# CHAPTER 1

## General introduction and review

## 1.1 General introduction

The content of this thesis includes two types of observations based on the synthesis of quinoline derivatives and some nitrogen containing reaction intermediates such as β-amino carbonyl compounds and β-nitroalcohol via one pot multicomponent/multistep approach using reusable greener catalyst or medium.

### 1.1.1 One pot reactions

One pot reactions can be defined as those reactions where several bond formation or several consecutive steps of reactions occur in a single vessel without isolating the reaction intermediates involve in various steps [1]. These reactions may be multicomponent (MCR) or multistep which makes provisions for the creation of complex library of products with high level of molecular complexity and diversity with the variation of substrate molecules [2]. Thus one pot protocols have emerged as a highly valuable synthetic tool in the context of modern drug discovery to prepare drug-like compounds. In multistep synthesis, all the consecutive steps occur separately with the isolation of each reaction intermediate. This process becomes laborious, time consuming, formation of less yields of target product and generates large volume of chemical wastes during purification steps [3]. As a consequence, the organic preparation has got more attention towards the development of one pot transformations to reduce the drawbacks of multistep synthesis. Multicomponent reactions are convergent, operationally simple, reduce reaction time, giving higher overall chemical yields and therefore can reduce the use of energy and cost [4]. Minimization of chemical waste and decrease of energy consumption are also possible by omitting the purification of individual reaction intermediates in the multistep one pot process [5]. The one pot reaction will give maximum selectivity of target product by combining two or more stages within the pot, if the individual reaction steps are compatible with one another [3, 6]. Thus one pot strategy contributes an improved method in synthesis from the economic view point as well as

sustainable synthetic routes. Additionally, such direct synthetic routes can help to avoid the side reactions and loss of starting material and can enhance stereo chemical control.

### 1.1.2 Significance of quinoline derivatives as N-heterocycles

Quinoline derivatives represent an important group of nitrogen heterocycles that possess a variety of commercial applications, such as pharmaceuticals, fragrances and dyes [7]. These nitrogen compounds are widely found in natural products including the isolation of quinine alkaloids from the bark of cinchona tree [8] to the antitumoral agent dynemicin A [9] (**Figure 1.1**). Quinoline is a weak tertiary base with p*K*a 4.85 and shows both electrophilic and nucleophilic substitution reactions. This N-heterocycle is harmless to human on oral absorption and inhalation [10].

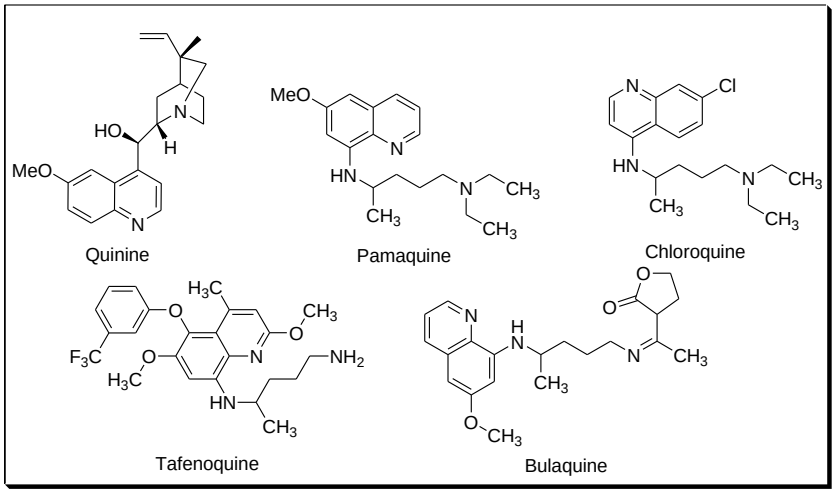



**Figure 1.1** Bioactive natural products with quinoline nucleus

The quinoline nucleus has gathered significant attention from synthetic and pharmacological chemistry as they are the key framework in innumerable biologically active compounds [11]. They exhibit various physiological properties and pharmacological activities (**Figure 1.2**), such as antiparasitic [12], antitubercular [13], antifilarial [14-15], anti-platelet [16], HMG-CoA reductase inhibiting [17], anti-allergic [18], anti-inflammatory [19], antioxidant [20], anti-asthmatic [21], antibacterial [22-23], antihypertensive

[24-25], anticancer [26-28], tyrosine kinase inhibitory agents [29], anti-proliferative [30], antimalarial [31], antifungal [32], anti-hepatitis B virus (HBV) activities [33]. Furthermore, these compounds find applications in chemistry of transition metal catalysts for uniform polymerization and luminescence chemistry [34]. They also act as antifoaming agents in refineries [35-36]. They are used in a variety of nano-structures and meso-structures with enhanced electronic and photonic functions [37-38].

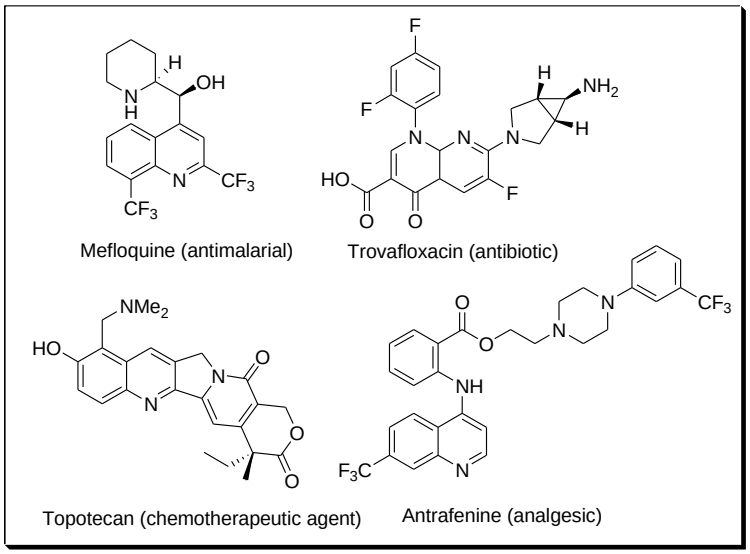



**Figure 1.2** Examples of quinoline derivatives with medicinal properties

From literature, it has been observed that among various quinoline derivatives, 2-styrylquinoline is one of the most interesting compound having novel and promising application in AIDS therapy [39], lipoxygenase inhibition [40], leukotriene $D_4$ antagonists [41], useful imaging agent for β-amyloid plaques on Alzheimer disease [42] in addition to other pharmacological activities including antitumor [43], anti-allergic and anti-inflammatory agents [44].

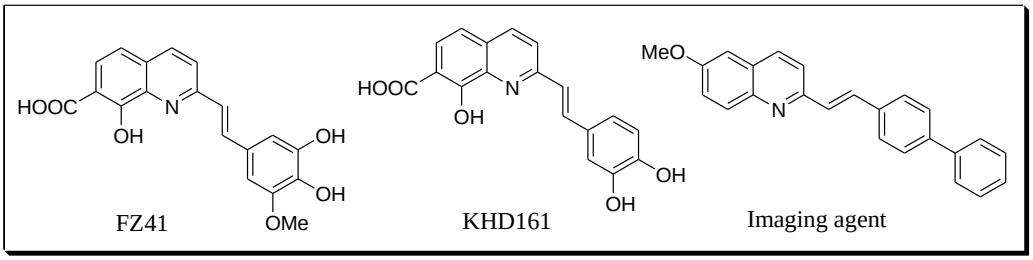



**Figure 1.3** Structure of bioactive 2-styrylquinoline derivatives

Two such polyhydroxylated styrylquinoline, FZ41 and KHD161 are exemplified as anti-HIV integrase inhibitors (**Figure 1.3**). They are also applicable for the construction of different molecular logic devices and in supramolecular chemistry [45].

### 1.1.3 Significance of β-amino carbonyl compounds and β-nitro alcohols as reaction intermediates

β-Amino carbonyl compounds are nitrogen containing intermediates which are considered as valuable building blocks for the preparation of 1,3-amino alcohols [46-47], β-amino acids [48], synthesis of various bioactive products [49], plant growth regulators [50], pharmaceutical compounds [51]. They are also useful for the preparation of β-peptides and β-lactams, which are present in several bioactive molecules such as taxol (antitumour agent), bestatine (immunological response modifier), SCH48461 (anti-cholesterol agent) (**Figure 1.4**) [52-56] and some marketed drugs like artane and ondansetron [57].

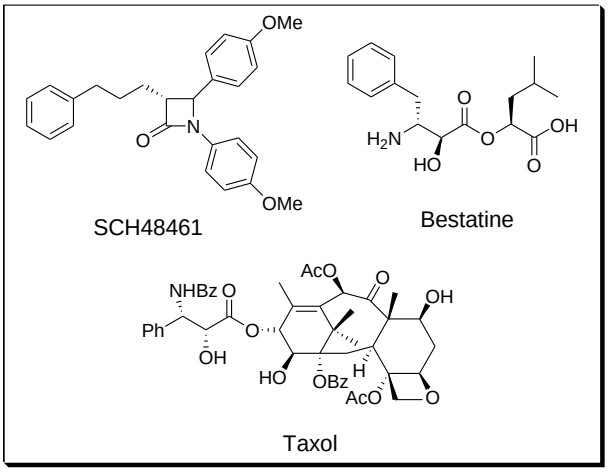



**Figure 1.4** Structure of SCH48461, bestatine and taxol

Tramadol, osnervan and moban are bioactive β-amino carbonyl derivatives with analgesic, antiparkinson and neuroleptic properties (**Figure 1.5**) [58].

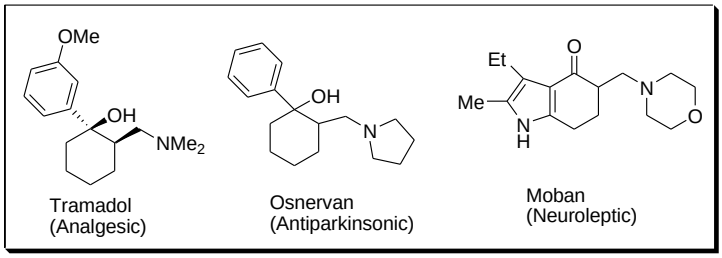
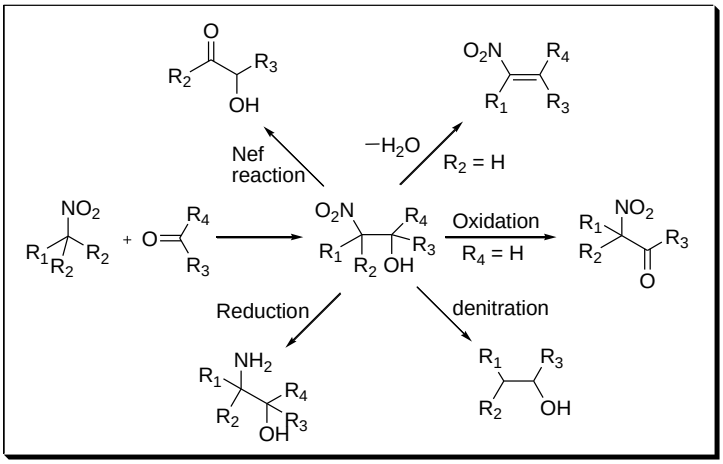



**Figure 1.5** Examples of bioactive β-amino carbonyl derivatives

The different β-amino carbonyls and its derivatives exhibit broad range of medicinal properties such as anticonvulsant [59-63], antimicrobial [64-65], anticancer [66], cytotoxic properties [67-70], anti-herpes [71], anti-psychotic [72], anti-HIV [73-74], antibacterial, antifungal [75-77], analgesic, anti-inflammatory [78-79], non-steroidal PR antagonists [80], antioxidant [81], antiepileptic [82], and antidiabetic activity [83]. Various β-amino carbonyl compounds have been investigated as reactive, potential dyes for synthetic fibers and also as surface active compounds [84].

β-Nitro-alcohol is one of the versatile intermediate for the synthesis of nitro alkenes, 2-aminoalcohols, α-nitro ketones, α-hydroxy carboxylic acids and α-hydroxy ketones through dehydration, reduction, oxidation and denitration reactions (**Scheme 1.1**) [85-88]. In Diels-Alder reactions nitro alkenes are used as a strong dienophiles and can readily undergo addition reaction with various nucleophiles [89-90].




**Scheme 1.1** Various transformations from β-nitro-alcohol

In addition, nitro alcohols are also utilized as reaction intermediates in the development of biologically active derivatives [91-92] which include the β-receptor antagonists (-)-denopamine and (-)-arbutamine; the β-blockers (S)-propanolol [93] and antibiotics [94-95] such as norephedrine and anthracycline (**Figure 1.6**).

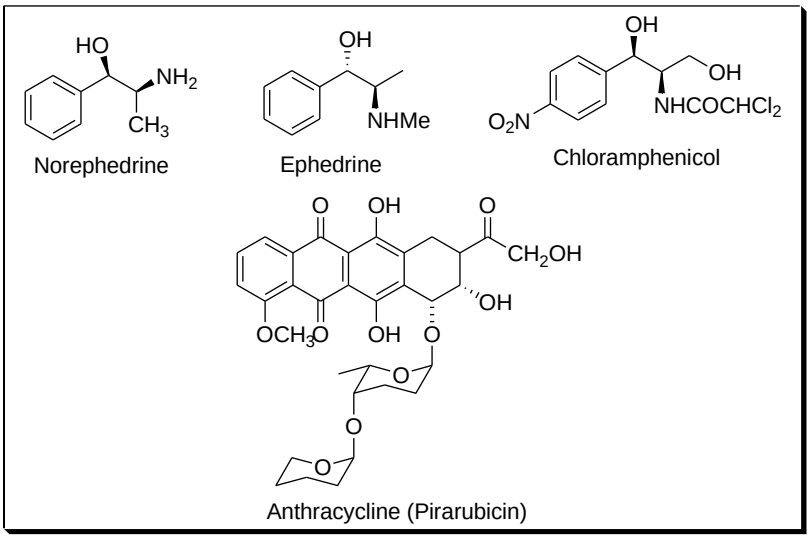



**Figure 1.6** Structure of some important antibiotics

### 1.1.4 Ionic liquids as greener solvent or catalyst in organic synthesis

Ionic liquids (ILs) are a class of organic salts composed of an organic cation and an inorganic or organic anion. These salts are liquid at room temperature or below 100 °C. Ionic liquids have unique properties such as lack of measurable vapor pressure, high thermal stability and recyclability [96-97]. Their properties can be tuned like a "designer solvent" by changing the anions and cations which provides vital role in ionic liquid chemistry [98]. Interest in room temperature ionic liquids (RTILs) continues to grow because of their potential as greener solvent alternatives to conventional environmentally hazardous organic solvents [99-100]. The environmental-friendly properties make ILs relatively benign solvents for cleaner processes to minimize toxic chemical wastes which have become a priority for chemical industries [101]. Room temperature ILs have been used in various applications such as replacing conventional organic solvents in organic synthesis, solvent extractions, electrochemical reactions, liquid-liquid extractions and in

enzymatic reactions [102]. Most of the common room temperature ionic liquids are available from alkylammonium, alkylphosphonium, *N*-alkylpyridinium, *N*,*N*-dialkylimidazolium, pyrazolium, triazolium, sulfonium and pyrrolidinium cations in combination with various anions (**Figure 1.7**) [103-107].

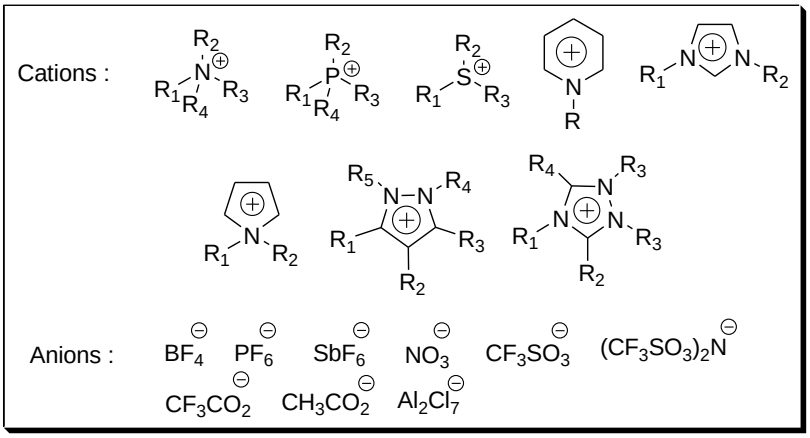



**Figure 1.7** Structure of room temperature ionic liquids

One of the green chemistry principles describes the design of environmentally benign reusable catalyst with high activity and selectivity for the reduction of chemical waste [108]. The synthesis and application of task-specific ionic liquids (TSILs) with special functions for a particular organic reaction has become an interesting field in the context of green chemistry. The incorporation of this functionality imbued the ionic liquid with a capacity to behave not only as reaction medium but also as a reagent or catalyst in some reactions or processes [109]. All these studies offer the possibility of designing suitable catalysts for a given reaction [110]. The design of TSILs focuses on preparing acidic or basic ILs to replace traditional liquid acids, such as sulfuric acid and hydrochloric acid, and bases like sodium hydroxide, potassium hydroxide in chemical processes. The applications of traditional Lewis and Brønsted catalysts are often toxic, corrosive, and non-reusable despite their high catalytic activity [111-112]. The reactions in ILs provide good reactivity and selectivity in homogeneous phases by dissolving many of the organic and inorganic substrates. Acidic or basic ionic liquids have potential application as dual solvent-catalyst nature in organic reactions which are easily recyclable

and reusable for several times without decomposition. From the economic and ecological reasons, TSILs are very attractive in organic synthesis and some of them have even been applied to the chemical industry. The unique properties of task-specific ionic liquids can be utilized to develop one pot multicomponent/multistep synthesis of quinoline derivatives without isolating any intermediate to get the desired product selectively.

### 1.1.5 Water as greener solvent in organic synthesis

The cycloaddition of furan and maleic anhydride in water was the first known example of organic reaction reported by Diels and Alder in 1931, which was limited only for the Diels-Alder reaction [113]. The exploration of water as solvent in organic chemistry was again started in 1980s by Breslow [114-115], who showed that hydrophobic effects could strongly enhance the rate of several organic reactions. Before that, the limited solubility of organic substrate in water solvent restricted the use of aqueous media in organic reactions. Such type of studies developed the high temperature water (HTW) as convenient greener procedure in organic reactions [116-118]. Water behaves as a "pseudo-organic solvent'' under near-critical and supercritical conditions due to lower dielectric constant. As a result the solvating power of water for organic compounds becomes comparable with that of ethanol or acetone at room temperature.

The water mediated organic reactions have attracted significant interest in synthetic chemistry based on [119-123]:

- It is safer, cheaper, non-flammable, and abundantly available.
- The unique and unusual physical properties of water such as high specific heat, high surface tension, high dielectric constant, large cohesive energy, amphoteric nature and ability to form H-bonds can facilitate the reaction rate and the selectivity of chemical reactions.
- Its flexibility to form strong hydrogen bonds that give it a significant surface tension (three times more than that of liquid ammonia) which could favour the aggregation of reactants.
- Its ability to engage in electron transport reactions as exemplified by many biological and synthetic reactions.

- Recycling of heterogeneous and homogeneous catalysts is possible in water solvent.

Although, water has several interesting properties as solvent for chemical reactions, at the same time the solubility problem of organic reactants in aqueous medium generally leads to immiscible and/biphasic reaction mixture. Several ways to solve this issue have been proposed such as by using surfactant combined phases, mixing with co-solvents, heating the reaction mixture, grinding the reactants [124-126] etc. Other drawbacks are the use of water incompatible organic reactants or reaction intermediates and formation of side products in organic synthesis. For heterogeneously or homogeneously catalyzed protocols, aqueous phases require stable and water tolerant catalysts which need to be designed to work under these conditions [127-128]. Such stable catalysts can be recycled for several runs in heterogeneous or homogeneous phases without loss of catalytic activity [129]. The amount of water in aqueous phase reactions can also range widely, from sub stoichiometric quantities to a large volume in which the reactants are suspended or dissolved. Depending on the associated experimental conditions, the water mediated organic reactions were classified into "*in water*", "*on water*" and "*in the presence of water*" by Butler and Coyne [130-131].

### 1.1.6 Solid acids or bases as greener catalysts

The design and application of environmentally benign solid catalyst in chemical reactions reduces the overall cost of chemical industry by producing less side product and higher yields of required product [132-133]. Most of the chemical processes generate wastes during separation stage of the products and release large volume of volatile organic solvents/hazardous chemicals to the environment. For cleaning up the waste materials, it requires more expenditure. Heterogeneous catalysts have a lot of advantageous properties as compared to homogeneous material in terms of high versatility, easy treatment and work-up, mild reaction conditions, high yields and selectivity, and reusability [134-136]. The appropriate use of non-toxic and more selective solid catalyst is very desirable and represents an important route for the clean organic synthesis.

There may be several forms of heterogeneous catalyst such as transition metal, metal oxide, metal salts, metal alloys and other supported solid acids or bases [137-141]. For each type of solid catalysts, the activity depends on the number of active sites on its surface for activation of the substrate molecules through adsorption process. The number of active sites of solid catalysts can be increased by immobilizing the catalysts over high surface area, using inert materials such as silica, alumina, polymer and zeolite etc. [142-143]. The direct use of conventional Lewis/Brønsted acids or bases as catalysts is not favourable because of vigorous reaction condition, corrosive nature, toxicity, hygroscopicity, difficulty in separation, recovery and recyclability. All the problems with the traditional acids or bases can be solved by immobilizing these catalysts on inert materials which will generate supported solid catalysts. The simple separation of supported solid catalysts from the reaction mixture by filtration will aid another facility to generate complex library of molecules in multicomponent reaction.

The use of polymers in organic synthesis was designed by Merrifield in 1963 by introducing his "solid-phase technique" for the synthesis of peptides [144-146] in which an insoluble cross-linked macromolecule was used as a protecting group. After that functionalized polymers have been employed widely in organic synthesis as stoichiometric reagents, catalysts, protecting groups, substrate carriers, in analytical chemistry, ion exchange, the detection of reaction intermediates and related fields [147]. They have chemically bound functional groups which can be utilized as reagents, catalysts, protecting groups etc. In a suitable solvent, a linear polymer can easily form molecular solution; on the other hand a cross-linked polymer or so-called resin remains macroscopically insoluble in spite of readily being solvated by that solvent. The use of functionalized cross-linked polymer as a reagent or catalyst facilitates its separation from the reaction mixture by filtration process and thus it simplifies the product work-up and isolation steps instead of the complex chromatographic techniques. The activity of resin catalysts have been found to be higher in organic reactions, since they have high surface area [148].

## 1.2 Methods for the synthesis of –$SO_3H$ functionalized Brønsted acidic ionic liquids (BAILs)

The synthesis of first imidazolium Brønsted acidic ionic liquids (BAILs) tethered with alkane sulfonic acid group (**Figure 1.8**) was reported by Cole *et al.* [149] in 2002 and screened them as dual solvent-catalysts system in organic reactions such as Fischer esterification, alcohol dehydrodimerization and the pinacol/benzopinacole rearrangement. This IL was prepared by the reaction of trifluoromethane sulfonic acid with zwitterions of 1-butylimidazole and 1,4-butane sultone. After this protocol, a resurgence of the chemistry of sulfoimidazolium ionic liquids began.

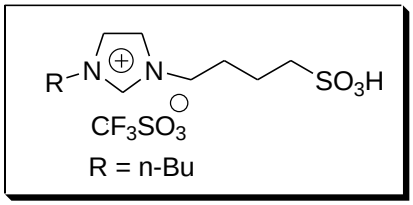



**Figure 1.8** The structure of first -$SO_3H$ functionalized IL

The initiation of Brønsted acidic functional groups into cations or anions of the ILs, especially -$SO_3H$-functional group, has evidently enhanced their properties like acidity and water solubility, and provides great potential for using ILs as green catalyst or media in many typical acid-catalyzed organic reactions with good catalytic activities [150-151]. This type of acidic IL combines the advantageous characteristics of solid acids and mineral acids by which the traditional mineral liquid acids, such as sulfuric acid and hydrochloric acid, can be replaced [152].

To expand the scope of the synthesis of sulfoimidazolium ILs, Gui *et al.* (2004) [153] discovered the synthetic route for three new halogen-free Brønsted acidic ionic liquids (**Figure 1.9**) and utilized their catalytic activity for esterification of alcohols. The synthesis of these ILs were carried out by reacting 1-methyl imidazole, pyridine and triethylamine with 1,4-butane sultone stirred at 40 °C for 10 h. They found high conversion rate and

selectivity for the esterification of ethanol by acetic acid. The ILs could be reused directly after removal of water under vacuum.

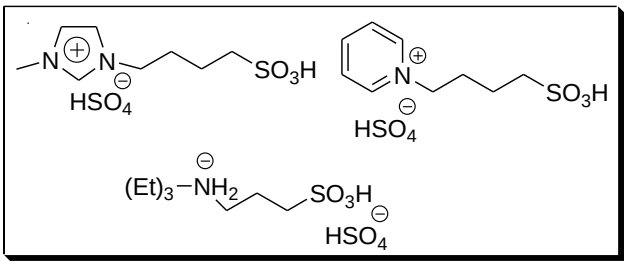



**Figure 1.9** Structure of three ILs

In 2005 & 2007, Xing *et al.* [154-155] synthesized several water-stable Brønsted-acidic task-specific ionic liquids (TSILs) with an alkane sulfonic acid group in a pyridinium cation (**Figure 1.10**) by treating an equimolar mixture of *N*-propane sulfone pyridinium (PSPy) with Brønsted acids ($HBF_4$, p-toluene sulfonic acid, $H_2SO_4$, $H_3PO_4$) at 40-80 °C for 24 h. All these ILs were characterized by $^{1}H$, $^{13}C$ and $^{19}F$ NMR spectroscopy. These TSILs show good catalytic activities in the esterification reactions of benzoic acid with methanol, ethanol, and butanol. The catalytic activity of such acidic IL depends on the nature of anion. The TSILs can be reused further after removal of water.

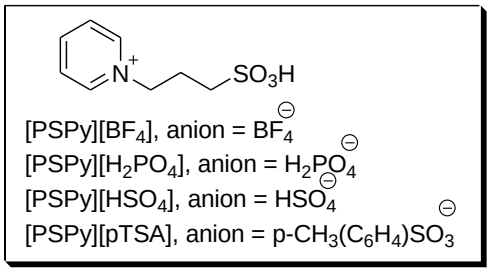
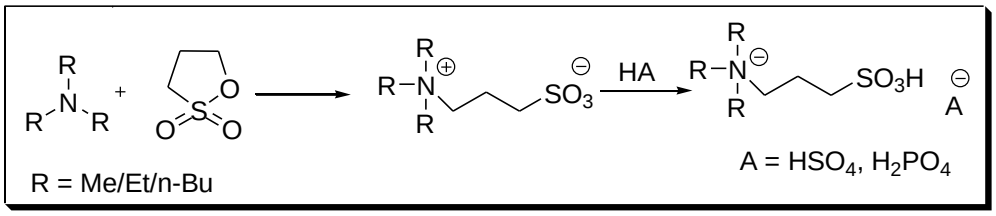



**Figure 1.10** Structures of TSILs

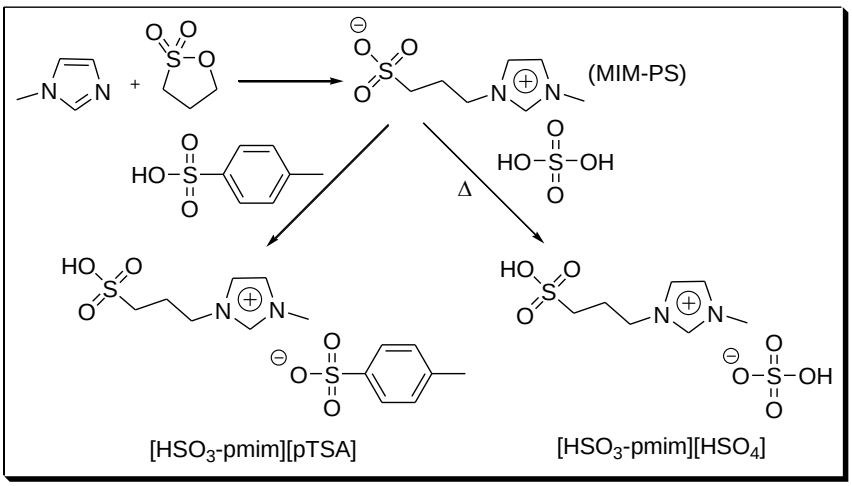
In 2006, Liu and co-workers [156] synthesized some sulfonic acid functionalized ILs containing acyclic trialkanylammonium cation and applied them as dual solvent-catalysts for Fischer esterification reaction of acetic acid, metacetonic acid, and benzoic acid with ethanol, butanol, and benzyl alcohol (**Scheme 1.2**). All the synthesized TSILs are soluble in water, methanol,

ethanol and acetone and they are partially immiscible with esters, alkanes, and aromatic hydrocarbons. The ionic liquids were stable at high temperature and could be reused at least six times without loss of catalytic activity.




**Scheme 1.2** Synthetic method of TSIL

In another report, Li *et al.* (2007) [157] designed few members of sulfonic acid functionalized imidazolium ILs according to the synthetic **Scheme 1.3** and used them as catalyst in the preparation of dioctyl phthalate. Moreover the stability and reuse performance of these TSILs were compared with those of non-functionalized ionic liquids and found better catalytic activity and reusability.




**Scheme 1.3** Structure of functionalized IL

Cheng *et al.* (2008) [158] prepared three ILs based on N-(4-hydroxysulfonylbutyl)pyridinium cation [BSPy] containing different anions available from three Brønsted acids ($H_2SO_4$, $CF_3SO_3H$, pTSA) (**Figure 1.11**) by following the similar synthetic route as described by Gui *et al.* (2004) [153]. The acidity of these ILs were studied by using Hammett method with

UV-visible spectrometer and observed the trend of acidity as [BSPy][OTf] > [BSPy][$HSO_4$] > [BSPy][pTSA]. They tested the catalytic activities for nitration of aromatic compounds with $NO_2$/air and found good efficiency in terms of conversion and selectivity.

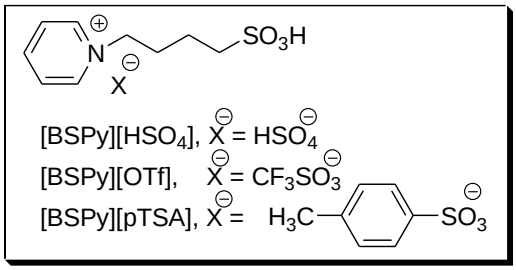



**Figure 1.11** Structure of three sulfonic acid functionalized ILs

In 2009, Wang and co-workers [159] synthesized a series of heteropoly anion (HPA) containing task-specific ionic salts of organic cations—$[MIMPS]_3PW_{12}O_{40}$, $[PyPS]_3PW_{12}O_{40}$, and $[TEAPS]_3PW_{12}O_{40}$ (**Figure 1.12**) and investigated their catalytic behavior in various esterification reactions.

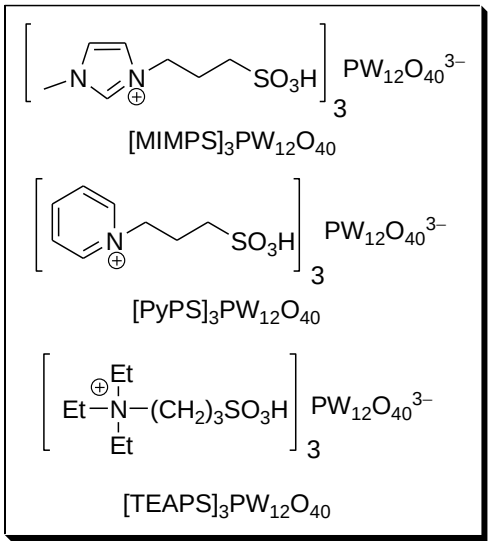
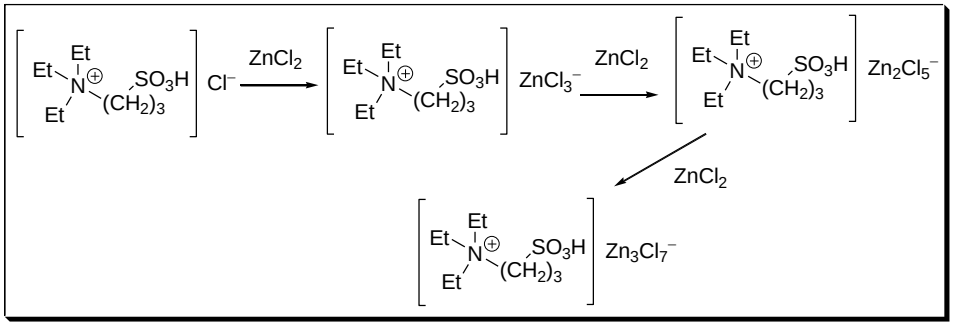


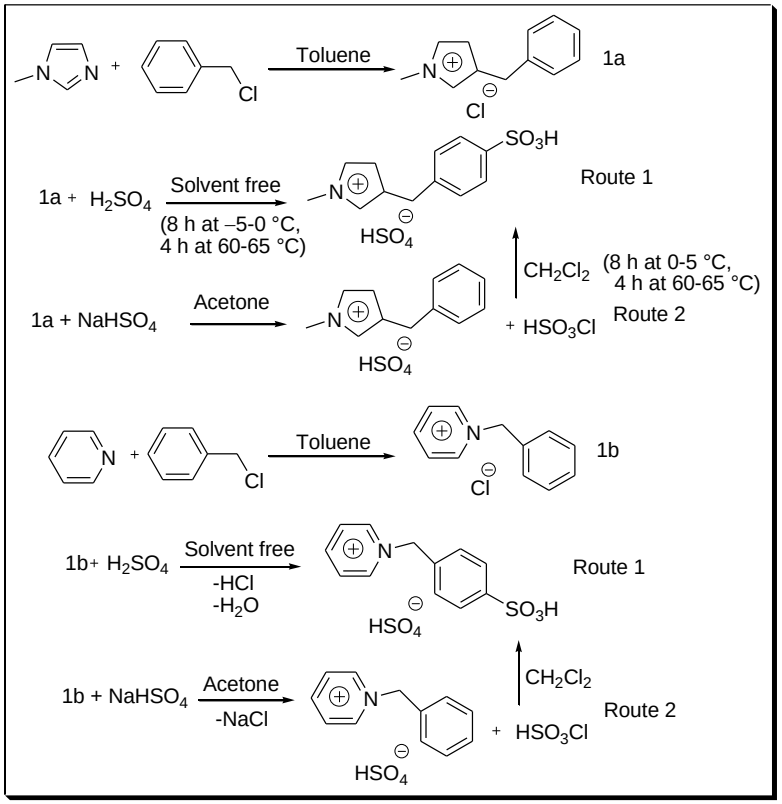

**Figure 1.12** Structure of three HPA containing ILs

The ionic salts were found to switch their properties from homogeneous to heterogeneous which were proved by high melting points of the same and also recovery and catalytic reuse of this kind of catalyst was found to be very convenient.




**Scheme 1.4** ILs based on trichlorozincinate anions

Working in this field, Liu *et al.* (2008) [160] reported the design and characterization of Brønsted–Lewis acidic ILs (3-sulfonic acid) propyl triethyl ammonium chloro zincinates. The synthetic route involved the reaction of 1 equivalent of $[HSO_3–(CH_2)_3–NEt_3][Cl]$ ionic liquid with 3 equivalent of $ZnCl_2$ under vigorous stirring for 4 h at 100 °C (**Scheme 1.4**). The resulted viscous ILs at room temperature was then characterized using $^{1}H$ NMR, $^{13}C$ NMR, FT-IR, ESI-MS and employed as efficient reusable catalyst for the dimerization of rosin.




**Scheme 1.5** Synthetic route of Brønsted acidic ILs

Eli and coworker (2008) [161] described the synthesis of two novel Brønsted acidic ionic liquids that bear an aromatic sulfonic acid group on the imidazolium or pyridinium cation by following two different routes (**Scheme 1.5**) and observed their catalytic activity towards Fischer esterification of long chain aliphatic acids with methanol and ethanol.

Wang *et al.* (2008) [162] prepared a new group of Brønsted acidic task-specific ILs based on benzimidazolium cations (**Figure 1.13**) and explored their use as catalysts for acetalization of aromatic aldehydes with diols. The ionic liquid [PSebim][$HSO_4$] was found to be more acidic among the studied ILs and was efficient for the acetalization.

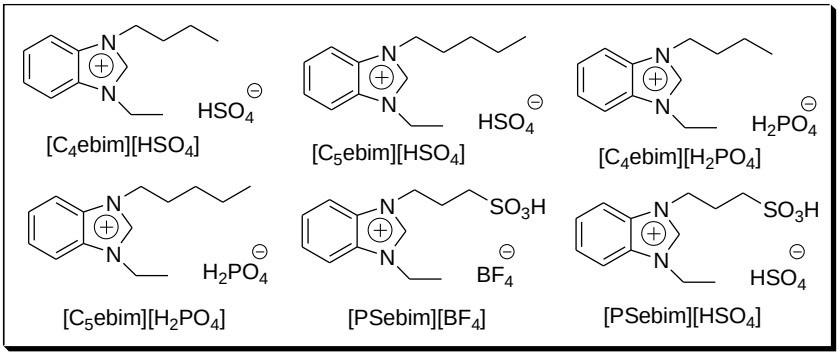
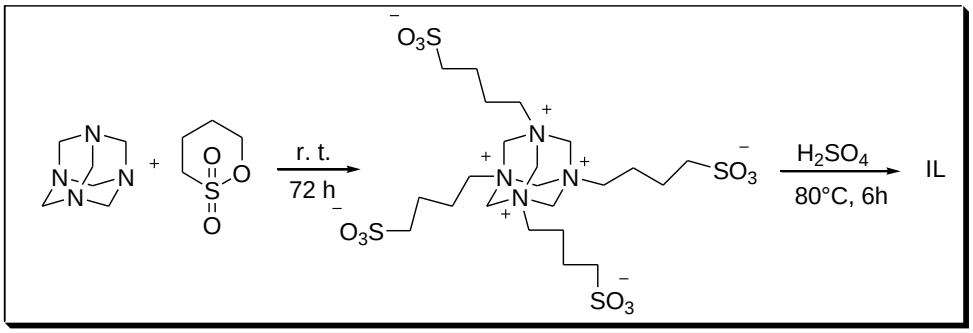



**Figure 1.13** A group of benzimidazolium based ILs

In order to improve the acidity of functionalized ILs, Jing *et al.* (2009) [163] developed novel multi -$SO_3H$ functionalized strong Brønsted acidic ionic liquid (**Scheme 1.6**) with more acid sites and introduced as catalysts for acetalization reactions. This IL was also successfully applied for the synthesis of biodiesel from rapeseed oil and methanol [164].




**Scheme 1.6** The synthetic route of multi acid site IL

Xu *et al.* (2009) [165] investigated the synthesis of novel $–SO_3H$ functionalized ionic liquids containing two alkyl sulfonic acid groups in the imidazolium cations (**Figure 1.14**) which were investigated as catalysts for the one-pot Fischer indole synthesis in water. This IL was synthesized from the reaction of *N*-trimethylsilylimidazole with 1,3-propane or 1,4-butane sultone, respectively, followed by the acidification. The obtained acidic ILs consist of some important properties like water-stability, non-volatility, and immiscible with non-polar organic solvents. These ILs were found to be more acidic than the other Brønsted acidic ionic liquids (BAILs) investigated and also $H_2SO_4$.

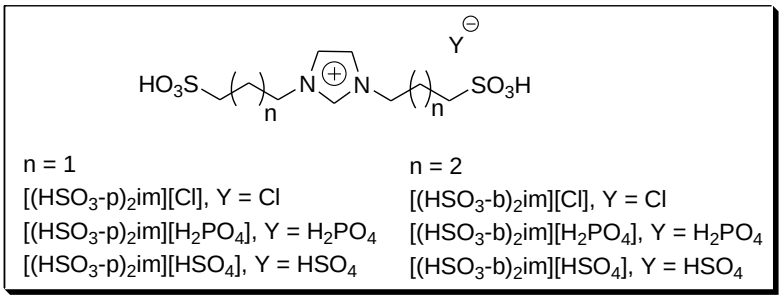
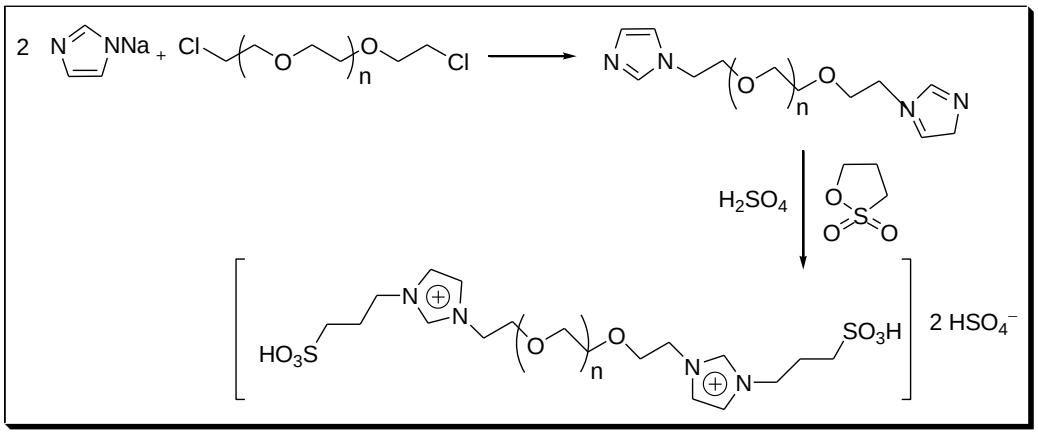



**Figure 1.14** Structure of BAIL bearing two alkyl sulfonic acid groups

Zhi *et al.* in 2009 [166] developed a new recyclable temperature-dependent phase-separation system comprised of PEG-1000-based dicationic acidic ionic liquid (**Scheme 1.7**) and toluene and used in one pot three component condensations to prepare benzopyrans in excellent yields.




**Scheme 1.7** Synthesis of PEG-1000 based DAIL

In 2010, Yang *et al.* (2010) [167] studied the acidity and thermal stability of three –$SO_3H$ functionalized reported ILs ([MIMPs][X], [PyPs][TsO] and [MIM][TsO]) and one new ionic liquid [1,2-DiMIMPs][TsO] of similar type (**Figure 1.15**). After knowing their acidities, they were utilized as recyclable promoter for the hydroesterification of olefins catalyzed by $PPh_3$-Palladium complex.

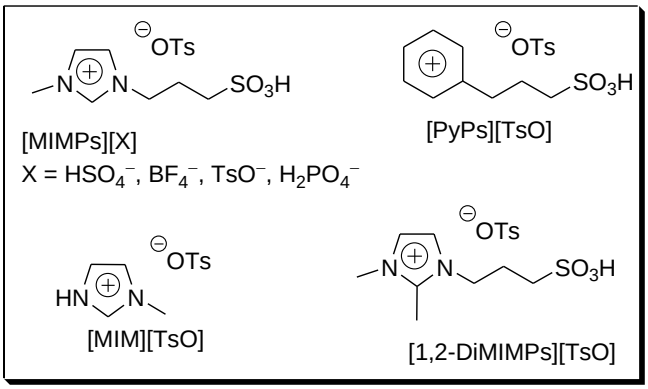
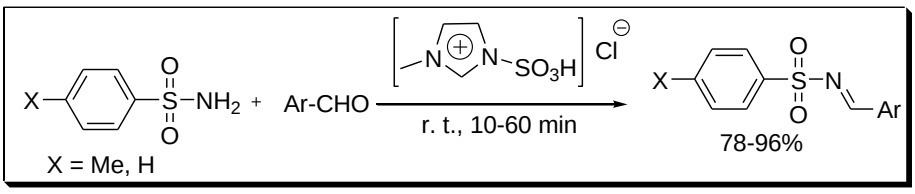



**Figure 1.15** Structure of synthesized ILs

A new Brønsted acidic ionic liquid, 3-methyl-1-sulfonic acid imidazolium chloride {[Msim][Cl]}, was reported in 2010 by Zolfigol *et al.* [168]. This IL was prepared by the reaction of equimolar mixture of 1-methyl imidazole and chlorosulfonic acid in $CH_2Cl_2$ over a reaction period of 20 min at room temperature. The ionic liquid [Msim][Cl] was obtained as viscous colorless oil after washing and decanting several times with $CH_2Cl_2$ solvent. They utilized this IL as dual solvent-catalyst system for the efficient synthesis of *N*-sulfonyl imines (**Scheme 1.8**).




**Scheme 1.8** Synthesis of *N*-sulfonyl imines using IL [Msim][Cl]

Zolfigol *et al.* (2011) [169] again extended their study for preparation of new member of sulfonic acid functionalized imidazolium salts including 1,3-disulfonic acid imidazolium chloride IL [Dsim][Cl] and 3-methyl-1-sulfonic

acid imidazolium tetrachloroaluminate [Msim][$AlCl_4$] (a solid) (**Figure 1.16**). These ILs efficiently catalyze the one pot multicomponent condensation of 2-naphthol with aromatic aldehydes and amide derivatives under solvent-free conditions to afford 1-amidoalkyl-2-naphthols in excellent yields (81–96%) and in very short reaction times (1-40 min).

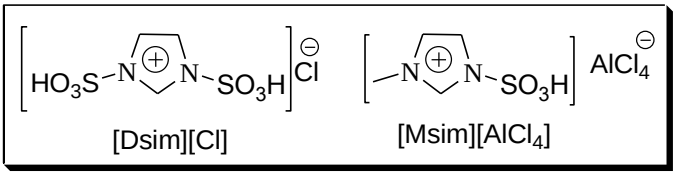
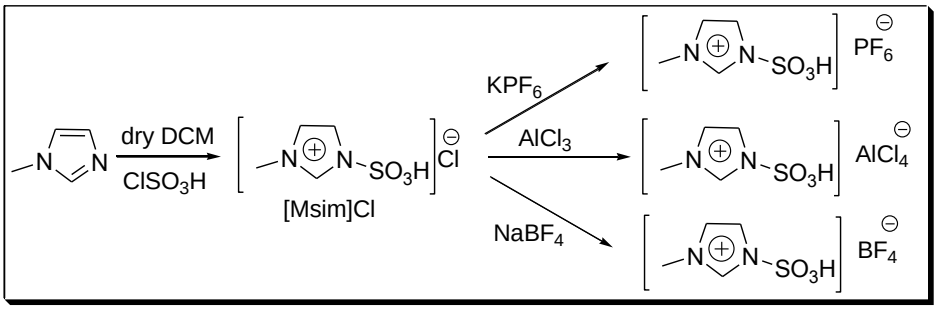



**Figure 1.16** Structure of two BAILs

Again in 2012, the same group [170] prepared two sulfonic acid functionalized ILs [Msim][$PF_6$] and [Msim][$BF_4$] by the metathesis of [Msim][Cl] ionic liquid with two alkali metal salts $KPF_6$ and $NaBF_4$ respectively (**Scheme 1.9**). The TGA study showed their thermal stability up to 200-230 °C. Both these ILs were efficiently applied for the preparation of xanthene derivatives.

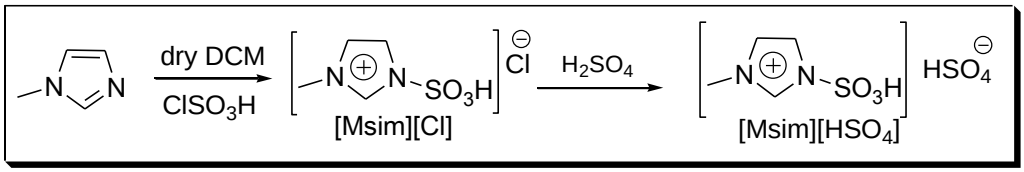



**Scheme 1.9** Synthesis of sulfonic acid functionalized ILs

Again in 2011, Khaligh [171] synthesized novel ionic liquid (3-methyl-1-sulfonic acid imidazolium hydrogen sulfate) [Msim][$HSO_4$] as recyclable and eco-benign catalyst for the chemoselective trimethylsilyl protection of hydroxyl groups under solvent free conditions to afford trimethylsilanes in excellent yields (92-100%) and in very short reaction times (1-8 min).

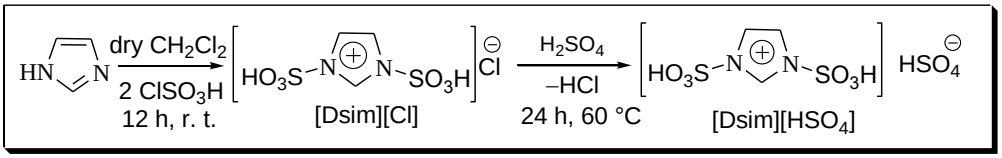
This IL was prepared from the reaction of [Msim][Cl] ionic liquid obtained by the method of Zolfigol *et al.* (2010) [168] with sulfuric acid at room temperature during 8 h stirring (**Scheme 1.10**). After washing with

$CH_2Cl_2$, the IL was obtained as viscous pale yellow oil which was characterized by NMR and FT-IR spectroscopy.



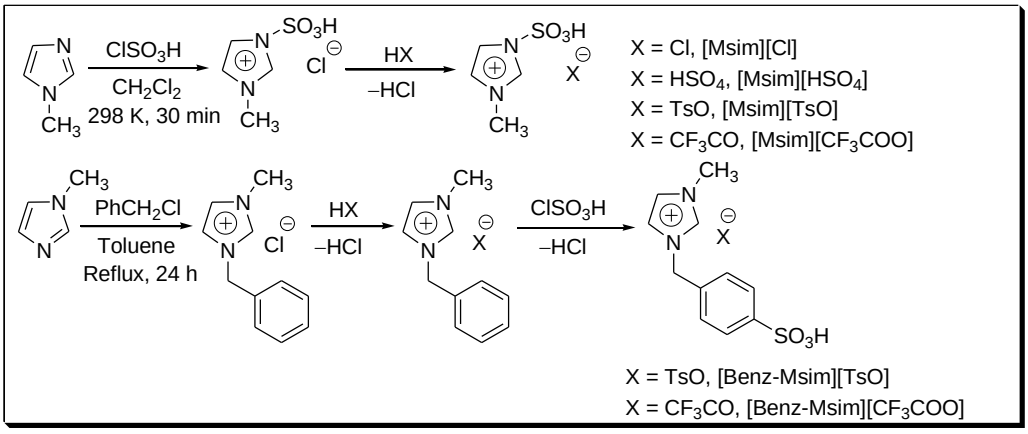

**Scheme 1.10** Synthesis of [Msim][$HSO_4$] IL

After the synthesis of [Dsim][Cl], Shirini *et al.* (2012) [172] designed 1,3-disulfonic acid imidazolium hydrogen sulfate [Dsim][$HSO_4$] as halogen free novel IL (**Scheme 1.11**) which was efficiently used as catalyst for the trimethylsilyl protection of hydroxyl groups at room temperature under solvent free conditions to afford trimethylsilanes. Zare *et al.* [173] also synthesized this IL in 2013 and characterized by using FT-IR, $^{1}H$ NMR, $^{13}C$ NMR, MS, TGA, DTG and XRD spectra. From the TGA study the molecular decomposition of the IL [Dsim][$HSO_4$] was observed after 350 °C.




**Scheme 1.11** Synthesis of [Dsim][$HSO_4$] IL

Kore and his group in 2012 [174] prepared a series of novel BAILs along with known ILs for hydration of alkynes under mild conditions to give high yields of ketones as a selective product. They synthesized three acidic ILs [Msim][$HSO_4$], [Msim][$CF_3COO$] and [Msim][TsO] from the reaction of [Msim][Cl] with three Brønsted acids ($H_2SO_4$/pTSA/$CF_3COOH$) in $CH_2Cl_2$ respectively (**Scheme 1.12**). The other two ILs [Benz-Msim][TsO] and [Benz-Msim][$CF_3COO$] were obtained from the reaction of 1-benzyl-3-methylimidazolium chloride with stoichiometric amount of pTSA/$CF_3COOH$ in dichloromethane followed by sulfonation with chlorosulfonic acid (**Scheme 1.12**).




**Scheme 1.12** Synthetic approach of sulfonic acid functionalized ILs

A series of reusable quaternary ammonium geminal Brønsted acidic ionic liquids based on zwitterionic 1,2-bis[*N*-methyl-*N*-(3-sulfopropyl)-alkylammonium]ethane and p-toluene sulfonic acid monohydrate were designed by He *et al.* (2014) [175] (**Figure 1.17**) and applied in three-component Mannich reactions in water.

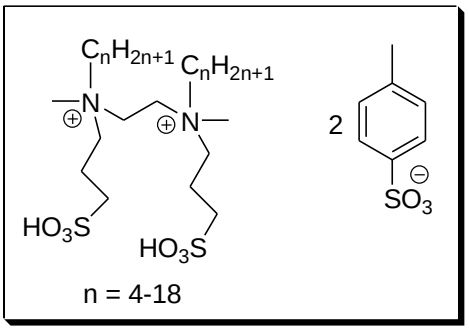
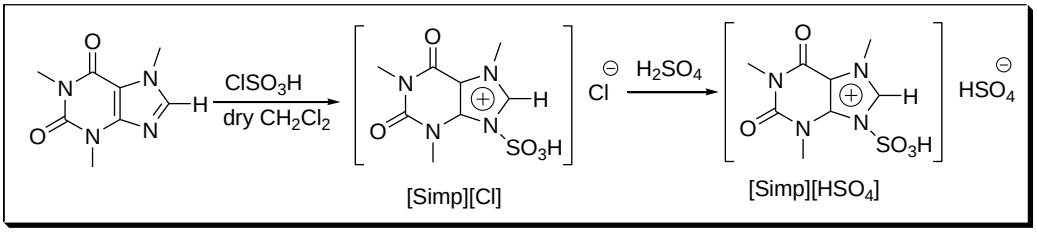



**Figure 1.17** Structure of geminal Brønsted acid ionic liquids

In 2014, three 1,3-disulfonic imidazolium IL [Dsim][X] (where X = $CH_3COO$, $CCl_3COO$, $CF_3COO$) were synthesized by Dutta *et al.* [176]. Further these ILs were applied for the preparation of 14*H*-dibenzo[a,j]xanthene and 1,8-dioxo-decahydroacridine derivatives within short time under solvent-free condition.

Recently, in 2015, Tayebee *et al.* [177] reported the synthesis and characterization of a novel BAIL 3-sulfonic acid 1-imidazolopyridinium hydrogen sulfate [Simp][$HSO_4$]. The IL was prepared by treating equivalent amount of caffeine and chlorosulfonic acid as pale yellow viscous oil (**Scheme 1.13**). The structure of [Simp][$HSO_4$] was confirmed by FT-IR, $^1$H NMR, $^{13}$C

NMR, UV–Vis, and fluorescence spectra. After that the IL was efficiently utilized for the synthesis of 2*H*-indazolo[2,1-b]phthalazine-trione derivatives via three-component condensation of phthalhydrazide, aromatic aldehydes, and dimedone under solvent free conditions.




**Scheme 1.13** Preparation of IL [Simp][$HSO_4$]

## 1.3 Review of ionic liquid mediated/catalyzed synthesis of quinoline derivatives from the Friedländer annulations

Quinoline derivatives play an indispensable role in medicinal and organic chemistry, as this ring system is the key backbone of many natural products and biologically active molecules [10]. Owing to diverse utilization, the synthesis of this N-heterocycle has been a fascinating target for chemists.The most common way of constructing the quinoline system involves the cyclization of a substituent in the side chain of a benzene ring. There are several classical name reactions that can be used to assemble the quinoline structural core, such as; Skraup [178-180], Doebner-Miller [181-182], Friedländer [183], Combes [184], Conrad-Limpach [185] and Pfitzinger [186]. All these reactions involve a cyclo condensation of aniline or aniline derivatives with carbonyl compound, followed by aromatization reactions. Only in the Skraup reaction, glycerol is used as one of the starting material for in situ generation of acrolein through dehydration reaction.

Most of the classical methods for quinoline synthesis consist of some drawbacks which include the use of stoichiometric amounts of acid catalysts, harsh reaction condition resulting lack of environmental safety and longer reaction time [187-188]. Further, many of these methods produce large amount of undesirable side-products whose removal become more tedious and

time consuming process with the release of large volume of waste materials to the environment.

Thus, it has become very important to follow methods which could be considered as a better and eco-friendly viable 'green synthetic methods'. Among the various methods, the protocol reported by Friedländer is one of the most simple and straightforward routes for the synthesis of poly substituted quinolines [183].

The Friedländer method involves the acid or base catalyzed or thermal condensation between a 2-aminoaryl ketone and another aldehyde or ketone compound possessing a reactive α-methylene functionality followed by cyclodehydration. The Friedländer annulations without catalyst proceed under drastic condition with temperature ranging from 150-200 °C [189-191]. Furthermore, under thermal or base-catalyzed conditions, *o*-aminobenzophenone fails to react with simple ketones such as cyclohexanone and β-ketoesters [191]. It has been observed that acid catalysts are more effective than base catalysts for the Friedländer annulations [192].

The common examples of Brønsted acid catalysts are HCl [193-194], sulfamic acid [195], oxalic acid [196], triflouroacetic acid [197], *p*-toluene sulphonic acid [198] etc. Several Lewis acid catalysts have been reported for the synthesis of quinolines which include $FeCl_3.6H_2O$ [199], $SnCl_2/ZnCl_2$ [200], $Mg(ClO_4)_2$ [201], $Bi(OTf)_3$ [202], $Y(OTf)_3$ [203], $CeCl_3 \cdot 7H_2O$ [204], zirconium tetrakisdodecyl sulfate [205], silver phosphotungstate [206], molecular iodine [207], sodium fluoride [208], $NaAuCl_4 \cdot 2H_2O$ [209], $Zr(NO_3)_4$, $Zr(HSO_4)_4$ [210], $BiCl_3$ [211], $Nd(NO)_3$ [212], $NiCl_2$ [213], diphosgene/ acetonitrile solvent [214] etc.

However, in spite of their potential utility, some of these catalysts exhibit limitations such as use of toxic and corrosive reagents, tedious workup procedures, necessity of neutralization of the strong acidic media, requirement of stoichiometric and/or relatively expensive reagent, producing undesired wastes, more reaction time and high temperature. Some of the above methods also utilizes THF, DMF and DMSO as reaction medium and thus leads to complex isolation and recovery procedures. The main disadvantage of almost all existing methods is that the catalysts are destroyed in the work-up procedure and cannot be recovered or reused.

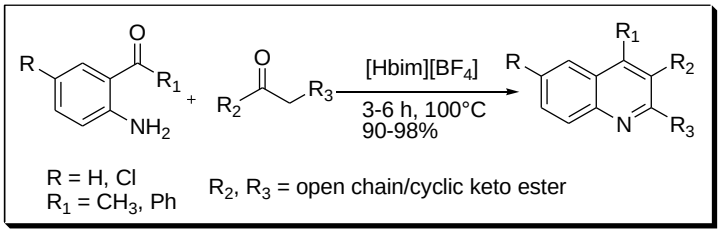
Since, quinoline derivatives are useful in drugs and pharmaceuticals; the development of simple, convenient and high yield protocols are desirable in the context of ideal synthesis. To solve the problem of catalyst recycle, a number of silica supported acid catalysts have been developed under thermal and microwave (MW) energies in solvent-free or solution methods. Some examples of such type of catalyst are $SiO_2$-indium(III) chloride [215], $NaHSO_4$- $SiO_2$ [216-217], $H_2SO_4$-$SiO_2$, Amberlyst-15 and $HClO_4$-$SiO_2$ [218], silica supported phosphomolybdic acid [219], silica-propylsulfonic acid [220], silica supported $P_2O_5$ [221]. Poly (ethylene glycol)-4000 supported sulfonic acid [222] was also used as a heterogeneous catalyst for the preparation of quinolines.

Few reports involved with the use of safer recyclable Brønsted or Lewis acid catalysts like *o*-benzenedisulfonimide [223], pentafluorobenzoates [$RE(Pfb)_3$] [224], dodecylphosphonic acid (DPA) [225], phosphotungstic acid ($H_3PW_{12}O_{40}$) [226], zeolites [227] in solvent-free medium or aqueous solution at different temperature.

In organic synthesis, ionic liquids have occupied a prominent position as reaction medium or catalyst because of their excellent chemical and thermal stability, low vapour pressure, good solvating capability, broad liquid range, and ease of recycling. Several task specific acidic ionic liquids have been successfully used in many organic reactions as catalyst or medium [97]. As a sustainable development technology, the applications of ionic liquids in the Friedländer annulation were reported by several groups in the form of reaction medium, promoter or catalysts [228-229]. Ionic liquids are proved to be great catalytic system or promoter since a considerable number of catalytic reactions become feasible in ionic liquids due to their ability to dissolve a wide range of materials. The use of ionic liquids has added various greener components in the quinoline synthesis like recycling of IL as catalyst or medium, formation of lesser number of side products, high yield of quinoline products, shorter reaction time and simplification of work-up procedures. The literature search on the Friedländer annulations in ionic liquids has covered the development of following methodologies till 2014.

In 2003, Palimkar and his co-workers [230] synthesized several room temperature ionic liquids based on 1-butylimidazolium salts with varying

anions and evaluated for the preparation of biologically active substituted quinolines and fused polycyclic quinolines (**Scheme 1.14**) using the Friedländer heteroannulation reaction. The reactions proceed very well in [Hbim][$BF_4$] at 100 °C without any added catalyst during 3-6 h reaction time. The IL acts as a promoter for this regiospecific synthesis and can be recycled. By this green approach, various quinolines were prepared in excellent yields and purity and well-characterized.




**Scheme 1.14** Synthesis of quinoline derivatives using [Hbim][$BF_4$]

Perumal and co-worker (2004) [231] investigated the Friedländer synthesis of quinolines at room temperature stirring for 24 h by using 1-butyl-3-methyl imidazolium chloride and $ZnCl_2$ melt (1:2 molar ratio) that can act both as a solvent and Lewis acid catalyst to get good to excellent yields of product (55-92%). Along with the reactants used by Palimkar *et al.* they also carried out the reaction between 2-amino, 3-acyl benzofuran and ethylacetoacetate to yield the corresponding quinoline at 80 °C (**Scheme 1.15**).

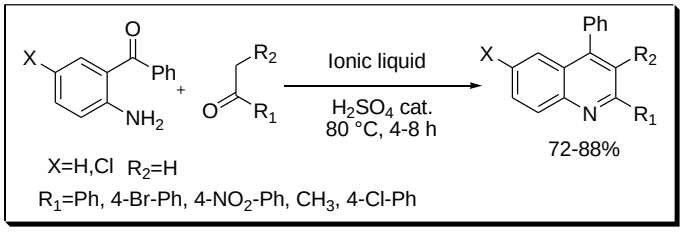

**Scheme 1.15** Synthesis of quinoline using [Bmim][Cl]:$ZnCl_2$


**Scheme 1.16** Friedländer quinoline synthesis using IL [Bmim][$BF_4$]

Wang and his group (2004) [11] carried out the preparation of substituted quinoline derivative (**Scheme 1.16**) in [Bmim][$BF_4$] IL as reaction medium and $FeCl_3 \cdot 6H_2O$ as catalyst at 100 °C within 5-8 h to give 72-90% yields.

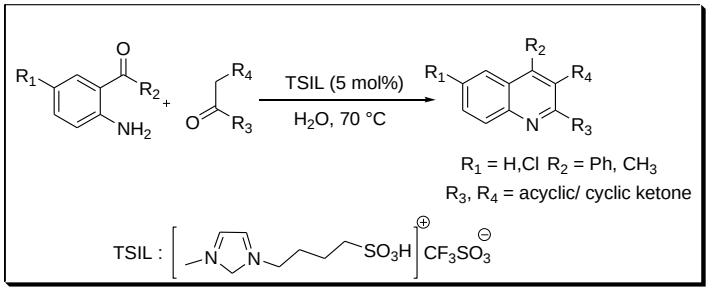
Zhang *et al.* (2004) [232] reported a novel and efficient protocol for the synthesis of quinoline derivatives through acid-catalyzed Friedländer reaction using ionic liquid [Bmim][$BF_4$]. Both the reaction media and catalyst were recoverable.

Zhang *et al.*(2004) [233] modified the classical Friedländer approach (**Scheme 1.17**) using sulfuric acid catalyst for the synthesis of 4-phenylquinoline derivatives in [Bmim][$BF_4$] ionic liquid as medium within 4-8 h at 80 °C.



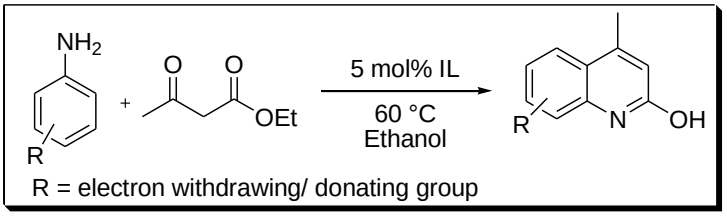

**Scheme 1.17** Ionic liquid promoted synthesis of quinoline

Akbari *et al.*(2010) [234] applied -$SO_3H$ functionalized task specific ionic liquid (TSIL) as water stable-acid catalyst for one-pot domino approach quinoline synthesis (**Scheme 1.18**) in aqueous medium at 70 °C. Various types of quinolines from 2-aminoaryl ketones and β-ketoesters/ketones were prepared with 85-98% yields during 1-8 hour time using 5 mol% of catalyst. After completion, the product can be separated from the aqueous IL solution by filtration. They observed that the catalyst could be easily recyclable for five times without any treatment.



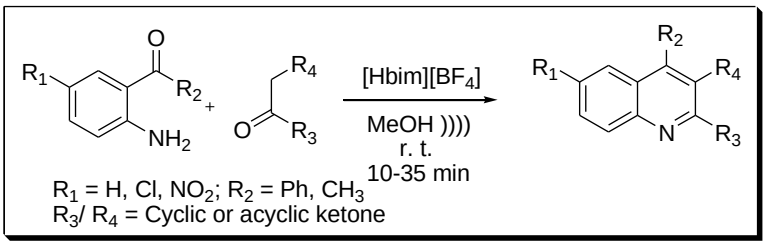

**Scheme 1.18** Quinoline synthesis using TSIL

Rajendran *et al.* (2012) [235] discussed an elegant one-pot synthesis of quinoline derivatives achieved by the reaction of substituted anilines with *β*-ketoester at 60 °C in ethanol (**Scheme1.19**) using 5 mol% of $[Et_3NH][BF_4]$ IL as reusable catalyst. All the reactions furnished excellent yield (78-93%) within the shorter span of time (20-65 min) than those reactions with conventional methods.




**Scheme 1.19** Synthesis of hydroxy quinoline derivatives using $[Et_3NH][BF_4]$

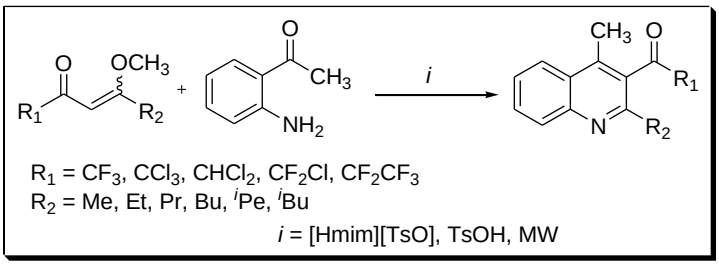
Heravi in 2009, [236] described an efficient method for the condensation of various *o*-aminoaryl ketones with α-methylene ketones via the tandem addition/annulation reaction (**Scheme 1.20**) under ultrasound irradiation in $[Hbim][BF_4]$ as solvent in presence of MeOH as a co-solvent at ambient temperature without any other catalyst within 10-35 min.




**Scheme 1.20** Reaction between *o*-aminoaryl ketones with α-methylene ketones in $[Hbim][BF_4]$

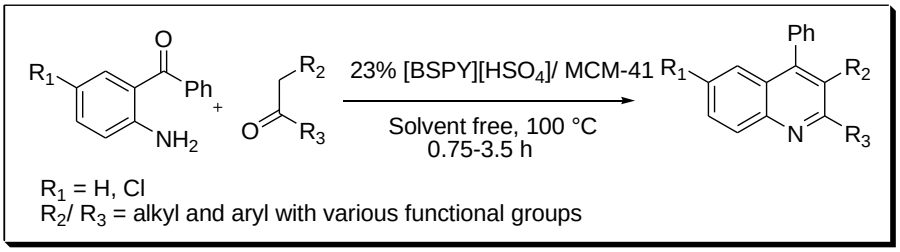
In 2012, Prola *et al.* [237] synthesized 3-haloacetyl-4-methylquinoline derivatives from the reaction of 4-alkoxy-3-alken-2-ones $[R_1C(O)CH=C(R_2)OCH_3$, where $R_1$= $CF_3$, $CCl_3$, $CHCl_2$, $CF_2Cl$, $CF_2CF_3$ and $R_2$= Me, Et, Pr, Bu, *i*-Bu and *i*-Pe] and 2-aminoacetophenone (**Scheme 1.21**). The reactions were performed in 1*H*-methylimidazolium toluene sulfonate [Hmim][TsO] as Brønsted acid ionic liquid and TsOH under microwave irradiation. The quinoline products were formed in a short time (10-20 min)

with good yields (70-91%). The effectiveness of the ionic liquid was observed from the recyclability of the same.




**Scheme 1.21** Synthesis of quinoline derivatives using IL [Hmim][TsO]

Alibeik and his co-workers (2012) [238] developed a supported catalyst by dispersing protic n-butanesulfonic acid pyridinium hydrogensulfate ionic liquid [BSPY][$HSO_4$] on the surface of MCM-41 nanoparticles. They studied the morphology of the MCM-41 and MCM-41 supported ionic liquid by SEM, XRD, BET and FT-IR techniques. The catalytic activity of the nanosized MCM-41 supported ionic liquid was investigated in the Friedländer synthesis of quinolines at 100 °C in solvent-free condition (**Scheme 1.22**).

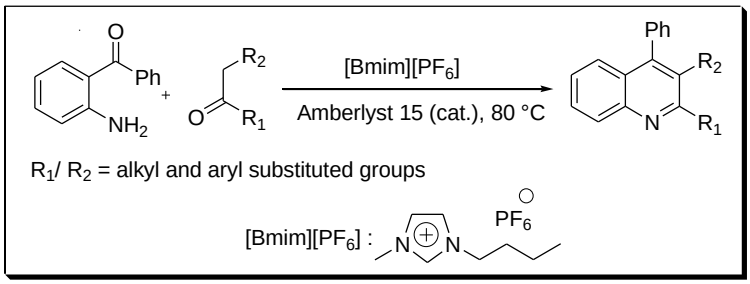



**Scheme 1.22** Synthesis of quinolines in the presence of 23% [BSPY][$HSO_4$]/MCM-41

In 2011, Tajik *et al.* [239] introduced an efficient synthesis of polysubstituted quinolines from the reaction of 2-aminobenzophenones and ethylacetoacetate or ketones using 50 mol% of acidic 1-butyl-3-methylimidazolium hydrogen sulfate [Bmim][$HSO_4$] ionic liquid at 70 °C under solvent-free conditions. This method produced 75-95% yields of product within 25 min to 10 h reaction time.

Hou *et al.* (2008) [240] synthesized various quinoline derivatives by the reaction of 2- aminobenzophenone and arylketones in [Bmim][$PF_6$]

(**Scheme 1.23**) ionic liquid in presence of Amberlyst-15 catalyst at 80 °C for 3 h. The ionic liquid plays dual role as solvent and promoter for this synthesis. The reactions were carried out with 72-84% yield.




**Scheme 1.23** Friedländer synthesis of quinoline using [Bmim][$PF_6$]

Wang *et al.* (2009) [241] reported the synthesis of quinolines via Friedländer annulation by using Lewis acidic ionic liquid choline chloride.2$ZnCl_2$ as efficient solvent and catalyst under mild conditions.

Recently Shirini and his group (2014) [36] presented a convenient, highly versatile and eco-friendly protocol for the Friedländer annulation in presence of 25 mol% of reusable 1,3-disulfonic acid imidazolium hydrogen sulfate (DSIMHS) (**Figure 1.18**) as IL catalyst under solvent-free medium at 70 °C. A variety of ketones afforded the substituted quinolines in excellent yields (88-94%) during relatively short reaction times (5-45 min).The acidic IL catalyst could be easily recovered and reused for four runs.

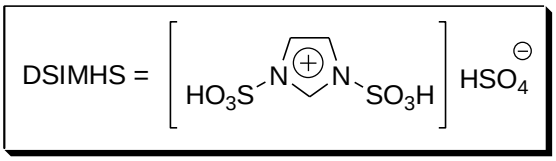
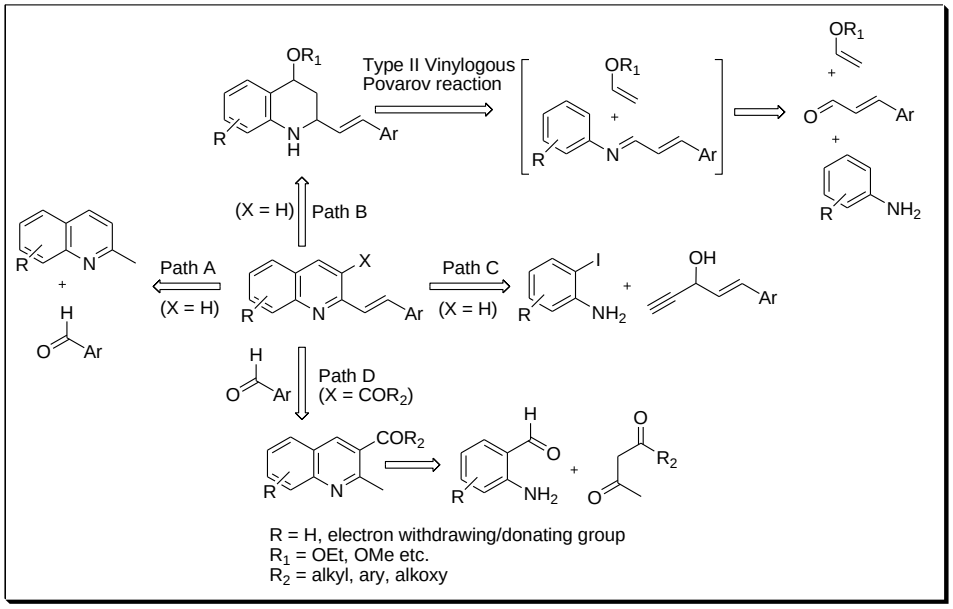



**Figure 1.18** Structure of ionic liquid DSIMHS

## 1.4 Reported methods for the synthesis of 2-styrylquinoline derivatives

The synthesis of 2-styrylquinolines have drawn attention from synthetic/medicinal chemists among the various quinoline derivatives due to

their immense potential as HIV-1 integrase inhibitors [39], activity against Alzheimer's disease, lipoxygenase inhibitors and leokotriene d4 antagonists [242] in addition to other biological activities [43, 243]. The retro-synthetic analysis of 2-styrylquinoline derivatives provides three different routes for the synthesis of target molecule according to **Scheme 1.24** [244].



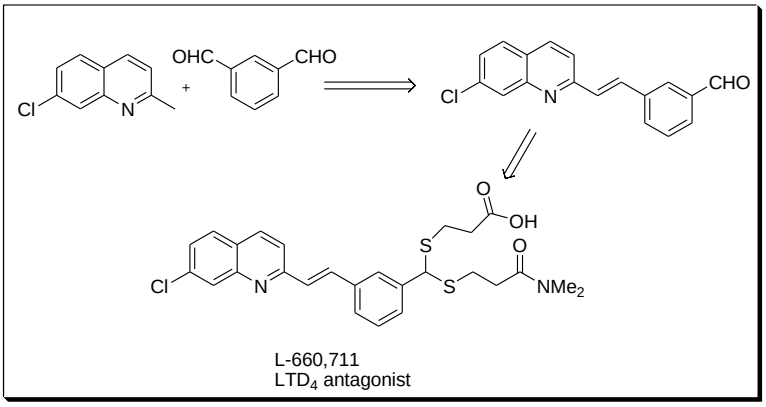

**Scheme 1.24** Various approaches for the synthesis of 2-styrylquinolines

However, the literature search offers few general methods for synthesizing these important derivatives. The most common method involves with the classical Knoevenagel condensation of 2-methylquinolines with an aldehyde in acetic anhydride at high temperature (100-140 °C) within 16-20 h reaction (Path-A, **Scheme 1.24**).

By following the above retrosynthetic route (Path-A, **Scheme 1.24**), Royer *et al.* in 1949 [245] designed the synthesis of 4-amino-2-styrylquinolines by treating a mixture of 4-amino-quinaldine, aromatic aldehydes in acetic anhydride at 155-160 °C for 3 h. The reaction also produced lower to moderate yields of some 4-amino-2-styrylquinolines at 180-185 °C using anhydrous $ZnCl_2$ as catalyst.

Rubtso and his co-workers in 1960 [246] investigated the preparation of 6-methoxy- and 7-chloro-2-styrylquinolines derivatives, with different substituents in the styryl group and in 4-position of the quinoline nucleus.

These derivatives were prepared by condensation of the corresponding substituted quinaldines with aldehydes in the presence of piperidine or acetic anhydride [245] at high temperature (170-185 °C) for prolonged reaction time (3-5 h). They also observed the antimicrobial activity of the synthesized compounds.




**Scheme 1.25** Synthesis of L-660,711

McNamara and co-workers (1989) [247] described a four-step synthesis of styrylquinoline derivative as potent $LTD_4$ antagonist. The product was synthesized via the intermediate aldehyde which was synthesized by the coupling of two readily available fragments 7-chloroquinaldine and 1, 3-benzenedicarboxaldehyde in presence of acetic anhydride (**Scheme 1.25**). The styryl product formed about 88% yield after the four steps of reactions. However this process was too long since all the steps are carried out by different procedure and involved with the isolation of each reaction intermediates.

In 1992, Zamboni *et al.* [248] developed a series of novel styrylquinoline compounds as high-affinity Leukotriene $D_4$ receptor antagonists by studying structure-activity relationship which led to the identification of (±)-3-[[[3-[2-(7-chloro-2-quinolinyl)-(E)-ethenyllphenyl][3-(dimethylamino)-3-oxopropyl]thio]-methyl]thio]propionic acid (**Figure 1.19**) (MK-571) as a potent and orally active antagonist.

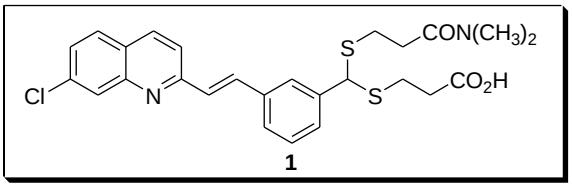
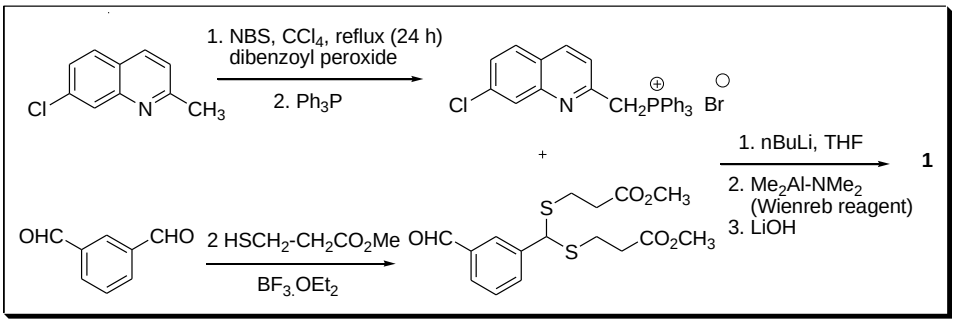



**Figure 1.19** Structure of MK-571

For the preparation of 2-styryl derivatives they utilized both $ZnCl_2$ as well as acetic anhydride methods at high temperature (120-160 °C) for longer time (8-18 h) to get good to excellent yields of product. They also applied Wittig reagent for the preparation of 2-styrylquinoline derivatives by following the reaction **Scheme 1.26**.




**Scheme 1.26** Synthesis of styrylquinoline **1**

Sidler *et al.* (1997) [249] reported the synthesis of a $LTD_4$ antagonist L-708,738 (**Figure 1.20**). They synthesized this product through the formation of 6, 7-difluoroquinaldine from 4-difluoroaniline and crotonaldehyde in a Skraup synthesis. Conversion of 6, 7-difluoroquinaldine to styryl derivative was readily effected by refluxing in xylene solution with isophthalaldehyde and acetic anhydride. After following several steps finally it transforms to $LTD_4$ antagonist L-708,738.

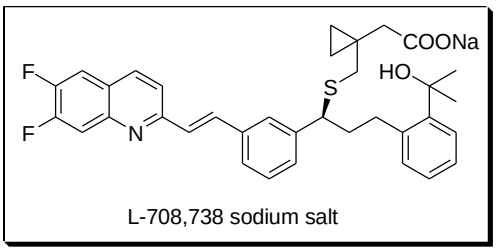



**Figure 1.20** Structure of styrylquinoline L-708,738

Mekouar *et al.* (1998) [250] outlined a method for the synthesis of these derivatives by using 8-hydroxyquinaldine as starting material which was subsequently converted to quinaldine derivatives. The condensation of quinaldine derivatives (**Figure 1.21**) with aromatic aldehydes in acetic anhydride produced the required 2-styrylquinolines (**Scheme 1.27**) at high temperature during longer reaction time (8-36 h).

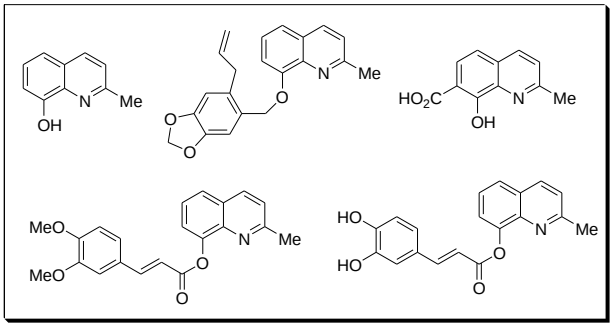
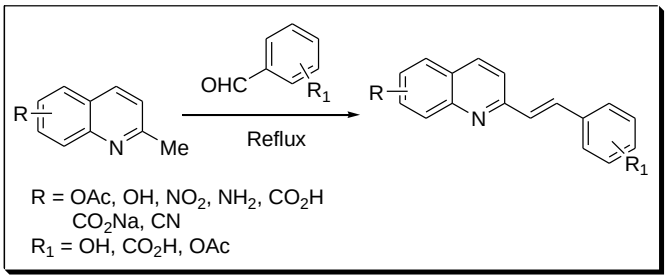



**Figure 1.21** Structure of 8-hydroxyquinaldine and their derivatives




**Scheme 1.27** Synthesis of styrylquinoline derivatives under reflux condition

Burdujan *et al.* (2001) [251] also prepared two styrylquinolines by following the same procedure as described by Mekouar *et al.* [250]. These compounds were found to possess photophysical and photochemical properties.

Zouhiri *et al.* (2000) [252] revealed some styryl derivatives by condensation of different starting quinaldine derivatives like 8-Hydroxy-7-quinaldic acid (**2**) and 5,7-dichloro-2-methyl-8-quinolinol (**3**) (**Figure 1.22**) with aromatic or hetreoaromatic aldehydes (mostly hydroxy derivatives) in acetic anhydride at high temperature. They studied the biological activity as potent inhibitors of HIV-I integrase.

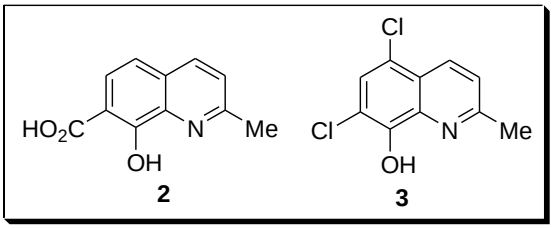



**Figure 1.22** Structure of quinaldine derivatives

A series of styrylquinoline derivatives were prepared by Polanski *et al.* (2002) [253] following the similar procedure as described by Mekouar *et al.* (1998) [250] and Zouhiri *et al.* (2000) [252]. They used different substituted quinaldic acids as starting material for the synthesis which were synthesized by condensation of substituted anilines with crotonaldehyde under standard Doebner-Miller conditions. Some of the compounds exhibit HIV-1 blocking activity.

Benard *et al.* (2004) [254] studied the biological activity of polyhydroxylated styrylquinoline derivatives (**4**) prepared from Perkin condensation of 8-hydroxyquinaldine-7-carboxylic acid (**5**) with aromatic aldehydes (**Figure 1.23**).

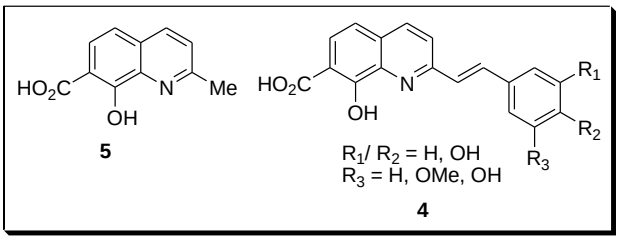
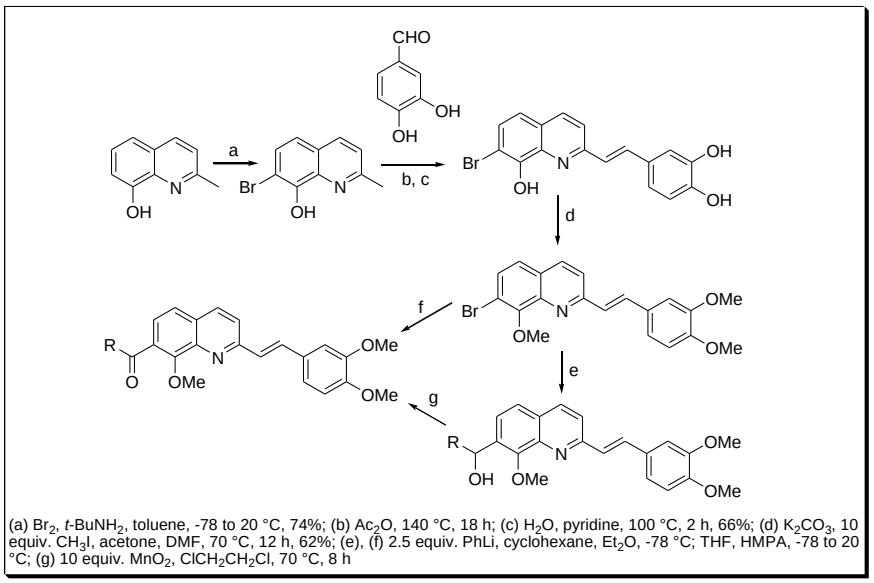


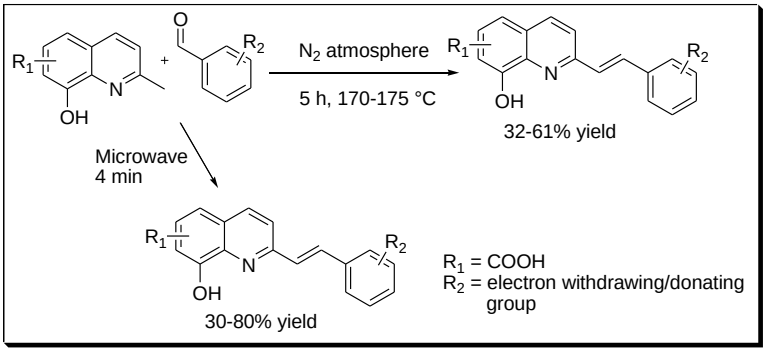

**Figure 1.23** Structure of styrylquinoline derivatives with quinaldine

In 2005, d'Angelo and his group [255] prepared a new class of 2-styrylquinolines bearing aroyl/acyl group at the C-7 position starting from Perkin-type reaction of 7-bromo-8-hydroxyquinaldine with 3,4-dihydroxybenzaldehyde in refluxing $Ac_2O$ followed by several steps of reactions according to **Scheme 1.28**.




**Scheme 1.28** Synthesis of aroyl/acyl substituted styrylquinoline derivatives

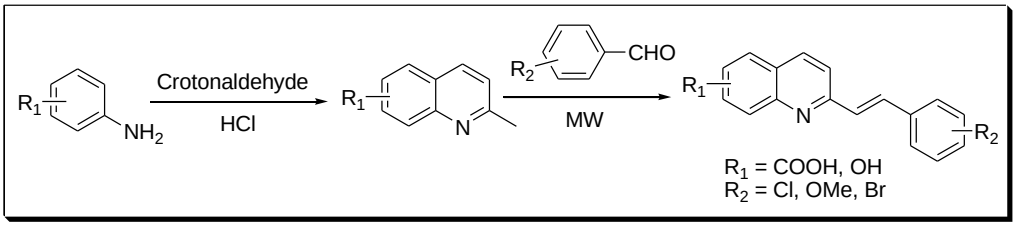
Polanski and co-workers (2006) [256] observed a comparative study for the condensation of quinaldine with aromatic aldehyde to 2-styrylquinoline under microwave as well thermal energy in solvent-free medium. The microwave method completed the reaction within 4 min to give good to moderate yields whereas the thermal method required 5 h at 170-175 °C to show 32-61% product (**Scheme 1.29**).




**Scheme 1.29** Microwave assisted synthesis of styrylquinoline derivatives

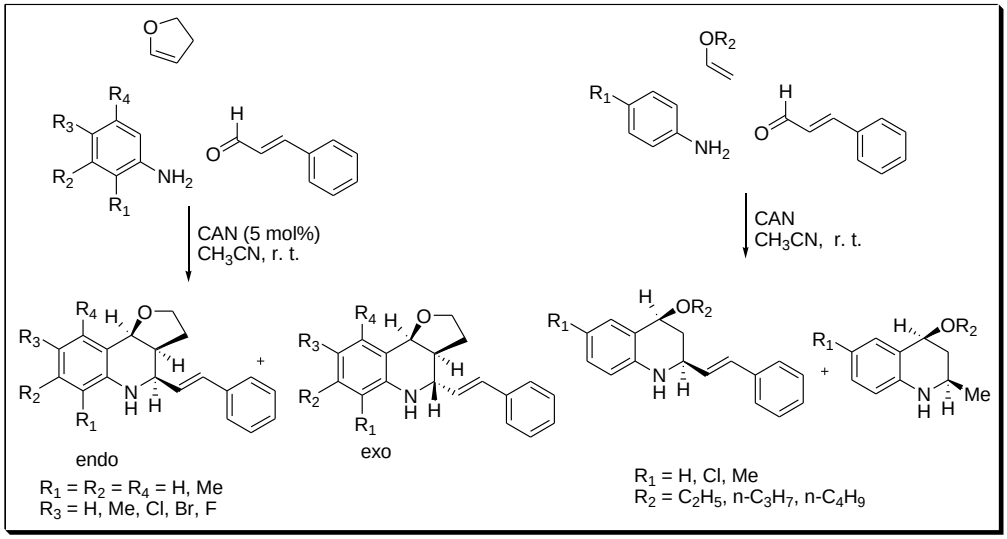
The same group (2006) [32] also reported the study related to antifungal activity of some halo substituted styryl derivatives which were obtained by conducting the microwave assisted reaction in presence of silica. Polanski and co-workers also (2007) [257] described the synthesis of styrylquinolines via condensation of anilines with crotonaldehyde containing HCl, followed by

microwave irradiation of the resulting quinaldine with aldehydes (**Scheme 1.30**). Some of the synthesized compounds possess photosynthesis inhibiting activity.




**Scheme 1.30** Synthesis of substituted styrylquinolines

Sridharan *et al.* (2007) [258] did the first implementation of type II vinylogous Povarov reaction by CAN catalyzed (5 mol%) three component reactions of anilines, cinnamaldehyde and vinyl ethers in acetonitrile at mild condition to afford 2-styryl-1,2,3,4-tetrahydroquinolines (**Scheme 1.31**).




**Scheme 1.31** CAN catalyzed synthesis of styrylquinoline derivatives

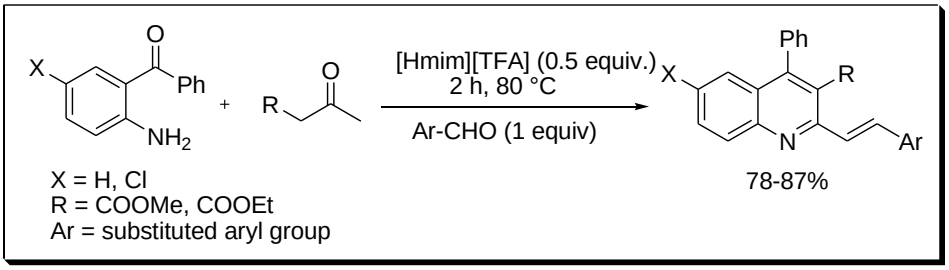
In the case of non-cyclic vinyl ethers, these reactions are completely stereoselective and furnish exclusively the diastereomer with a *cis* relationship between the styryl and alkoxy groups. With cyclic vinyl ethers the reaction completed within 1.5-6 h and formed good to moderate yields of products (70-85%). However, the reactions of non-cyclic vinyl ethers furnish 55-65% yield

along with small amount of 2-methyl-1, 2, 3, 4-tetrahydroquinoline derivatives within 2-3 h.

The same group again in 2009 [259] reported a simple synthesis of 2-styrylquinolines using a two-step sequence based on a CAN-catalyzed three-component type-II vinylogous Povarov reaction from aryl amines, cinnamaldehydes, and electron-rich cyclic and noncyclic vinyl ethers. The tetrahydroquinolines thus obtained were subsequently aromatized to styrylquinolines by DDQ-promoted dehydrogenation.

Podeszwa *et al.* (2007) [43] also employed his previous microwave assisted method to prepare some styrylquinolines possessing antiproliferative activity starting from 8-hydroxyquinaldine or quinaldic acids which were obtained from the Skraup reaction for condensation with aromatic aldehydes.

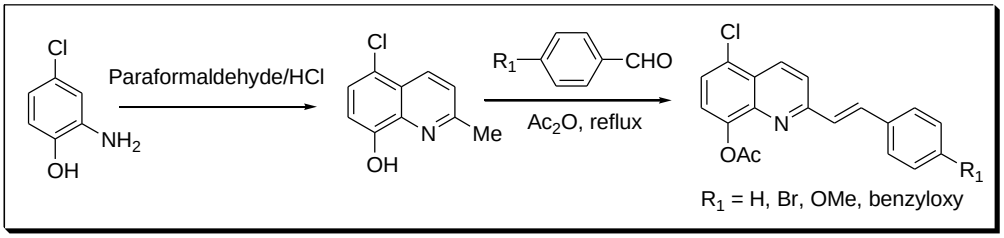
Dabiri *et al.* in 2008 [260] for the first time used task specific ionic liquid for the synthesis of 2-styrylquinolines via consecutive Friedländer annulations followed by Knoevenagel condensation. They first prepared 2-methylquinoline derivatives from 2-aminoaryl ketone and methylketone using [Hmim][TFA] ionic liquid at 80 °C for 2 h. After that reaction of another equivalent of aryl aldehydes to the crude reaction mixture at the same temperature for 2 h form the styryl derivatives with good results (78-87%) (**Scheme 1.32**).




**Scheme 1.32** Synthesis of 2-styrylquinoline using ionic liquid [Hmim][TFA]

In 2010, Jiao *et al.* [261] synthesized *N*-[(2-substituted-styryl)-5-chloro-8-hydroxyquinolin-7-yl]-benzenesulfonamide derivative by the Perkin condensation of 5-chloroquinolin-8-ol with various aromatic aldehydes which generate 5-chloro-2-styrylquinolin-8-yl acetates (**Scheme 1.33**) which were further hydrolyzed in pyridine/water to give 5-chloro-2-styrylquinolin-8-ols.

After nitration and reduction followed by reaction with benzenesulfonyl chloride derivatives provided the derivatives of styrylquinolin-7-yl-benzenesulfonamide (**Figure 1.24**) in 16-56% yield. Some of the compounds exhibit HIV IN inhibitory activity.




**Scheme 1.33** Synthetic method for 5-chloro-2-styrylquinolin-8-yl acetates

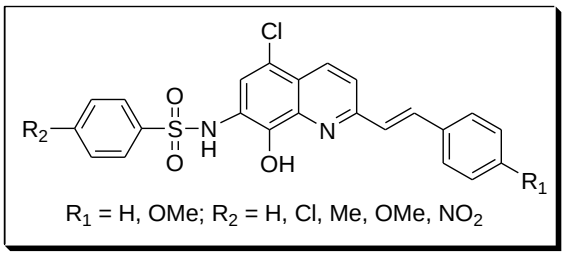
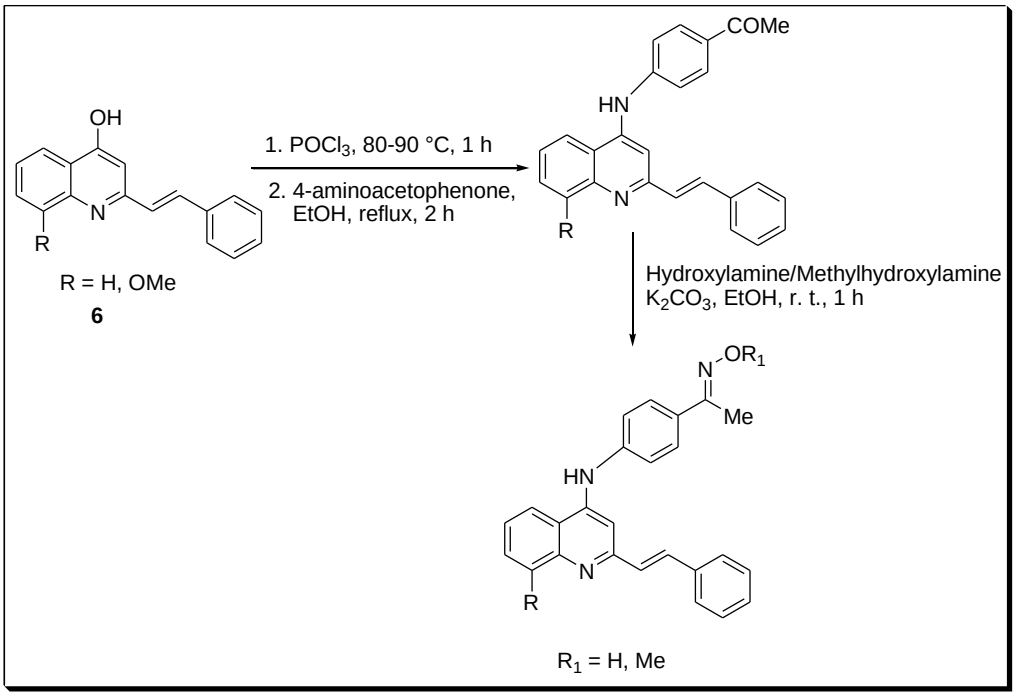



**Figure 1.24** Structure of styrylquinolin-7-yl-benzenesulfonamide




**Scheme 1.34** Synthetic route of oxime derivatives of 2-styrylquinolines

Chang *et al.* (2010) [262] revealed the synthesis of some substituted styrylquinoline derivatives (**6**) from 4-hydroxy-2-methyl-8-methoxyquinoline for evaluation of antiproliferative activities which was prepared from aniline and acetoacetic ester at 80 °C in acetic acid over 24 h. Condensation of this derivative with benzaldehyde in $Ac_2O$ at 150 °C for 30 h gave (E)-4-hydroxy-8-methoxy-2-styrylquinoline. Modification of this 2-styrylquinoline through various steps yielded the oxime derivatives of 2-styrylquinolines (**Scheme 1.34**). They also prepared several other oxime derivatives of 2-furylnyl quinoline derivatives by following the same multistep reactions (**Figure 1.25**).

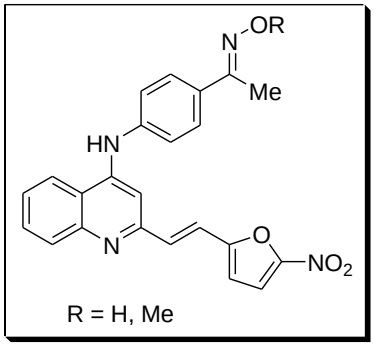
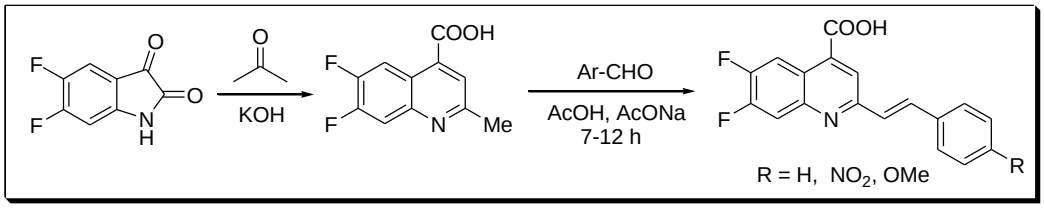



**Figure 1.25** Structure of oxime derivatives of 2-furylnyl quinoline derivatives

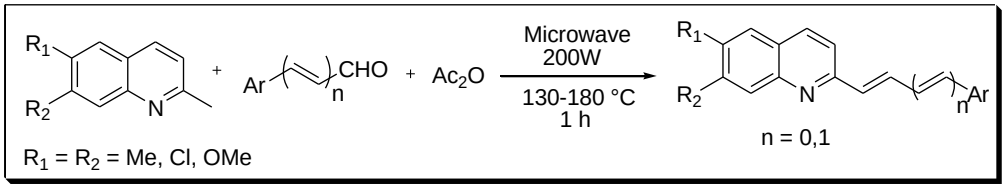
In another report, Li *et al.* (2011) [263] utilized microwave energy for the condensation of 2-methylquinolines with various aromatic and heterocyclic aldehydes in presence of 0.45 equiv. zinc chloride under MW irradiation without solvent. Apart from quinaldine, the above condensation was extended with benzo-fused derivatives of 2-methylquinolines, 3-methylbenzo[*f*]quinoline and 4-chloro-2-methylbenzo[*g*]quinoline.

Nosova *et al.* (2011) [264] developed a synthetic approach to 6,7-difluoro-2-styrylquinolines from the condensation of 6,7-difluoro-2-methylquinoline-4-carboxylic acid which was prepared by the Pfitzinger reaction, with aromatic aldehydes in acetic acid in the presence of sodium acetate under reflux for 7-12 h (**Scheme 1.35**). They also utilized another starting material 6,7-difluoroquinaldine under the same reaction condition for the formation of new series of (*E*)-2-(arylvinyl)-6,7-di-fluoroquinolines via reaction with aryl aldehydes which gave poor yields of product (31-45%).




**Scheme 1.35** Synthesis of (*E*)-2-(arylvinyl)-6, 7-di-fluoroquinolines derivatives

Staderini *et al.* (2011) [265] also used microwave energy for the synthesis of 2-styrylquinoline derivatives according to scheme 1.30 in acetic anhydride in the temperature range of 130-180 °C for 1 h (**Scheme 1.36**).




**Scheme 1.36** Microwave assisted synthesis of 2-styrylquinoline derivatives

Another microwave assisted method was reported by Gavrishova and co-workers (2011) [266] for the synthesis of derivatives of 2-(4-hydroxystyryl)quinoline by condensation of appropriate quinalidin derivatives with 4-hydroxybenzaldehyde in water. The reaction time was 10-16 min which provided 35-90% yield.

The same group in 2011 [45], also synthesized bichromophoric dyads containing 2-(4-oxystyryl)quinoline moiety under microwave irradiation from the mixture of quinaldine with 4-hydroxybenzaldehyde within 9-12 min (**Figure 1.26**). Further, alkylation of the styryl compound with different dibromo alkanes followed by treatment with 2,3-dihydroxy naphthalene furnishes the dyad.

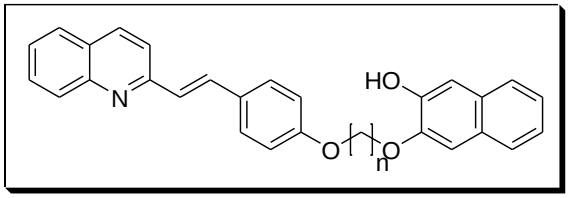
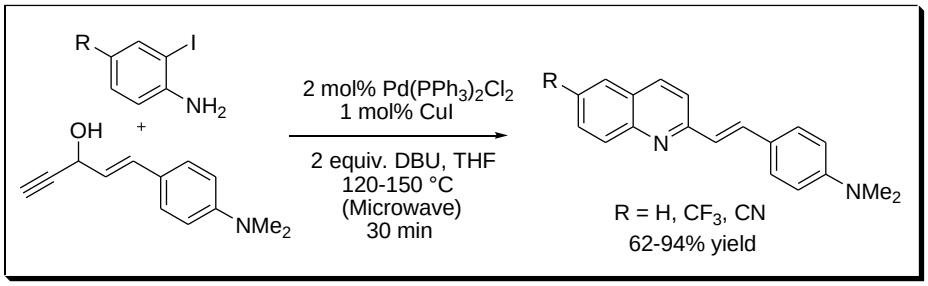



**Figure 1.26** Structure of bichromophoric dyad containing styrylquinoline moiety

Musiol and co-workers (2012) [267] studied the antimicrobial activity of some novel halogenated styrylquinoline derivatives formed by the condensation of corresponding quinaldine and aromatic aldehydes under microwave irradiation.

A synthetic approach to three styryl derivatives was studied by Cinar *et al.* (2013) [268] upon microwave-assisted coupling-isomerization reaction (MACIR) of ortho-iodo anilines, bearing a hydrogen atom or electron withdrawing substitutents in the 4-position. 4-N,N-dimethylamino-2-trans-styryl propargyl alcohols and 6-substituted 4′-N,N-dimethylamino-2-trans-styrylquinolines were obtained in 62-94% yield (**Scheme 1.37**). These compounds were found as luminescent pH sensors.




**Scheme 1.37** Synthesis of 2-styrylquinolines possessing luminescent properties

In 2013, Nosova *et al.* [269] reported the synthesis of 6,7-difluoro derivative of 2-styryl substituted 8-hydroxyquinoline and its Zn(II) complex (**Figure 1.27**). They first prepared 2-methyl-6,7-difluoro-8-oxyquinoline from 2,3-difluoro-6-nitrophenol. The acetoxy derivative was obtained by condensation with *p*-anisaldehyde in acetic anhydride in presence of HCl at 0 °C. After that hydrolysis of acetoxy group was carried out by heating with hydrochloric acid in ethanol and then treated the reaction with triethylamine to form the title product providing 46% yield. They also studied the fluorescent properties of these compounds.

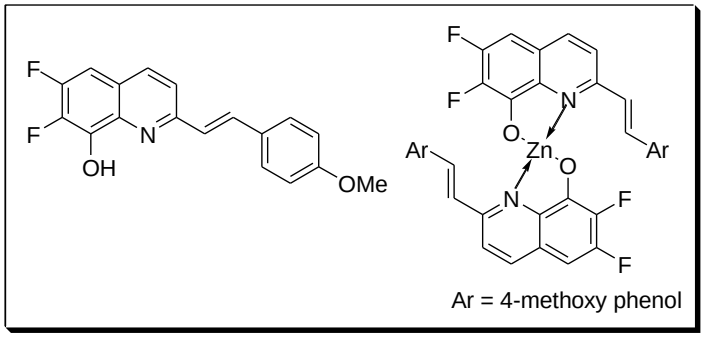
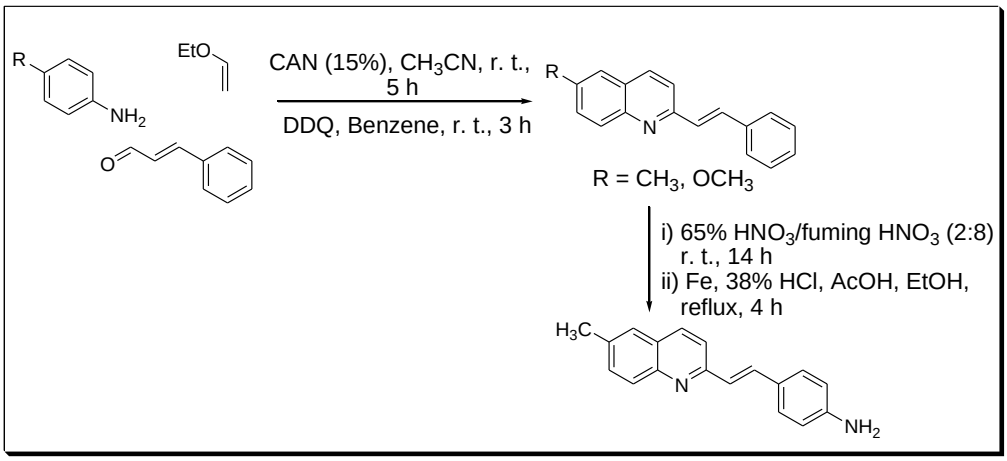


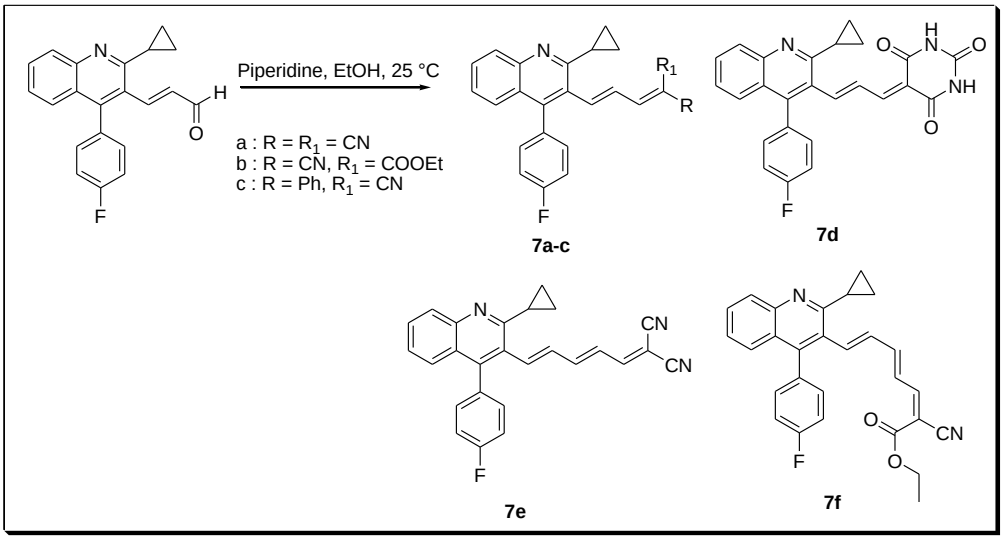

**Figure 1.27** The structure of 6,7-difluoro derivative of 2-styryl substituted 8-hydroxyquinoline and its Zn(II) complex



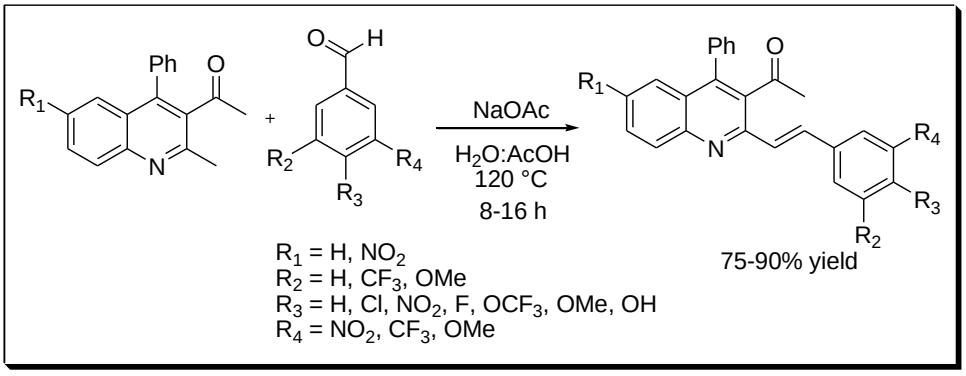

**Scheme 1.38** Synthetic route for 2-styrylquinolines possessing biological activities

Bolognesi and co-workers (2013) [270] prepared two styrylquinoline derivatives (65-70%) via a vinylogous variation of the Povarov reaction [258]. In next step, the amino derivative of 2-styrylquinolines was prepared by treating the initially formed 2-styrylquinoline with conc. nitric acid followed by reduction of the crude nitration product with iron powder in conc. HCl (**Scheme 1.38**). These derivatives have florescent properties in combination with therapeutic and diagnostic activities against Alzheimer's and Prion diseases.

Sekar and co-worker (2014) [271] synthesized six novel styryl dyes (**7a-f**) containing 4-flurophenyl along with quinoline ring as an electron donor and cyano-carbethoxy group as electron acceptors conjugated through a π–bridge. These compounds were obtained by the classical Knoevenagel condensation of 3-substituted aldehyde with the active methylene compounds (**Scheme 1.39**).



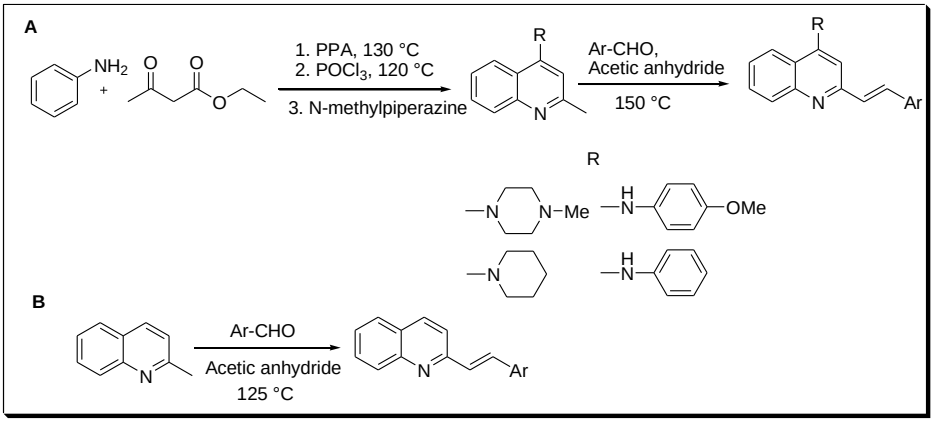

**Scheme 1.39** Synthesis of styrylquinoline derivatives **7a-f**




**Scheme 1.40** Synthesis of substituted 2-styrylquinolines

Recently, Kamal *et al.* (2015) [272] generated a series of biologically active 2-styrylquinolines regioselectively from quinaldine in binary solvent (water–acetic acid) using sodium acetate as base at 120 °C for 8-16 h to produce 75-90% yield (**Scheme 1.40**).

Kumar and co-workers (2015) [244] explored a general method for the synthesis of a series of these derivatives by using 10 mol% of $In(OTf)_3$ by one pot mechanism via the synthesis of quinaldine derivatives followed by addition of aryl aldehydes. The first step completed within 15 min at 100 °C and second step completed within 2-4 h giving 70-84% of the desired 2-styrylquinoline.




**Scheme 1.41** Synthesis of 2-styrylquinoline derivatives

Recently Wang *et al.* (2015) [273] evaluated a four step synthetic route of 2-styrylquinolines (**Scheme 1.41**). The synthesis of 2-methyl-4-hydroxy quinoline was observed from the cyclocondensation of aniline and ethylacetoacetate in presence of polyphosphoric acid (PPA) at 130 °C followed by chlorination with $POCl_3$ at 120 °C. The reaction of 4-chloroquinaldine with various amino compounds produced 8-aminoquinaldine derivatives using TsOH as catalyst at 120 °C. The target compounds were obtained by the addition of aldehydes to the quinaldine in acetic anhydride at 150 °C for 36 h. They observed that the synthesized compounds act as anti Alzheimer agents.

From the above discussion we have observed several drawbacks of the above mentioned methods. Some of them are: (a) commercial lack of starting material such as 2-methylquinoline derivatives, 2-styryl propargyl alcohols and thus they require additional synthetic steps for formation; (b) the requirement of high reaction temperature, prolonged reaction period, use of expensive catalyst and volatile organic solvents (such as THF, $CH_2Cl_2$, $CH_3CN$) along with excess amount of toxic reagents like $Ac_2O$ as medium, DBU as organic base, DDQ as dehydrogenating agent in various steps of reaction in different methods; (c) few methods give moderate yield of required product along with side products.

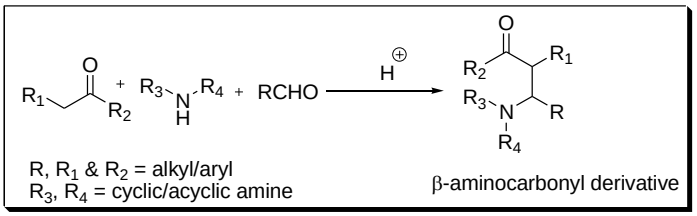
Some of the original methods modified with the reduction of reaction time under microwave irradiation for the condensation of quinaldine and aldehydes to the 2-styrylquinolines. Many of these methods are multistep reactions involving with the isolation of various reaction intermediates by

applying common purification techniques which decreases the yields of final product. Only two methods completed the synthesis of 2-styrylquinolines via two-step one pot approach in acidic ionic liquids at 80 °C as well as neat condition at 100 °C using $In(OTf)_3$ as Lewis acid catalyst. As a result there is a scope for development of strong acidic IL as medium or catalyst for the one pot synthesis of 2-styrylquinoline via Friedländer-Knoevenagel condensation reaction.

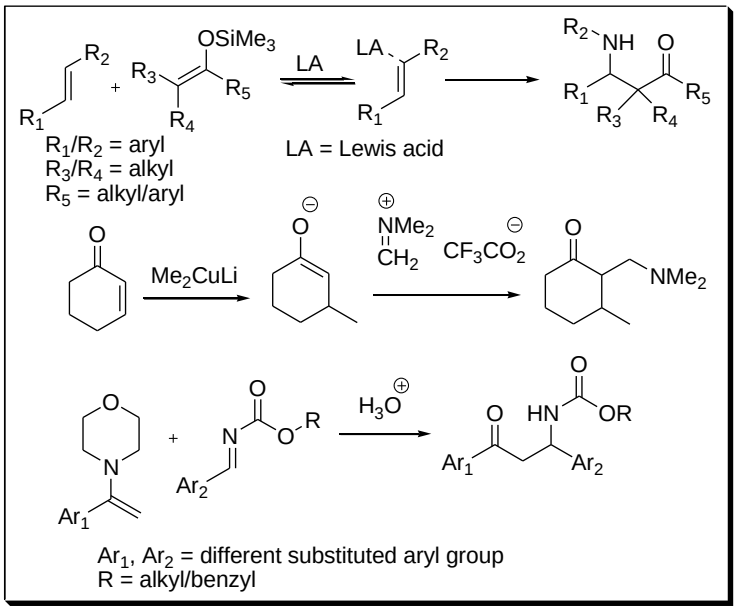
## 1.5 Heterogeneous acid catalyzed synthesis of β-amino carbonyl compounds via Mannich-type reactions

Mannich reaction is one of the fundamental carbon–carbon bond forming reactions in organic synthesis to prepare β-amino carbonyl compounds, which are important synthetic intermediates for various pharmaceuticals and natural products [274-277]. The products of the Mannich reaction are used for the synthesis of amino alcohols, peptides and lactams and as precursors to synthesize amino acids [278-280]. The literature on this reaction provides an outstanding evidence for the diversity and applications of the reaction. The three component classical Mannich reaction is the simplest one step method for incorporation of several elements in to the molecule of β-amino carbonyl compounds from the mixture of keto compound, aldehydes and primary or secondary amines using various acid catalysts (**Scheme 1.42**). This method has various limitations such as lack of selectivity, competitive Aldol reaction, longer reaction time and high temperature reaction. To overcome these limitations, modified Mannich reactions have been developed (**Scheme 1.43**) based on two-step reactions which utilize preformed electrophiles like imines and stable nucleophiles such as enolates, enol ethers and enamines in combination with appropriate use of catalyst and reaction conditions [281-284]. In spite that also the one pot multicomponent reaction is the preferred path for the preparation of β-amino carbonyl compounds rather than two steps procedure [285]. Furthermore, various development of the three component Mannich-type reactions have also been observed in literature from the

reactions of aldehydes, amines and silyl enolates or enol ethers or enamine [286-288] which greatly extended their synthetic utility.




**Scheme 1.42** Synthesis of β-aminocarbonyl derivatives using three component routes




**Scheme 1.43** Reaction using silyl enol ether, enolate and enamines

Conventional catalysts for the classical Mannich reaction of aldehydes, ketone and amines involve mainly Lewis acids [289], Brønsted acids [290] and Lewis base catalysis [291]. Some of these common Brønsted or Lewis acid catalysts are acetic acid [292], HCl [293], sulfamic acid [294], ceric ammonium nitrate [295], $Bi(OTf)_3$ [296], $SnCl_2$ [297], $InCl_3$ [298], $Y(OTf)_3$ [299], $Zn(BF_4)_2$ [300] etc. Several synthetic methods and catalysts have been developed to improve and modify this classical reaction. These include assistance of microwave [301] or ultrasound irradiation [302-303] and rare metal salts [304-305], organocatalysts [306-308], ionic liquids [309-310], Cu-nanoparticles [311], heteropoly acids [312] and supported acids [313].

However, many of them often suffer from the drawbacks of excess amount of non-recyclable catalysts, use of expensive heavy metal salts, toxic solvents such as 1,2-dichloroethane, acetonitrile or dichloromethane, harsh reaction condition and difficulty in product isolation which limit their use for the synthesis of complex molecules. Also most of the reported procedures are relevant to aliphatic amines and failed to cooperate with the aromatic amines. In context with sustainable technology, heterogeneous catalysts have played an important role in chemical industry from the economic and environmental point of view in terms of less sensitivity to moisture and oxygen, ready availability, low cost and low toxicity as compared to other traditional catalysts. In addition, the easy separation of catalyst by filtration makes the procedure more convenient for isolation of product and recycling of the catalyst. Heterogenizations of homogeneous catalytic systems also facilitate the recovery of the catalyst and minimize the waste material which is currently the subject of a great deal of research in green chemistry [314-315].

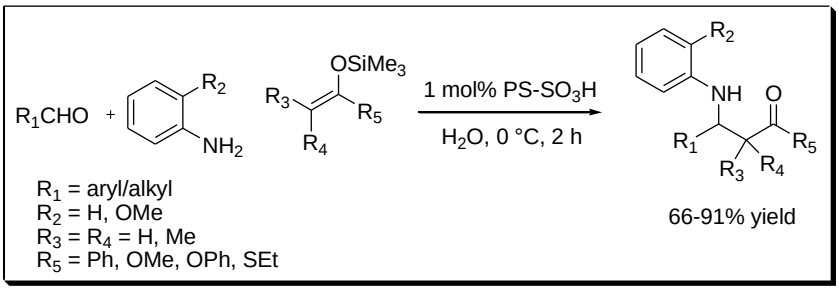
The immobilization technique utilizes various materials such as metal oxide (e.g. $SiO_2$, $Al_2O_3$, alumina, $WO_x$ etc.), zeolite, clay and polymer as inert supports for carrying the homogeneous catalytic system on its surface by secondary interaction or direct bond formation [316-317].

Development of polymer-supported catalysts is an important area in the design of heterogeneous catalyst due to their ease of workup and of separation of products and catalysts, from the economical point of view, and in application to industrial processes, recyclability, easier handling, greater selectivity, enhanced stability, non toxicity, and non corrosiveness [318]. The catalysts are heterogenized on polymers via coordinate or covalent bonds. Its hydrophobic nature protects water-sensitive Lewis acids from hydrolysis by atmospheric moisture until it is suspended in an appropriate solvent where it can be used in a chemical reaction [319].

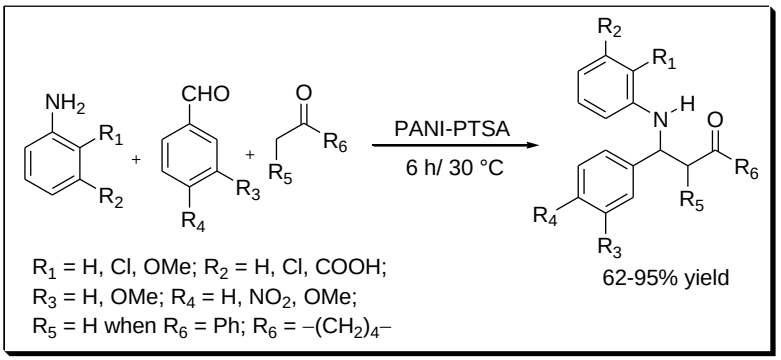
This section has discussed the review of various methods till date for the synthesis of β-amino carbonyl compounds or their derivatives through the three components Mannich (or Mannich-type) reactions using heterogeneous acid catalysts.

In 2003, Kobayashi and co-workers [320] studied several types of three-component Mannich-type reactions efficiently catalyzed by hydrophobic

polystyrene-supported sulfonic acid (PS–$SO_3H$) in water under mild conditions. They successfully used variety of nucleophile sources such as keto compounds, silicon enolates (derived from a ketone, esters, and a thioester), vinyl ether and phosphite for reaction with aldehyde and aromatic amines using 1 mol% of catalyst during different time intervals (2-24 h) in water (**Scheme 1.44**).




**Scheme 1.44** PS-$SO_3H$ catalyzed Mannich reaction




**Scheme 1.45** Synthetic route of β-amino carbonyl compounds using PANI-PTSA

Palaniappan *et al.* (2004) [321] also investigated a three component Mannich-type reaction catalyzed by reusable polyaniline salts of Brønsted and organic acids and polyaniline complexes of Lewis acids in solvent-free medium at 30 °C for 6 h. The polyaniline salts were prepared by doping of polyaniline base with different Brønsted ($H_2SO_4$, HCl, $HClO_4$, $HBF_4$) and organic acids (5-sulfosalicylic acid, p-toluene sulfonic acid). Polyaniline complexes were prepared by using Lewis acids ($ZnI_2$ and $FeCl_3$). The optimized reaction conditions were carried out using substituted aldehydes, aniline and cyclohexanone in the presence of polyaniline salt of p-toluene sulfonic acid

(25% with respect to weight of benzaldehyde) as catalyst to provide β-amino carbonyl compounds in the range of 62-95% yields (**Scheme 1.45**).

In 2012, Suling *et al.* [322] utilized Nafion-H (8 mol%) as heterogeneous catalyst in ethanol at ambient temperature for the Mannich-type reactions of aromatic aldehydes, aromatic amines and acetophenone or cyclohexanone to furnish corresponding β-amino carbonyl product during 2-24 h. The catalyst could be easily recovered and reused without loss of activity for at least four times.

Massah *et al.* (2012) [323] applied sulfonated polystyrene/montmorillonite nanocomposite (OMMT/PS-$SO_3H$) (**Figure 1.28**) as heterogeneous catalyst in the Mannich reaction of ketones, aromatic aldehydes and aniline derivatives under solvent-free conditions. This method provides corresponding Mannich products in high yield within time range 45-125 min.

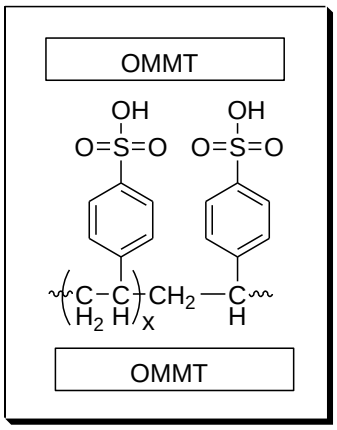



**Figure 1.28** Structure of catalyst OMMT/PS-$SO_3H$

In 2014, Li *et al.* [324] utilized sulfonated poly(4-vinylpyridine) heteropolyacid salts (**Figure 1.29**) to effectively catalyze the one-pot synthesis of β-amino carbonyl compounds via the Mannich reaction of variety of aromatic aldehydes, aromatic ketone and aromatic amines. The reaction requires longer reaction time (6-16 h) to yield the corresponding β-amino carbonyl compounds. In addition, the catalyst could be easily recovered by the filtration and reused six times without significant loss of catalytic activity.

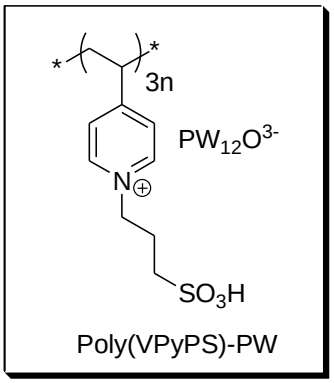
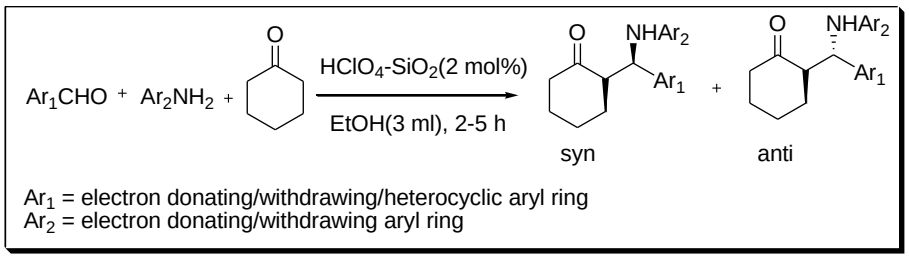



**Figure 1.29** Structure of sulfonated poly(4-vinylpyridine) heteropolyacid salts

Recently, Sachdev *et al.* (2015) [325] reported the use of mesoporous silica–polymer nanocomposites (SBA/PS) as catalyst for the synthesis of β-amino carbonyl compounds. The reactions were carried out using 90 mg of the catalyst at 52 °C for 24 h. They observed good selectivity of the Mannich products using the SBA/PS catalyst.

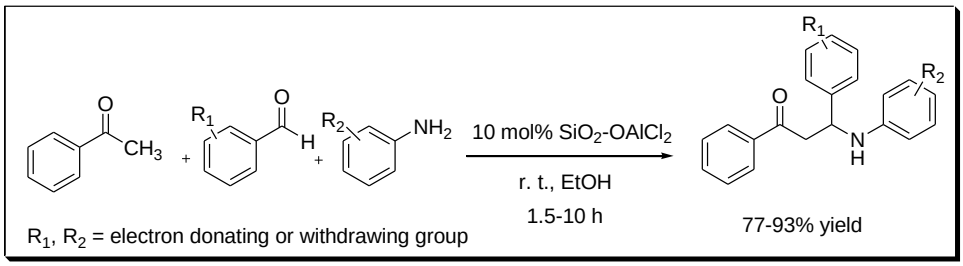
Several reports discussed the efficient applications of metal oxide supported solid acid catalyst for the Mannich-type reactions. Bigdeli *et al.* (2007) [326] developed $HClO_4$–$SiO_2$ (2 mol%) catalyzed three-component, one-pot Mannich reaction of ketones, aromatic aldehydes and aromatic amines (**Scheme 1.46**) in ethanol to afford the corresponding β-amino ketones in good yields and high stereoselectivities in favour of the *anti*-isomer.




**Scheme 1.46** One pot three component Mannich reaction catalyzed by $HClO_4$-$SiO_2$

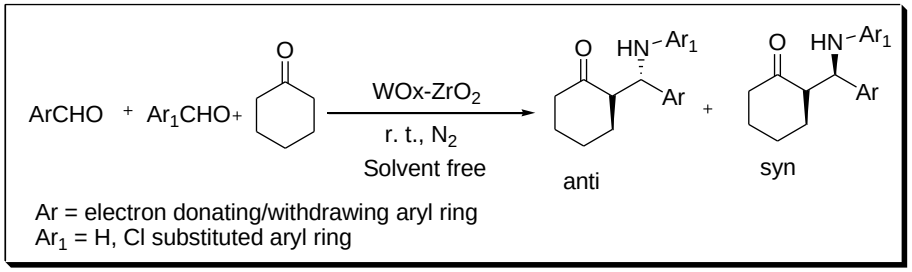
Li *et al.*, in 2007, [327] investigated one-pot Mannich-type reactions of acetophenone with aromatic aldehydes and aromatic amines using silica-supported aluminum chloride as catalyst (**Scheme 1.47**). 10 mol% of the catalyst provides good yields (77-93%) with various substituted aryl aldehydes and amines within 1.5-10 h. However, ortho substituted aryl amines give trace

amount of product and the catalyst had found no catalytic activity against the aliphatic aldehydes or amines.




**Scheme 1.47** $SiO_2$-$OAlCl_2$ catalyzed Mannich reaction

In 2008, an efficient $WO_x$–$ZrO_2$ solid acid catalyst was synthesized by Reddy *et al.* [328] from zirconium hydroxide gel obtained by a coprecipitation method, and impregnating with ammonium metatungstate. After characterization, the synthesized catalyst was found to be efficiently catalyse the three component Mannich-type reaction of aromatic aldehyde, aniline and keto compounds (cyclohexanone or acetophenone or acetone) under solvent-free conditions at ambient temperature in 1-4 h (**Scheme 1.48**). In this method, acetophenone was less reactive than cyclohexanone and required longer time to afford the desired product.

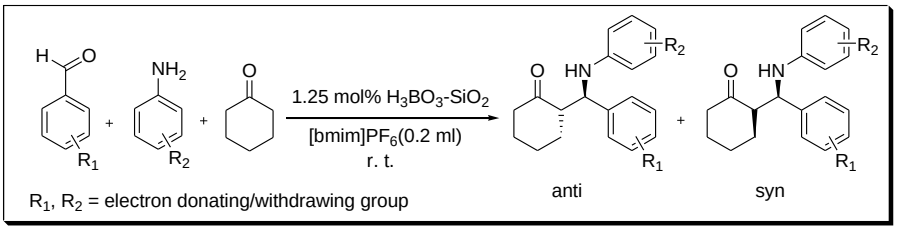



**Scheme 1.48** Three component Mannich reaction catalyzed by tungsted zirconia

Nagrik *et al.* (2010) [329] utilized $MgO/ZrO_2$ as inexpensive and effective catalyst for the one-pot Mannich reaction of aldehydes, ketones, and amines to furnish β-amino carbonyl compounds. The present methodology offers good yield with the optimized 0.35/0.65 wt% mole ratio of $MgO/ZrO_2$ in acetonitrile at 80 °C within 4-12 h.

Yelwande *et al.* [330] used 10 mol% of polyaniline/$SiO_2$ as catalyst for the Mannich-type reaction of acetophenone, aromatic aldehydes and aromatic amines in ethanol under reflux for 3-4 h to furnish 87-92% of product.

A novel and efficient silica-supported boric acid ($H_3BO_3$–$SiO_2$) in ionic liquid ([bmim][$PF_6$]) system was applied in the Mannich-type reactions by Kumar *et al.* (2011) [331] for the three types of ketones such as cyclohexanone, ethyl methyl ketone and acetophenone (**Scheme 1.49**). In case of ethyl methyl ketone and acetophenone the reactions require longer time for completion. The reaction afforded desired product at room temperature with different amount of supported catalyst for different types of ketones.




**Scheme 1.49** Mannich reaction catalyzed by silica-supported boric acid in IL

Sharma *et al.* (2012) [332] designed an inorganic–organic hybrid silica based tin (II) catalyst (**Figure 1.30**) and examined the catalytic activity for the Mannich reaction of ketones with aromatic aldehydes and different amines in dry dichloromethane at ambient temperature.

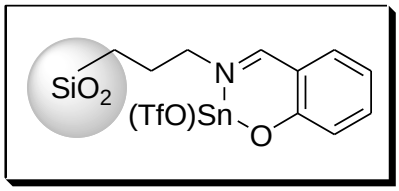



**Figure 1.30** Structure of silica based tin(II) catalyst

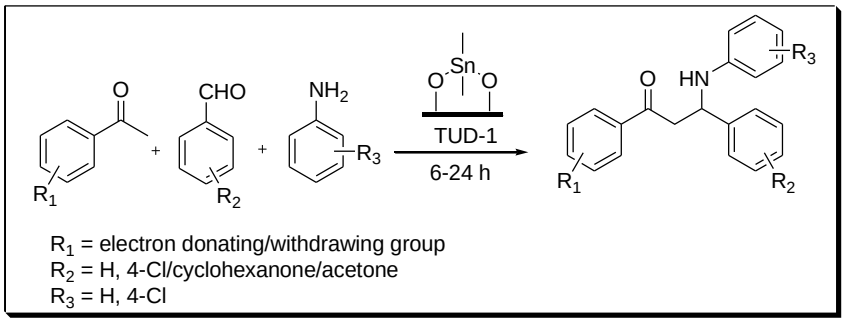
In 2011, Rajbangshi *et al.* [333] employed iodine-alumina as catalyst in the coupling reactions of aldehydes, enolizable ketones, or 1, 3-dicarbonyls with methylcarbamate or aromatic amines under microwave irradiation to afford β-amino carbonyl compounds in good to excellent yields.

Boumoud *et al.* (2012) [334] investigated an easy operational method for the synthesis of β-amino carbonyl compounds using silica-supported antimony (III) chloride ($SiO_2$-$OSbCl_2$) as heterogeneous catalyst. This protocol uses 2 mol% of catalyst to provide good yield but it requires longer time (3-5 h) for completion.

Most recently, in 2015, a facile synthesis of β-amino carbonyl compounds was developed by Liu *et al.* [335] through the condensation of cyclohexanone, aromatic aldehydes and anilines at 25 °C in the presence of 5 mol% silica supported phenylphosphinic acid against 10 mmol of ketone. They observed that the resulting products were formed in moderate to good yields with reasonable diastereoselectivities.

The application of mesoporous sulfated MCM-41 was observed by Vadivel *et al.* (2013) [336] for the three-component reaction of aniline, ketone and aldehyde in ethanol under reflux condition within 5-8 h to afford the corresponding products.

Pachamuthu *et al.* (2013) [337] explored the synthesis of a novel wormhole structured mesoporous material containing tin, SnTUD-1 and characterized by different techniques. The catalyst showed interesting Lewis acidity as measured by FT-IR of pyridine adsorption which furnished good activities using 100 mg in Mannich-type reactions of ketones with aldehydes and amines at room temperature (**Scheme 1.50**). The main drawback of this reaction is that it requires prolonged reaction time (6-24 h) for completion.




**Scheme 1.50** Sn TUD-1 catalyzed synthesis of β-amino carbonyl compounds

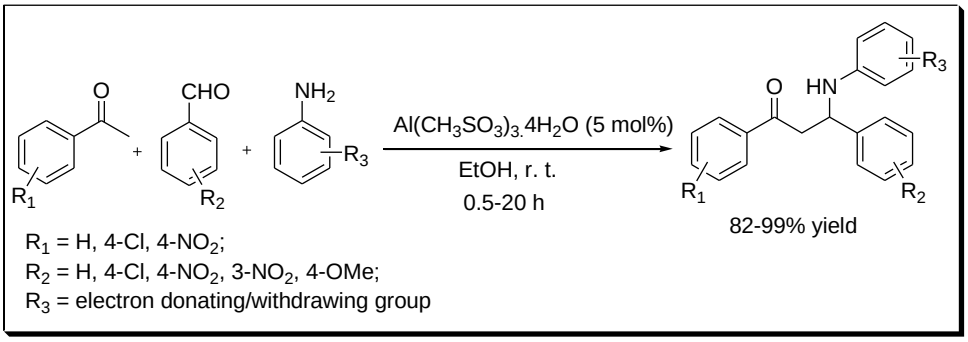
In 2006, Azizi *et al.* [338] successfully utilized heteropoly acid (HPA) $H_3PW_{12}O_{40}$ as catalyst for three component Mannich reaction of various ketones with aromatic aldehydes and different amines in water at ambient

temperature. The reactions afforded the corresponding β-amino carbonyl compounds in good to excellent yields with moderate diastereoselectivity using 10-20 mg of the catalyst.

In 2010, Rafiee *et al.* [339] observed the Mannich-type reaction of aldehyde, aromatic amine and cyclohexanone or acetophenone in water using insoluble salts of Keggin heteropoly compounds $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ as recyclable heterogeneous catalyst in water at room temperature. This procedure afforded structurally diverse β-amino ketones with major *anti*-diastereoselectivity. The reactions were completed within 30-210 min for various substituted reactants. The catalyst was recovered and reused for subsequent five runs.

The efficient utilization of metal salts or complexes as heterogeneous catalyst was observed in various reports [340-341]. Some examples of such catalysts include $InCl_3$, $Fe(HSO_4)_3$, copper(II) triflate, $Bi(NO_3)_3$ and $FePO_4$ [298, 342-345]. The reactions carried out with these catalysts took longer time and provide low yield with ortho substituted aldehydes. In addition, $FePO_4$ was not applicable for aliphatic amine or aldehydes and also with aliphatic ketone like cyclohexanone the reaction did not proceed.

In 2009, Wang *et al.* [346] described the synthesis of β-amino ketones via the reaction of aromatic aldehydes, aromatic amine and substituted acetophenone in presence of catalytic amount of 5 mol% of reusable aluminium methane sulphonate $[Al(CH_3SO_3)_3.4H_2O]$ in ethanol at room temperature (**Scheme 1.51**). In all the cases the reactions completed within 0.5-20 h providing 82-99% yield of β-amino carbonyl compounds.




**Scheme 1.51** Synthesis of β-amino ketones using $[Al(CH_3SO_3)_3.4H_2O]$

Dai *et al.* (2010) [347] applied 10 mol% of recyclable cerium trichloride heptahydrate ($CeCl_3.7H_2O$) as catalyst for three-component direct Mannich reaction of anilines and benzaldehydes with acetophenone in ethanol at room temperature stirring within 3-16 h to produce excellent yields.

Khalifeh *et al.* (2013) [348] synthesized one heterogeneous complex of zinc with N,N-bis(2-hydroxyphenyl) pyridine-2,6-dicarboxamide (BHPPDAH) (**Figure 1.31**) for the three-component coupling reactions of aldehydes, alkynes, and amines (A3 coupling) via C–H activation (**Scheme 1.52**). The catalyst was found to be efficient for both aromatic and aliphatic aldehydes and alkynes. The catalyst could be recycled and reused for subsequent reactions. The reactions were performed at 70 °C with 2 mol% of catalyst.

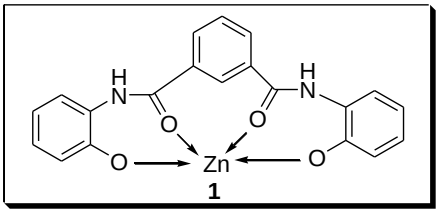
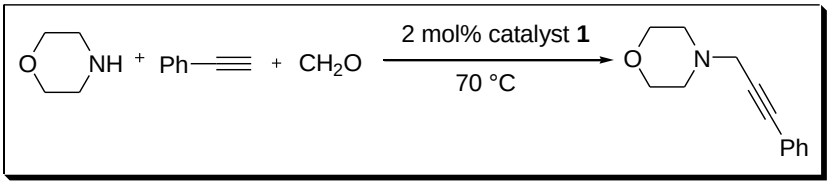



**Figure 1.31** Structure of catalyst [Zn(II)BHPPDAH]

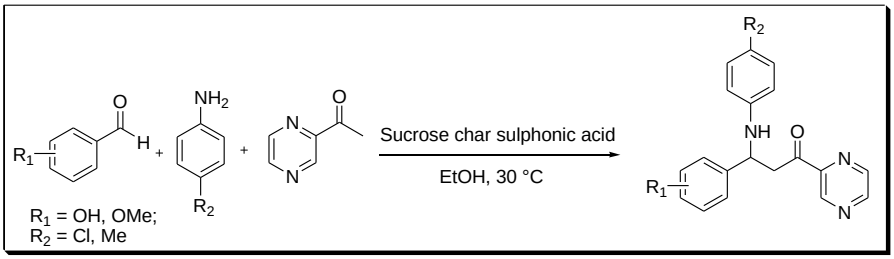



**Scheme 1.52** Mannich reaction using [Zn(II)BHPPDAH]

The use of various organocatalysts as solid acid catalysts has also been observed for the Mannich-type reactions. In 2007, Wu *et al.* [349] conducted the direct Mannich-type reaction of a variety of in situ generated aldimines at room temperature using aldehydes and anilines with ketones in a three-component reaction catalyzed by silica sulfuric acid (SSA) in EtOH. This rapid reaction afforded the corresponding β-amino ketones in good yields with excellent stereoselectivities and catalyst was recyclable.

Xu *et al.* (2009) [350] utilized 2-6 mol% of sucrose char sulfonic acid as recyclable solid catalyst in ethanol at 30 °C for the reaction of aromatic

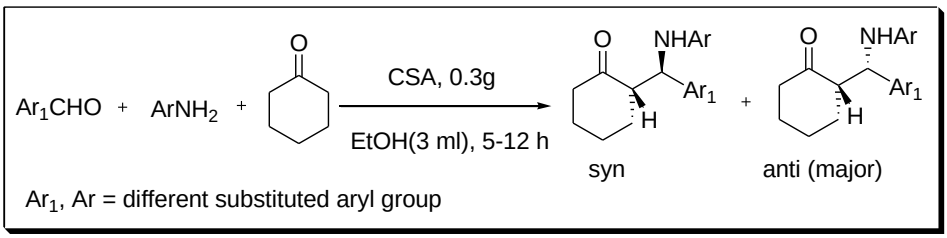
aldehydes, aromatic amines and ketones to afford the corresponding β-amino carbonyl compounds. A series of heteroaromatic β-amino carbonyl compounds were also obtained by using 2-acetylpyrazine as keto compound (**Scheme 1.53**). They provide good to high yield of product during 10-40 h reaction.




**Scheme 1.53** Sucrose char sulfonic acid catalyzed Mannich reaction

Carbon-based solid acid (CBSA) was used as a reusable catalyst for the synthesis of β-amino carbonyl compounds by Davoodnia *et al.* (2011) [313] following the reaction of acetophenone, aromatic aldehydes and aromatic amines in ethanol at mild condition 3.45-7 h to show 84-93% of products.

Nemati *et al.* (2011) [351] used cellulose sulphuric acid as biodegradable, efficient and recyclable heterogeneous catalyst in ethanol at room temperature for the highly stereoselective synthesis of β-amino ketones from the mixture of aromatic aldehydes, aromatic amines and various types of ketones within 5-16 h (**Scheme 1.54**).




**Scheme 1.54** One pot three component Mannich reaction

For the Mannich–type reaction, many reports have described metal-nanoparticle material as reusable catalysts in different reaction conditions. The Cu-nanoparticles catalyzed synthesis of β-amino carbonyl compounds from various ketones, aromatic aldehydes and amines was exploited by Kidwai *et*

*al.* (2009) [311] in methanol at ambient temperature under nitrogen atmosphere. They used 10 mol% of catalyst to afford corresponding products within 8-12 h.

Another ZnO-nanoparticle was developed by MaGee *et al.* (2011) [352] and investigated as recyclable catalyst for the Mannich reaction of ketones, aromatic aldehydes and amines in water to afford good yields of β-amino carbonyl compounds with moderate diastereoselectivity. They have observed that electron withdrawing groups were more active than electron donating groups. All the reactions were carried out using 0.5 mmol of catalyst for 10 h at 60 °C.

In 2011, Kassaee *et al.* [353] observed that $TiO_2$ nano particles (20 mol% of $TiO_2$ NPs) act as an efficient reusable catalyst for the solvent-free Mannich reaction of substituted aldehydes, amines and ketones in 2-6 h reaction time.

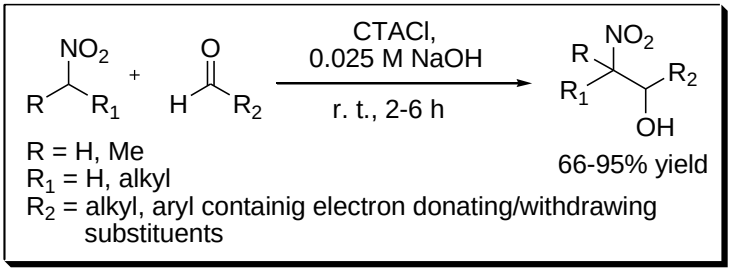
Shirini *et al.* (2013) [354] developed rice-husk-supported $FeCl_3$ nano-particles ($FeCl_3$–RiH) and used as an environmentally friendly catalyst in the synthesis of β-amino carbonyl compounds from simple and readily available precursor molecules. All the reactions completed within time period of 8-14 h.

## 1.6 Review on water mediated Henry reaction

The classical Henry reaction represents the condensation of a carbonyl compound with a nitroalkane in the presence of variety of basic reagents which include alkali metal hydroxides, alkaline earth oxides, carbonates, bicarbonates, alkoxides, alkaline earth hydroxides, or magnesium and aluminum alkoxides in organic solvent at different temperatures [355-359]. Depending on the strength of base, Aldol and Cannizaro reactions may occur as side reactions. Sometimes base catalyzed elimination of water molecule leads to the formation of nitroolefin which polymerize readily [360]. Moreover, during work-up step, Nef reaction may happen by acidification of the reaction mixture for complete removal of the base [87]. Thus it is necessary to control the activity of the base as well as the reaction condition to provide only the nitroaldol product exclusively. For reduction of toxic waste

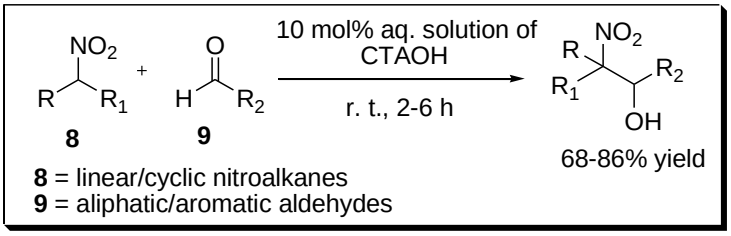
and byproducts arising from any chemical process requires increasing emphasis on the use of less toxic and environmentally compatible materials in the design of new synthetic methods [361]. Within this context the water mediated Henry reaction in the presence of reusable heterogeneous or homogeneous basic catalyst is of considerable significance. The aqueous medium with respect to organic solvent is less expensive, less dangerous, and environment-friendly and also it allows the control of the pH of the solution [362-363]. The low solubility of most reagents in water is generally increased in combination with a co-solvent. The increasing demand of water as reaction medium in many organic reactions have developed research interest in studying the Henry reaction in aqueous medium.

In 1997, Ballini *et al.* [364] studied the nitroaldol reaction using cetyltrimethylammonium chloride (CTACl) as cationic surfactant in aqueous medium for the first time in presence of 0.025M NaOH at room temperature during 2-6 h time (**Scheme 1.55**). This method produced good to excellent yields of 2-nitroaldol (66-95%) without any side products from variety of substrate molecules.




**Scheme 1.55** Nitroaldol reaction using CTACl

Again, the same author (2004) [365], successfully utilized 10 mol% of cetyltrimethylammonium hydroxide (CTAOH) in water solution for the nitroaldol reaction at room temperature stirring within 2-6 h (**Scheme 1.56**). A series of linear and cyclic nitroalkanes were tested with both of aliphatic and aromatic aldehydes under the optimized conditions to produce 68-86% yield. In both methods, the catalyst could not be recycled.




**Scheme 1.56** Synthesis of nitroaldol using CTAOH

The chemoselective nitroaldol reaction of aldehyde in aqueous medium was observed by Zhou *et al.* (2003) [366] at mild condition using triethylamine as base within 3-12 h stirring. Both aliphatic and aromatic keto compounds were found to be inactive under the reaction condition of aldehydes.

Later on, in 2005, Wang *et al.* [367] synthesized a series of 1-aryl-2-nitroalkan-1-ols utilizing dual catalytic system consisting phase-transfer catalyst polystyrene-supported tributylammonium chloride (PsTBAC) (**Figure 1.32**) and KOH either in $H_2O$ containing 10% of THF (biphasic system) or in neat $H_2O$ at room temperature. A variety of substituted aryl aldehydes were reacted with nitromethane and nitroethane for a time period 6-9 h. The catalyst could be recycled and no appreciable change in activity was observed up to 4 runs.

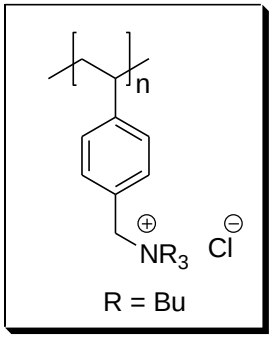



**Figure 1.32** Structure of catalyst PsTBAC

An enantioselective catalysis of the nitroaldol reaction between α-keto-carboxylates and nitromethane was carried out by Parker and co-workers [368], in 2007, by using a chiral macrocyclic ytterbium cationic complex (**Figure 1.33**) in aqueous medium (**Scheme 1.57**). The reactions proceeded at room temperature in 4:1 MeOH:$H_2O$ solvent system using 10 mol% of the catalyst. However, the reactions took much time (48 h) to provide good yield and the catalyst system was also not reusable.

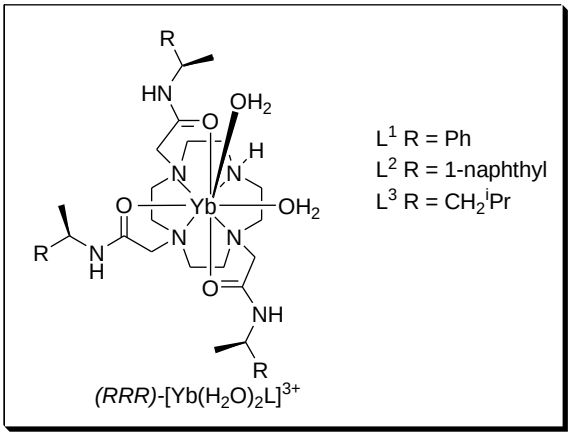
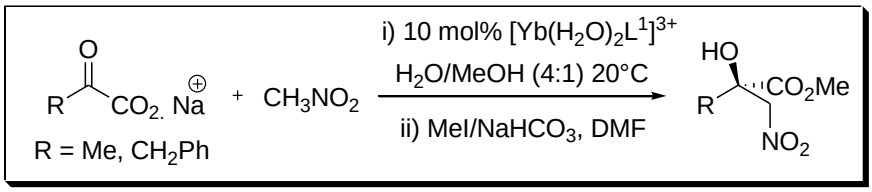


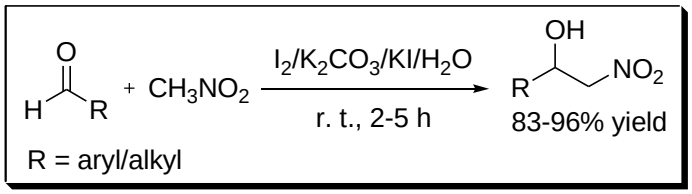

**Figure 1.33** Structure of complex *(RRR)*-$[Yb(H_2O)_2L]^{3+}$




**Scheme 1.57** Nitroaldol reaction using ytterbium cationic complex

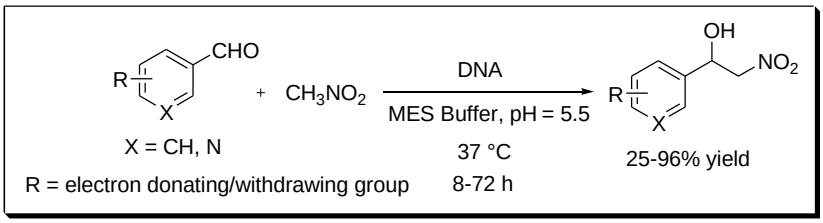
Reddy *et al.* (2007) [369] explored 10 mol% of zinc–proline complex as an effective reusable homogeneous catalyst for the nitroaldol reaction of aromatic aldehydes and nitromethane at room temperature in water. This method needed excess amount of nitromethane to give 71-98% of product within 0.25-15 h time. Otherwise the reaction took longer time (18 h) with 1:1 mixture of the aldehyde and nitroalkane.

Ren and Cai (2007) [370] developed an inexpensive and environmentally benign reagent $I_2/K_2CO_3$ for the nitroaldol reaction in aqueous medium at room temperature (**Scheme 1.58**). Both aromatic and aliphatic aldehydes were effective to complete the reaction with nitromethane in aqueous medium. The reaction was found to be better in aqueous medium than organic solution.




**Scheme 1.58** Henry reaction using $I_2$ and $K_2CO_3$ in water

In 2008, Fan *et al.* [371] reported the use of double stranded DNA from natural sources as catalyst to facilitate the Henry reaction in aqueous medium (**Scheme 1.59**). They studied the influence of DNA on various substituted aldehydes and found 25-96% yield within 8-72 h. They also studied the recycling of the catalytic DNA and found the catalyst can be reused.




**Scheme 1.59** Application of DNA as catalyst

Phukan *et al.* [128], in 2008, explored imidazole catalyzed method for the synthesis of nitroaldol in aqueous medium. The reaction proceeds smoothly for a series of aliphatic and aromatic aldehydes at room temperature in water with 55-98% yield within 0.25-12 h. The catalyst could be reused without loss of activity.

Punniyamurthy and co-worker (2009) [372] synthesized recyclable catalyst copper (II) open cubane (**Figure 1.34**) and used in nitroaldol reaction. A series of aryl aldehydes were reacted with nitromethane using 2.5 mol% of the catalyst in water to furnish 72-95% product within 1-12 h. However the reaction was not feasible with nitroethane or nitropropane.

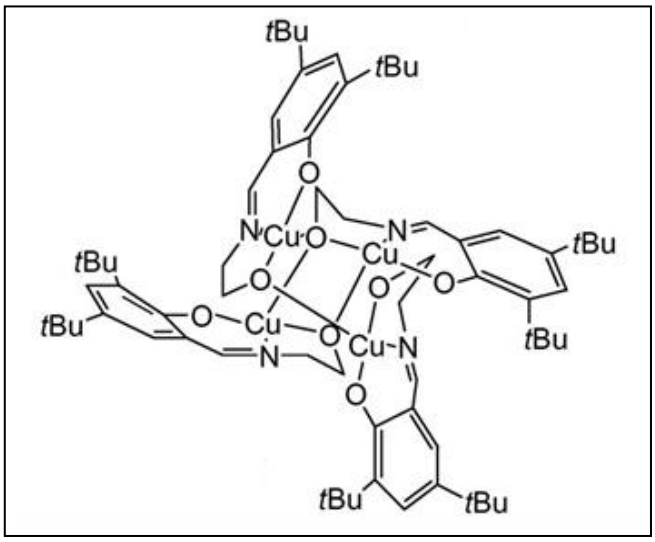



**Figure 1.34** Catalyst copper(II) open cubane

Later on in 2011, Lai *et al.* [373] discovered the enantioselective Henry reaction catalyzed by in situ copper tertiary amine complex of proline derivatives with copper acetate (**Figure 1.35**) in aqueous medium. All the reactions were carried out at 0 °C with electron withdrawing, donating, hetero, naphthyl aldehydes for a time period 12-72 h. Although the catalyst was recoverable but the method consumes more time to afford the required product.

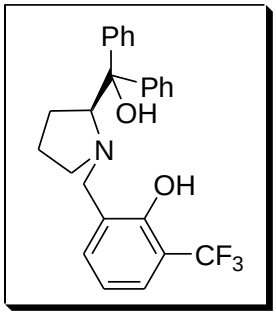



**Figure 1.35** Structure of catalyst used for Henry reaction

Gotor and co-workers (2011) [374] applied protein Bovine serum albumin (BSA) or L-lysine as catalyst for Henry reaction in water medium. A wide family of arylaldehydes was screened using 50 mg BSA and the products obtained within 16-72 h at room temperature. They also investigated the reusability of BSA and the catalyst was found to be recyclable up to $5^{th}$ cycle.

Mhamdi *et al.* (2011) [375] described the use of phase transfer catalyst TBAB, TEBAC and Aliquat-336 in water medium for the formation of nitroaldol from nitroalkane and carbonyl compounds. They screened three different quaternary salts and found Aliquat-336 to be the most successful one in terms of yield. They have also found that addition of the PTC leads to an increase in the yield. However along with PTC, a base $Et_3N$ was required to promote the reaction.

Bez and co-workers (2013) [376] investigated aqueous phosphate buffer catalyzed Henry reaction under neutral pH at room temperature in aqueous medium. In case of higher nitro alkanes, they observed good diastereoselectivity to provide *syn* β-nitro alcohols. A number of aldehydes were reacted with nitromethane to provide good yield (61-96%) but the reaction took longer time (12-96 h). In addition, with higher alkanes also the

yield was satisfactory but the reaction time was very long. The buffer cannot be recycled for further reaction.

In 2013, Tamaddon *et al.* [377] discovered the utilization of Dolomite ($CaMg(CO_3)_2$) as neutral catalyst for Henry reaction in 50% water and PEG medium. The optimized condition utilized various aldehydes, nitroalkanes and 0.1g of dolomite at 40 °C during 2-20 h to produce 68-95% of nitroaldol product. Dolomite can be reused easily for further study.

An enzyme catalyst, Lipase A from *Aspergillusniger* was used by Le *et al.* [378], in 2013, to study Henry reaction in aqueous/organic medium. They observed 10 mg of catalyst at 30 °C was favorable for the reactions of different aromatic aldehydes and nitroalkanes. All the reactions furnish acceptable yield (24-94%) but the reactions were time consuming (24-120 h) and also the catalyst was not recoverable.

In 2014, Matsumoto and Asakura [379] outlined the use of non recoverable human serum albumin (HSA) in water at neutral pH to promote the asymmetric Henry reaction. An array of aldehydes were reacted with nitromethane at 0 °C to observe the efficiency of the catalyst and 44-93% yield was observed at 168 h with fair enantioselectivities.

Karmakar *et al.* (2014) [380] synthesized and characterized two isostructural mono nuclear copper complexes $[Cu(L1)(H_2O)_4]$ (**10**) and $[Cu(L2)(H_2O)_4]$ (**11**) of terephthalic acid derivatives bearing amide side functional groups, viz. 2-propionamidoterephthalic acid ($H_2L1$) and 2-acetamidoterephthalic acid ($H_2L2$) (**Figure 1.36**).

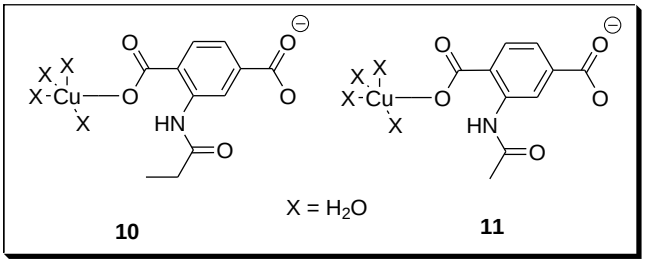



**Figure 1.36** Structure of complex **10** and **11**

Complexes **10** and **11** act as heterogeneous catalysts for the diastereoselective nitroaldol (Henry) reaction in aqueous medium, providing high yields (up to

77%) and good diastereoselectivities under ambient conditions during 30 h reaction period. These catalysts can be recycled without significant loss of activity, and the catalytic process is efficient, simple, and easy to work-up and operates under 'green' conditions.

Sutradhar *et al.* (2014) [381] reported the synthesis of a stable recyclable heterogeneous catalyst cyclic binuclear Ni(II) complex, $[Ni_2(H_2L)_2]\cdot 4MeOH$ (**Figure 1.37**) and utilized it for Henry reaction in water. The optimized condition gives 93% yield by treating the reactants with 1 mol% catalyst at 60 °C for 24 h.

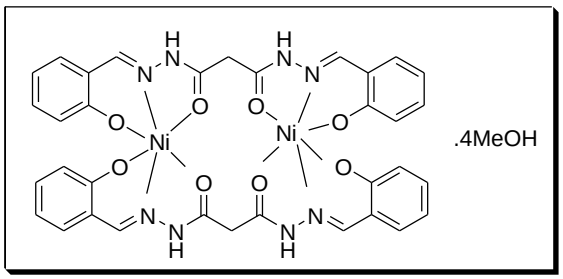



**Figure 1.37** Structure of $[Ni_2(H_2L)_2]$ .4MeOH

Microwave assisted nitroaldol synthesis was described by Devi *et al.* (2014) [382] which was catalyzed by KF modified NaY zeolite. A methanol-water solvent system was used for the reactions to complete within 15 min by using 10% of the catalyst under 40% MW power.

Recently in 2015, Arunachalam *et al.* [383] applied two binuclear Cu(II) complexes (**Figure 1.38**) catalyzed diastereoselective Henry reaction in a mixed water and methanol medium. The complex $Cu_2A_2$ worked efficiently as catalyst for both substituted benzaldehyde and pyridine carboxaldehyde, whereas $Cu_2B_2$ is highly substrate specific and showed activity towards nitro-substituted aldehydes and pyridine carboxaldehyde. All the reactions were carried out using 8 mol% of catalyst at 45 °C for 8 h which provided good yield.

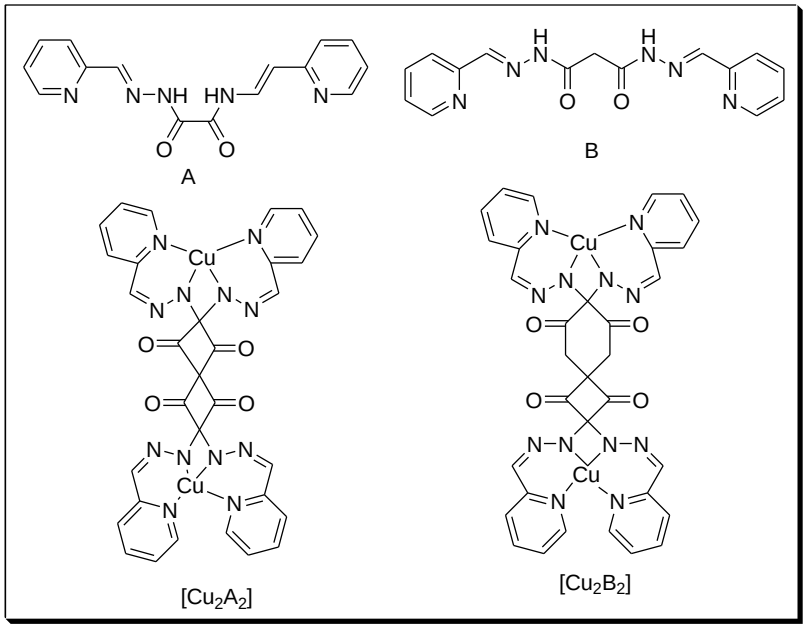



**Figure 1.38** Structure of binuclear Cu(II) complexes

Most recently, again natural DNA catalyzed Henry reaction at physiological temperature in pure water was exploited by Häring *et al.* (2015) [384]. Both heteroaromatic aldehydes and aromatic aldehydes bearing strong or moderate electron-withdrawing groups reacted satisfactorily with nitromethane within 24 h. In contrast, aliphatic and aromatic aldehydes having electron-donating groups either did not react or were poorly converted.

After detailed observation of the reaction conditions and catalysts it can be inferred that most of the homogeneous or heterogeneous catalysts utilized in different methods were not recyclable. Although in most cases, the reaction conditions were mild with less side product; good to excellent yields have been observed using longer reaction time. Therefore there is a scope to enhance the rate of reaction or recycling of catalyst to overcome the drawbacks associated with the literature methods.

After detail discussion of the literature survey, the following objectives have been considered.

1. Design of some Brønsted acidic ionic liquids based on imidazole derivatives and their characterization using various techniques viz. FT-IR, $^{1}$H NMR, $^{13}$C NMR, TGA and UV.
2. Application of the synthesized ionic liquids for the preparation of biologically important nitrogen heterocycles quinoline and its derivative 2-styrylquinoline under solvent free thermal condition via one pot approach.
3. Synthesis of novel silica supported carboxylic acids as heterogeneous solid acid catalysts and characterization using FT-IR, TGA, SEM-EDX and powder XRD.
4. Development of efficient one pot synthetic route of β-amino carbonyl compounds in presence of recyclable silica supported heterogeneous catalysts at room temperature.
5. Investigation of modified greener pathways using polymer poly(4-vinylpyridine) as basic catalyst for the synthesis of β-nitroaldol compounds.
6. Characterization of all the known and unknown products by using different spectroscopic tools such as FT-IR, $^{1}$H NMR, $^{13}$C NMR, CHN analyzer etc. and also by melting point determination.

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