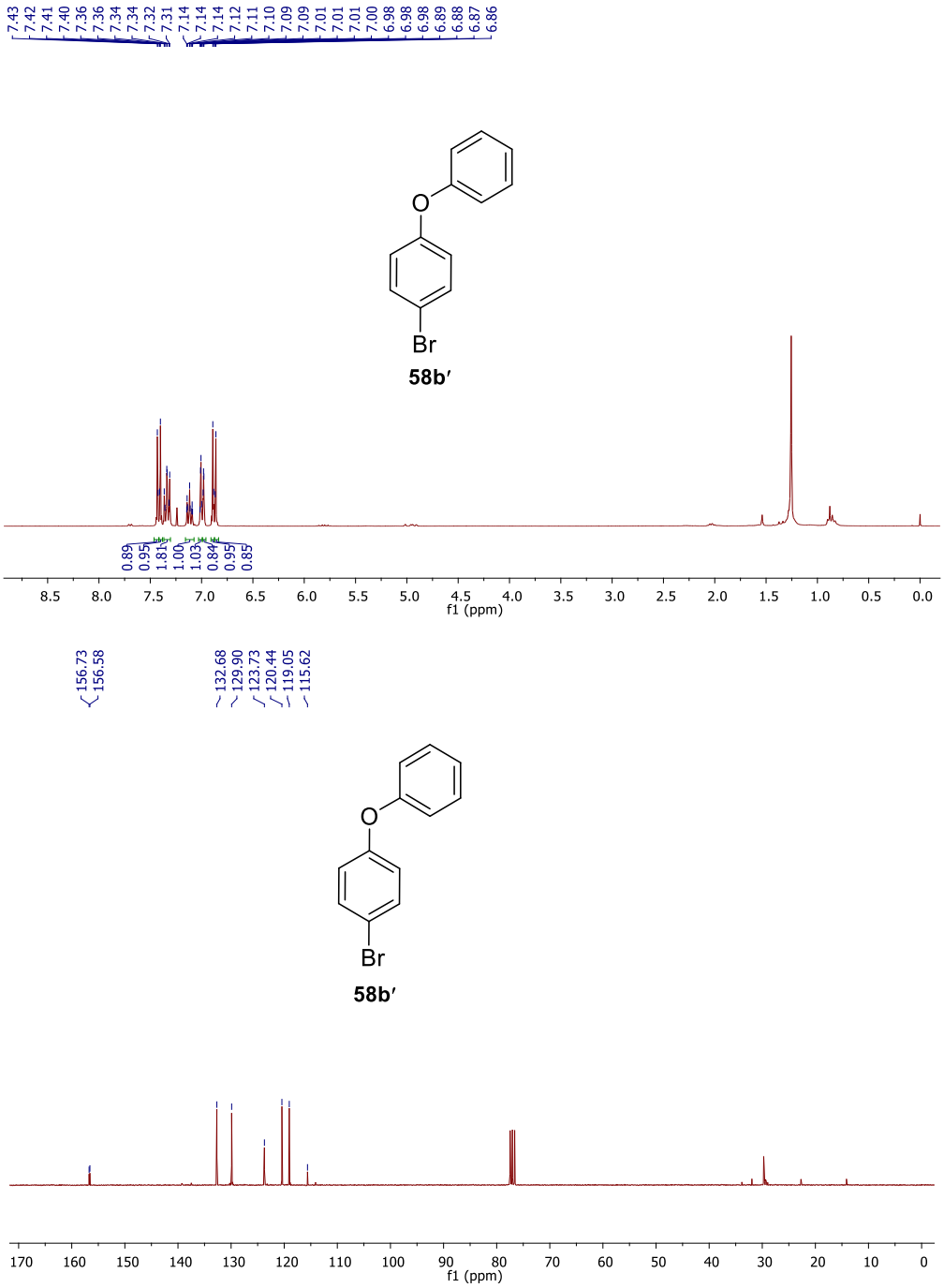
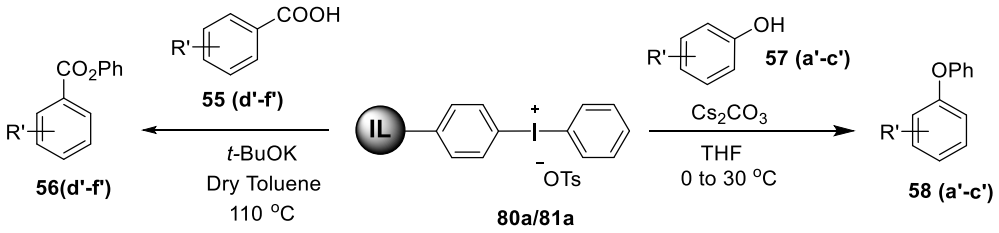
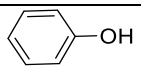
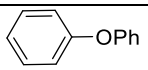
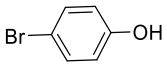
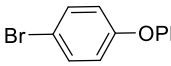
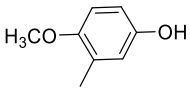
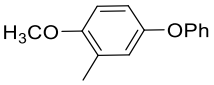
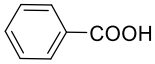
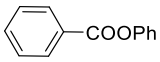
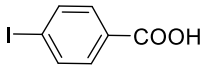
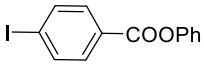
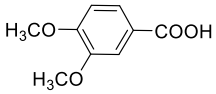
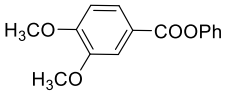
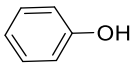
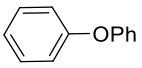
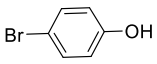
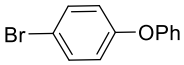
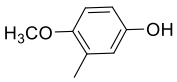
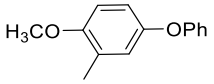


Figure 3.13: ^{1}H and ^{13}C NMR spectrum of **58b′**

Table 3.7: *O*-Arylation of substituted phenols and carboxylic acids using ionic liquid-supported diaryl iodonium salts **80a** and **81a**



Entry	Substrate	Reagent	Product		Yield (%)
1		**81a**		**58a′**	75[a]
2		**81a**		**58b′**	85[a]
3		**81a**		**58c′**	70[a]
4		**81a**		**56d′**	72[b]
5		**81a**		**56e′**	72[b]
6		**81a**		**56f′**	77[b]
7		**80a**		**58a′**	37[c]
8		**80a**		**58b′**	44[c]
9		**80a**		**58c′**	44[c]

Reagents and reaction conditions: (a) **58a′–58c′** (1 mmol), Cs_2CO_3 (1.5 mmol), THF (5 mL), **81a** (1.1 mmol), 0–30 °C, 4 h; (b) **55d′–55f′** (1 mmol), *t*-BuOK (1.5 mmol), **81a** (1.1 mmol), dry toluene (5 mL), 110 °C, 3 h. (c) Yields of **58a′–58c′** when **80a** was used as arylating agent.

3.14 Conclusions

In summary, we designed and synthesized ionic liquid-supported diaryliodonium salts by two approaches: i) using HTIAs and ii) using (diacetoxyiodo)-arenes and *p*-toluenesulfonic acid, where the HTIAs were generated *in situ*. One of the salient features of this protocol is that chromatographic purification is avoided. The electrophilic phenylation of phenols and carboxylic acids by ionic liquid-supported diaryliodonium salt **81a** was demonstrated, and the products were

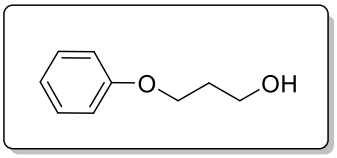
purified by simple extraction with hexane/ethyl acetate mixture. The by-product of the reaction, ionic-liquid-supported iodophenyl **82**, was easily isolated, and can be further reused as a reagent in different organic transformations.[48-50]

3.15 Experimental Section

Procedure for synthesis of 3-phenoxypropan-1-ol (70)

A mixture of phenol **68** (5.00 g, 53 mmol), 3-bromo-1-propanol **69** (4.77 mL, 53 mmol) and K_2CO_3 (7.33 g, 53 mmol) in dry acetone (50 mL) was stirred for 12 h at 60 °C. After completion of reaction, acetone was evaporated, and water (100 mL) was added to the residue. The mixture was extracted by ethyl acetate (3 × 50 mL). The organic layer was dried over anhydrous sodium sulfate. Ethyl acetate was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (60-120 mesh) using hexane and ethyl acetate as eluents to yield as colorless liquid. (6.79 g, yield 84%).

3-Phenoxypropan-1-ol (70)

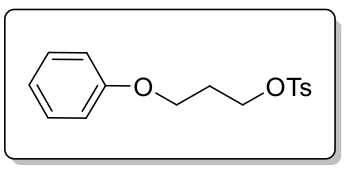


Colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.22 (m, 2H), 6.97-6.85 (m, 3H), 4.08 (t, J = 6.0 Hz, 2H), 3.81 (t, J = 6.0 Hz, 2H), 2.00 (m, J = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 129.5, 120.9, 114.5, 65.5, 60.3, 32.0.

Procedure for synthesis of 3-phenoxypropyl 4-methylbenzene sulfonate (71)

To the stirred reaction mixture of **70** (6.79 g, 44 mmol) and triethylamine (9.19 mL, 66 mmol) in dichlorormethane (DCM) (50 mL) at 0 °C, *p*-toluenesulfonyl chloride (13.59 g, 66 mmol) was added portion wise. The resulting reaction mixture was stirred at room temperature for 4 hours. After completion of the reaction, reaction mixture was washed with water and dried over anhydrous sodium sulfate. DCM was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (60-120 mesh) using hexane and ethyl acetate as eluents to yield **71** as a pure product (8.20 g, yield 60%).

3-phenoxypropyl 4-methylbenzenesulfonate (71)



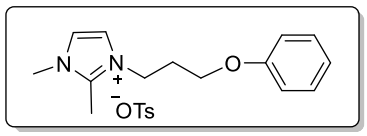
Colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J = 8.3 Hz, 2H), 7.28-7.19 (m, 4H), 6.96-6.89 (m, 1H), 6.76 (d, J = 1.1 Hz, 1H), 6.73 (d, J = 0.9 Hz, 1H), 4.23 (t, J = 6.0 Hz, 2H), 3.92 (t, J = 5.9 Hz,

2H), 2.36 (s, 3H), 2.09 (m, J = 5.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 144.8, 132.7, 129.8, 129.4, 127.8, 120.8, 114.3, 67.1, 62.9, 28.8, 21.6.

Procedure for synthesis of 76

1,2-Dimethylimidazole **15** (2.70 g, 28 mmol) was added to **71** (8.20 g, 53 mmol) and the resulting reaction mixture was heated up to 80 °C till the reaction completes. The resulting residue was washed with diethyl ether (3 × 15 mL) to remove unreacted starting materials, which upon drying under reduced pressure gave **76** as colorless solid. (10.34 g, yield 96 %).

3-(3-Phenoxypropyl)-1,2-dimethyl-1H-imidazol-3-ium 4-methylbenzenesulfonate (76)



Colorless solid (10.35 g, 60%); mp: 85-90 °C ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.68 (d, J = 2.1 Hz, 1H), 7.63 (d, J = 2.1 Hz, 1H), 7.48 (d, J = 8.1 Hz, 2H), 7.33-7.24 (m, 2H), 7.10 (d, J = 7.8 Hz, 2H), 6.95 (dd, J = 8.7, 2.3 Hz, 1H), 6.90 (dd, J = 8.6, 0.9 Hz, 2H), 4.29 (t, J = 6.9 Hz, 2H), 3.98 (t, J = 6.0 Hz, 2H), 3.73 (s, 3H), 2.54 (s, 3H), 2.28 (s, 3H), 2.18 (m, J = 6.5 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.5, 146.2, 144.9, 138.0, 129.9, 128.5, 125.9, 122.8, 121.4, 121.2, 114.8, 64.4, 45.2, 35.1, 29.1, 21.2, 9.5.

Procedure for synthesis of 2-(chloromethyl)thiophene

To the thiophene-2-carboxaldehyde (**72**, 5 mL, 53 mmol) in methanol (25 mL) sodium borohydride (4.04 g, 107 mmol) was added slowly portion wise for 5 min at 0 ºC. The resulting reaction mixture was stirred at room temperature. Progress of reaction was monitored by TLC. After completion of the reaction, methanol was evaporated and water was poured in order to cleave boron complex product was extracted with ethyl acetate (2×15 mL) dried over anhydrous sodium sulfate. Ethyl acetate was evaporated under reduced pressure to give a colorless liquid (5.98 g, yield 98%).

Thionyl chloride ($SOCl_2$, 5.65 mL, 78 mmol) was added drop-wise to the thiophen-2-ylmethanol (5.98 g, 52 mmol) at 0 °C. The resulting mixture was slowly heated to 75 °C for 4 h. After completion of the reaction, excess thionyl chloride was removed by addition of cold water at 0 °C and product was extracted with ethyl acetate (2×15 mL) dried over anhydrous sodium sulfate. Ethyl acetate was evaporated under reduced pressure to give a brown liquid 2-(chloromethyl)thiophene (6.6 g, yield 96%), was pure enough to use further organic transformations.

Procedure for synthesis of 2-(Thiophen-2-ylmetoxy) ethanol (73)

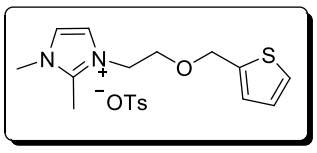
To a stirred solution of 1,2-ethanediol (14.056 mL, 240 mmol) in DMSO at 0 °C potassium *tert*-butoxide (7.37 g, 65 mmol) was added slowly portion wise for 10 min. The resulting solution was further stirred for 30 min at same temperature before adding tetrabutylammonium iodide (TBAI, 10 mmol). A homogeneous solution of 2-(chloromethyl)thiophene (6.6 g, 50 mmol) in DMSO (15 mL) was added drop-wise to the above reaction mixture and stirred at room temperature for 3 hours. After completion of the reaction, cold water (50 mL) was added and compound was extracted with ethyl acetate (2 × 25 mL) and dried over anhydrous sodium sulfate. Ethyl acetate was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (60-120 mesh) using hexane and ethyl acetate as eluents to get pure product as brown liquid **74** (5.41 g, yield 69%).

Procedure for synthesis of 2-(Thiophen-2-ylmethoxy)ethyl-4-methylbenzenesulfonate (74)

To the stirred solution of 2-(thiophen-2-ylmetoxy)ethanol (**73**, 5.41g, 34 mmol) in DCM (25 mL) triethylamine (14.28 mL, 102 mmol) and *p*-toluenesulfonyl chloride (9.78 g, 51 mmol) was added slowly at 0 °C. The resulting reaction mixture was stirred at room temperature for 4 hours. After completion of the reaction, the reaction mixture was washed with water and dried over anhydrous sodium sulfate. DCM was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (60-120 mesh) using hexane and ethyl acetate as eluents to get pure product as dark yellow liquid **74** (6.62 g, yield 62%).

Procedure for synthesis of ionic liquid-supported thiophene (75)

Mixture of 2-(thiophen-2-ylmethoxy)ethyl 4-methylbenzenesulfonate **74** (6.62 g, 21 mmol) and 1,2-dimethylimidazole **15** (2.24 g, 23 mmol) was heated to 80 °C under solvent free conditions up to 6 hours. After completion of reaction as indicated by TLC, the resulting product was washed with hexane:ethyl acetate (1:1 *v/v,* 20 mL× 3) to remove unreacted materials followed by drying under reduced pressure gave compound 75 as brown viscous liquid (8.31 g, yield 96%).



Compound 75: Brown viscous liquid (8.31 g, yield 96%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.61 (d, J = 2.1 Hz, 1H), 7.58 (d, J = 2.1 Hz, 1H), 7.53-7.48 (m, 3H), 7.11 (d, J = 7.9 Hz, 2H), 7.02-6.99 (m, 2H),

4.64 (s, 2H), 4.39-4.25 (m, 2H), 3.74-3.71 (m, 5H), 2.53 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 146.0, 145.1, 140.7, 138.2, 128.5, 127.2, 127.2, 126.9, 125.9, 122.6, 121.7, 67.8, 67.0, 47.9, 35.1, 21.2, 9.8.

General procedure for the synthesis of HTIAs from iodoarenes

To a stirred solution of iodoarene (3 mmol) in dichloromethane/trifluoroethanol (TFE) (8 mL, 1:1 *v/v*) *m*CPBA was added (3 mmol) and stirred for 15-20 min, followed by the addition of *p*-TsOH (3 mmol). The resulting solution was stirred at room temperature till the reaction completed and the resulting solid was filtered off and washed with diethyl ether:hexane mixture (1:1 *v/v*, 10 mL) to remove impurities. The product was dried in vacuum to give compound **78** as a solid.

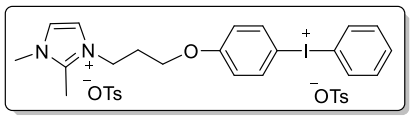
General procedure for the synthesis of (diacetoxyiodo)arenes from iodoarenes (79)

To a mixture of acetic acid (6 mL) and acetic anhydride (0.60 mL), sodium acetate (6.6 mmol), sodium periodate (3 mmol) and iodoarene (3 mmol) were added simultaneously. The resulting reaction mixture was heated up to 120 ^{o}C for 3 hours. After completion of the reaction as indicated by TLC, the reaction mixture was cooled to room temperature, 10% acetic acid solution was added and the resulting solution was stirred at room temperature for 10 min. The precipitated out solid was filtered and washed with 10% acetic acid solution and dried under reduced pressure to get corresponding (diacetoxyiodo)arenes.

General procedure for the synthesis of ionic liquid-supported diaryliodonium salts (81a-i & 80a-f) (Method A)

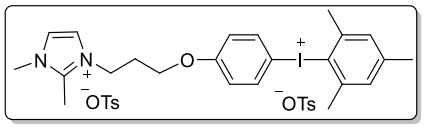
HTIA (1.0 mmol) was added to the ionic liquid-supported arene **75** or **76** (1.0 mmol) in $CHCl_3$ (10 mL), and the resulting reaction mixture was heated at reflux for 10 h. The progress of the reaction was monitored by TLC. After the reaction was complete, the $CHCl_3$ was decanted, and the crude product was washed with THF (3 × 5 mL) to remove unreacted starting materials. The resulting compound was dried under reduced pressure to give the pure desired product.

3-(3-(4-(Phenyliodonio)phenoxy)propyl)-1,2-dimethyl-1*H*-imidazol-3-ium-di-(4-methylbenzenesulfonate) (81a)



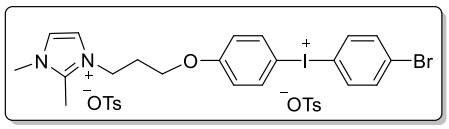
White solid (648 mg, yield 80%); mp 149-157 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.28 – 8.09 (m, 4H), 7.65 (d, J = 2.1 Hz, 1H), 7.63 (d, J = 7.4 Hz, 1H), 7.60 (d, J = 2.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.1 Hz, 4H), 7.10 (d, J = 7.9 Hz, 4H), 7.03 (d, J = 9.1 Hz, 2H), 4.25 (t, J = 6.9 Hz, 2H), 4.03 (t, J = 5.9 Hz, 2H), 3.71 (s, 3H), 2.52 (s, 3H), 2.28 (s, 6H), 2.23-2.11 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.3, 146.1, 144.9, 138.1, 137.7, 135.3, 132.3, 132.1, 128.5, 125.9, 122.8, 121.4, 118.3, 117.5, 106.2, 65.3, 45.1, 35.1, 28.9, 21.2, 9.6; HRMS (ESI-TOF) (*m/z*) calculated for $C_{20}H_{23}IN_2O^{2+}$: 434.0844, found: 434.0842 $[M - OTs]^+$.

3-(3-(4-(Mesityliodonio)phenoxy)propyl)-1,2-dimethyl-1*H*-imidazol-3-ium-di-(4-methylbenzenesulfonate) (81b)



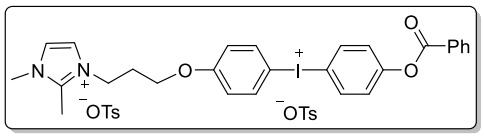
Off white viscous liquid (588 mg, yield 72%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.90 (d, J = 8.9 Hz, 2H), 7.65 (d, J = 1.8 Hz, 1H), 7.60 (d, J = 1.7 Hz, 1H), 7.46 (d, J = 7.9 Hz, 4H), 7.18 (s, 2H), 7.10 (d, J = 7.8 Hz, 4H), 7.00 (d, J = 8.9 Hz, 2H), 4.25 (t, J = 6.8 Hz, 2H), 4.02 (t, J = 5.8 Hz, 2H), 3.71 (s, 3H), 2.59 (s, 6H), 2.53-2.52 (m, 2H), 2.28 (s, 9H), 2.22-2.09 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.0, 146.1, 144.9, 143.3, 141.8, 138.1, 137.0, 130.1, 128.5, 125.9, 123.6, 122.8, 121.4, 118.3, 104.1, 65.3, 55.4, 45.1, 35.1, 28.9, 26.7, 21.2, 20.9, 9.6; HRMS (ESI-TOF) (*m/z*) calculated for $C_{23}H_{29}IN_2O^{2+}$: 476.1314, found: 476.1310 $[M - OTs]^+$.

3-(3-(4-((4-Bromophenyl)iodonio)phenoxy)propyl)-1,2-dimethyl-1*H*-imidazol-3-ium-di-(4-methylbenzenesulfonate) (81c)



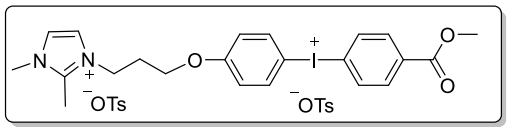
White solid (683 mg, yield 80%); mp 152-159 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.18-8.15(m, 4H), 7.72 (d, J = 8.6 Hz, 2H), 7.65 (d, J = 1.9 Hz, 1H), 7.60 (d, J = 1.9 Hz, 1H), 7.47 (d, J = 8.0 Hz, 4H), 7.10 (d, J = 7.9 Hz, 4H), 7.04 (d, J = 9.0 Hz, 2H), 4.26 (t, J = 7.0 Hz, 2H), 4.04 (t, J = 5.9 Hz, 2H), 3.72 (s, 3H), 2.53 (s, 3H), 2.28 (s, 6H), 2.12-2.10 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.3, 146.1, 144.9, 138.1, 137.7, 137.3, 134.9, 128.5, 126.41, 125.9, 122.8, 121.4, 118.3, 116.1, 106.5, 65.3, 45.1, 35.1, 28.9, 21.2, 9.6; HRMS (ESI-TOF) (*m/z*) calculated for $C_{20}H_{22}BrIN_2O^{2+}$: 511.9949, found: 511.9940 $[M - OTs]^+$ and 513.9849 $[M + 2 - OTs]^+$.

3-(3-(4-((4-(Benzoyloxy)phenyl)iodonio)phenoxy)propyl)-1,2-dimethyl-1*H*-imidazol-3-ium-di-(4-methylbenzenesulfonate) (81d)



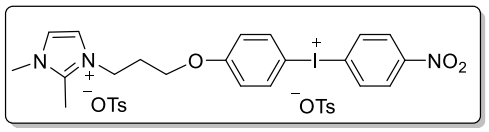
White solid (761 mg, yield 85%); mp 155-162 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.32 (d, J = 7.1 Hz, 2H), 8.21 (d, J = 6.9 Hz, 2H), 8.11 (d, J = 5.5 Hz, 2H), 7.82-7.72 (m, 1H), 7.63 (d, J = 11.5 Hz, 4H), 7.47 (d, J = 5.6 Hz, 6H), 7.16-6.99 (m, 6H), 4.33-4.19 (m, 2H), 4.11-4.01 (m, 2H), 3.71 (s, 3H), 2.50 (s, 3H), 2.27 (s, 6H), 2.22-2.12 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.7, 161.3, 153.6, 146.1, 144.9, 138.1, 137.7, 137.1, 134.9, 130.4, 129.5, 128.8, 128.5, 126.1, 125.9, 122.84, 121.4, 118.3, 113.8, 106.6, 65.3, 45.1, 35.1, 28.9, 21.2, 9.6; HRMS (ESI-TOF) (*m/z*) calculated for $C_{27}H_{27}IN_2O_3^{2+}$: 554.1055, found: 554.1044 [M –OTs]$^{+}$.

3-(3-(4-((4-(Methoxycarbonyl)phenyl)iodonio)phenoxy)propyl)-1,2-dimethyl-1*H*-imidazol-3-ium-di-(4-methylbenzenesulfonate) (81e)



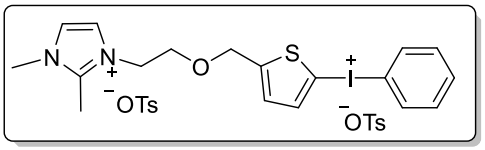
Brown viscous liquid (633 mg, yield 76%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.32 (d, J = 7.8 Hz, 2H), 8.20 (d, J = 8.0 Hz, 2H), 7.99 (d, J = 7.5 Hz, 2H), 7.65 (d, J = 2.0 Hz, 1H), 7.60 (d, J = 2.0 Hz, 1H), 7.48 (d, J = 7.1 Hz, 4H), 7.10 (d, J = 7.2 Hz, 4H), 7.05 (d, J = 8.3 Hz, 2H), 4.26 (t, J = 7.0 Hz, 2H), 4.04 (t, J = 5.9 Hz, 2H), 3.86 (s, 3H), 3.71 (s, 3H), 2.53 (s, 3H), 2.28 (s, 6H), 2.23-2.11 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.6, 161.4, 146.1, 144.9, 138.1, 137.9, 135.7, 132.8, 132.2, 128.5, 125.9, 122.8, 122.3, 121.4, 118.4, 106.2, 65.3, 53.2, 45.0, 35.1, 28.9, 21.2, 9.6; HRMS (ESI-TOF) (*m/z*) calculated for $C_{22}H_{25}IN_2O_3^{2+}$: 492.0899, found: 492.0944 [M –OTs]$^{+}$.

3-(3-(4-((4-Nitrophenyl)iodonio)phenoxy)propyl)-1,2-dimethyl-1*H*-imidazol-3-ium-di-(4-methylbenzenesulfonate) (81f)



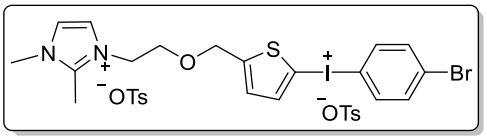
Light brown viscous liquid (590 mg, yield 72%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.44 (d, J = 9.0 Hz, 2H), 8.29-8.20 (m, 4H), 7.65 (d, J = 2.0 Hz, 1H), 7.60 (d, J = 2.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 4H), 7.10 (d, J = 7.9 Hz, 4H), 7.06 (d, J = 9.1 Hz, 2H), 4.26 (t, J = 7.0 Hz, 2H), 4.05 (t, J = 5.9 Hz, 2H), 3.72 (s, 3H), 2.53 (s, 3H), 2.28 (s, 6H), 2.22 – 2.25 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.5, 149.7, 146.1, 144.9, 138.1, 138.1, 136.6, 128.5, 126.5, 125.9, 123.7, 122.8, 121.4, 118.4, 106.5, 65.3, 45.1, 35.1, 28.9, 21.2, 9.6; HRMS (ESI-TOF) (*m/z*) calculated for $C_{27}H_{27}IN_2O_3^{2+}$: 554.1055, found: 554.1044 [M –OTs]$^{+}$.

3-(2-((5-(Phenyliodonio)thiophen-2-yl)methoxy)ethyl)- 1,2-dimethyl-1*H*-imidazol-3-ium-di-(4-methylbenzenesulfonate) (80a)



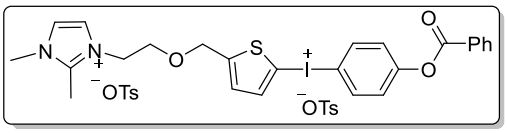
Yellow viscous liquid (562 mg, yield 72%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.24 (d, J = 7.7 Hz, 2H), 7.94 (d, J = 3.7 Hz, 1H), 7.70-7.51 (m, 5H), 7.48 (d, J = 8.0 Hz, 4H), 7.11 (d, J = 7.8 Hz, 4H), 7.04 (d, J = 3.6 Hz, 1H), 4.74 (s, 2H), 4.33 (t, J = 4.6 Hz, 2H), 3.79-3.65 (m, 5H), 2.53 (s, 3H), 2.28 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.2, 146.0, 145.2, 140.5, 138.2, 135.1, 132.5, 132.1, 128.6, 128.4, 125.9, 122.7, 121.7, 119.9, 100.7, 68.5, 66.8, 47.8, 35.2, 21.2, 9.8; HRMS (ESI-TOF) (*m/z*) calculated for $C_{18}H_{21}IN_2SO^{2+}$: 440.0408, found: 440.0403 $[M - OTs]^+$.

3-(2-((5-((4-Bromophenyl)iodonio)thiophen-2-yl)methoxy)ethyl)-1,2-dimethyl-1*H*-imidazol-3-ium 4-methylbenzenesulfonate (80c)



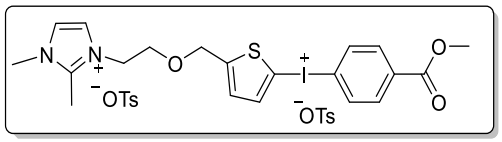
Brown viscous liquid (602 mg, yield 70%); mp 173-177 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.18 (d, J = 8.6 Hz, 2H), 7.95 (d, J = 3.8 Hz, 1H), 7.74 (d, J = 8.6 Hz, 2H), 7.60 (d, J = 1.9 Hz, 1H), 7.57 (d, J = 2.1 Hz, 1H), 7.48 (d, J = 8.0 Hz, 4H), 7.11 (d, J = 7.9 Hz, 4H), 7.06 (d, J = 3.8 Hz, 1H), 4.75 (s, 2H), 4.34 (t, J = 4.8 Hz, 2H), 3.79-3.70 (m, 5H), 2.53 (s, 3H), 2.28 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.4, 146.0, 145.2, 140.7, 138.2, 137.1, 135.0, 128.5, 128.4, 126.6, 125.9, 122.7, 121.7, 118.5, 101.0, 68.5, 66.8, 47.8, 35.2, 21.2, 9.8; HRMS (ESI-TOF) (*m/z*) calculated for $C_{18}H_{20}IBrN_2SO^{2+}$: 517.9513, found: 517.9413 $[M - OTs]^+$ and 519.9512 $[M + 2 - OTs]^+$.

3-(2-((5-((4-(Benzoyloxy)phenyl)iodonio)thiophen-2-yl)methoxy)ethyl)-1,2-dimethyl-1*H*-imidazol-3-ium-di-(4-methylbenzenesulfonate) (80d)



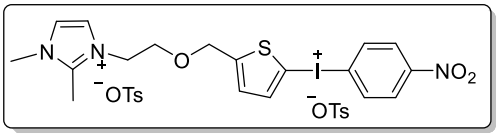
Brown viscous liquid (685 mg, 76% yield); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.36 (d, J = 7.9 Hz, 2H), 8.11 (d, J = 7.4 Hz, 2H), 7.98 (s, 1H), 7.77 (t, J = 6.9 Hz, 1H), 7.60 (dd, J = 15.5, 6.4 Hz, 4H), 7.48 (d, J = 6.1 Hz, 6H), 7.11 (d, J = 7.4 Hz, 4H), 7.06 (d, J = 3.7 Hz, 1H), 4.76 (s, 2H), 4.31-4.37 (m, 2H), 3.69-3.79 (m, 5H), 2.53 (s, 3H), 2.27 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.7, 153.7, 152.4, 145.9, 145.2, 140.7, 138.3, 136.9, 134.9, 130.4, 129.5, 128.8, 128.6, 128.4, 126.0, 125.9, 122.7, 121.7, 116.1, 101.0, 68.5, 66.9, 47.8, 35.2, 21.2, 9.8; HRMS (ESI-TOF) (*m/z*) calculated for $C_{25}H_{25}IN_2SO_3^{2+}$: 560.0620, found: 560.0610 $[M - OTs]^+$

3-(2-((5-((4-(Methoxycarbonyl)phenyl)iodonio)thiophen-2-yl)methoxy)ethyl)-1,2-dimethyl-1*H*-imidazol-3-ium-di-(4-methylbenzenesulfonate) (80e)



White solid (587 mg, yield 70%); mp 170-173 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.36 (d, J = 8.4 Hz, 2H), 8.03 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 3.7 Hz, 1H), 7.60 (d, J = 1.7 Hz, 1H), 7.56 (d, J = 1.6 Hz, 1H), 7.47 (d, J = 7.9 Hz, 4H), 7.11 (d, J = 7.8 Hz, 4H), 7.07 (d, J = 4.0 Hz, 1H), 4.76 (s, 2H), 4.34 (t, J = 4.6 Hz, 2H), 3.87 (s, 3H), 3.75-3.70 (m, 5H), 2.54 (s, 3H), 2.28 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.6, 160.0, 158.1, 152.6, 146.1, 145.2, 141.0, 138.1, 135.4, 133.0, 132.3, 128.5, 125.9, 124.5, 122.7, 121.7, 68.5, 66.9, 53.2, 47.8, 35.2, 21.2, 9.8; HRMS (ESI-TOF) (*m/z*) calculated for $C_{20}H_{23}IN_2SO_3^{2+}$: 498.0463, found: 498.0390 $[M - OTs]^+$

3-(2-((5-((4-Nitrophenyl)iodonio)thiophen-2-yl)methoxy)ethyl)-1,2-dimethyl-1*H*-imidazol-3-ium-di-(4-methylbenzenesulfonate) (80f)

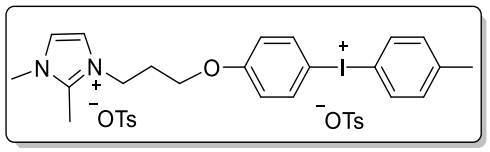


Light brown viscous liquid (562 mg, 68% yield); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.49 (d, J = 8.7 Hz, 2H), 8.28 (d, J = 8.7 Hz, 2H), 8.02 (d, J = 3.6 Hz, 1H), 7.63-7.60 (m, 1H), 7.59-7.55 (m, 1H), 7.47 (d, J = 7.8 Hz, 4H), 7.11 (d, J = 7.8 Hz, 4H), 7.08-7.06 (m, 1H), 4.76 (s, 2H), 4.38-4.30 (m, 2H), 3.75-3.70 (m, 5H), 2.54 (s, 3H), 2.28 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.9, 149.7, 146.0, 145.2, 141.3, 138.2, 136.4, 128.5, 128.5, 126.6, 125.9, 122.7, 121.7, 101.0, 68.6, 66.9, 47.8, 35.2, 21.2, 9.8; HRMS (ESI-TOF) (*m/z*) calculated for $C_{18}H_{20}IN_3SO_3^{2+}$: 485.0259, found: 485.0300 $[M - OTs]^+$

General procedure for the synthesis of ionic liquid-supported diaryliodonium salts (103g-j & 104a-f) (Method B)

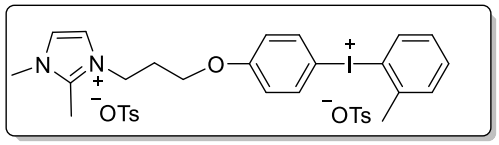
p-Toluenesulfonic acid (1.0 mmol) was added to the suspension of (diacetoxyiodo)arene (1.0 mmol) in MeCN giving an intense yellow colour solution, which was further diluted with $CHCl_3$. Ionic liquid-supported arene (**99** or **100**) (1.0 mmol) was added to the reaction mixture and resulting pale yellow solution was refluxed for 12 h. After completion of the reaction, as indicated by TLC, solvent was evaporated and washed with diethyl ether (2 × 5 mL), THF (3 × 5 mL) and the residue was dried under reduced pressure to obtained pure ionic liquid-supported diaryliodonium salts.

3-(3-(4-(*p*-Tolyliodonio)phenoxy)propyl)-1,2-dimethyl-1*H*-imidazol-3-ium-di-(4-methylbenzenesulfonate) (81g)



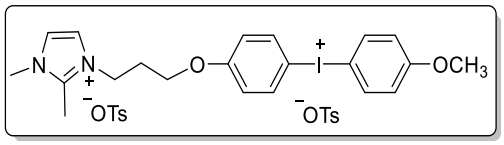
White solid (687 mg, yield 87%); mp 160-166 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.14-8.06 (m, 4H), 7.65 (d, J = 2.2 Hz, 1H), 7.60 (d, J = 2.1 Hz, 1H), 7.48 (d, J = 8.1 Hz, 4H), 7.31 (d, J = 8.2 Hz, 2H), 7.10 (d, J = 7.8 Hz, 4H), 7.02 (d, J = 9.1 Hz, 2H), 4.25 (t, J = 6.9 Hz, 2H), 4.03 (t, J = 6.0 Hz, 2H), 3.71 (s, 3H), 2.52 (s, 3H), 2.33 (s, 3H), 2.28 (s, 6H), 2.24-2.11 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.2, 146.2, 144.9, 142.7, 138.1, 137.6, 135.3, 132.7, 128.5, 125.9, 122.8, 121.4, 118.21, 113.9, 106.4, 65.3, 45.1, 35.1, 28.9, 21.3, 21.2, 9.6; HRMS (ESI-TOF) (*m/z*) calculated for $C_{21}H_{25}IN_2O^{2+}$: 448.1001, found: 448.0985 [M –OTs]$^{+}$.

3-(3-(4-(o-Tolyliodonio)phenoxy)propyl)-1,2-dimethyl-1*H*-imidazol-3-ium-di-(4-methylbenzenesulfonate) (81h)



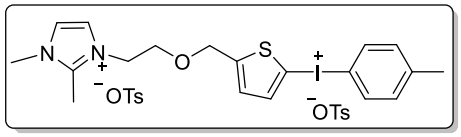
Colorless viscous liquid (679 mg, yield 86%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.36 (d, J = 7.9 Hz, 1H), 8.12 (d, J = 8.9 Hz, 2H), 7.65 (d, J = 2.0 Hz, 1H), 7.60 (d, J = 2.0 Hz, 1H), 7.54 (d, J = 6.5 Hz, 2H), 7.48 (d, J = 8.0 Hz, 4H), 7.32-7.23 (m, 1H), 7.10 (d, J = 7.9 Hz, 4H), 7.00 (d, J = 9.0 Hz, 2H), 4.25 (t, J = 6.8 Hz, 2H), 4.02 (t, J = 5.9 Hz, 2H), 3.70 (s, 3H), 2.60 (s, 3H), 2.51 (s, 3H), 2.27 (s, 6H), 2.22-2.09 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.2, 146.0, 144.9, 140.8, 138.2, 137.57, 137.4, 133.1, 131.7, 129.6, 128. 6, 125.9, 122.8, 122.5, 121.4, 118.3, 105.6, 65.3, 45.0, 35.1, 28.9, 25.4, 21.2, 9.5; HRMS (ESI-TOF) (*m/z*) calculated for $C_{21}H_{25}IN_2O^{2+}$: 448.1011, found: 448.0984 [M –OTs]$^{+}$.

3-(3-(4-((4-Methoxyphenyl)iodonio)phenoxy)propyl)-1,2-dimethyl-1*H*-imidazol-3-ium-di-(4-methylbenzenesulfonate) (81i)



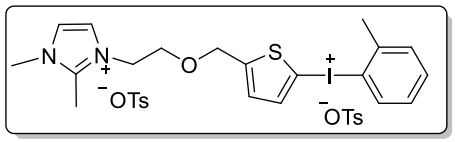
Light yellow viscous liquid (604 mg, yield 75%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.12 (d, J = 8.7 Hz, 4H), 7.64 (s, 1H), 7.59 (s, 1H), 7.47 (d, J = 7.2 Hz, 4H), 7.10 (d, J = 7.4 Hz, 4H), 7.03 (t, J = 7.9 Hz, 4H), 4.25 (t, J = 6.5 Hz, 2H), 4.09-3.94 (m, 2H), 3.78 (s, 3H), 3.71 (s, 3H), 2.52 (s, 3H), 2.27 (s, 6H), 2.22-2.11 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.3, 161.1, 146.1, 144.9, 138.1, 137.4, 137.4, 128.5, 125.9, 122.8, 121.4, 118.2, 117.8, 106.8, 106.5, 65.2, 56.2, 45.1, 35.1, 25.59, 21.2, 9.6; HRMS (ESI-TOF) (*m/z*) calculated for $C_{21}H_{25}IN_2O_2^{2+}$: 464.0950, found: 464.0935 [M –OTs]$^{+}$.

3-(2-((5-(*p*-Tolyliodonio)thiophen-2-yl)methoxy)ethyl)-1,2-dimethyl-1*H*-imidazol-3-ium-di-(4-methylbenzenesulfonate) (80g)



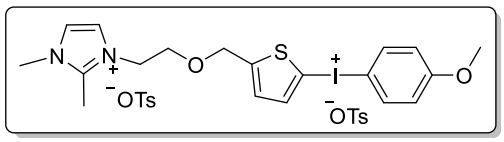
Light brown viscous liquid (636 mg, yield 80%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.11 (d, J = 7.2 Hz, 2H), 7.90 (s, 1H), 7.57 (d, J = 9.3 Hz, 2H), 7.48 (d, J = 7.2 Hz, 4H), 7.32 (d, J = 7.6 Hz, 2H), 7.11 (d, J = 7.3 Hz, 4H), 7.03 (s, 1H), 4.73 (s, 2H), 4.27-4.38 (m, 2H), 3.81-3.67 (m, 5H), 2.52 (s, 3H), 2.33 (s, 3H), 2.28 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.0, 145.9, 145.2, 143.0, 140.3, 138.2, 135.1, 132.7, 128.6, 128.4, 125.9, 122.7, 121.7, 116.3, 100.9, 68.5, 66.8, 47.8, 35.2, 21.32, 21.2, 9.8; HRMS (ESI-TOF) (*m/z*) calculated for $C_{19}H_{23}IN_2SO^{2+}$: 454.0565, found: 454.0560 $[M - OTs]^+$.

3-(2-((5-(*o*-Tolyliodonio)thiophen-2-yl)methoxy)ethyl)-1,2-dimethyl-1*H*-imidazol-3-ium-di-(4-methylbenzenesulfonate) (80h)



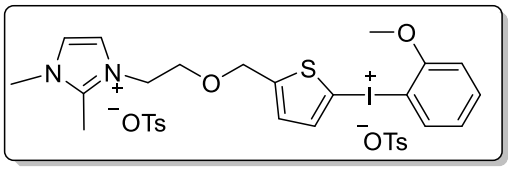
Light brown viscous liquid (612 mg, 77% yield); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.41 (d, J = 7.9 Hz, 1H), 7.91 (d, J = 3.8 Hz, 1H), 7.60 (t, J = 2.5 Hz, 2H), 7.57 (t, J = 2.5 Hz, 2H), 7.47 (d, J = 8.0 Hz, 4H), 7.35-7.28 (m, 1H), 7.11 (d, J = 7.9 Hz, 4H), 7.03 (d, J = 3.8 Hz, 1H), 4.73 (s, 2H), 4.33 (t, J = 4.9 Hz, 2H), 3.75-3.72 (m, 5H), 2.63 (s, 3H), 2.53 (s, 3H), 2.28 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 151.9, 146.1, 145.2, 140.4, 140.2, 138.1, 137.2, 133.4, 131.9, 129.8, 128.5, 128.4, 125.9, 124.9, 122.7, 121.7, 100.1, 68.5, 66.8, 47.8, 35.2, 25.4, 21.2, 9.8; HRMS (ESI-TOF) (*m/z*) calculated for $C_{19}H_{23}IN_2SO^{2+}$: 454.0560, found: 454.0562 $[M - OTs]^+$.

3-(2-((5-((4-Methoxyphenyl)iodonio)thiophen-2-yl)methoxy)ethyl)-1,2-dimethyl-1*H*-imidazol-3-ium 4-methylbenzenesulfonate (80i)



Light brown viscous liquid (568 mg, yield 70%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.17 (d, J = 9.1 Hz, 2H), 7.89 (d, J = 3.8 Hz, 1H), 7.60 (d, J = 2.2 Hz, 1H), 7.56 (d, J = 2.1 Hz, 1H), 7.47 (d, J = 8.1 Hz, 4H), 7.14-7.06 (m, 5H), 7.07-7.01 (m, 2H), 4.74 (s, 2H), 4.34 (t, J = 4.9 Hz, 2H), 3.80 (s, 3H), 3.77-3.72 (m, 5H), 2.54 (s, 3H), 2.28 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.4, 151.8, 146.2, 145.2, 140.0, 138.1, 137.3, 128.5, 128.3, 126.0, 122.7, 121.7, 117.8, 108.9, 101.4, 68.5, 66.8, 56.2, 47.8, 35.2, 21.2, 9.8; HRMS (ESI-TOF) (*m/z*) calculated for $C_{19}H_{23}IN_2SO_2^{2+}$: 470.0514, found: 470.0510 $[M - OTs]^+$.

3-(2-((5-((2-Methoxyphenyl)iodonio)thiophen-2-yl)methoxy)ethyl)-1,2-dimethyl-1*H*-imidazol-3-ium-di-(4-methylbenzenesulfonate) (80j)

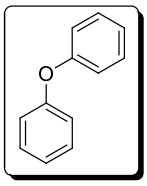


Brown viscous liquid (543 mg, yield 67%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.11 (d, J = 7.2 Hz, 2H), 7.90 (s, 1H), 7.57 (d, J = 9.3 Hz, 2H), 7.48 (d, J = 7.2 Hz, 4H), 7.32 (d, J = 7.6 Hz, 2H), 7.11 (d, J = 7.3 Hz, 4H), 7.03 (s, 1H), 4.73 (s, 2H), 4.33 (s, 2H), 3.97 (s, 3H), 3.75-3.74 (m, 5H), 2.52 (s, 3H), 2.28 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.3, 151.6, 145.9, 145.2, 140.2, 138.3, 137.3, 135.5, 128.6, 128.2, 125.9, 123.9, 122.7, 121.7, 113.4, 109.9, 100.0, 68.5, 66.8, 57.5, 47.8, 35.2, 21.2, 9.8; HRMS (ESI-TOF) (*m/z*) calculated for $C_{19}H_{23}IN_2SO_2^{2+}$: 470.0520, found: 470.0512 [M –OTs]$^{+}$.

General procedure for *O*-phenylation of substituted phenols:

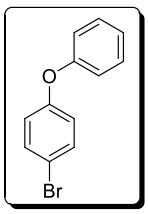
Substituted phenol **68** (1.0 mmol) was dissolved in THF (5.0 mL), and Cs_2CO_3 (1.5 mmol) was added slowly at 0 °C. The mixture was stirred for 20 min, then it was treated with ionic-liquid-supported iodonium salt **80a** or **81a** (1.1 mmol). The resulting solution was stirred at room temperature for 4 h. After the reaction was complete, the THF was evaporated, and the product was extracted with hexane/ethyl acetate (1:1 v/v). The organic phase was washed with water, dried with anhydrous sodium sulfate, and concentrated to give the desired products.

1,1′-Oxydibenzene (58a′)



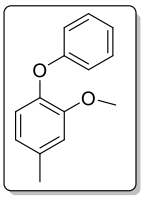
Colorless liquid (121 mg, yield 75%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (t, J = 2.2 Hz, 1H), 7.32-7.29 (m, 2H) , 7.29-7.26 (m, 1H), 7.10-7.04 (m, 2H), 7.01 (t, J = 1.6 Hz, 2H), 6.99-6.97 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 129.8, 123.3, 119.0.

1-bromo-4-phenoxybenzene (58b′)



Colorless liquid (211 mg, yield 85%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, J = 2.2 Hz, 1H), 7.40 (d, J = 2.2 Hz, 1H), 7.37-7.30 (m, 2H), 7.12 (dt, J = 7.0, 1.08 Hz, 1H), 7.01 (q, J = 1.8 Hz, 1H), 6.99-6.97 (m, 1H), 6.89 (d, J = 2.2 Hz, 1H), 6.86 (d, J = 2.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 156.6, 132.7, 129.9, 123.7, 120.4, 119.0, 115.6.

2-Methoxy-4-methyl-1-phenoxybenzene (58c′)

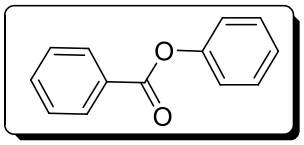


White solid (149 mg, yield 70%); mp 70-72 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.22 (m, 2H), 7.04-6.96 (m, 1H), 6.93 (t, J = 1.6 Hz, 1H), 6.90 (dd, J = 3.1, 2.1 Hz, 1H), 6.86 (s, 1H), 6.81 (d, J = 1.6 Hz, 1H), 6.72 (dd, J = 8.0, 1.2 Hz, 1H), 3.79 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 151.3, 142.4, 134.9, 129.4, 122.1, 121.5, 121.3, 116.7, 113.8, 55.9, 21.3.

General procedure for *O*-phenylation of substituted benzoic acids

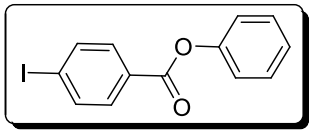
Mixture of substituted benzoic acid (**75**, 1 mmol), *t*-BuOK (1.5 mmol) and ionic liquid-supported diphenyliodonium salt (**81a**, 1.1 mmol) in dry toluene (5 mL) was heated to reflux temperature under nitrogen atmosphere. The progress of the reaction was monitored by TLC. After completion of the reaction toluene was evaporated and the residue was extracted using hexane:ethyl acetate (1:1 *v/v*) mixture. The organic layers were combined, washed with saturated sodium bicarbonate solution and dried over anhydrous sodium sulfate. The organic layers were evaporated under reduced pressure to give pure *O*-phenylated products.

Phenyl benzoate (56d′)



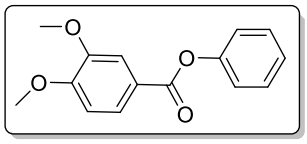
White solid, mp 58-60 ºC; (142 mg, yield 72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 7.5 Hz, 2H), 7.64 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.7 Hz, 2H), 7.44 (t, J = 7.8 Hz, 2H), 7.27 (dd, J = 12.7, 5.1 Hz, 1H), 7.22 (d, J = 8.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3, 151.1, 133.7, 130.3, 129.7, 129.6, 128.7, 126.0, 121.8.

Phenyl-4-iodobenzoate (56e′)



Light brown solid; mp 119-124 °C (233 mg, yield 72%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 4H), 7.42 (d, J = 6.7 Hz, 2H), 7.35-7.14 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 150.8, 138.0, 131.5, 129.5, 129.1, 126.1, 121.6, 101.6.

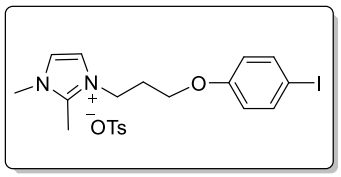
Phenyl-3, 4-dimethoxybenzoate (56f′)



Colorless solid (198 mg, yield 72%); mp 129-132 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (dd, J = 8.4, 2.0 Hz, 1H), 7.68 (d, J = 1.9 Hz, 1H), 7.43 (t, J = 7.8 Hz, 2H), 7.30-7.17 (m, 3H), 6.95 (d, J = 8.5 Hz, 1H),

3.97 (s, 3H), 3.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 153.6, 151.1, 148.8, 129.5, 125.8, 124.4, 121.9, 121.8, 112.4, 110.4, 56.1, 56.1.

3-(3-(4-iodophenoxy)propyl)-1,2-dimethyl-1*H*-imidazol-3-ium 4-methylbenzenesulfonate 82



Off-white solid; mp 71-75 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, J = 8.1 Hz, 2H), 7.44 (d, J = 8.9 Hz, 2H), 7.35 (s, 2H), 7.06 (d, J = 8.0 Hz, 2H), 6.54 (d, J = 8.9 Hz, 2H), 4.20 (t, J = 6.9 Hz, 2H), 3.78 (t, J = 5.6 Hz, 2H), 3.69 (s, 3H), 2.47 (s, 3H), 2.27 (s, 3H), 2.18-2.05 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 143.9, 143.6, 139.4, 138.3, 128.7, 125.8, 122.9, 121.2, 116.9, 8.12, 6.1, 45.3, 35.3, 28.9, 21.9, 9.6.

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Chapter IV

Conclusions

Summary

4.1 General Conclusions

Ionic liquids (ILs) are salts, with melting points below the boiling point of water (100 ^{o}C). They are termed as 'designer solvents' because their physical properties such as melting point, viscosity, density and hydrophobicity can be modified by altering their cationic or anionic part depending upon the nature of the desired reactions. Ionic liquids possess versatile physical and chemical properties such as high thermal stability, good solvating ability, negligible vapor pressure, recyclability and non-coordinating nature.

Functionalized ionic liquids (FILs) which could be synthesized through incorporation of additional functional groups in cationic and/or anionic parts of ionic liquid. They have been utilized in electrochemistry, catalyst anchoring, metal ion extraction, synthesis of nano-materials and ion conducting material. Incorporation of a functional group to ionic liquids imparts specific properties to the ionic liquid while retaining some of the characteristic properties.

In this thesis we have synthesized two type of sulfonyl based functionalized ionic liquid (a) ionic liquid-supported sulfonyl hydrazine (b) ionic liquid-supported iodine reagent. The synthesized functionalized ionic liquids (FILs) have been effectively used as a reagents in selected organic transformation.

4.2 Specific conclusions

The thesis entitled "**Ionic Liquid-supported Sulfonyl Hydrazine and Iodine Reagents: Synthesis and Application in Selected Organic Transformations**" is divided in four chapters. A brief overview of these chapters is presented below.

The **first chapter** of the thesis deals with brief overview on application of functionalized ionic liquids in organic synthesis. Synthesis of various functionalized ionic liquids (Figure 4.1) and their use as soluble support has been described in detail.

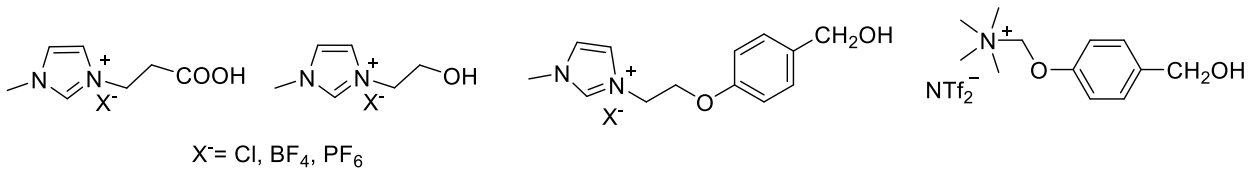
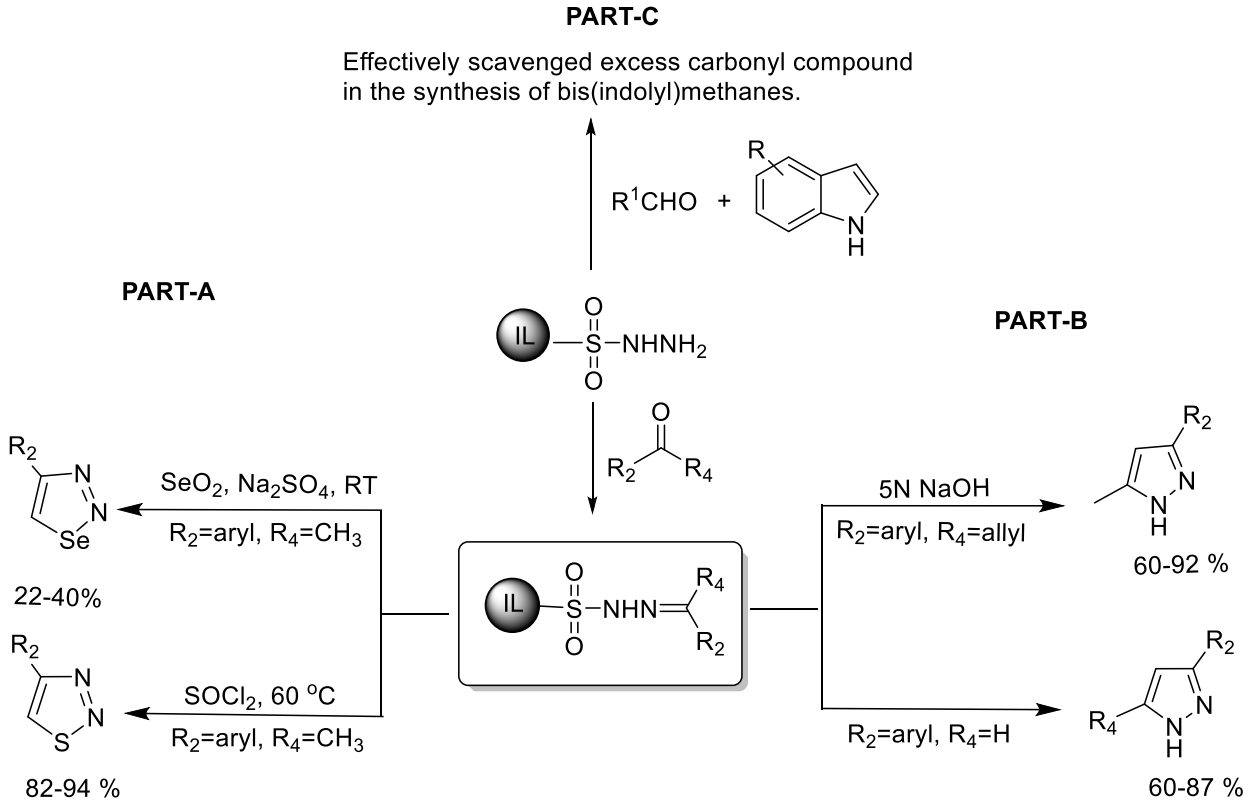


Figure 4.1: Various functionalized ionic liquids

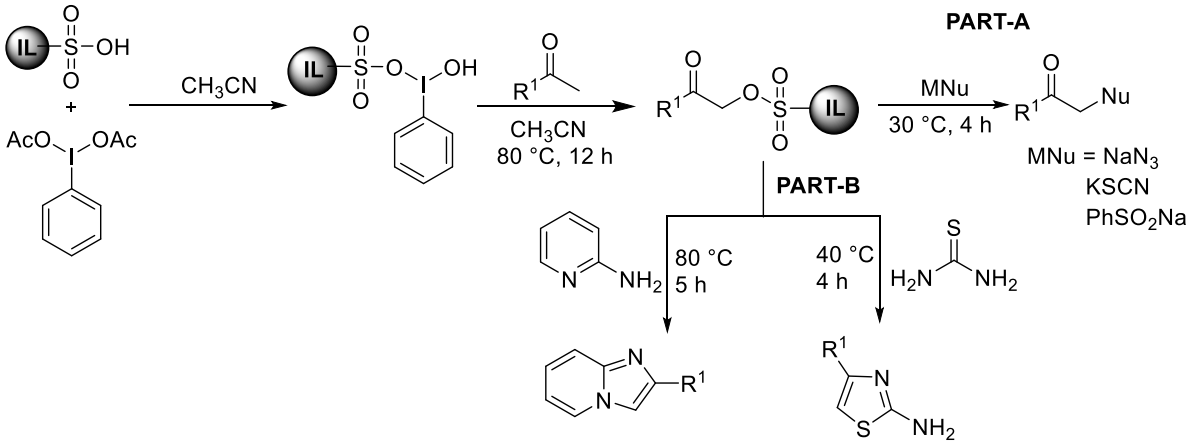
The **second chapter** of thesis deals with synthesis of novel ionic liquid-supported sulfonyl hydrazine and exploration of its applications in selected organic transformations (Scheme 4.1). Synthesized ionic liquid-supported sulfonyl hydrazine has been characterized by ^{1}H NMR, ^{13}C NMR and mass data. Stability of ionic liquid-supported sulfonyl hydrazine has been studied by DSC and TGA analysis. The chapter is divided in three parts. In **part-A**, a convenient synthesis of 1,2,3-thiadiazoles and 1,2,3-selenadiazoles was achieved using an ionic liquid as a soluble support. Ionic liquid-supported sulfonyl hydrazine was reacted with a number of ketones to afford the corresponding ionic liquid-supported hydrazones that were converted to 1,2,3-thiadiazoles (80-91%) in the presence of thionyl chloride. The reaction of ionic liquid-supported hydrazones with selenium dioxide in acetonitrile afforded 1,2,3-selenadiazoles (22-40%). The advantages of this methodology are the ease to workup, simple reaction conditions, and high purity. Indeed, 1,2,3-thiadiazoles were obtained pure enough by neutralization with sodium hydrogen carbonate, isolation with organic solvents, and subsequent evaporation of the organic solvent. Thus, this methodology provides access toward the synthesis of diverse 1,2,3-thiadiazole and 1,2,3-selenadiazole derivatives under simple reaction conditions. This study provides insights for using ionic liquid-supported reagents for the synthesis of other heterocyclic compounds. In **part-B**, a facile and economical approach for the traceless synthesis of highly substituted pyrazoles has been developed *via* two different routes using ionic liquid-supported

sulfonyl hydrazine as a soluble support. The first one is by the condensation of α,β-unsaturated carbonyl compounds to ionic liquid-supported sulfonyl hydrazine followed by cyclization in the presence of a base and the second one by the 1,3-dipolar cycloaddition of alkynes with ionic liquid-supported sulfonyl hydrazones, which were obtained by reacting ionic liquid-supported sulfony hydrazine with the corresponding aldehydes. Substituted pyrazoles were achieved in moderate to excellent yield (40-93%). In **part-C**, a facile and convenient chromatography free synthesis of *bis*(indolyl)methanes has been developed using sulfonic acid and sulfonyl hydrazine functionalized ionic liquids as catalysts and scavenger, respectively. The *bis*(indolyl)methanes were obtained in good to excellent yield (67-97%) with high purity. The employed excess of aldehyde for completion of the reaction was scavenged by sulfonyl hydrazine functionalized ionic liquid. Purification of products without column chromatography, ease of monitoring the progress reaction by ^{1}H NMR, ^{13}C NMR, IR spectroscopy and HPLC, high loading of catalyst/scavenger, low dosage and shorter reaction time are the salient feature of the developed protocol. The reuse and regeneration of the catalyst and scavenger have been achieved up to 5 times and 2 times, respectively without significant loss of activity.



Scheme 4.1: Application of ionic liquid-supported sulfonyl hydrazine

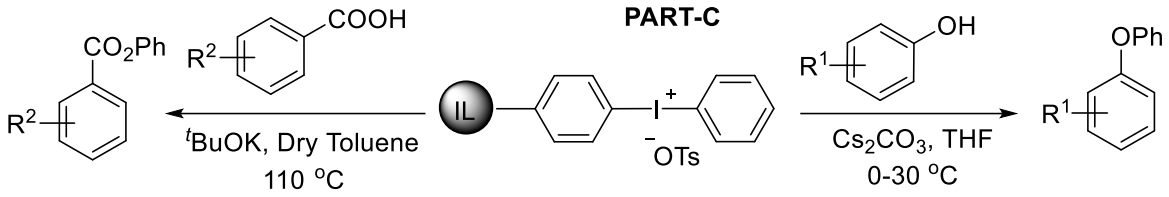
The **third chapter** of the thesis describes the synthesis of novel ionic liquid-supported hypervalent iodine reagent and its applications in organic synthesis (Scheme 4.2). The chapter is divided in three parts. In part-A, imidazolium-based ionic liquid-supported hypervalent iodine reagent has been synthesized and employed for a 'catch and release' strategy with substituted acetophenones to generate various α-substituted acetophenones (α-azidoketone, α-thiocyantoketone and β-ketonesulfone) in good to excellent yields (Scheme 4.2). The use of an ionic liquid-supported hypervalent iodine reagent avoids chromatographic separation for the purification of α-substituted acetophenones. The scope and utility of the ionic liquid-supported reagent is general and can be used for the synthesis of various substituted ketones and heterocyclic compounds. In part-B, an efficient and practical ionic liquid phase synthesis (IoLiPS) of aza-heterocycles has been developed through a 'catch-and-release' strategy using an ionic liquid-supported hypervalent iodine reagent. The hypervalent iodine played dual role as a reagent and as a soluble support. This strategy provided a combinatorial approach for the synthesis of 2-aminothiazoles and imidazo[1,2-*a*]pyridines directly from substituted acetophenones in good to excellent yields. The use of an ionic liquid supported reagent offered better isolation of the products by simple extraction with organic solvents. This combinatorial approach could be a good alternative for the synthesis of 2-aminothiazoles and imidazo[1,2-*a*]pyridines (Scheme 4.2).



Scheme 4.2: Synthesis of IL-supported hypervalent reagent and application in organic synthesis

The synthesis of ionic-liquid-supported diaryliodonium salts is described in **part-C**. The ionic-liquid-supported diaryliodonium salts were prepared by two approaches: i) using hydroxy(tosyloxy)iodo arenes (HTIAs); and ii) using (diacetoxyiodo)-arenes and *p*-toluenesulfonic acid, where the HTIAs were generated *in situ*. The synthesis is simple and

practical, and the ionic liquid products require no chromatographic purification. The reactivity of these salts was explored in the phenylation of substituted phenols and carboxylic acids. Corresponding diaryl ethers and aryl esters, respectively, were synthesized in good to excellent yields with high purities (Scheme 4.3). The by-product of the reaction, ionic liquid-supported iodophenyl, was easily isolated, and can be further reused as a reagent in different organic transformations.

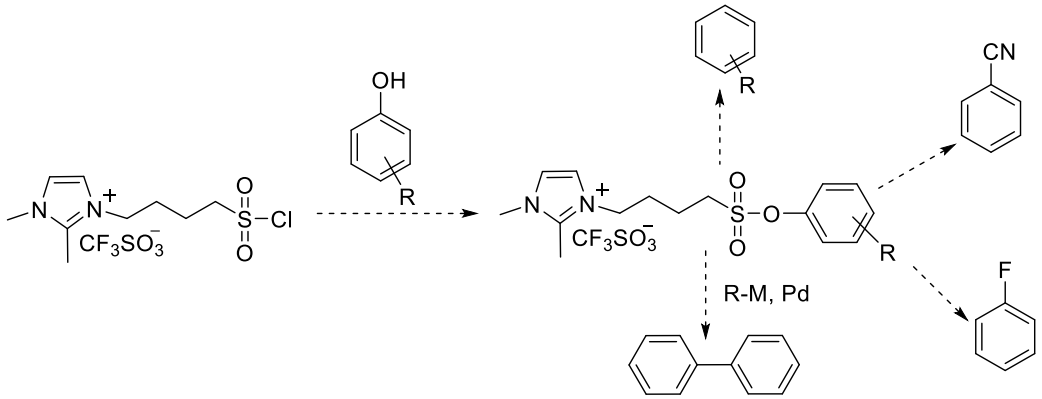


Scheme 4.3: Synthesis and application of ionic liquid-supported diaryliodonium salt

4.3 Future scope of the research work

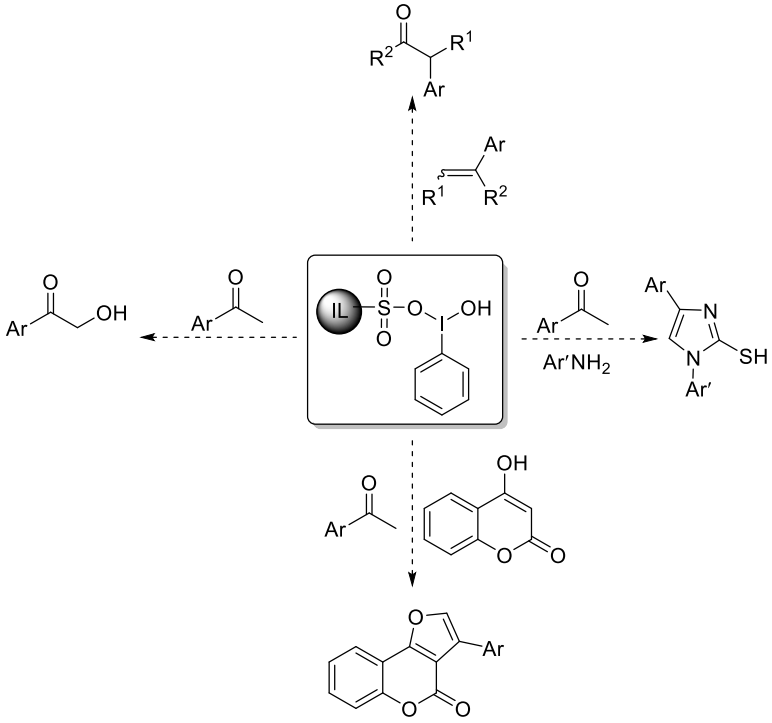
Ionic liquid-supported reagents have many advantages over solid-supported reagents such as high loading capacity, homogeneity, tuneable solubility and easy monitoring of the reaction by various analytical techniques such as IR, NMR and mass spectrometery. These reagents can be used to achieve the desired products without column chromatography and can contribute in developing green and eco-friendly methods for various organic transformations.

For instance IL-supported sulfonic acid (IL-SO_3H) can be used as efficient Bronsted acid for various acid catalyzed reaction conditions to synthesize several heterocyclic molecules. Similarly, IL-supported sulfonyl chloride can used as a sulfonylating reagent for phenol derivative which can be further undergo cross-coupling reactions to form C-H, C-N, C-O, C-P, and C-CN bonds (Scheme 4.4).



Scheme 4.4: Proposed schemes for the application of ionic liquid-supported sulfonyl chloride

Ionic liquid-supported hypervalent iodine reagent can also be used for the various organic transformations such as halotosylation of alkynes, palladium catalyzed cross coupling reactions, oxidation of alcohols and also used for the synthesis of substituted oxazoles, dihydroimidazothiazoles, 3-phenylthiazolobenzimidazoloes, furo-coumarins and α-hydroxylation of acetopheneone (Scheme 4.5) .



Scheme 4.5: Proposed schemes for the application of ionic liquid-supported iodine reagent

Appendices

APPENDICES

LIST OF PUBLICATIONS *[A-1]*

1. **S Choudhary,** M K Muthyala, A Kumar, Synthesis of ionic liquid-supported hypervalent iodine reagent and its application as 'catch and release' reagent for α-substituted acetophenones, *RSC Adv.* **2014,** 4, 14297–14303.
2. **S Choudhary,** M K Muthyala, A Kumar, Ionic liquid phase synthesis (IoLiPs) of 2-aminothiazoles and imdazo[1,2-*a*]pyridines, *RSC Adv.* **2014,** 4, 47368–47372.
3. **S Choudhary,** M K Muthyala, K Parang, A Kumar, Ionic liquid-supported sulfonyl hydrazine: A useful reagent for traceless synthesis of pyrazole, *Org. Chem. Front.,* **2014**, 1, 683–688.
4. M K Muthyala, **S Choudhary**, A Kumar, Synthesis of ionic liquid-supported sulfonyl azide and its application in diazotransfer reaction, *J. Org. Chem.,* **2012,** *77,* 8787–8791**.**
5. A Kumar, M K Muthyala, **S Choudhary**, R. K. Tiwari, K Parang, Ionic liquid as soluble support for synthesis of 1,2,3-thiadiazoles and 1,2,3-selenadiazoles, *J. Org. Chem.,* **2012,** *77,* 9391–9396.
6. **S Choudhary,** M K Muthyala, K Panday, G M Shelke, M Jha, A Kumar, Synthesis of ionic-liquid-supported diaryliodonium Salts, *Eur. J. Org. Chem.* **2014**, 2365–2370.
7. K Panday, M K Muthyala, **S Choudhary,** A Kumar, Imidazolium salt-supported mukaiyama reagent: An efficient condensation reagent for amide bond formation, *RSC Adv*. **2015,** 5, 13797–13804.
8. **S Choudhary,** Saroj, K Panday, A Kumar, Ionic liquid-supported benzyl azide: An efficient soluble scavenger for alkyne, *RSC Adv.* **2015,** 5, 67049–67053.
9. S M A Shakoor, **S Choudhary,** M K Muthyala, A Kumar, R Sakhuja, Imidazolium supported benzotriazole: an efficient and recoverable activating reagent for amide, ester and thioester bond formation in aqueous media, *RSC Adv.* **2015,** 5, 82199–82207
10. **S Choudhary,** K Panday, Saroj, A Kumar, Functionalized ionic liquid-assisted chromatography-free synthesis of *bis*(indolyl)methanes, *Mol. Div.* **2016** (Accepted).
11. K Panday, **S Choudhary,** Saroj, A Kumar, Sulfonic acid functionalized onium salt-mediated condensation of phenols with acetophenones: Synthesis of chromene derivatives (Submitted).

JOC The Journal of Organic Chemistry

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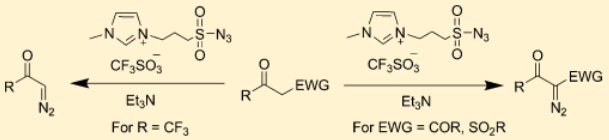
Synthesis of Ionic Liquid-Supported Sulfonyl Azide and Its Application in Diazotransfer Reaction

Manoj Kumar Muthyala, Sunita Choudhary, and Anil Kumar*

Department of Chemistry, Birla Institute of Technology and Science, Pilani 333031, Rajasthan, India

Supporting Information

ABSTRACT: The paper describes synthesis of a novel ionic liquid-supported sulfonyl azide and its applications as diazotransfer reagent of active methylene compounds as well as deformylative diazo transfer reagent. The diazo compounds were isolated in excellent yields (82−94%) and high purity. The method offers better separation of product and reagent. This method is experimentally simple and mild, and requires very short reaction time.



JOC The Journal of Organic Chemistry

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Ionic Liquid as Soluble Support for Synthesis of 1,2,3-Thiadiazoles and 1,2,3-Selenadiazoles

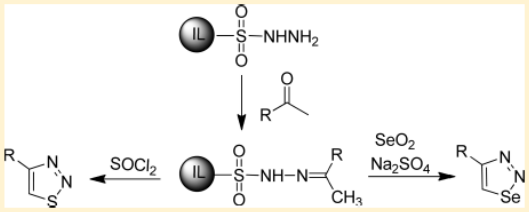
Anil Kumar,*[,†] Manoj Kumar Muthyala,[†] Sunita Choudhary,[†] Rakesh K. Tiwari,[‡] and Keykavous Parang*[,‡]

[†]Department of Chemistry, Birla Institute of Technology and Science, Pilani 333031, Rajasthan, India

[‡]Department of Biomedical and Pharmaceutical Sciences, College of Pharmacy, University of Rhode Island, Kingston 02881, USA

Supporting Information

ABSTRACT: A convenient synthesis of 1,2,3-thiadiazoles and 1,2,3-selenadiazoles was achieved using an ionic liquid as a novel soluble support. Ionic liquid-supported sulfonyl hydrazine was synthesized and reacted with a number of ketones to afford the corresponding ionic liquid-supported hydrazones that were converted to 1,2,3-thiadiazoles in the presence of thionyl chloride. The reaction of ionic liquid-supported hydrazones with selenium dioxide in acetonitrile afforded 1,2,3-selenadiazoles. The advantages of this methodology were the ease of workup, simple reaction conditions, and high purity.



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RESEARCH ARTICLE

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Ionic liquid-supported sulfonyl hydrazine: a useful reagent for traceless synthesis of pyrazoles†

Cite this: *Org. Chem. Front.*, 2014, **1**, 683

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Accepted 20th May 2014

DOI: 10.1039/c4qo00092g

rsc.li/frontiers-organic

Sunita Choudhary,[a] Manoj Kumar Muthyala,[a] Keykavous Parang[b] and Anil Kumar*[a]

Ionic liquid-supported sulfonyl hydrazine has been synthesized and used as a soluble support for the traceless synthesis of highly substituted pyrazoles from two different routes. Various substituted pyrazoles were synthesized in high yields. A key feature of the protocol is an easy and convenient purification process that avoids chromatographic separation of products and thus makes the method eco-friendly and economical.

EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201301920

Synthesis of Ionic-Liquid-Supported Diaryliodonium Salts

Manoj Kumar Muthyala,[a][‡] Sunita Choudhary,[a][‡] Khima Pandey,[a] Ganesh M. Shelke,[a,b] Mukund Jha,[b] and Anil Kumar*[a]

Keywords: Ionic liquids / Hypervalent compounds / Iodine / Supported reagents / Arylation

The synthesis of ionic-liquid-supported diaryliodonium salts is described. The synthesis is simple and practical, and the ionic liquid products require no chromatographic purification. The ionic-liquid-supported diaryliodonium salts are quite stable, and they did not show any sign of decomposition or loss of reactivity, even after being stored for one month at 5 °C. The reactivity of these salts was explored in the phenylation of substituted phenols and carboxylic acids, and the corresponding diaryl ethers and aryl esters, respectively, were synthesized in good to excellent yields and with high purities.

RSC Advances

PAPER

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Synthesis of ionic liquid-supported hypervalent iodine reagent and its application as a 'catch and release' reagent for α-substituted acetophenones†

Cite this: *RSC Adv.*, 2014, **4**, 14297

Manoj Kumar Muthyala,‡ Sunita Choudhary‡ and Anil Kumar*

Received 14th January 2014
Accepted 4th February 2014

DOI: 10.1039/c4ra00063c

www.rsc.org/advances

A novel imidazolium-based ionic liquid-supported hypervalent iodine reagent has been synthesized and employed for a 'catch and release' strategy with substituted acetophenones to generate various α-substituted acetophenones in good to excellent yields. The use of an ionic liquid-supported hypervalent iodine reagent avoids chromatographic separation for the purification of α-substituted acetophenones and thus makes the method greener.

RSC Advances

PAPER

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Ionic liquid phase synthesis (IoLiPS) of 2-aminothiazoles and imidazo[1,2-*a*]pyridines†

Cite this: *RSC Adv.*, 2014, **4**, 47368

Sunita Choudhary,‡ Manoj Kumar Muthyala‡ and Anil Kumar*

Received 2nd August 2014
Accepted 18th September 2014

DOI: 10.1039/c4ra08009b

www.rsc.org/advances

An efficient and practical ionic liquid phase synthesis (IoLiPS) of aza-heterocycles has been developed through a 'catch-and-release' strategy using an ionic liquid-supported hypervalent iodine reagent. The hypervalent iodine played a dual role as a reagent and as a soluble support. This strategy provided a combinatorial approach for the synthesis of 2-aminothiazoles and imidazo[1,2-*a*]pyridines directly from substituted acetophenones in good to excellent yields. The use of an ionic liquid supported reagent offered better isolation of the products by simple extraction with organic solvents.

RSC Advances

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Cite this: *RSC Adv.*, 2015, **5**, 13797

Imidazolium salt-supported Mukaiyama reagent: an efficient condensation reagent for amide bond formation†

Khima Pandey, Manoj Kumar Muthyala, Sunita Choudhary and Anil Kumar*

Received 19th November 2014
Accepted 13th January 2015

DOI: 10.1039/c4ra14856h

www.rsc.org/advances

A novel imidazolium salt-supported Mukaiyama reagent (2-chloropyridinium salt) has been developed and explored as an efficient coupling agent for amide bond formation. The use of an ionic liquid-supported reagent enabled isolation of the amide products by simple extraction with organic solvents in high purity and avoiding column chromatography purification.

RSC Advances

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Cite this: *RSC Adv.*, 2015, **5**, 67049

Ionic liquid-supported benzyl azide: an efficient soluble scavenger for alkynes†

Sunita Choudhary, Saroj, Khima Pandey and Anil Kumar*

Received 19th May 2015
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DOI: 10.1039/c5ra09407k

www.rsc.org/advances

An ionic liquid functionalized with benzyl azide was synthesized and its synthetic utility was evaluated by scavenging excess alkynes in the synthesis of 2,4-disubstituted quinoline *via* the Povarov reaction. The ionic liquid-supported benzyl azide gave excellent efficiency in alkyne scavenging (85–100%). Purification of the products without column chromatography, ease of monitoring, high loading of the scavenger and shorter scavenging time are some of the advantages of this approach over solid-supported scavengers.

RSC Advances

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Cite this: *RSC Adv.*, 2015, **5**, 82199

Imidazolium-supported benzotriazole: an efficient and recoverable activating reagent for amide, ester and thioester bond formation in water†‡

S. M. Abdul Shakoor, Sunita Choudhary, Kiran Bajaj, Manoj Kumar Muthyala, Anil Kumar and Rajeev Sakhuja*

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Accepted 15th September 2015

DOI: 10.1039/c5ra18749d

www.rsc.org/advances

An efficient and recyclable imidazolium-supported benzotriazole reagent (Im-CH_2-BtH) as a novel synthetic auxiliary has been synthesized and its utility as a carboxyl group activating reagent *via* the formation of stable imidazolium-supported acyl benzotriazoles was explored for the synthesis of amides, esters and thioesters in water under microwave conditions. The reagent was reused five times without any noticeable loss in activity. It is moisture insensitive and highly stable under thermal and aerobic conditions. The application of imidazolium-supported *N*-acetyl benzotriazole leads to synthesis of paracetamol on the gram scale under greener conditions in 93% yield.

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2. **S Choudhary**, M K Muthyala, A Kumar, An efficient synthesis of indolo[3,2-*a*]carbazole using ionic liquid sulfonic acid, National Symposium on Recent Trends in Chemical Science and Technology, Department of Chemistry, IIT Patna, March 3-4, 2012.
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7. **S Choudhary**, M K Muthyala, Anil Kumar, Ionic liquid-supported sulfonyl hydrazine: A novel 'catch and release' reagent for synthesis of pyrazoles, at Nascent Developments in Chemical Sciences (NDCS), Department of chemistry, Birla Institute of Technology and Science Pilani, Pilani Campus, Rajasthan, October 16-18, 2015.

BRIEF BIOGRAPHY OF THE CANDIDATE ***[A-3]***

Sunita Choudhary obtained her Master degree in General Chemistry from Banasthali University, Tonk (Rajasthan), India. She joined Prof. Anil Kumar group, BITS Pilani as junior research fellow by CSIR New Delhi in the PhD program of the institute in August 2011. She has published ten research articles in peer reviewed international journals and presented papers in seven conferences/symposiums. Her research interest lies in developing new task specific ionic liquids and using in selected organic transformations.

Dr. Anil Kumar is Associate Professor of Chemistry at the Birla Institute of Technology and Science, Pilani. He obtained his Ph.D degree from Department of Chemistry, University of Delhi, Delhi, India under the supervision of Prof. S. M. S. Chauhan in 2004. Dr. Anil Kumar worked on development of heterogeneous catalyst for organic synthesis with emphasis on green chemistry for his doctoral studies. During May 2004 to April 2006, he worked in Prof. Keykavous Parang's group as postdoctoral fellow at Department of Biomedical and Pharmaceutical Sciences, University of Rhode Island, Kingston, USA. He joined Department of Chemistry, Birla Institute of Technology and Science, Pilani, India as Assistant Professor in 2006 and was promoted to Associate Professor in February 2013. He served as Head of Department of Chemistry from September 2014-August 2016. He has visited University of Rhode Island, Kingston, USA and Chapman University as visiting scientist and Acadia University, Wolfville, Canada as Harrison McCain visiting Professor.

Dr. Kumar is recipient of Harrison McCain Foundation award from Acadia University, Canada for 2012, ISCB Young Scientist award in Chemical Sciences from Indian Society of Chemists and Biologists, Lucknow for 2013 and Dr. Aravind Kumar memorial award from Indian Council of Chemist for 2014. He has 16 year of research experience and 10 year of teaching experience. He has published over 135 research papers in international journals of repute and contributed two book chapters and one US patent. He has participated in more than 75 national and international symposia/conferences and delivered more than 30 invited lectures. He has guided four Ph.D students and currently supervising 9 Ph.D students. He is editor for Canadian Chemical Transactions and member of editorial advisory board for The Open Catalysis Journal. He has completed three research projects as Principle Investigator and one as Co-PI sponsored by DST, CSIR and UGC. Currently, he has one research project from CSIR and one industry project from Ranbaxy in collaboration with Prof. Dalip Kumar. He is member of American Chemical Society and life member of Chemical Research Society of India, Bangalore; Indian Society of Chemists and Biologists, Lucknow and Indian Council of Chemists, Agra.

His research interest lies in transition metal catalyzed C−H activation, green chemistry, ionic liquids and medicinal chemistry.