

ABSTRACT

Background of the present work

Modern chemists are mainly focused in search of technique of syntheses which has minimal impact on environment and human health. Multicomponent reaction (MCRs) is one of such “one-pot” approach of chemical syntheses involving more than two components of different types. The main advantages of one-pot protocol are simple operation, higher yields, low cost and formation of fewer side products. It avoids the isolation of unstable reaction intermediate, and increases the rate of reaction to form the selective product. Multicomponent reactions are convergent, atom economic, high bond forming efficiency and experimental simplicity. They are devoid of several steps which mean less waste production. Multicomponent reactions have the ability to generate a library of compounds with efficient structure-activity relationship for studies and synthesis of drug-like compound as pharmaceutical and agrochemical. Therefore, the development of new multicomponent reaction for heterocyclic compound is rapidly gaining one of the frontier position in organic syntheses such as Hantzsch pyridine synthesis, Skarup quinoline synthesis etc.

Nitrogen and oxygen containing heterocyclic compounds are key building blocks used to develop compounds of biological or medicinal interest to chemists. The majority of pharmaceutical products that mimic natural products with biological activity are heterocyclic. A vast number of nitrogen containing heterocyclic building blocks have applications in pharmaceuticals and agrochemical research and drug discovery. The 5-membered *N*-heterocycles are of exceptional interest in the pharmaceutical industry, as they appear in the core structure of several drugs. Six membered heterocycles such as substituted pyrimidines exhibit a broad range of biological activity. They are used to modulate hypertension, angina pectoris, act as Ca²⁺ channel blockers and are anti-diabetic, hepatoprotective and show antitumor properties. Heterocyclic compounds also have a practical use as components in dyes, antioxidants, copolymers, bases, and ligands. Finally, as an applied science, heterocyclic chemistry is an inexhaustible resource of novel compounds. A vast number of combinations of carbon, hydrogen, and heteroatoms can be designed, providing compounds with the most diverse physical, chemical, and biological properties. Oxygen containing xanthene derivatives, tetrahydropyran compounds are also well known for their biological and chemical properties.

Nowadays synthetic organic chemists have been developing methodologies either avoiding volatile organic solvents (VOCs) or using alternate greener solvents such as ionic liquids, water, and super critical fluids etc. which reduce the burden of solvent disposal and also enhance the rate of reactions. They also prefer to conduct organic reaction under solvent-free method for its higher efficiency, operational simplicity and environmentally benign conditions. The use of task-specific ionic liquid as catalyst or medium is also another environmental benign approach for replacement of traditional Brønsted or Lewis acidic catalysts. Their characteristics feature include almost no vapor pressure, non-flammability, non-combustibility, high thermal stability, relatively low viscosity, wide temperature range for being liquids, and high ionic conductivity, can be synthesized in research laboratory easily. Furthermore, their properties can be designed with proper combination of functionalized cation or anion which leads to the generation of task-specific ionic system possessing variable thermal stability, water sensitivity, acidity, basicity as well as viscosity. The nature of ionic liquids can also modified by supporting with acid, base, polymer, or metallic substances as per requirement of the reaction. Thus ionic liquids are highly efficient and specific materials for dual applications as recyclable catalyst and medium that reduces various harmful effects of traditional Brønsted or Lewis acid catalysts or organic solvents. Thus, the new synthetic methodologies should be designed in such a way that they have less harmful effect to the living being and as well as environment.

Objectives

- [1] Exploration of Brønsted/Lewis acidic catalysts for the one-pot synthesis of oxygen and nitrogen heterocycles such as naphthoxazine, xanthene and acridine derivatives under environmentally benign approach.
- [2] Synthesis and characterization of task specific Brønsted acidic ionic liquids and their application as reusable homogeneous catalyst for the synthesis of heterocycles in solution or solvent-free medium.
- [3] Synthesis and characterization of task specific Brønsted-Lewis acidic chlorometallate ionic liquid system and their uses as reusable heterogeneous catalysts for the preparation of heterocycles in solution or solvent-free medium.

- [4] Characterization of complex molecules of naphthoxazines, xanthenes and acridines with NMR, FT-IR, elemental analysis, single crystal XRD and melting point determination.
- [5] Investigation of fluorescence properties of novel heterocyclic compounds.

Plan of work

To fulfil the above mentioned objectives, the following plan of works have been adopted:

- [1] Investigation of efficient Brønsted/Lewis acidic catalysts for the one-pot synthesis of oxygen and nitrogen heterocycles such as naphthoxazine, xanthene and acridine derivatives under environmentally benign methods.
- [2] Synthesis of Brønsted and Brønsted-Lewis acidic novel ionic liquids and their characterization by NMR, FT-IR, TGA, UV-visible, Powder XRD, SEM, EDX, Raman, solid UV, ICP and CHN elemental analyses.
- [3] Studies on the catalytic activity of novel ionic liquid systems as reusable homogeneous/heterogeneous catalyst for the one pot multicomponent synthesis of above heterocycles.
- [4] Synthesis of the complex library of each heterocyclic compound by varying the substrates molecules and their characterization via $^1\text{H-NMR}$, $^{13}\text{C-NMR}$, FT-IR, and CHN analyser.
- [5] Study of fluorescence property of novel heterocycle compounds *viz.* naphthoxazine and dibenzoacridine derivatives.

Outline of the thesis

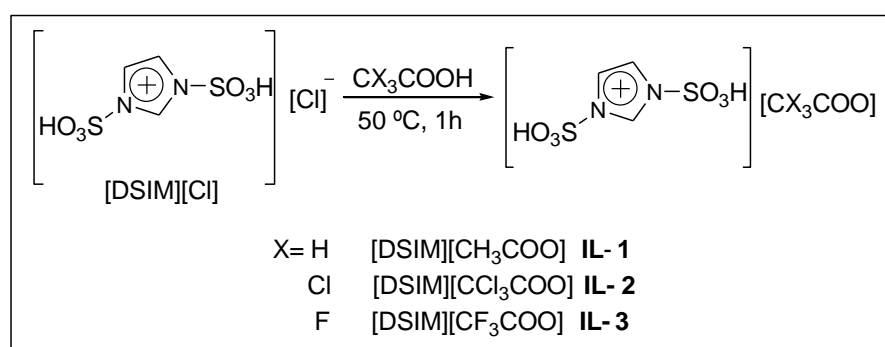
The present work explains the development of various Brønsted or Brønsted-Lewis acidic ionic liquid system, their characterization and applications for the one-pot synthesis of different nitrogen or oxygen (or both) containing heterocycles. Entire works have been divided into **six chapters**.

Chapter 1: Introduction and review of literature

This chapter includes general introduction and pharmacological significances of three types of heterocycles such as naphthoxazines, acridines and xanthenes as natural products

or synthesized molecules. It also contains a brief discussion on general experimental methodologies, review for preparation of $-\text{SO}_3\text{H}$ functionalized IL system, review for the synthesis of up to date literature of trisubstituted naphthoxazines, xanthenes and acridines derivatives in presence of ionic liquid as catalysts/medium or other methods.

Chapter 2: Investigation of 1, 3-disulfonic acid imidazolium carboxylate ionic liquids as task-specific Brønsted acidic catalysts for one-pot synthesis of 1, 8-dioxo-decahydroacridine and 14-substituted-14*H*-dibenzo[*a,j*]xanthene derivatives



Scheme-1: Synthesis of ionic liquids [DSIM][CX₃COO]

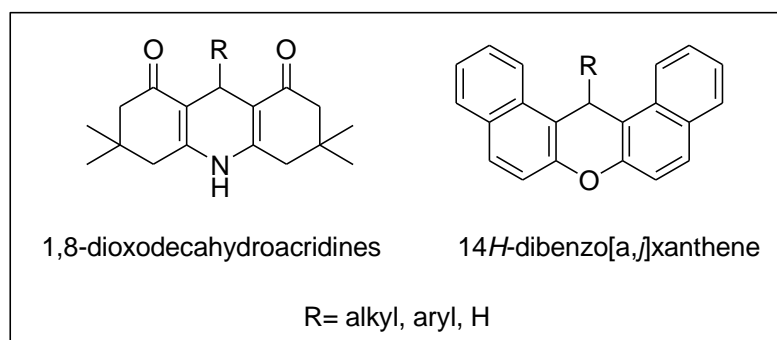


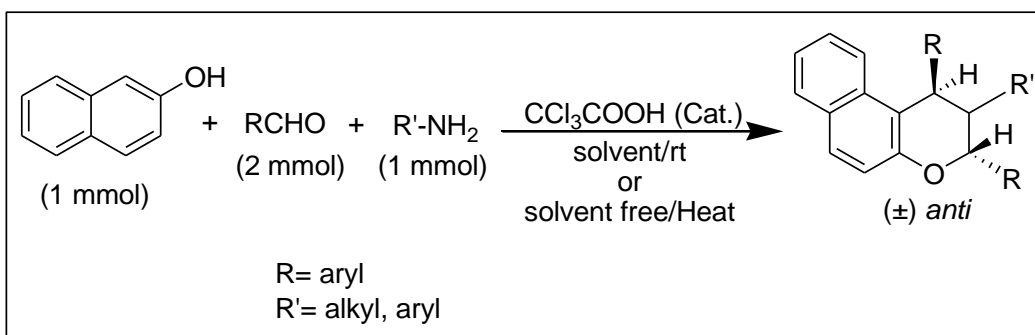
Fig.1: Structure of decahydroacridinediones and dibenzoxanthenes

In this chapter three new 1, 3-disulfonic acid imidazolium carboxylate ionic liquids [DSIM][CX₃COO] (where X = H, Cl, F) were prepared (**Scheme-1**) and characterized via NMR, FT-IR, TGA, UV-Visible and elemental analysis. The ILs with higher acidity [DSIM][CCl₃COO] and [DSIM][CF₃COO] have been effectively utilized as reusable homogeneous catalysts for one-pot synthesis of 14*H*-dibenzo[*a,j*]xanthene and 1,8-dioxo-decahydroacridine derivatives (**Fig.1**). Both sets of ILs produced excellent yields within short times under solvent-free conditions at 80–100 °C. Moreover the synthesis of 1, 8-dioxo-decahydroacridine derivatives have also been carried out in water under the same

condition. Both the ILs was recycled and reused upto 3rd run for model reaction. All products were characterized by melting points, ¹H and ¹³C NMR, FT-IR, and elemental analysis.

Chapter 3A: Studies on acid catalyzed multicomponent synthesis of *anti*-2, 3-dihydro-1, 2, 3-trisubstituted-1*H*-naphth[1, 2-*e*][1, 3]oxazine derivatives as single diastereomer

In the **Chapter 3A**, a series of *anti*-2,3-dihydro-1,2,3-trisubstituted-1*H*-naphth[1,2-*e*][1,3]oxazine derivatives were synthesized from the multicomponent synthesis of 2-naphthol, aldehyde and electron rich primary amine in 1:2:1 molar ratio at room temperature in ethanol as well as solvent free heating at 100 °C using trichloroacetic acid (TCA) as catalyst (**Scheme-2**). Initially three acetic acid derivatives *viz.* trichloroacetic acid (TCA), trifluoroacetic acid (TFA) and acetic acid were employed to study the model reaction under optimized condition. Acetic was less effective compared to the others while TFA was very reactive under the reaction condition which gave multiple side products. TCA however produced excellent yields of 1,2,3-trisubstituted naphthoxazine derivatives within short reaction time in both the condition. Furthermore the exact orientation of the two hydrogen atom connected to C-2 and C-4 positions of the oxazine ring are identified as *anti*- through COSY and NOESY analysis along with single crystal XRD analysis. All the synthesized naphthoxazine derivatives were characterized via melting points, ¹H and ¹³C NMR, FT-IR, and elemental analysis.

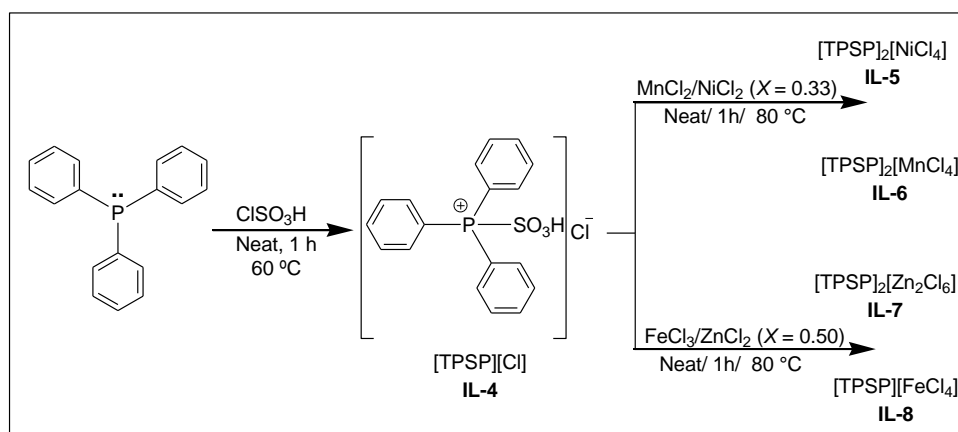


Scheme-2: Synthesis of *anti*-2,3-dihydro-1,2,3-trisubstituted-1*H*-naphth[1,2-*e*][1,3]oxazine

Chapter 3B: Development of environmentally benign Brønsted acidic catalytic system for multicomponent synthesis of *anti*-2,3-dihydro-1,2,3-trisubstituted-1*H*-naphth[1,2-*e*][1,3]oxazines

This chapter demonstrates a comparative studies for the preparation of *anti*-2,3-dihydro-1,2,3-trisubstituted-1*H*-naphth[1,2-*e*][1,3]oxazine derivatives in presence of six different conventional Brønsted/ Lewis acid catalysts such as sulfamic acid, *p*-toluene sulfonic acid (PTSA), I₂, FeCl₃ and BF₃.OEt₂ in aqueous ethanol at room temperature and solvent-free medium at different temperature. Out of these six acidic catalysts, only sulfamic acid and *p*-toluene sulfonic acid were optimized as reusable acid catalyst in 25 % aqueous ethanol at room temperature and in solvent free heating at 80 °C with good yields in short time. The same reaction was also conducted successfully with 1, 3-disulfonic acid imidazolium trifluoroacetate ([DSIM][CF₃COO]) IL as reusable homogeneous catalyst in both methods. All the known and new naphthoxazine derivatives were characterized via melting points, ¹H and ¹³C NMR, FT-IR, and elemental analysis.

Chapter 3C: Exploration of triphenylsulfophosphonium chlorometallates as heterogeneous catalyst for the synthesis 1, 2, 3-trisubstituted naphthoxazines

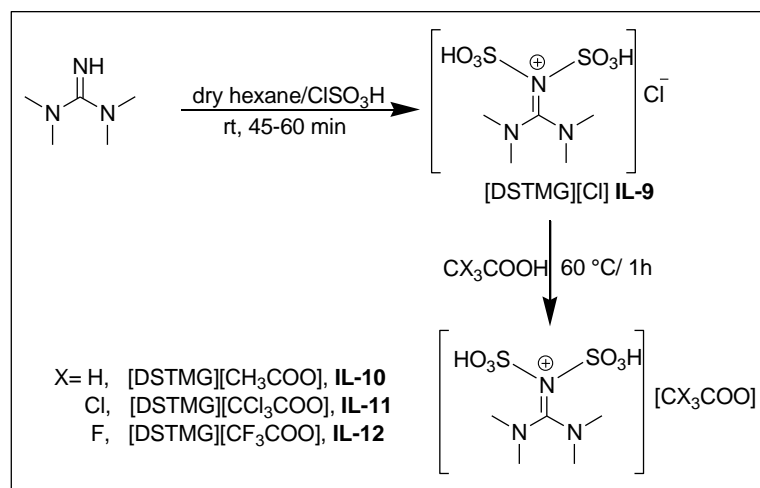


Scheme-3: Synthesis of triphenylsulfophosphonium chlorometallates

Four new –SO₃H functionalized triphenylsulfophosphonium chlorometallates [TPSP]_n[X], were prepared from the reaction of triphenylsulfophosphonium chloride [TPSP][Cl] with FeCl₃ ([TPSP][FeCl₄]), ZnCl₂ ([TPSP]₂[Zn₂Cl₆]), NiCl₂ ([TPSP]₂[NiCl₄]) and MnCl₄ ([TPSP]₂[MnCl₄]) as solid material (**Scheme-3**) and characterized via NMR, FT-IR,

Raman, TGA, powder XRD, UV-visible, SEM-EDX, ICP and CHN elemental analyses. Their catalytic activities were evaluated as task specific acidic heterogeneous catalysts for diastereoselective synthesis of *anti*-2,3-dihydro-1,2,3-trisubstituted-1*H*-naphth[1,2-*e*][1,3]oxazines as did in **Chapter 3A** and **3B** in 50 % aqueous EtOH at room temperature and under neat condition at 80 °C. The best catalysts were also reused for eight consecutive cycles for the model reaction. In addition fluorescence property of the naphthoxazine derivatives were also studied and emission were observed in the region of 370-440 nm with fluorescence emission maxima around $\lambda_{\text{emi}} = 420\text{-}430$ nm. Melting points, NMR, FT-IR, and elemental analysis was used to characterise the synthesized trisubstituted naphthoxazines.

Chapter 4: Evaluation of N, N-disulfo-1, 1, 3, 3-tetramethylguanidinium carboxylate ionic liquids as reusable homogeneous catalysts for multicomponent synthesis of tetrahydrobenzo[*a*]xanthene and tetrahydrobenzo[*a*]acridine derivatives



Scheme-4: Synthesis N, N-disulfo-1, 1, 3, 3-tetramethylguanidinium carboxylate ionic liquids

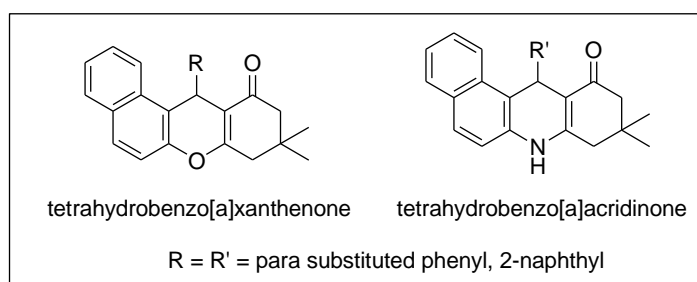
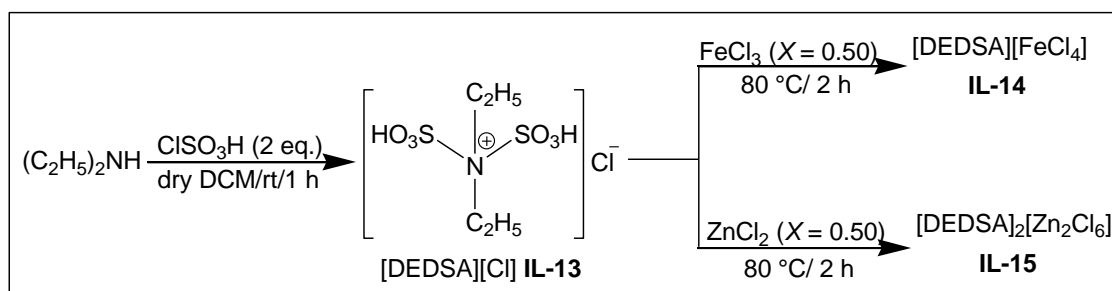


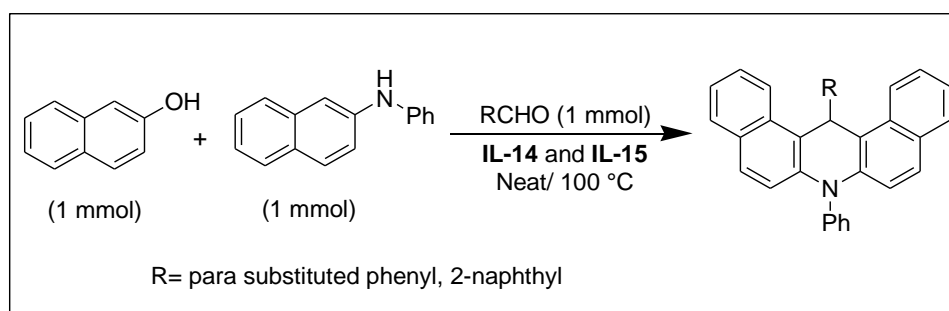
Fig.2: Structure of tetrahydrobenzo[*a*]xanthenone and tetrahydrobenzo[*a*]acridinone derivatives

In the **Chapter 4** a new series of task specific Brønsted acidic ionic liquid N, N-disulfo-tetramethylguanidinium carboxylate [DSTMG][CX₃COO], (where X= H, Cl, F) was developed from the reaction between N, N-disulfo-tetramethylguanidinium chloride and corresponding acetic acid derivatives in 1:1 molar ratio at 60 °C for 1 hour (**Scheme-4**). These ILs were characterized via NMR, FT-IR, TGA, UV-visible and CHN elemental analyses. The most acidic ILs [DSTMG][CCl₃COO] and [DSTMG][CF₃COO] were successfully utilized as reusable homogeneous catalysts for the multicomponent synthesis of tetrahydrobenzo[a]acridinone and tetrahydrobenzo[a]xanthenone derivative (**Fig.2**). Both the catalyst produced excellent yields of the two heterocycle within short time under solvent free condition at 75-85 °C. The reusability tests of the catalyst were also studied and found reusable for six consecutive run. Moreover this is for the first time that tetrahydrobenzo[a]acridinone was synthesized via four component reaction in presence of ionic liquid catalyst.

Chapter 5: Diethyl disulfo-ammonium chlorometallates: A novel and reusable heterogeneous acidic catalyst for the multicomponent synthesis of 14-aryl-7-(N-phenyl)-14H-dibenzo[a,j]acridine derivatives



Scheme-5: Synthesis of diethyldisulfoammonium chlorometallates



Scheme-6: Synthetic route of 14-aryl-7-(N-phenyl)-14H-dibenzo[a,j]acridine

The content of this chapter contains development of disulfoammonium chlorometallate ionic liquids system and their application for the multicomponent synthesis of dibenzo[a,j]acridine derivatives. Two diethyldisulfoammonium chlorometallate ILs [DEDSA]_n[X] (where n= 1 and 2 for X= FeCl₄⁻ and Zn₂Cl₆²⁻) were explored as solid material by treating diethyldisulfoammonium chloride with FeCl₃ and ZnCl₂ in equimolar ratio at 80 °C for 2 h (**Scheme-5**). All these new materials were characterized via different analytical tool such as FT-IR, NMR, TGA, UV-visible, Raman, powder XRD, SEM-EDX, ICP and CHN elemental analyses. Both the chlorometallates were successfully utilized as reusable heterogeneous catalyst for the multicomponent synthesis of 14-aryl-7-(N-phenyl)-14*H*-dibenzo[a,j]acridine derivatives at 100 °C (**Scheme-6**) under neat condition and the catalysts were reused up to 6th consecutive cycle. The fluorescence properties of synthesized naphthoxazine derivatives were also studied and found to be fluorescence active. All the products were characterized using FT-IR, NMR and elemental analysis.

Chapter 6: Summary and future scopes of the present work

This chapter describes the overall summary of each chapter and future scopes of our present work in different directions.