

## ABSTRACT

The work reported in the thesis entitled “**Greener approach for one pot synthesis of quinoline derivatives and some nitrogen containing reaction intermediates**” has been described under two parts.

The first part of the work consists of the synthesis, characterization and application of Brønsted acidic ionic liquids (BAILs) towards the synthesis of quinoline derivatives. Development of newer methods towards organic synthesis is important features of sustainable chemistry. Due to various advantageous properties, ionic liquids (ILs) have been utilized as catalyst/medium for this work. One pot multistep synthesis is one of the very important strategies to achieve the target where a number of individual reactions are brought about in a single pot through various steps. Since such process has useful impact on minimization of chemical waste and decrease of energy consumption by omitting the separation and purification steps of the intermediates, this process has been utilized in this study. In the series of quinoline derivatives, 2-styrylquinolines are found to possess variety of promising applications. Keeping this in mind, various compounds have been synthesized along with parent quinoline moiety using ILs. For this purpose, some active sulfonic acid functionalized BAILs were synthesized and characterized by using various spectral techniques and applied them for the synthesis of these derivatives under solvent free condition.

The second part of the work includes the synthesis of some important reaction intermediates. Taking into account the wide advantages of heterogeneous catalysts  $\beta$ -amino carbonyl compounds and  $\beta$ -nitroaldol were synthesized. Under heterogeneous catalysts nitrogen bound polymer compound poly (4-vinyl pyridine) was directly used as basic catalyst. In addition, some silica supported carboxylic acid catalysts were synthesized, characterized and applied for this work. During the whole work, the greener components such as simplicity in methods and techniques, milder reaction condition, enhancement in reaction rates, higher yields and selectivity of products, and reusability of catalysts were envisaged.

The content of the thesis is divided into five chapters.

## **Chapter 1: General introduction and review**

Nitrogen containing heterocycles are basic unit of several natural products which have found application in various fields. This chapter emphasizes the synthesis of N-containing compound quinoline and its derivatives, as they exhibit vast range of applicability in synthetic and pharmacological field. In addition, among various quinoline derivatives 2-styrylquinoline was found to have promising application in AIDS therapy. Herein importances of various quinoline derivatives were discussed. Now a day, ionic liquid plays an important role in various organic synthesis as they possess different unique properties viz. non-volatility, recyclability, non-explosive, excellent thermal stability and intrinsic physicochemical characteristics. Among the various acidic ionic liquids,  $-\text{SO}_3\text{H}$  functionalized ILs are most attractive as they combine advantageous properties like higher acidity and water solubility along with other properties. There are variety of methods which describe the synthesis of sulfonic acid functionalized ILs and application as catalyst/medium. The detailed review of synthetic methodologies leading to quinoline derivatives using ILs and various  $-\text{SO}_3\text{H}$  functionalized ILs was highlighted in this chapter.

The literature review offers few general methods for synthesizing 2-styrylquinoline derivatives. The most common classical method involves the use of acetic anhydride at high temperature with longer reaction time starting with quinaldine which was prepared through other methods. Only two methods were found in the literature to synthesize 2-styrylquinoline by using one pot two step process via Friedländer annulation. One of which used acidic ionic liquids (50 mol%) at 80 °C and the other employed  $\text{In}(\text{OTf})_3$  as Lewis acid catalyst at 100 °C by consuming longer time. Therefore, there is a scope for development of strong acidic IL as medium or catalyst for the one pot synthesis of these important derivatives.

This chapter also discusses the importance of reaction intermediates  $\beta$ -amino carbonyl compounds and  $\beta$ -nitroaldol. The  $\beta$ -amino carbonyl and its

derivatives exhibit broad range of medicinal and industrial use as intermediate for the synthesis of various important organic molecules.  $\beta$ -Nitroalcohol is also found to be one of the versatile intermediate for the synthesis of variety of compounds like nitro alkenes, 2-aminoalcohols,  $\alpha$ -nitro ketones,  $\alpha$ -hydroxy carboxylic acids etc. This chapter intensifies the reported methods for synthesis of  $\beta$ -amino carbonyl compounds and nitroaldol using heterogeneous catalysts.

Designing of heterogeneous acidic/basic catalysts, e.g. polymer as well as polymer supported catalysts, offers innovative route to synthesize organic molecules as they are compatible to environment, can be recovered and recycled which simplifies the product work-up and isolation steps and reduce waste and pollution. To explore the aspects of environment safety and economics, efforts have been applied towards decreasing the usage of toxic organic solvents in chemical laboratories and industrial processes. To fulfill this purpose, water is considered as a solvent of choice as it possesses interesting properties like safety, low cost, non-flammability, and abundant availability. Also solvating power of water for organic compounds becomes comparable with that of ethanol or acetone at room temperature.

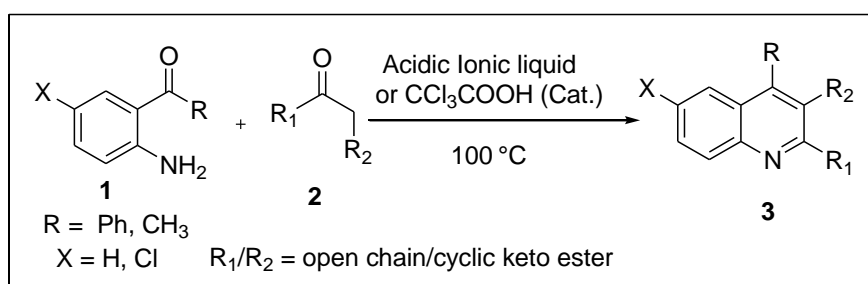
## **Chapter 2: Synthesis, characterization and applications of Brønsted acidic ionic liquids (BAILs) as catalyst/medium for the preparation of quinoline derivatives**

This chapter is divided into two sub sections, **Section 2A** and **Section 2B**.

### **Section 2A: Studies on Brønsted acidic imidazolium task-specific ionic liquids (TSILs) for the synthesis of quinoline derivatives via Friedländer annulation**

The Friedländer annulation for the synthesis of quinoline derivatives commonly involves acid or base catalyzed thermal condensation of 2-aminoaryl ketone with carbonyl analogue possessing a reactive  $\alpha$ -methylene group followed by cyclodehydration (**Scheme 1**). Although other methods are also available for quinoline synthesis; however, Friedländer annulation is the

most favorable one. The literature search disclosed that a variety of metal salts have been employed as Lewis acid catalysts for the Friedländer synthesis in addition to traditional Brønsted acids. However, most of them are not fully satisfactory, as they are associated with some drawbacks like complexity in operational process, use of large amount of relatively toxic or expensive non-reusable catalysts, volatile organic solvents and low yields. The distinctive properties of Brønsted acidic ionic liquids make them recyclable catalyst/medium in various organic transformations. Therefore, new modified methods can be applied for the quinoline synthesis using ionic liquids.

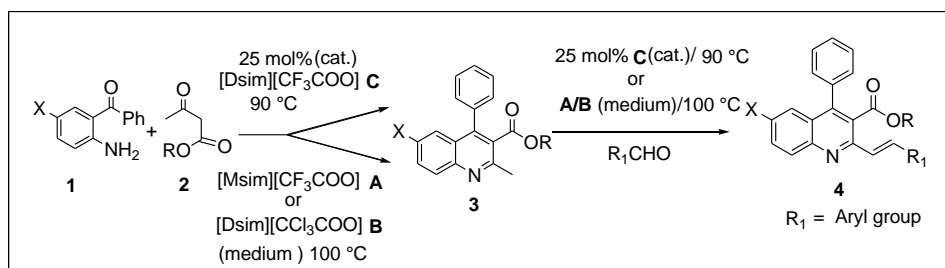


**Scheme 1.** Synthesis of quinoline derivatives

This section describes the synthesis and characterization of some imidazolium based Brønsted acidic ILs and applied them as catalyst and medium for quinoline (**3**) synthesis by the condensation of 2-aminoarylketone (**1**) with a variety of ketones and keto esters (**2**) under solvent free thermal condition (**Scheme 1**). The synthesized ILs [Msim][OOCCL<sub>3</sub>], [Msim][Cl] and [Hmim][OOCCL<sub>3</sub>] were characterized using FT-IR and NMR spectroscopy. In addition, the acidity of these ILs was compared using UV spectrophotometer with Hammett equation. Along with the ILs, the above synthesis has been explored using the Brønsted acid (trichloroacetic acid) as catalyst. The IL mediated method provides excellent yield of product formation (96-100%) within short time. Additionally, the ionic liquids as well as trichloroacetic acid can be reused for further reactions.

## **Section 2B: Studies on -SO<sub>3</sub>H functionalized Brønsted acidic imidazolium ionic liquids (BAILs) for one pot synthesis of 2-styrylquinolines via Friedländer annulation followed by Knoevenagel condensation**

This section emphasized the exploration of four sulfoimidazolium ILs as catalyst/medium for the synthesis of 2-styrylquinoline derivatives. A few methods were found in literature which could describe the general synthesis of 2-styrylquinolines.



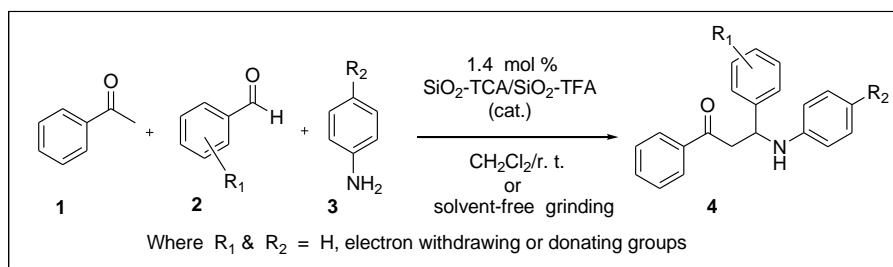
**Scheme 2.** Synthesis of 2-styrylquinoline derivatives

This section elucidated the synthesis of titled compound using sulfoimidazolium ILs viz. [Msim][OOCFF<sub>3</sub>], [Dsim][OOCFF<sub>3</sub>], [Dsim][OOCCL<sub>3</sub>] and [Dsim][OTs] after measuring their acidity and thermal stability. The novel IL [Dsim][OTs] was characterized using spectral analysis FT-IR and NMR. The acidity of these ILs was compared using UV spectroscopy through Hammett function. Further, after characterization and comparison of acidity, these ILs were applied for the one pot two step synthesis of 2-styrylquinolines (**4**) via the formation of appropriate quinaldine (**3**) which was prepared from 2-aminoarylketone (**1**) and β-keto ester (**2**) (**Scheme 2**). The results indicated that IL [Dsim][OOCFF<sub>3</sub>] acts as efficient catalyst for this synthesis. This procedure provides an efficient and improved method through single product formation, high yield, recycling of ILs and easy work up process.

In both the sections, all known and unknown products were characterized using melting points, FT-IR, <sup>1</sup>H and <sup>13</sup>C NMR, and elemental analysis techniques after recrystallized with ethanol. Some products were confirmed using single crystal X-ray diffraction technique.

### **Chapter 3: Designing of silica supported organocatalysts from carboxylic acids for the Mannich-type synthesis of β-amino carbonyl compounds**

The Mannich reaction is a multicomponent acid catalyzed condensation of a non-enolizable aldehyde, an amine and an enolizable carbonyl compound to afford  $\beta$ -amino carbonyl compounds as product. This chapter demonstrates the synthesis of silica supported carboxylic acids {CH<sub>3</sub>COOH (AA), CCl<sub>3</sub>COOH (TCA) and CF<sub>3</sub>COOH (TFA)} which were used as heterogeneous catalyst. These were characterized by different spectral analysis viz. FT-IR, SEM-EDX, TGA and powder XRD. After characterization, they were investigated as catalyst for the synthesis of  $\beta$ -amino carbonyl compounds (**4**) from the reaction of acetophenone (**1**), aryl aldehydes (**2**) and aryl amines (**3**) using CH<sub>2</sub>Cl<sub>2</sub> as solvent or under solvent free grinding condition at room temperature (**Scheme 3**). Among the three catalysts SiO<sub>2</sub>-TCA and SiO<sub>2</sub>-TFA were found to be more active compared to SiO<sub>2</sub>-AA.



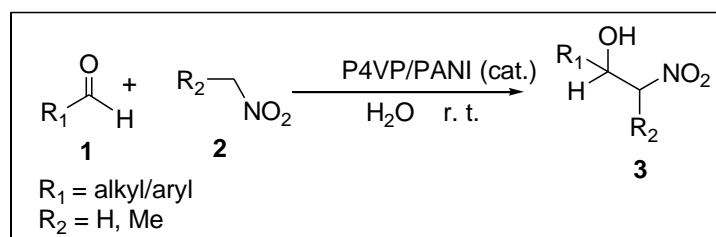
**Scheme 3.** Synthetic approach of  $\beta$ -amino carbonyl compounds

The reusability was also examined for the two silica supported catalysts SiO<sub>2</sub>-TFA and SiO<sub>2</sub>-TCA. The activity was almost found to be unchanged up to five consecutive cycles.

#### **Chapter 4: Nitrogen bound polymers as heterogeneous basic catalysts for the synthesis of $\beta$ -nitroaldol in aqueous medium**

The classical Henry reaction represents the condensation of a carbonyl compound with a nitroalkane in the presence of variety of basic reagents which were associated with various drawbacks like non-recyclable catalyst, harsh reaction condition etc. In this chapter, two nitrogen containing basic polymers: poly(4-vinylpyridine) (P4VP) and polyaniline (PANI) were investigated as heterogeneous catalysts for the nitroaldol reaction in aqueous medium without any added base. The synthesis involves the reaction between aliphatic/aromatic aldehydes (**1**) and nitroalkane (**2**) in water at room

temperature stirring (**Scheme 4**). Poly(4-vinylpyridine) was found to act as an efficient heterogeneous Lewis base catalyst for the diastereoselective synthesis of *syn*-nitroaldols from aromatic aldehydes and nitroethane. The recyclability of the catalyst P4VP was studied and found to be active after reactivation. This protocol provides greener synthetic route with water as reaction medium, high yields, simple separation of reusable polymer catalyst and mild reaction condition.



**Scheme 4.** Synthesis of  $\beta$ -nitroaldol derivatives

## Chapter 5: Summary and future scopes of the present work

This chapter summarizes the entire work described in this thesis and the future scope of the work.