# Ionic Liquids: A Class of Versatile Green Reaction Media for the Syntheses of Nitrogen Heterocycles

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**Abstract:** Ionic liquids have been emerging as a versatile class of green solvents with many projected advantages compared with conventional media. They have been described as "designer solvents" whose properties such as solubility, density, refractive index, and viscosity can be adjusted to suit requirements simply by making changes to the structure of either anion or cation or both. In organic synthesis, ionic liquids have been extensively used for the variety of synthetic transformations. Recently, plethoras of nitrogen heterocycles have been synthesized using variety of structurally diverse ionic liquids. In the present review, I would account the synthesis of various kinds of nitrogen heterocycles using variety of ionic liquids from the beginning to the recent reports.

**Keywords:** Nitrogen heterocycles, Ionic liquids.

## 1. INTRODUCTION

Ionic liquids are defined as pure compounds consisting of cations and anions (*i.e.* salts), which exist in liquid state at ambient temperature *i.e.* they are salts that do not normally melt by means of any external heat source [1]. Ionic liquids typically consist of organic nitrogen containing heterocyclic cations and inorganic anions. Most of the ionic liquids are liquid at room temperature that is why they are also referred to as room temperature ionic liquids (RTILs) [2].

The non-volatile nature of ionic liquids gives them significant advantage in minimizing solvent consumption. Their polarity renders them good solvents for homogenous catalysis. Their vague solubility properties, *i.e.* miscibility gap between water and organic solvents, have made them interesting candidates for separation process by simple liquid–liquid extraction with either aqueous or conventional organic solvents for immobilizing catalysts. Ionic liquids have attracted increasing interest recently in the context of green organic synthesis. Although, ionic liquids were initially introduced as alternative green reaction media because of their unique chemical and physical properties of non-volatility, non-inflammability, thermal stability, and controlled miscibility. Today they have marched far beyond this boundry, showing their significant role in controlling reactions as solvent or catalyst. Another feature of ionic liquids is their ability to be reused many times.

Heterocycles form the largest class of organic compounds and are of immense importance not only both biologically and industrially but also to the functioning of any developed human society as well [3]. The majority of pharmaceutical products that mimic natural products with potential biological activities are heterocycles. Most of the significant advances against various diseases have been made by designing and testing new structures, which are often heterocycles. In addition, a number of pesticides, antibiotics, alkaloids, and cardiac glycosides are heterocyclic natural products of significance for human and animal health [4]. Therefore, researchers are on a continuous pursuit to design and produce better pharmaceuticals, pesticides, insecticides, rodenticides, and weed killers by following natural models. A significant part of such biologically active compounds is composed of heterocycles. These compounds play major part in biochemical processes and the side groups of the most typical and essential constituent of the living cells. Other important practical applications of heterocycles can also be cited for instance, additives and modifiers in a wide variety of industries including cosmetics, reprography, information storage, plastics, solvents, antioxidants, and vulcanization accelerators. Recently, a number of review articles have been reported by various researchers on the different aspects of ionic liquids in literature [5, 6]. The main aim of this review is to focus on the synthesis of various kinds of nitrogen heterocycles using variety of structurally diverse ionic liquids from beginning to recent reports.

## 2. SYNTHESES OF NITROGEN HETEROCYCLS USING IONIC LIQUIDS

### 2.1. Aziridines

The aziridine functionality also called the azaethylene or ethylenimine unit, represents one of the most valuable three-membered ring system in modern synthetic chemistry because of its widely recognized versatility as a significant building block for chemical bond elaborations and functional group transformations [7]. Its powerful synthetic utility has been demonstrated by an overwhelming amount of documentation on the methodologies for the preparation of aziridine, especially those including asymmetric approaches. It also has a broad spectrum of applications in other syntheses [8]. In recent years, many researchers have attracted much attention for the synthesis of substituted aziridines using ionic liquids.

Xia and coworkers have reported [9] the first ionic liquid promoted efficient synthesis of aziridines **3** through the reaction of equamolar amounts of imines **1** and ethyl diazoacetate (EDA) **2** using ionic liquid [Bmim]$PF_6$ **(**Scheme **1)** afforded only *cis*-isomer in 93% yield. However, when a catalytic amount of [Bmim]$PF_6$ was used, there was no formation of aziridine **3**. The remaining ionic liquid was recovered and used five times with only a gradual decrease in activity observed (93% to 91% yield). The formation of **3** in an ionic liquid proceeded in a shorter reaction time, but it has been suggested to occur in a manner similar to that previously proposed for typical Lewis acids ($BF_3.OEt_2$) in molecular solvent such as hexane in 15h at 25$^o$C [10].

Recently, Mayer *et al.* have reported [11] another new synthesis of substituted aziridines **3,** through the reaction of imines **1** with phenyl diazomethane **4** using various kinds of ionic liquids **5,** specifically pyridinium and viologen species (**5a-5f**). Out of several ionic liquids used, **5f** was found to be best for specifically in the formation of *cis*-aziridines **3** (Scheme **2**).

### 2.2. Azetidines

Azetidines constitute an important class of small-ring aza-heterocycles with interesting pharmacological activities. Further-

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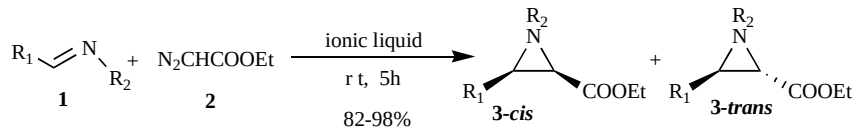
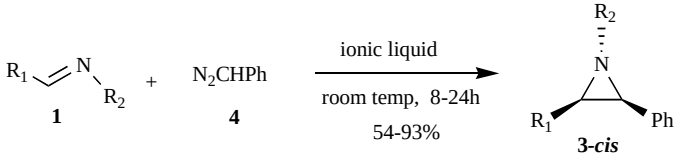



**1** **2** **3-*cis*** **3-*trans***

$R_1$ = Ph, 4-Me-Ph, 2-MeO-Ph, 4-Cl-Ph, = 2Cl-Ph, 4-$NO_2$-Ph, 4-Br-Ph
$R_2$ = Ph, 4-Me-Ph

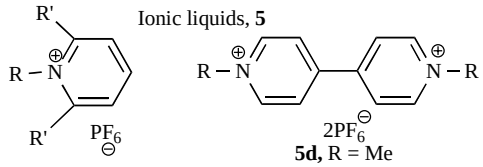
**Scheme 1.**




**1** **4** **3-*cis***

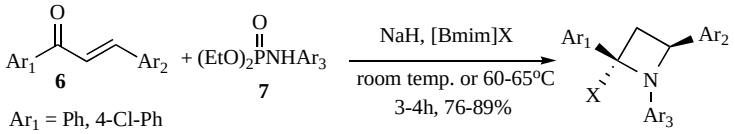
$R_1$ = Ph, 4-MeO-Ph, 4-$NO_2$-Ph, COOEt, *t*-Bu
$R_2$ = Ph, 4-MeO-Ph,4-$NO_2$-Ph, 4-Br-Ph, 2-Br-Ph, n-Bu, $Ph_2CH$

Ionic liquids, **5**



**5a,** R = Me, R' = H
**5b,** R = Bn, R' = H
**5c,** R = Me, R' = Me
**5d,** R = Me
**5e,** R = Bn
**5f,** R = Ph

**Scheme 2.**




**6** **7** **8**

$Ar_1$ = Ph, 4-Cl-Ph
$Ar_2$ = Ph, 4Cl-Ph, 4MeO-Ph X = SCN, SPh
$Ar_3$ = Ph, 4MeO-Ph

**Scheme 3.**

more, some of other compounds incorporating azetidine structure have been reported to exhibit remarkable biological activity against influenza virus [12], and possesses anti-HIV-1, anti-HSV-2 potential [13]. Whereas the strain associated with the azetidine ring system leads to difficulties in its synthesis, functionalizations, and modifications. It is advantageous for its synthetic applications involving ring-opening reactions. Over the past few years, several functionalized azetidines have been utilized as masked 1,4-dipoles for the construction of five and six membered aza-heterocycles [14]. Among the various general procedures available for the synthesis of azetidines, the most general method involves cyclization of *γ*-amino alcohols or their derivatives [15]. In recent years, researchers have directed their efforts for the synthesis of substituted azetidines using ionic liquids.

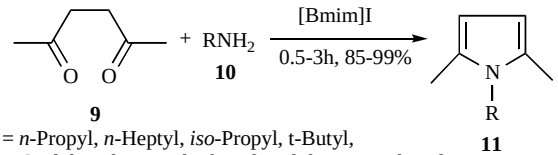
Recently, Yadav *et al.* have reported [16] first ionic liquid promoted synthesis of *C*-sulfur functionalized azetidines **8**, which involves aza-Michael addition of diethyl *N*-arylphosphoramidates **7** to chalcones **6,** afforded diethyl *N*-aryl-*N*-(1,3-diaryl-3-oxapropyl)phosphoramidates intermediate, which undergo cyclization to functionalized azetidines **8** (Scheme **3**). The cyclization is induced by anions ($NCS^-$, $PhS^-$) of task-specific ionic liquids (TSIL), and afforded excellent yields with high diastereoselectivity in a one-pot procedure. The use of KSCN or PhSNa instead of the corresponding TSIL, [Bmim]SCN or [Bmim]SPh, resulted in significantly lower yields of the products. After isolation of products, ionic liquid could be recycled for further use.

### 2.3. Pyrroles

Pyrroles are an important class of heterocyclic compounds that displayed remarkable pharmacological activities and have been widely used in synthetic organic chemistry and material science [17]. Due to their distinctive properties, extensive investigations have been made to develop preparative methods for substituted pyrroles. In general, 1,2,3,4-tetra-substituted pyrroles have been prepared by Paal-Knoor synthesis [18], Hantzsch-pyrrole synthesis [19], or the 1,3-dipole addition of azomethyne ylides with alkynes [20]. Classical methods to access pyrrole derivatives also involve condensation reactions of 1,4-dicarbonyl reactants [21]. In recent years, many researchers have directed their efforts for the synthesis of substituted pyrroles using ionic liquids.

Wang and their coworkers have reported [22] an efficient and green protocol for the synthesis of *N*-substituted 2,5-dimethylpyrrole **11** through Paal-Knorr condensation of 2,5-hexadione **9** with primary amines **10** using variety of ionic liquids (Scheme **4**). Out of several ionic liquids used, [Bmim]I was found to be best in caring out this transformation.

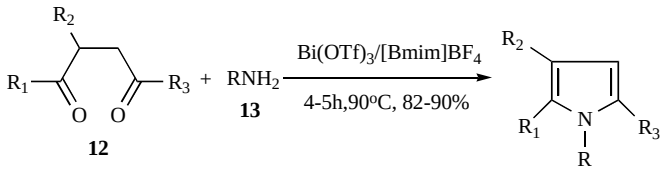
Later on, Yadav and coworkers have reported [23] synthesis of substituted pyrroles **14,** through the Paal-Knoor methodology using $Bi(OTf)_3$/$[Bmim]BF_4$ system. Thus, aryl/hetero aryl substituted pyrroles **14** were synthesized through the condensation reaction of substituted 1,4-dicarbonyl compounds **12,** with aryl amines **13** using $Bi(OTf)_3$/$[Bmim]BF_4$ system (Scheme **5**). The recovered ionic




R = *n*-Propyl, *n*-Heptyl, *iso*-Propyl, t-Butyl, Cyclohexyl, Benzyl, Phenyl, Tolyl, *p*-Nitrophenyl, *p*-Methoxyphenyl, 2-Pyridinyl

**Scheme 4.**

liquid containing bismuth triflate can be reused for subsequent runs with only a gradual decrease in activity.




R = 4-F-Phenyl, Phenyl;
$R_1$ = Fur-2-yl, 4-F-Phenyl, *n*-Bu, *n*-Hexyl;
$R_2$ = Phenyl, Thienyl, Pyrid-2-yl;
$R_3$ = Phenyl, 3-OH-Phenyl

**Scheme 5.**

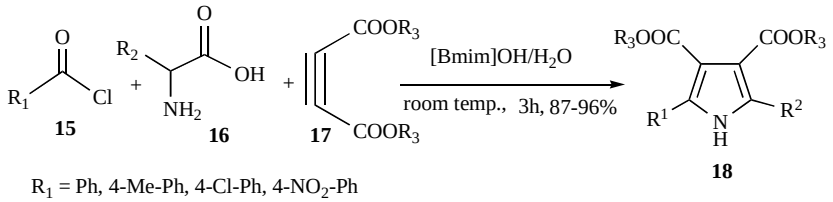
Recently, Yavari *et al*. have reported [24] an efficient and green protocol for the synthesis of highly functionalized pyrroles **18,** through the three-component coupling reaction of acid chlorides **15,** amino acids **16** and dialkyl acetylene dicarboxylates **17** in aqueous medium using a task-specific basic functionalized ionic liquid, 1-*n*-butyl-3-methylimidazolium hydroxide [Bmim]OH (Scheme **6**). The attractive features of this protocol are simple procedure, short reaction time, use of cheap, and benign solvent, the reuse of reaction medium and its adaptability for synthesis of diverse set of pyrroles.

### 2.4. Pyrazoles

The vast majority of medicinal drugs or agrochemicals incorporate at least one heterocyclic ring in their molecular structure. Among these, there are many halo-substituted 1*H*-pyrazoles and their derivatives are known to exhibit important biological activities [25]. The synthesis of pyrazoles by so called [3+2] atom fragments has been relatively well investigated. In this method, *β*-diketones or their derivatives, such as the three atom fragment, are condensed with hydrazine and its derivatives (by two atom fragment) to close the five-membered ring [26]. Many reseachers have attracted their attention towards the synthesis of pyrazole derivatives using ionic liquids in recent years.

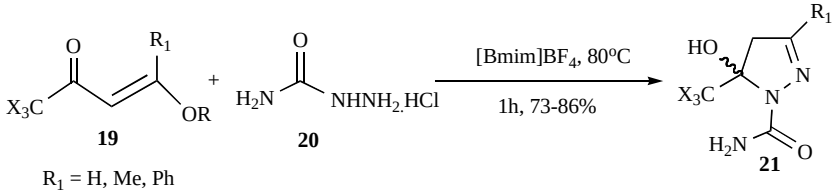
Martins and coworkers have reported [27] first an efficient synthesis of 4,5-dihydropyrazoles **21,** through the reaction of enones **19,** with hydrazine derivative **20** in the presence of equimolar quantities of ionic liquid [Bmim]$BF_4$ (Scheme **7**). These reactions have some advantages over the same experiment carried out in the absence of an ionic liquid. The yields were higher and the reaction time was shorter in comparison to those for the conventional method performed in absence of pyridine.

Recently, Martins group have also demonstrated [28] another efficient and mild synthesis of 1-cyanoacetyl-5-hydroxy-5-halomethyl-4,5-dihydro-1*H*-pyrazoles **24,** through the reaction of 4-alkoxy-3-alken-2-ones **22**, with cyanoacetohydrazide **23** using ionic liquid [Bmim]$BF_4$ (Scheme **8**). The use of ionic liquid in the reac-



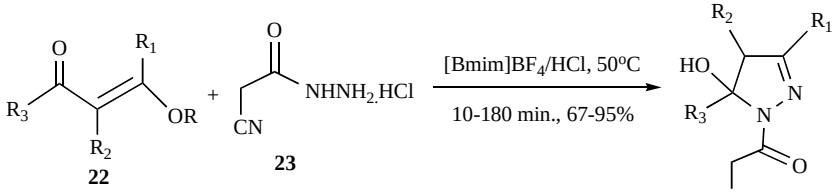

$R_1$ = Ph, 4-Me-Ph, 4-Cl-Ph, 4-$NO_2$-Ph
$R_2$ = Ph, Bn, *i*-Bu
$R_3$ = Me, Et

**Scheme 6.**



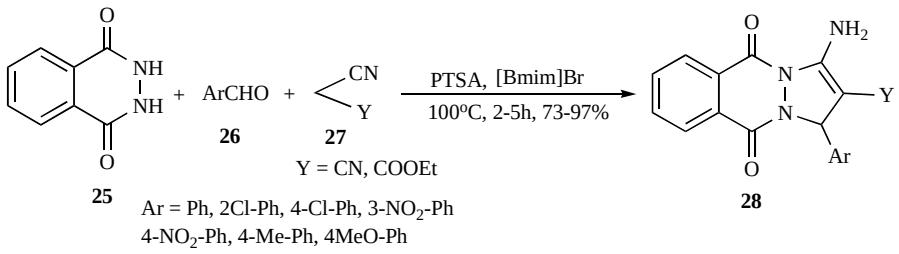

$R_1$ = H, Me, Ph
R = Et, Me
X = F, Cl

**Scheme 7.**



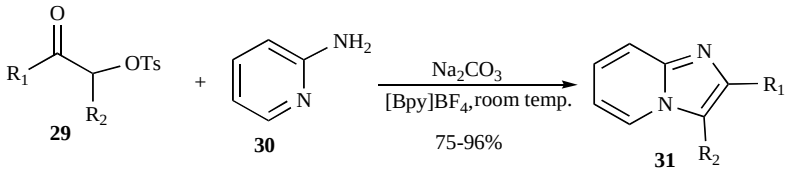

$R_1$ = H, Me, Et, Pr
$R_2$ = H, Me,
R = Et, Me
$R_3$ = $CF_3$, $CCl_3$, $CHCl_2$, COOEt

**Scheme 8.**



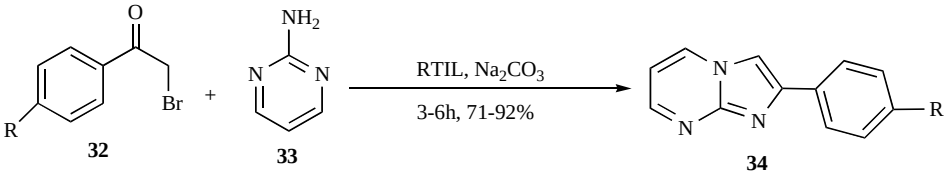

**25** **26** **27** **28**

**Scheme 9.**



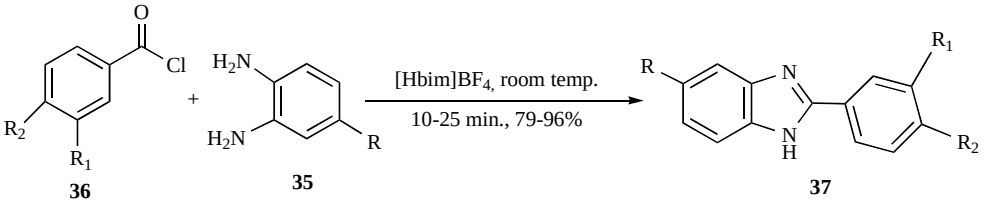

**29** **30** **31**

**Scheme 10.**




**32** **33** **34**

**Scheme 11.**




**36** **35** **37**

**Scheme 12.**

tion medium affects reaction time was drastically decreased and the yield was improved.

Recently, Bazgir *et al*. have reported [29] an efficient one-pot synthesis of 1*H*-pyrazolo [1,2-*b*]-phthalazine-5,10-dione derivatives **28,** through the three-component reaction between phthalhydrazine **25**, aromatic aldehydes **26**, and malononitrile or ethyl cyanoacetate **27** in presence of *p*-toluene sulfonic acid (PTSA) using an ionic liquid, 1-*n*-butyl-3-methyl imidazolium bromide [Bmim]Br as solvent at 100°C (Scheme **9**).

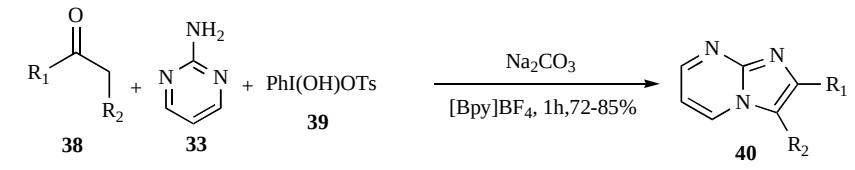
### 2.5. Imidazoles

Compounds with an imidazole ring systems have displayed many pharmacological properties and played important role in biochemical processes [30]. Several methods of substituted imidazoles synthesis have been reported in the literature, including hetero-Cope rearrangement [31], four-component condensation of aryl-glyoxals, the combination of primary amines, carboxylic acids, and isocyanates on Wang resin [32], the reaction of *N*-(2-oxo)-amides with ammonium trifluoroacetate [33], the use of 1,2-amino alcohols in the presence of $PCl_5$ [34], and finally the combination of diketones, aldehydes amines, and ammonium acetate in one of five possible media-phosphoric acid [35], acetic acid [36], acetic acid or $H_2SO_4$ with organo-catalysts [ 37], or DMSO [38]. In recent years, there has been much interest for the synthesis of diverse kinds of imidazole derivatives using ionic liquids.

Xie and coworkers have first demonstrated [39] an efficient and green synthesis of substituted-imidazol-[1,2-*a*]-pyridine **31** by cyclo-condensation of *α*-tosyloxyketones **29**, with 2-aminopyridine **30**, using *n*-butylpyridinium tetraflouroborate $[Bpy]BF_4$ as an ionic liquid (Scheme **10**).

Later on, Xu and coworkers have reported [40] an efficient and green protocol for the synthesis of 2-arylimidazo-[1,2-*a*]pyrimidines **34**, through the Tschotschibabin reaction in which *α*-bromoacetophenonen **32,** and 2-aminopyrimidine **33** undergoes cyclization using a room temperature ionic liquid (RTIL) (Scheme **11**). Out of several RTILs used, $[Bpy]BF_4$ was found to be most effective for caring out this transformation.

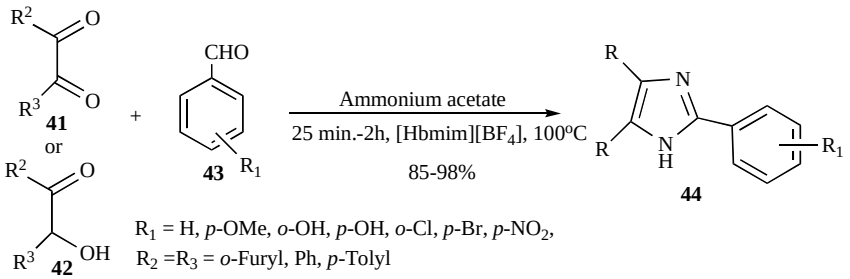
Later on, Srinivasan *et al.* have reported [41] an efficient and green protocol for the synthesis of 2-aryl benzimidazoles **37**, through reaction between substituted 1,2-phenylendiamine **35**, with substituted benzoyl chloride **36**, using room temperature ionic liquid, $[Hbim]BF_4$ (Scheme **12**).




38 33 39 40

$R_1$ = Ph, *p*-F-Ph, *p*-Cl-Ph, *p*-Br-Ph, *p*-Me-Ph, *p*-MeO-Ph, 2-furyl
$R_2$ = H, Me

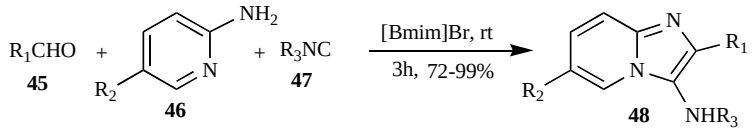
**Scheme 13.**




41 or 42 43 44

$R_1$ = H, *p*-OMe, *o*-OH, *p*-OH, *o*-Cl, *p*-Br, *p*-$NO_2$,
$R_2$ =$R_3$ = *o*-Furyl, Ph, *p*-Tolyl

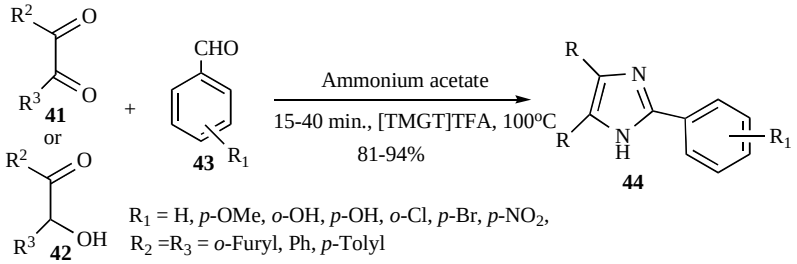
**Scheme 14.**




45 46 47 48

$R_1$ = Ph, 4-$CH_3$-Ph, 4-Cl-Ph, 3-$NO_2$-Ph,4-Py
$R_2$ = Br, Me; $R_3$ = Cyclohexyl, *tert*-Butyl, 2,6$(Me)_2$-Ph

**Scheme 15.**




41 or 42 43 44

$R_1$ = H, *p*-OMe, *o*-OH, *p*-OH, *o*-Cl, *p*-Br, *p*-$NO_2$,
$R_2$ =$R_3$ = *o*-Furyl, Ph, *p*-Tolyl

**Scheme 16.**

Later on, Xie and coworkers have reported [42] an efficient and green protocol for the synthesis of 2-arylimidazo-[1,2-*a*]-pyrimidines **40** through the reaction of ketones **38**, [hydroxyl(tosyloxy)iodo]benzene **39**, with 2-aminoprimidine **33** using room temperature ionic liquid (*i.e. n*-butylpyridinium tetraflurobo-rate [BPy]$BF_4$), and sodium carbonate (Scheme **13**).

Srinivasan and coworkers have also reported [43] an improved and rapid one-pot synthesis of 2,4,5-triarylimidazoles **44,** through reacting an aryl aldehydes **43,** with 1,2-diketone **41** or $\alpha$-hydroxy ketone **42** using room temperature ionic liquids without using any catalyst (Scheme **14**). Different ionic liquids based on 1-*n*-butyl and 1,3-di-*n*-butyl imidazolium salts were screened and their efficacy in term of acidity and polarity have been correlated with yields and reaction period. Ionic liquids have been recovered and recycled in this methodology.

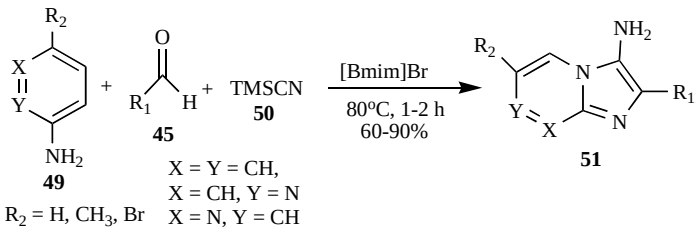
Later on, Shaabani *et al*. have reported [44] an efficient and green synthesis of 3-aminoimidazo [1,2-*a*]pyridines **48,** through the reaction of isocyanides **47**, an aldehyde **45,** and 1,2-amino-5-methylpyridine or 2-amino-5-bromopyridine **46,** using [Bmim]Br as an ionic liquid (Scheme **15**).

Later on, Shaabani and coworkers have also reported [45] an efficient and improved protocol for the synthesis of trisubstituted imidazoles **44,** in high yields (which was first reported by Srinivasan *et al.* [43], through the cyclization of diketone **41**, or hydroxy-ketone **42,** and substituted aldehyde **43,** using 1,1,3,3-*N*,*N*,*N*',*N*'-tetramethyl guanidinium triflouroacetate, [TMGT]TFA, as an ionic liquid (Scheme **16**).

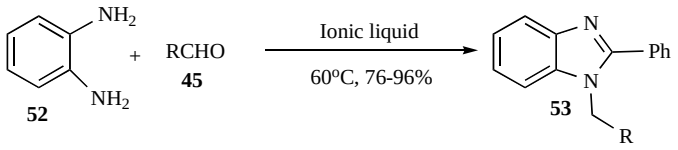
Recently, an efficient and green protocol for the synthesis of imidazo[1,2-*a*]azines **51**, through the one-pot, three-component cyclization of 2-aminoazine **49**, an aldehyde **45**, and trimethylsilyl-cyanide **50**, using 1-*n*-butyl-3-methylimidazolium bromide as a recyclable ionic liquid reported by Shaabani and coworkers [46] (Scheme **17**).

Recently, Ma and coworkers have reported [47] an efficient and green protocol for the synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles **53**, through the condensation of *o*-phenylenediamine **52**, with various aldehydes **45** using ionic liquid (Scheme **18**).

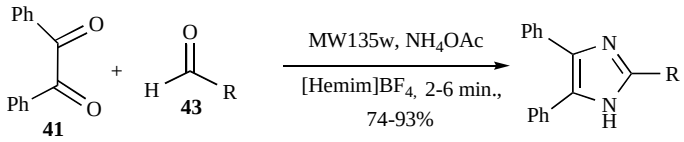
Recently, an improved and green protocol for the synthesis of 2,4,5-trisubstituted imidazoles by reaction of a diketone **41,** with an




**Scheme 17.**

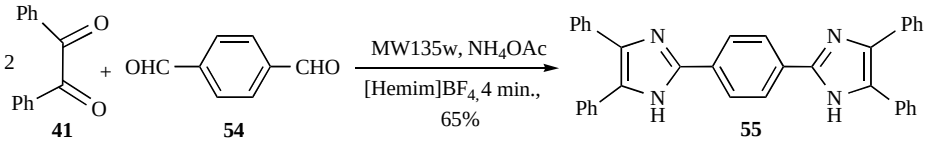



**Scheme 18.**

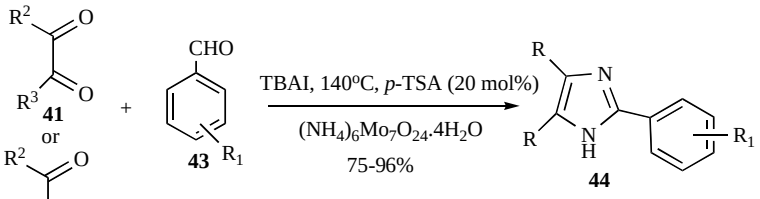



R = Ph, 4-F-Ph, 4-Cl-Ph, 4-Br-Ph, 4-$CF_3$-Ph, 2-Cl-Ph, 3-$NO_2$-Ph, 2,4-$Cl_2$-Ph, 4-$CH_3$-Ph, Piperonyl, 4-MeO-Ph, 4-*N*,*N*$(CH_3)_2$-Ph,4-OH-Ph, $(CH_3)_2$CH-'

**Scheme 19.**




**Scheme 20.**




$R_1$ = H, *p*-OMe, *o*-OH, *p*-OH, *o*-Cl, *p*-Br, *p*-$NO_2$,
$R_2$ =$R_3$ = *o*-Furyl, Ph, *p*-Tolyl

**Scheme 21.**

substituted aromatic aldehyde **43,** using neutral ionic liquid, 1-methyl-3-heptyl-imidazolium tetraflouroborate, [Hemim]$BF_4$ under microwave irradiation conditions reported by Xia and coworkers [48] (Scheme **19**). The combined merits of microwave irradiation and ionic liquid make the three-component condensation with safe operation, low pollution, rapid access to products and simple workup.

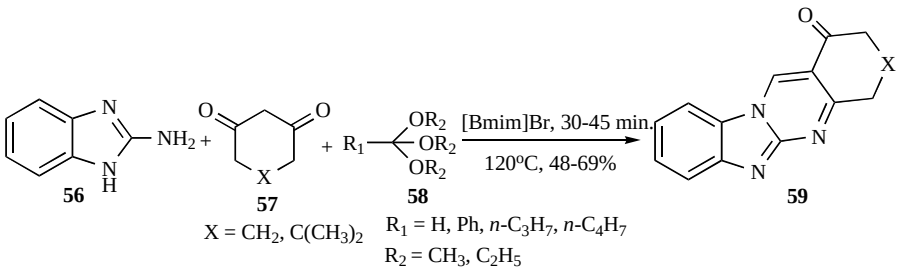
They have further synthesized 2,2'-(1,4-phenyllene)-*bis*-(4,5-diphenyl)-*1H*-imidazole, through refluxing the mixture of benzyl **41**, *bis*-aldehyde **54,** and ammonium acetate in acetic acid for 5h using same ionic liquid (Scheme **20)**.

Recently, Khodaei *et al*. have reported [49] an efficient, improved green protocol for the synthesis of 2,4,5-trisubstituted imidazoles **45,** by reacting 1,2-diketones **41,** or a $\alpha$-hydroxy ketones **42**, an aldehyde **43** and ammonium-heptamolybedate using ionic liquid, tetra-*n*-butyl ammonium iodide (TBAI) (Scheme **21**).

Recently, Shaabani and coworkers have reported [50] an efficient and green synthesis of 3,4-dihydrobenzimidazo-[2,1-*b*]-quinazoline-1(*2H*)-ones **59**, through the classical heating of a mixture 2-aminobenzimidazole **56**, cyclic-$\beta$-diketone **57**, and an ortho ester **58**, using 3-butyl-1-methyl imidazolium bromide, [Bmim]Br as an ionic liquid at 120°C (Scheme **22**). The ionic liquid can be recycled for subsequent reactions without any major loss of efficiency.

### 2.6. Triazoles

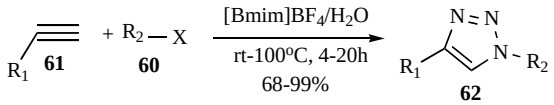
1,2,3-Triazoles are important five membered nitrogen heterocycles, frequently employed in a wide range of industrial applications such as agrochemicals, corrosion inhibitors, dyes, optical brighteners, and biologically active agents [51]. Generally, these triazole compounds can be prepared through the coupling reaction between alkynes and azides to form a mixture of 1,4-substituted and 1,5-




**Scheme 22.**

substituted-1,2,3-triazoles at high temperature [52]. The copper (I)-catalyzed Huisgen cycloaddition reaction of azides with terminal alkynes has emerged as a novel alternative, and received much attention since the discovery of Click Chemistry [53]. In recent years, researchers have directed their efforts for the synthesis of substituted triazoles using ionic liquids.

Liang *et. al.* have reported [54] first ionic liquid promoted synthesis of 1,4-disubstituted 1,2,3-triazoles **62,** through the one-pot, three-component reaction of various halides **60**, sodium azide with terminal alkynes **61** in $[Bmim]BF_4/H_2O$ system using a Cu(I) catalyst (Scheme **23**). Out of various Cu catalysts were used, CuI was found to be best in caring out this transformation.



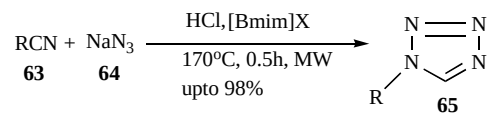

$R_1$ = Ph, cyclohexenyl, ferrocenyl
$R_2$ = Ph, $PhCH_2$, 4Me-Ph, 4-MeO-Ph, 4-$NH_2$Ph, Vinyl, alkyl, allyl
X = Cl, Br, I

**Scheme 23.**

### 2.7. Tetrazoles

Tetrazoles are an increasing popular functionality with wide range of applications [55]. This functional group has play pivotal role in coordination chemistry as a ligand, in medicinal chemistry as a metabolically stable surrogate for a carboxylic acid group [56], and in various applications in material science including propellants, and explosives [57]. Furthermore, tetrazole moieties are important synthons in synthetic organic chemistry [58]. The synthetic routes to substituted tetrazoles included acid-catalyzed cycloaddition reaction between hydrazoic acid and isocyanides [50], acid catalyzed cycloaddition between isocyanides and trimethyl azide [60], acetic acid or trifluoroacetic acid catalyzed cyclization between primary amines or their salts, with an orthocarboxyllic acid ester, and sodium azide [61], and $PCl_5$ and ytterbium triflate catalyzed cyclizations from an amine, triethyl orthophosphate, and sodium azide in highly polar solvents [62]. Recently, researchers have directed their efforts for the synthesis of tetrazoles using ionic liquids.

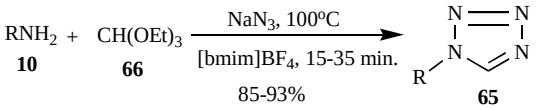
Schmidt *et al.* [63] have first reported an efficient and green protocol for the synthesis of tetrazoles **65**, through the [2+3] cycloaddition reaction of nitriles **63** with azides **64**, using imidazolium based ionic liquids under microwave irradiation conditions (Scheme **24**). Out of various alkylated imidazolium based ionic liquids have been used, 1-butyl-3-methyl imidazolium, [Bmim]Cl turned out to be superior affording excellent yields of desired products.




R = 4-MeO-Ph, 4-$NO_2$-Ph, 4-Me-Ph, 2-Pyrazoyl, 3-$NO_2$-Ph, 4-Br-Ph, 4-Py, $CH_2$Ph, Cy, *n*-$C_3H_7$, $CH_3CH{=}CH_2$,

**Scheme 24.**

Recently, Potewar and coworkers have reported [64] an efficient and green synthesis of 1-substituted-1,2,3,4-tetrazoles **65**, from the amines **10**, sodium azide **64** in stoichiometeric proportions, and triethyl orthophosphate **66**, using 1-*n*-butylimidazolium tetrafluroborate $[Bmim]BF_4$ as an ionic liquid (Scheme **25**).




R = Ph, 4-Me-Ph, 4-MeO-Ph, 4-Cl-Ph, 4-isopropyl-Ph, 2-Py, $PhCH_2$, 4-Aceto-Ph, 6-Me-Ph, 3-Cl, 4-F-Ph, 4-Me-2-Py

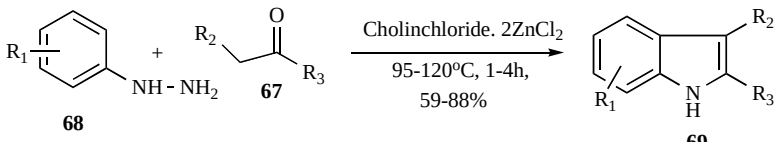
**Scheme 25.**

### 2.8. Indoles

The indole ring system is probably the most ubiquitous heterocycle that represents an important structural component in many pharmacologically active compounds [65]. Although, many methods have been developed for the synthesis of indoles [66], Fisher indole synthesis is still one of the most versatile, and widely employed methodologies for the preparation of indole intermediates, and biologically active compounds [67]. It can be regarded as the elimination of ammonia from the *N*-aryl hydrazone of a ketone through a [3,3] sigmatropic rearrangement with an acidic catalyst. Various other catalysts have been used to affect the cyclization of arylhydrazones derived from ketones. Alternative catalysts, includes Bronsted acids ($H_2SO_4$, HCl, PPA, AcOH) [68], Lewis acids ($ZnCl_2$, $TiCl_4$, $PCl_3$) [69], and solid acids (zeolite, montmorillonite clay) [70], have been reported for the synthesis of indole nucleus, but the search for new catalysts is still being actively pursued because the reported Bronsted and Lewis acids are not environmentally friendly, hazardous, or difficult to reuse and they are usually required in large amounts. Therefore, researchers have directed their efforts for the synthesis of indoles using ionic liquids in recent years.

Morels *et al.* have first reported [71] an efficient, green regiospecific protocol for the synthesis of substituted indoles **69**, in high yields employing Fisher-indole strategy, through the reaction of alkylethyl ketones **67**, and substituted hydrazines **68,** catalyzed by ionic liquid, choline chloride.$2ZnCl_2$ and the products readily sublime directly from the ionic liquid (Scheme **26**).

Recently, Xu and coworkers have reported [72] an improved and green protocol for the substituted indoles **69**, employing Fisher-indole strategy through the direct reaction of substituted hydrazines **68**, and alkyl methyl ketones **67** using Bronsted acidic ionic liquid $[Bmim]HSO_4$ (Scheme **27**). The ionic liquid can be readily reused without loss of efficiency after simple treatment involving only 1 equiv. of HCl for neutralization followed by filtration.

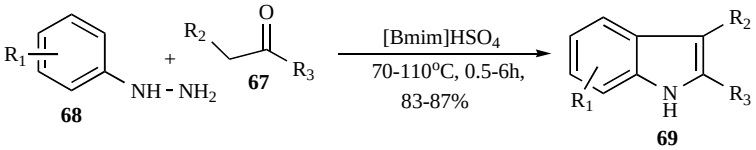



**68** **67** **69**

$R_1$ = H, 2,5-$Cl_2$, 4-Cl, 2-Me,

Ketone (**67**) = Butanone, 2-Pentanone, Cyclohexanone

**Scheme 26.**



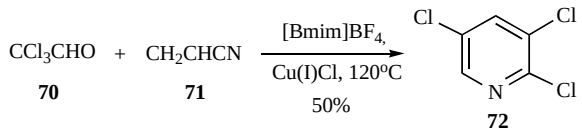

**68** **67** **69**

**Scheme 27.**

### 2.9. Pyridines

The pyridine nucleus is of considerable interest as this ring is the key constituent in a wide range of bioactive compounds, both naturally occurring and synthetic, and often of considerable complexity [73]. Thus, the synthesis of highly substituted pyridines has attracted much attention, and a number of procedures have been developed using a variety of protocols, such as hetero-Diels-Alder reaction of 3-siloxy-1-aza-1,3-butadienes with electron-deficient acetylenes [74], three-component condensation of aldehyde, malononitrile, and thiol [75], ruthenium-catalyzed cycloisomerization of 3-azadienynes [76], Mannich reaction of aldehydes with iminium salts [77], Vilsmeier-Haack reaction of $\alpha$-hydroxyketenedithioacetals [78], 6-$\pi$-azaelectrocyclization of azatrienes [79], catalytic oxidation of 1,4-dihydropyridines by $RuCl_3/O_2$ [80], carbon transfer reaction of functionalized oxazolidines and their open chain enamine tautomers to enamine nucleophiles [81], [4+2] cycloadditions of oximinosulfonates [82], conversion of conjugated oximes under Vilsmeier conditions [83], reaction of *N*-methylene-*tert*-butylamine with enamines [84], Diels-Alder reaction of 2*H*-1,4-oxazinones with acetylenic compounds [85], conversion of ketene dithioacetals to substituted pyridines [86]. Recently, researchers have directed their efforts for the synthesis of substituted pyridines using ionic liquids.

Zhong *et al.* have first reported [87] an efficient and green synthesis of 2,3,5-trichloropyridine **72**, through the hetero-cyclization reaction between trichloroacetaldehyde **70** and acrylonitrile **71**, in the presence of CuCl using [Bmim]$BF_4$ ionic liquid (Scheme **28**).

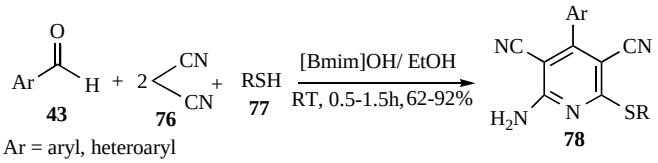



**70** **71** **72**

**Scheme 28.**

Later on, Perumal and Karthikeyan [88] designed a methodology for the synthesis of substituted pyridines **75**, through *in situ* heteroannulation *via* Bohlmann-Rahtz reaction, by generating the enaminone from the corresponding $\beta$-keto-esters **73** using an ionic liquid. This one-pot, three-component reaction of 1,3-dicarbonyl compounds **73**, ammonium acetate, and alkynones **74** afforded desired products in good yield using [Hmim]TFA as an ionic liquid and as a solvent (Scheme **29**).

Recently, Ranu *et al.* have reported [89] an improved and green protocol for the synthesis of highly substituted pyridines **78**, through one-pot, three-component condensation of aromatic aldehydes **43**, malononitrile **76**, and thiophenols **77** using basic ionic liquid [Bmim]OH, at room temperature (Scheme **30**). This reaction does not involve any hazardous organic solvent and toxic catalyst and ionic liquid is recovered and recycled for subsequent reactions.




**43** **76** **77** **78**

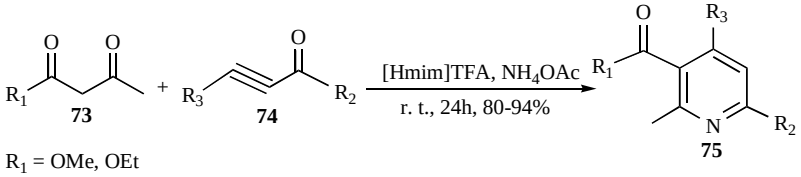
Ar = aryl, heteroaryl

R = aryl or benzyl

**Scheme 30.**

Recently, Zhang and coworkers have reported [90] an efficient and novel protocol for the synthesis of pyrazolo [3,4-*b*]-pyridine derivatives **80**, through the multi-component reaction of aromatic aldehyde **43**, 5-amino-3-methyl-1-phenylpyrazole **79,** and malononitrile **76** using [Bmim]$BF_4$ as an ionic liquid (Scheme **31**). Advantages of this method include mild reaction conditions, high yields together with a green nature and ease of recovery and reuse of the reaction medium. They have further extended the utility of this methodology for the synthesis of pyrazolo-[3,4-*b*]-pyridin-6-one **82**, using cyanoacetate **81** instead of malononitrile utilizing same ionic liquid promoted by $FeCl_3.6H_2O$ (Scheme **32**).

More recently, Wang *et al.* have reported [91] a novel and green method for the synthesis of indeno-[2,1-*c*]pyridine derivatives **84**, through one-pot, three-component reaction of 2-(2,3-

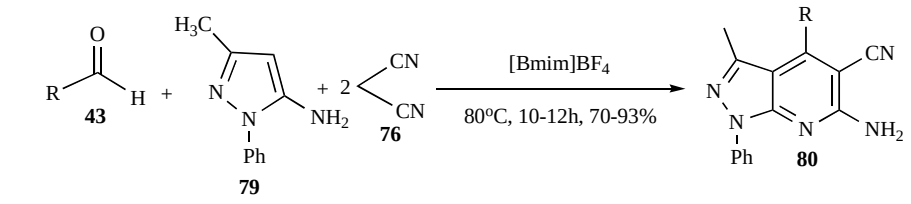



**73** **74** **75**

$R_1$ = OMe, OEt

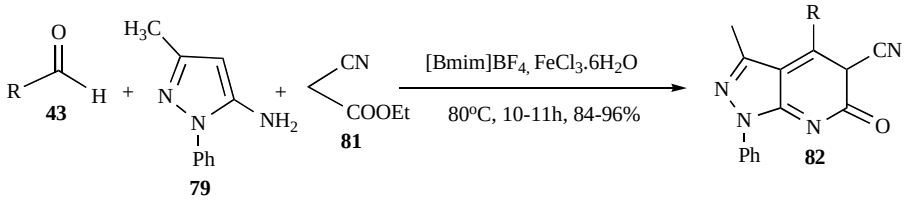
$R_2$ = Me, Ph; $R_3$ = H, Ph, $SiMe_3$

**Scheme 29.**



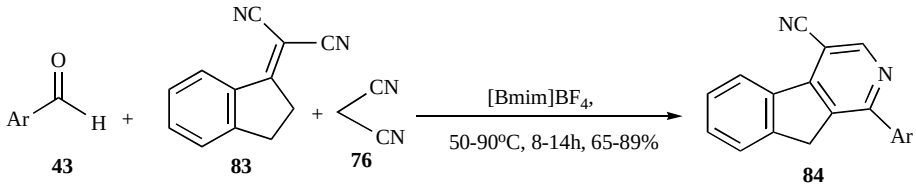

R = Ph, 4-Me-Ph, 4-$NO_2$-Ph, 4-Cl-Ph, 2-Cl-Ph, 4-Br-Ph, 3-Me-Ph
2-Br-Ph, 4-F-Ph, 3-$NO_2$-Ph, 4-MeO-Ph, 2-OH,3-MeO-Ph,

**Scheme 31.**



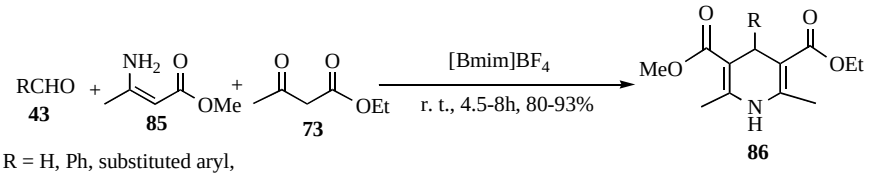

R = Ph, 4-Me-Ph, 4-$NO_2$-Ph, 4-Cl-Ph, 2-Cl-Ph, 4-Br-Ph, 3-Me-Ph
2-Br-Ph, 4-F-Ph, 3-$NO_2$-Ph, 4-MeO-Ph, 2-OH,3-MeO-Ph,

**Scheme 32.**




Ar = Ph, 4-Me-Ph, 4-$NO_2$-Ph, 4-Cl-Ph, 2-Cl-Ph, 4-Br-Ph, 3-Me-Ph,
2-Br-Ph, 4-F-Ph, 3-$NO_2$-Ph, 4-MeO-Ph, 2-OH,3-MeO-Ph,

**Scheme 33.**




R = H, Ph, substituted aryl,
heteroaryl, alkyl, cycloalkyl

**Scheme 34.**

dihydroinden-3-ylidine)-malononitrile **83**, benzaldehyde **43**, and malononitrile **76** in a ionic liquid, [Bmim]$BF_4$ at 90°C (Scheme **33**).

### 2.10. Dihydropyridines

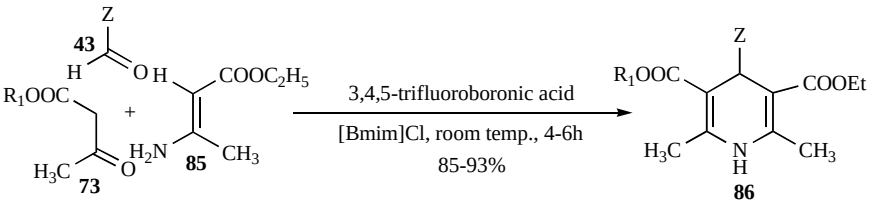
1,4-Dihydropyridines exhibit a wide range of biological activities, acting as potent vasodilators, anti-hypertensives, branchodilators, anti-atherosclerotics, hepatoprotective, antitumor, antimutagenic, geroprotective, and antidiabetic agents [92,93]. Generally, their synthesis has been achieved by Hantzsch method [94], which involves cyclocondensation of an aldehyde, keto ester, and ammonia either in acetic acid or by refluxing in alcohols for long reaction times leading to low yields. To overcome the associated problems in their synthesis, researchers have directed their efforts for the synthesis of 1,4-dihydropyridines using ionic liquids.

Yadav *et al*. have first reported [95] an improved and efficient protocol for the synthesis of 1,4-dihydropyridine derivatives **86**, through the three-component coupling reaction of aldehyde **43**, *β*-keto ester **73**, and methyl amino-crotonate **85,** using either [Bmim]$BF_4$ or [Bmim]$PF_6$ ionic liquids. Out of these ionic liquids used, [Bmim]$BF_4$ was found to be best in affording good yields of desired products (Scheme **34**).

Later on, Perumal and Sridhar have demonstrated [96] a modification of the original Hantzsh dihydropyridine synthesis, for the synthesis of 4-pyrazolyl-1,4-dihydropyridines **86**, at room temperature through the cyclo-condensation of ethyl-3-amino crotonate **85**, pyrazole aldehyde **43**, and a *β*-keto-ester **73,** using 3,4,5-trifluorobenzene boronic acid as catalyst mediated by ionic liquid [Bmim]Cl (Scheme **35**).

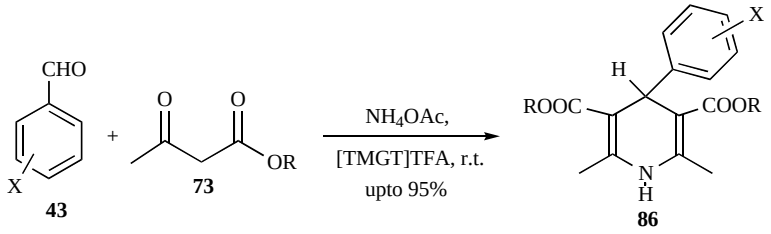
Shaabani *et al*. have also reported [97] a modified Hantshzsch method, which is an improved, efficient and green protocol for the synthesis of 1,4-dihydropyridines **86**, through the reaction of corresponding aldehyde **43,** and ethyl-acetoacetate **73**, using 1,1,3,3-*N,N,N'N'*-tetramethyl guanidinium trifluroacetate [TMGT]TFA as an ionic liquid in presence of ammonium acetate under ultrasonic conditions (Scheme **36**). The ionic liquid can be recovered conveniently and reused efficiently.

Recently, Zhang and coworkers have invented [98] the use of ionic liquid [Bmim]$BF_4$ as a reaction media for the synthesis of 1,4-dihydropyridines **88,** through four-component reaction between aldehydes **43**, 1,3-diketones **73**, and meldrum acid **87** using ammonium acetate (Scheme **37**).



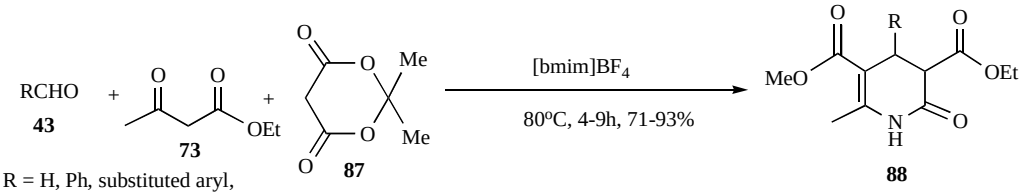

Z = Pyrazole, Ph, 3-$NO_2$-Ph
$R_1$ = Me, Et,

**Scheme 35.**



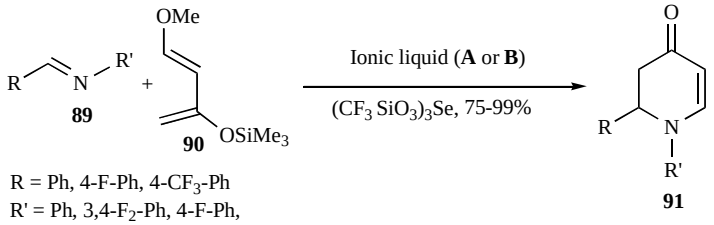

X = H, 4-MeO, 3-MeO, 4-Me, 2-MeO,
3-Cl, 3-$NO_2$, 4-$NO_2$, 4-Br, 4-$NO_2$

**Scheme 36.**




R = H, Ph, substituted aryl,
heteroaryl, alkyl, cycloalkyl

**Scheme 37.**




R = Ph, 4-F-Ph, 4-$CF_3$-Ph
R' = Ph, 3,4-$F_2$-Ph, 4-F-Ph,

**Scheme 38.**

### 2.11. Dihydropyridones

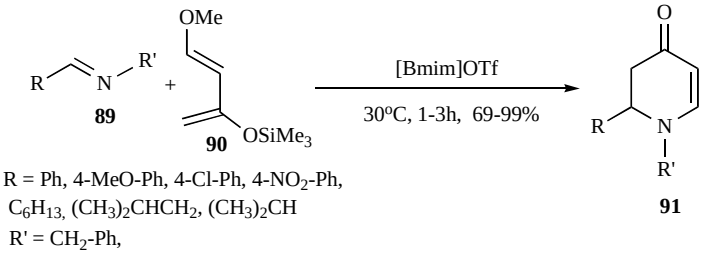
Substituted dihydropyridone skeleton is abundantly available in both natural and unnatural products and have displayed wide range of biological activities [99]. Aza-Diels-Alder reactions rank among the most powerful methodology for the construction of these dihydropyridone derivatives, which involve a reaction of Danishefsky's diene with imine. Various Lewis acids such as $BF_3.Et_2O$ [100], $ZnCl_2$ [101] or lanthanide triflate [102], and Bronsted acids including $HBF_4$ or TsOH [103] have been used to promote this reaction. In recent years, researchers have directed their efforts for the synthesis of substituted pyridones using ionic liquids.

Zulfiqar *et al.* [104] have first reported the synthesis of substituted 5,6-dihydro-4-pyridones **91**, through the reaction of imines **89**, and methoxy-3-[trimethylsilyl]-oxybuta-1,3-diene **90**, through a one-pot aza-Diels-Alder reaction catalyzed by scandium trifluoromethanesulphonate using 8-ethyl-1,8-diazabicyclo[5,4,0]-7-undecenium trifluoromethane sulphonate (**A**) or 1-ethyl-3-methyl-1*H*-imidazolium triflouro-methanesulphonate (**B**) as ionic liquid (Scheme **38**).

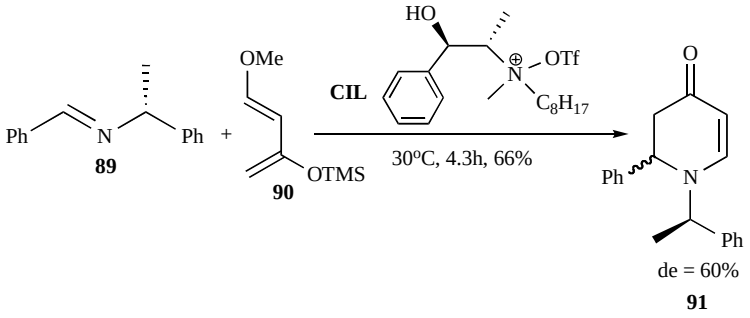
Later on, Pegot and coworkers have reported [105] a highly efficient, one-pot synthesis of 2-substituted-5,6-dihydro-4-pyridones derivatives **91**, through the aza-Diels-Alder reaction of Danishefky's diene **90**, with imines **89** at room temperature using $[Bmim]BF_4$ ionic liquid, which eliminates the use of an acidic catalyst and organic solvent (Scheme **39**). The ionic liquids can be recycled while their efficiency is preserved.

The asymmetric aza-Diels-Alder reaction of chiral imines **89,** with Danishefky's diene **90** using chiral ephedrinium derived ionic liquid (CIL) was investigated by Pegot and coworkers [106] (Scheme **40**). The corresponding cyclo-adduct **91** was obtained with diastereoselectivies upto 60% de in good yield without any use of co-solvent or Lewis acidic catalyst. The use of CIL resulted in a "matched" case of double stereo-induction and in a significant enhancement of diastereoselectivity compared to 32% de that was obtained when no CIL but a catalytic amount of $ZnCl_2$ was added.

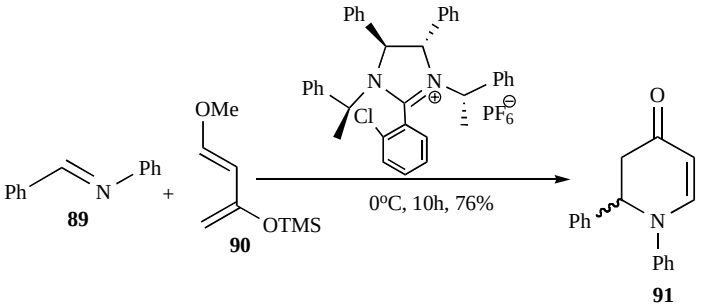
A range of new chiral mono and *bis*-imidazolium salts was prepared by Jurkik and Wilhelm [107] and applied as catalyst in normal and inverse electron demand aza-Diels-Alder reactions. In con-




**Scheme 39.**




**Scheme 40.**




**Scheme 41.**

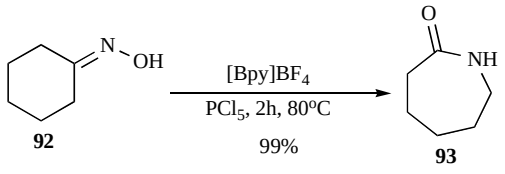
trast to previous report, CIL was used in catalytic amounts only. Generally 10 mol% of the imidazolium salts (ionic liquid) showed good catalytic activity in the reaction of Danishefky's diene **90** with imines **89** in acetonitrile but no asymmetric induction was obtained (Scheme **41**).

### 2.12. Lactams

Lactams are the key components of many biologically active compounds such as penicillin and cephalosporin antibiotics [108]. Although much progress has been made in the past few decades, the rapid increase of bacterial resistance against standard therapy has stimulated development of novel $\beta$-lactam agents that are stable to $\beta$-lactamase and possess high potency and broad spectrum activity. Apart from the clinical treatment of bacterial infection, $\beta$-lactams have also been clinically used as therapeutic agents for lowering the cholesterol level in plasma [109], as anticancer agents [110], and as enzyme inhibitors [111].

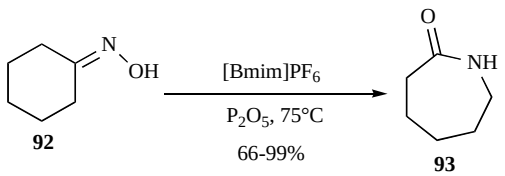
There are many methods for the synthesis of lactams have been reported such as rhodium-catalyzed carbonylation of aziridines [112], rhodium-catalyzed intra-molecular insertion of an $\alpha$-diazoamide into C-H bond [113], copper-catalyzed coupling of an alkyne with nitrone [114], amino-ether-catalyzed reaction of ester enolates with imines [115], and ketene-imine cycloaddition [116]. In recent years researchers have directed their efforts for the synthesis of lactams through various methodologies using ionic liquids.

Peng and Deng have first reported [117] an efficient synthesis of $\varepsilon$-caprolactum **93,** starting from cyclohexanone ketoxime **92,** through the Beckmann rearrangement using ionic liquid based on 1,3-dialkylimidazolium or alkylpyridinium salts, and phosphorated compounds. Out of various kinds of ionic liquids were used, *n*-butyl- pyridinium tetraflouroborate $[Bpy]BF_4$ was found to best in affording quantitative yield of desired product (Scheme **42**).



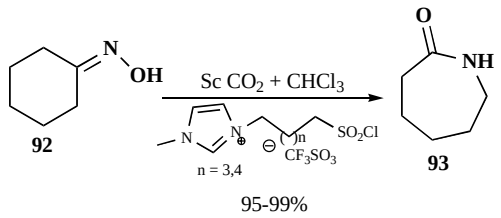

**Scheme 42.**

Later on, Ren *et al*. have reported [118] an improved catalytic Beckmann rearrangement of cyclohexanone oxime **92** into $\varepsilon$-caprolactam **93**, mediated by $P_2O_5$ or Eaton's reagent using ionic liquid, $[Bmim]PF_6$ (Scheme **43**).



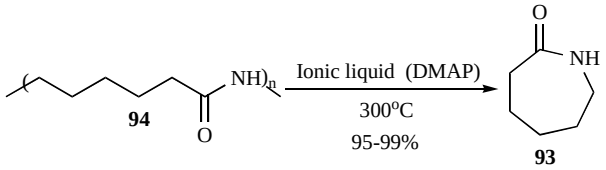

**Scheme 43.**

Later on, Qiao and coworkers have also reported [119] a recyclable liquid phase process for preparation of *ε*-coprolactam **93**, *via* Beckmann rearrangement of cyclohexanone oxime **92** using Lewis acidic ionic liquid as a catalyst and a mixture of supercritical $CO_2$ and chloroform as extractant (Scheme **44**).



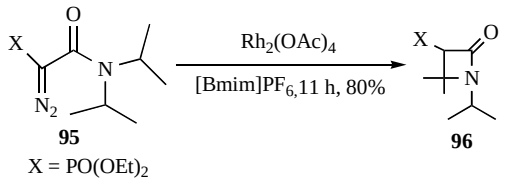

**Scheme 44.**

Recently, Kauimura *et al*. have reported [120] an interesting and efficient method for depolymerization of polyamide plastic **94**, into corresponding monomeric *ε*-lactam **93**, in good yield using ionic liquid at $300^0$C (Scheme **45**).




**Scheme 45.**

An efficient and green protocol for the synthesis of *α*-phosphonobutyrolactams *via* $Rh_2(OAc)_4$-catalyzed intra-molecular C-H insertion using an ionic liquid, $[Bmim]PF_6$ reported by Gois and coworkers (Scheme **46**) [121]**.**

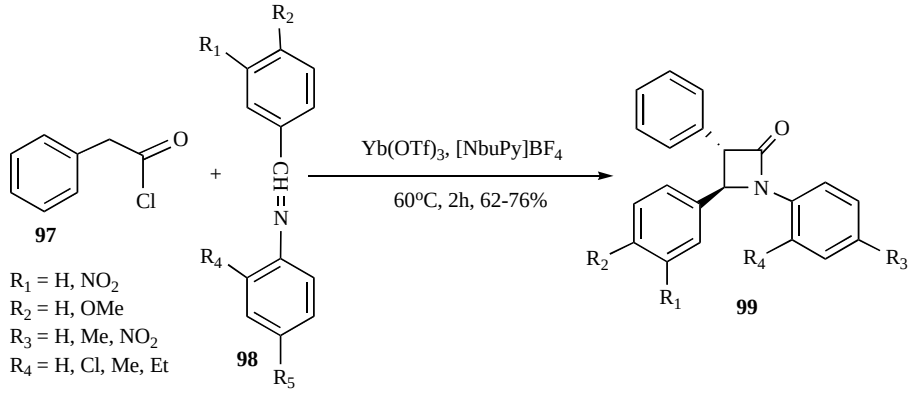



**Scheme 46.**

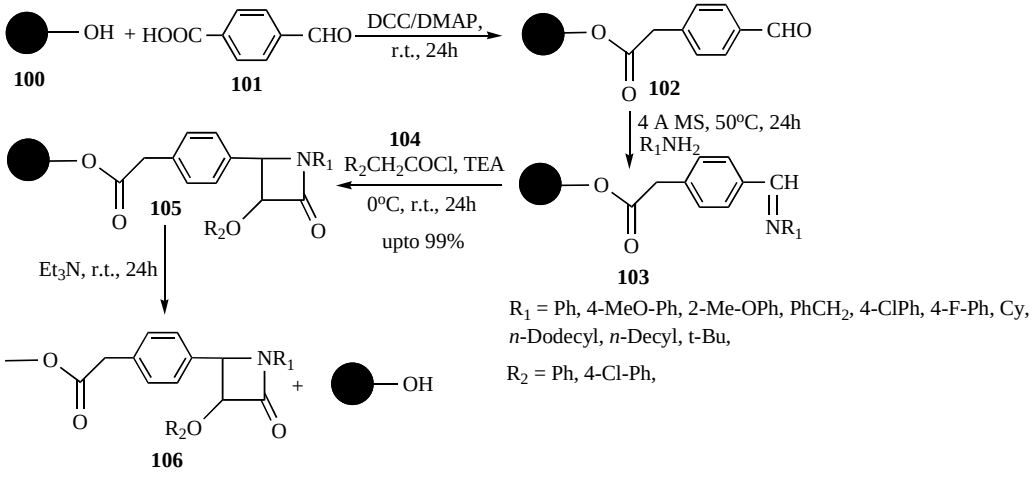
Recently, Chen *et al.* have reported [122] synthesis of *β*-lactams **99**, through the [2+2] cycloaddition reaction of imines **98**, with various acid chlorides **97** catalyzed by ytterbium (III) triflate using ionic liquid (Scheme **47**).

Recently, Tao and coworkers have reported [123] an efficient, green, and solid phase protocol for the synthesis of *β*-lactams **106**, library through multi-step synthetic reactions using $[Bmim]PF_6$ as an ionic liquid in each step (Scheme **48**). This method exhibited the advantages over soluble and insoluble polymeric support strategies, such as high loading capacity, avoiding of large excesses of reagents and easy purification and products were obtained in high yields.

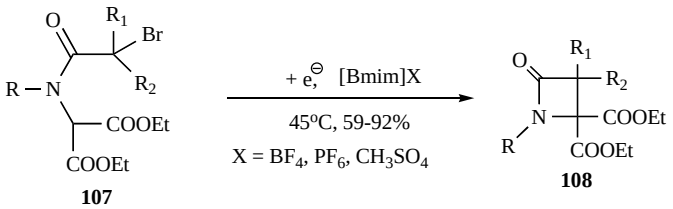
More recently, Feroci *et al.* have reported [124] an electrochemical synthesis of *β*-lactams **108**, starting from the corresponding haloamides **107** (*via* C-4-H deprotonation) under mild reaction conditions using room temperature ionic liquids (Scheme **49**). Out of various ionic liquids used, $[Bmim]BF_4$ was found to be best in affording good yields of desired products.




**Scheme 47.**

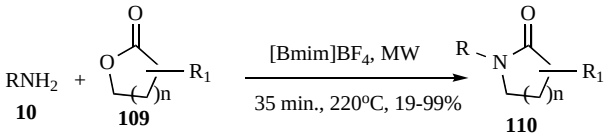



**Scheme 48.**



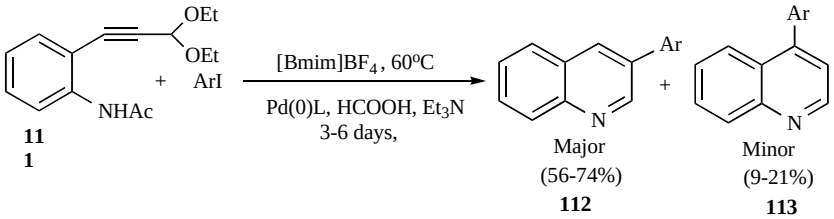

R = Ph, $PhCH_2$, 4-MeO-Ph, *c*-$C_5H_9$
$R_1$ = H, Me, $R_2$ = H, Me, Et

**Scheme 49.**

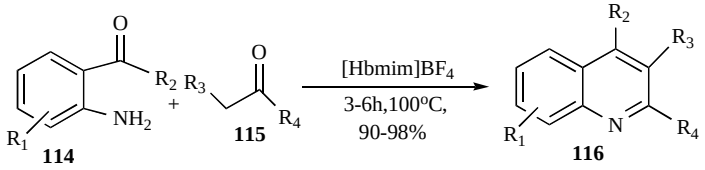



Amines = substituted aliphatic, aromatic, heterocyclic,
$R_1$ = H, Ph, alkyl

**Scheme 50.**




**Scheme 51.**




$R_1$ = H, Cl $R_3$ = $R_4$ = open chain/cyclic keto esters
$R_2$ = $CH_3$,

**Scheme 52.**

More recently, Larhed and coworkers have reported [125] a fast, acid free, and one-pot microwave methodology for the direct ionic liquid mediated preparation of lactams **110**, through the reaction of lactones **109**, with primary amines **10** using [Bmim]$BF_4$ ionic liquid (Scheme **50**). This protocol was investigated in acid sensitive substitutents. Both $\gamma$-lactams, and $\delta$-lactams were, despite the complete absence of a Bronsted acid, obtained in useful to excellent yields.

### 2.13. Quinolines

The quinoline nucleus occurs in several natural compounds, pharmacologically active substances, and displaying a broad range of biological activities [126]. They are also known for their formation of conjugated molecules, and polymers that combine enhanced electronic, optoelectronic, or non-linear optical properties with excellent mechanical properties [127]. Several methods such as Skraup, Doebner-von Miller, Friendlander, and Combe reactions have been developed for the preparation of quinolines [128], but due to their importance as substructures in a broad range of natural, and designed products, significant efforts have been continued to be directed into the development of new quinoline-based structures [129], and new methods for their constructions [130]. In recent years, researchers have directed their efforts for the synthesis of quinolines using ionic liquids.

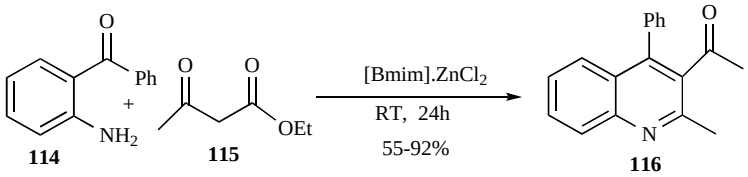
Cacchi *et al.* have first reported [131] an efficient and green synthesis of 3-arylquinolines **112** as a major product, through the hydroarylation of alkynes **111,** conducted in 1-butyl-3-methylimidazolium tetrafluroborate [Bmim]$BF_4$, in the presence of the (*E,E,E*)-1,6,11-*tris*(*p*-toluenesulfonyl)-1,6,11-triazacyclopentadeca-3,8,13-triene]Pd (0) complex ( Scheme **51**).

Later on, Srinivasan and coworkers have reported [132] an efficient, and ionic liquid mediated regiospecific Friedlander annulation reaction for the synthesis of substituted quinolines and fused polycyclic quinolines **116**, through reaction of from 2-aminoacetophenones **114,** with keto/keto esters **115**, using 1-*n*-butyl-imidazolium tetraflouroborate [Hbmim]$BF_4$ as an ionic liquid (Scheme **52**).

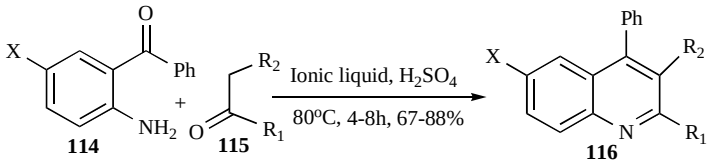
Later on, Perumal and Karthikeyan have reported [133] an efficient, mild, and green protocol for the Friedlander synthesis of quinolines **116,** using Lewis acidic ionic liquid *i.e.* zinc chloride-1-butyl-3-methyl imidazolium chloride $ZnCl_2$-[Bmim] (Scheme **53**).

Later on, Zhang *et al.* have reported [134] a novel and green protocol for the synthesis of quinolines derivatives **116** through acid-catalyzed Friedlander reaction using ionic liquid [Bmim]$BF_4$ (Scheme **54**).

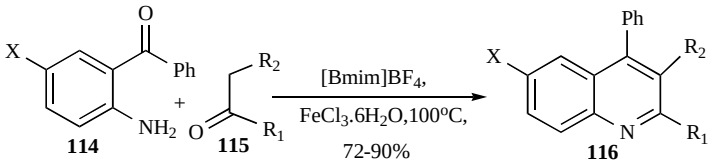
Later on, Wang group have reported [135] an efficient and green synthesis of substituted quinolines derivatives **116**, through



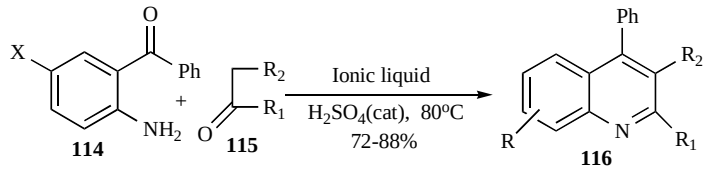

**Scheme 53.**




**Scheme 54.**



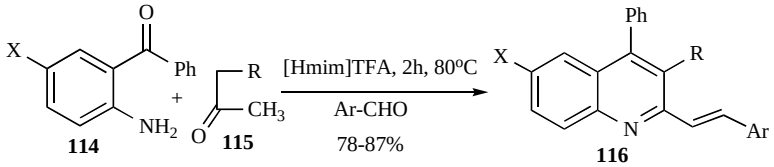

**Scheme 55.**




X = H, Cl $R_2$ = H

$R_1$ = Ph, 4-Br-Ph, 4-$NO_2$-Ph, $CH_3$, 4Cl-Ph,

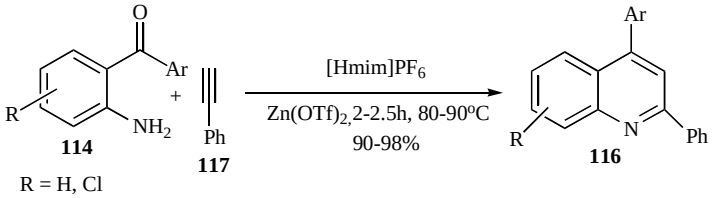
**Scheme 56.**




X = H, Cl R = COOEt, COOMe

Ar = 4-Cl-Ph, 4-OH-Ph, 4-MeO-Ph, 3-Pyridyl, 4-Pyridyl

**Scheme 57.**




R = H, Cl

Ar = Ph, 4-Br-Ph, 4-$NO_2$-Ph, $CH_3$, 4Cl-Ph,

**Scheme 58.**

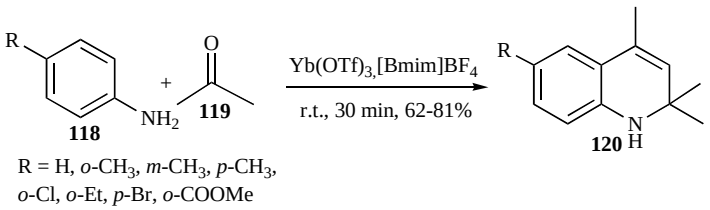
the Friedlander condensation of 2-aminoacetophenones **114**, with reactive methylene compound **115**, using ionic liquid [Bmim]$BF_4$, as reaction medium and iron chloride-hexahydrate ($FeCl_3.6H_2O$) as a catalyst (Scheme **55**).

Later on, Zhang *et al.* have reported [136] an efficient and green synthesis of 4-phenylquinoline derivatives **116,** through the acid catalyzed Friedlander reaction of *o*-amino substituted aryl ketones **114,** with carbonyl compounds **115** using [Bmim]$BF_4$ ionic liquid (Scheme **56**).

Recently, Dabiri and their coworkers have reported [137] an efficient and green synthesis of 2-styrylquinolines **116,** through the Friedlander annulation reaction of 2-aminoacetophenones **114,** with keto compounds **115** followed by a Knoevenagel condensation with aromatic aldehydes **26**, using 1-methylimidazolium trifluoroacetate, [Hmim]TFA as an ionic liquid (Scheme **57**).

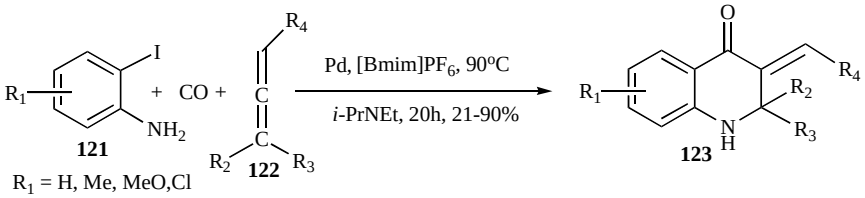
Recently, Prajapati and Sharma have reported [138] an efficient and green synthesis of 2,4-disubstituted quinolines **116**, *via* Meyer-Schuster rearrangement of 2-aminoaryl ketones **114,** and phenylacetylenes **117** in presence of zinc trifluoromethanesulfonate using [Hmim]$PF_6$ as an ionic liquid (Scheme **58**).

Li *et al.* have reported [139] a mild, convenient and efficient protocol for the synthesis of 2,2,4-trimethyl-1,2-dihydroquinolines




R = H, *o*-$CH_3$, *m*-$CH_3$, *p*-$CH_3$, *o*-Cl, *o*-Et, *p*-Br, *o*-COOMe

**Scheme 59.**

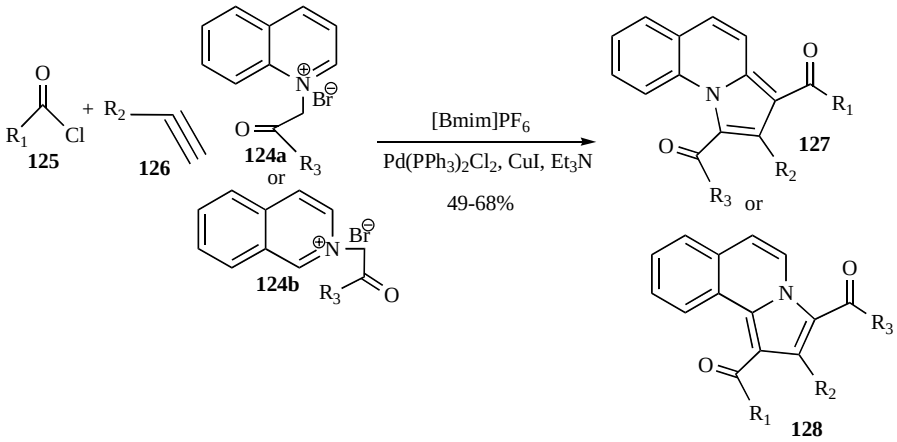



$R_1$ = H, Me, MeO,Cl

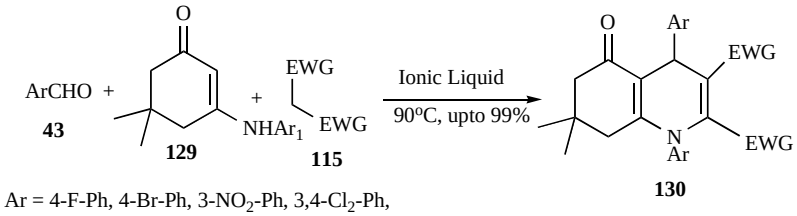
$R_2$ = $R_3$ = Me, Ar, COOEt, Cyclohexyl, Cyclooctyl

$R_4$ = H, $C_3H_7$, $PhCH_2$, $CH_3$,

**Scheme 60.**




**Scheme 61.**




Ar = 4-F-Ph, 4-Br-Ph, 3-$NO_2$-Ph, 3,4-$Cl_2$-Ph, 2,4-$Cl_2$-Ph, 4-$CH_3$-Ph, 4-Cl- 2-$NO_2$-Ph

$Ar_1$ = Ph, 4-Br-Ph, 4-Me-Ph

EWG = CN, COOEt, $COCH_3$

**Scheme 62.**

**120,** through the reaction of anilines **118**, with acetone **119** catalyzed by ytterbium (III) triflate [Yb(OTf)$_3$], and [Bmim]$BF_4$ as a recyclable ionic liquid (Scheme **59**).

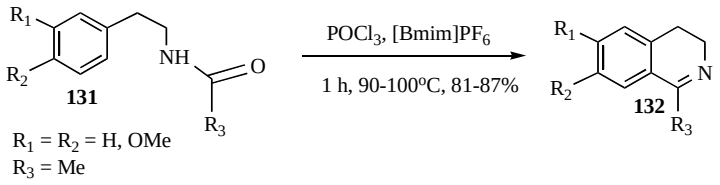
Recently, Alper and Ye have reported [140] a palladium catalyzed cyclocarbonylation reaction of *o*-iodo anilines **121,** with substituted allenes **122,** and CO using 1-*n*-butyl-3-methyl imidazolium hexaflourophosphate, [Bmim]$PF_6$ afforded 3-methylene-2,3-dihydro-1-*H*-quinolin-4-ones **123**, in moderate to good yields under low pressure (5 atm) of CO (Scheme **60**).

Ma and coworkers have reported [141] a novel one-pot synthesis of pyrroloquinolines **127** and pyrroloisoquinoline **128** derivatives through a Sonogashira coupling-1,3-dipolar cycloaddition sequence of a (hetero)-arene **124a** and **124b**, carbonyl chloride **125,** a terminal alkyne **126,** and a suitable quinolinium bromide or isoquinolinium bromide using ionic liquid (Scheme **61**).

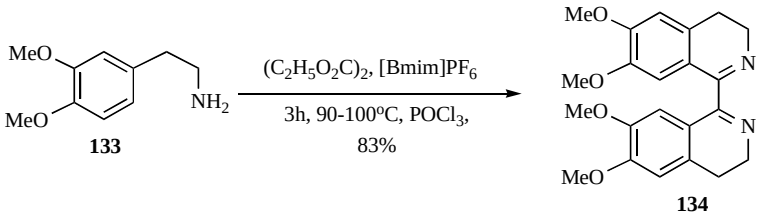
Wang *et al*. have reported [142] an efficient and green protocol for the synthesis of *N*-arylquinolines **130,** through the three-component reaction of aryl aldehydes **26**, 3-arylamino-5,5-dimethyl-cyclohex-2-enone **129,** and an active methylene compound including malanonitrile **115**, using [Bmim]$BF_4$ (Scheme **62**).

### 2.14. Isoquinolines

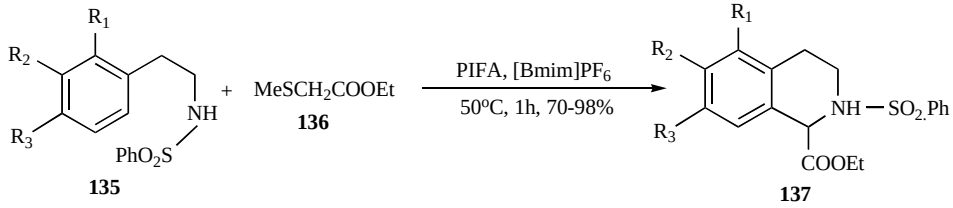
The isoquinoline nucleus is widespread in the alkaloid family, and is found in many biologically active compounds [143]. The



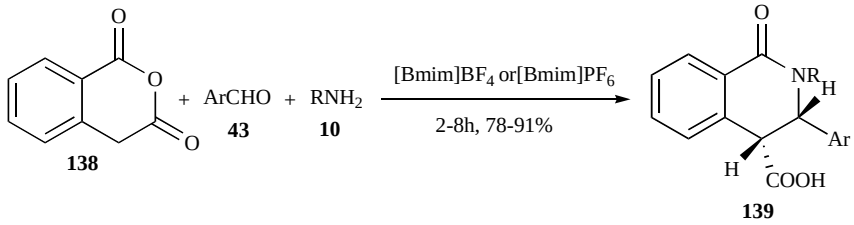

**Scheme 63.**




**Scheme 64.**




**Scheme 65.**




**Scheme 66.**

most widely used methods for the synthesis of isoquinolines are Bischler-Napieralski [144], and the Pictete-Spengler reactions [145]. The Bischler-Napieralski synthesis involves the cyclodehydration of *β*-phenylethanamides to 3,4-dihydroisoquinolines using a wide range of dehydrating agents [146]. The reaction often involves the use of toxic, and hazardous chlorinated and high boiling points solvents (e.g. 1,2-dichloroethane, 1,1',2,2'-tetrachloroethane, chlorobenzene, dioxane) at elevated temperatures. In recent years, researchers have directed their efforts for the synthesis of isoquinoline derivatives using ionic liquids.

Judeh *et al.* have first reported [147] an efficient and green synthesis of isoquinoline derivatives through Bischler-Napieralski cyclization of substituted phenylethanamides using room temperature ionic liquid, [Bmim]$PF_6$ (Scheme **63**).

They have further extended [147] the synthesis of *bis*-dihydroquinoline **134** from substituted phenethyl amine **133** mediated by $POCl_3$ using ionic liquid, [Bmim]$PF_6$ (Scheme **64**).

An efficient and green synthesis of 2-benzene sulfonyl-1,2,3,4-tetrahydro-isoquinoline-1-carboxyllic acid ethyl ester derivatives **137,** through the Pictet-Spengler cyclization of compound **135** with **136,** using phenyl( III) *bis*(trifluroacetate) PIFA under mild reaction conditions using room temperature ionic liquid, 1-butyl-3-methyl-imidazolium hexaflourophosphate [Bmim]$PF_6$ was reported by Wang and coworkers [148] (Scheme **65**).

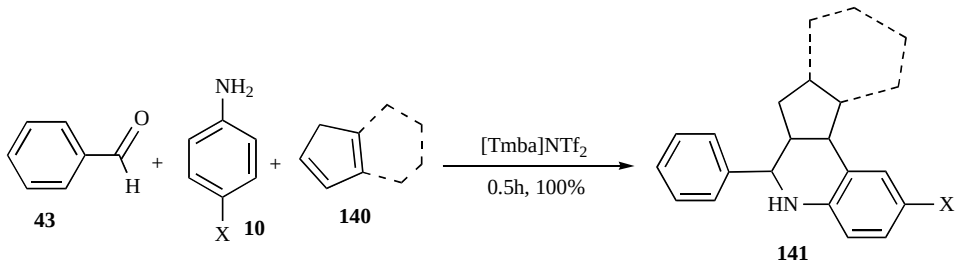
Yadav *et al.* have reported [149] an efficient and green protocol for the synthesis of *cis*-isoquinolinic acids **139,** *via* three-components coupling reaction of aldehydes **43**, amines **10**, and homophthalic anhydride **138** under mild reaction conditions using room temperature ionic liquid (Scheme **66**).

An efficient and green protocol for the synthesis of tetrahydroisoquinolines **141**, through the *Grieco's* multi-component reaction of corresponding amines **10**, aryl aldehydes **43**, and alkene **140** using a task specific ionic liquid, trimethylbutylammonium triflimide, [Tmba]$NTf_2$ by Hassine and coworkers [150] (Scheme **67**).

### 2.15. N-Aryl/Alkyl Phthalimides

Phthalimides and *N*-substituted phthalimides are an interesting class of compounds because they possess important biological activities, and substrates for important chemical applications [151]. Classical methods for the synthesis of phthalimides involve dehydrative condensation of an anhydride, and amines catalyzed by conc. $H_2SO_4$ with acetic anhydride as medium [152]. Other methods as with alcohol, nitrobenzene, and $CH_2Cl_2$ as medium in presence of $PPh_3$, THF to direct *N*-alkylation of imines [153]. These methods have been associated with drawbacks owing to using organic solvents, which are not environmental friendly. In recent years, many researchers have directed their efforts for synthesis of phthalimides using ionic liquids.

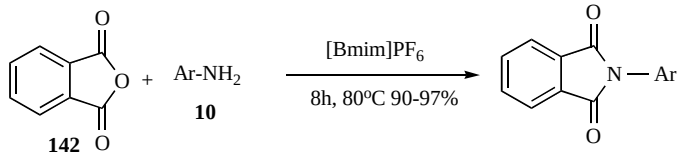
Li *et al.* have first reported [154] an efficient and green protocol for the synthesis of a series of *N*-aryl-phthalamides **143,** through the reaction of corresponding phthalic anhydride **142,** and aromatic




**43** **10** **140** **141**

X = H, $NO_2$, Cl, Br, OMe

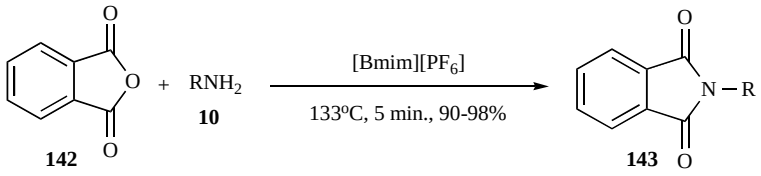
**Scheme 67.**




**142** **10** **143**

Ar = Ph, 2-MeO-Ph, 4-MeO-Ph, 4-$NO_2$-Ph, 4-Cl-Ph, 4-Br-Ph,

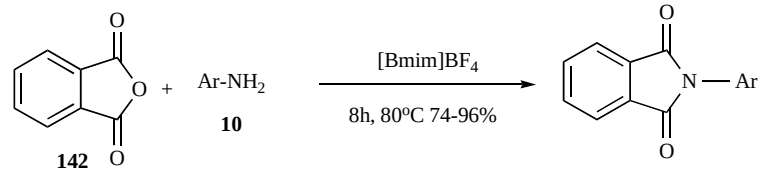
**Scheme 68.**




**142** **10** **143**

R = Ph, 2-MeO-Ph, 4-MeO-Ph, $PhCH_2$, *n*-$C_4H_9NH_2$ 4-$NO_2$-Ph, 4-Cl-Ph, 4-Br-Ph, $CH_2COOH$, $CH_2CH_2OH$

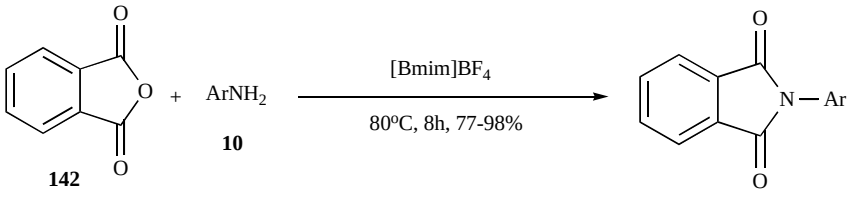
**Scheme 69.**




**142** **10** **143**

Ar = 4-F-Ph, 4-Cl-Ph, 3-F-Ph, 2-F-Ph, 3-Cl-Ph

**Scheme 70.**




**142** **10** **143**

Ar = Ph, 2-MeO-Ph, 4-MeO-Ph, 4-$NO_2$-Ph, 4-Cl-Ph, 4-Br-Ph,

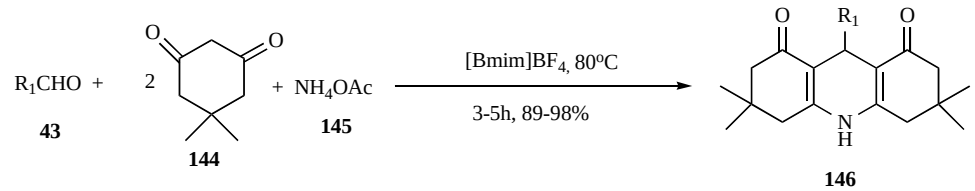
**Scheme 71.**

amines **10,** using room temperature ionic liquid, [Bmim]$PF_6$ (Scheme **68**).

Later on, Le and coworkers have reported [155] a synthesis of *N*-alkyl and *N*-aryl phthalimides **143**, through the direct dehydrative condensation reaction of phthalic anhydride **142** with the corresponding amines **10** using ionic liquid, [Bmim][$PF_6$] at 133°C (Scheme **69**).

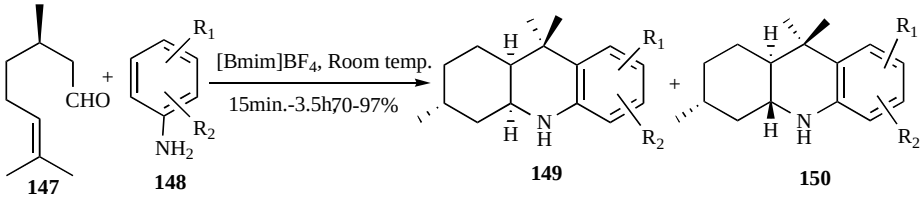
Recently, Chen group have reported [156] synthesis of *N*-aryl phthalimides **143**, through the reaction of phthalic anhydride **142,** and amines bearing halo group **10** using ionic liquid [Bmim]$BF_4$ which is acting as the dual role of solvent and promoter (Scheme **70**).

More recently, Chu and coworkers have also reported [157] an improved and efficient protocol for synthesis of *N*-aryl phthalimides **143**, through the *N*-alkylation of phthalic anhydride **142** with aromatic amines **10** using ionic liquid [Bmim]$BF_4$ (Scheme **71**).



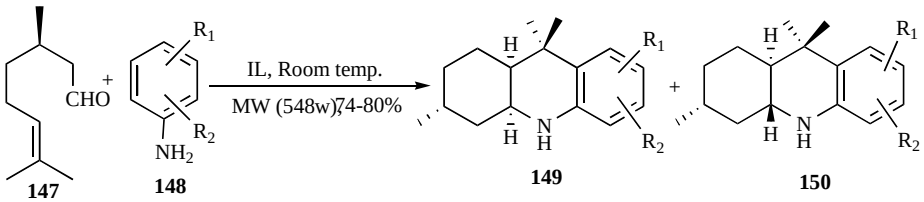

$R_1$ = Ph, 4-Br-Ph, 2Cl-Ph, 4Cl-Ph, 2,4-$Cl_2$-Ph, 4OH-Ph, 4-MeO-Ph, 3-$NO_2$-Ph, 4-$Me_2N$-Ph,3,4-$OCH_2O$-Ph, 3,4-$(MeO)_2$-Ph, 3-MeO-4-OH-Ph

**Scheme 72.**




$R_1$ = $R_2$ = 2-Me, 4-F, 4-Cl, 2-Br-4-Me, 4-MeO, 4-EtO, 4-Me, 2,6-$(Me)_2$, 2-$CF_3$, 4$NO_2$, 4-$NH_2$

**Scheme 73.**




$R_1$ = $R_2$ = 2-Me, 4-F, 4-Cl, 2-Br-4-Me, 4-MeO, 4-EtO, 4-Me, 2,6-$(Me)_2$, 2-$CF_3$, 4$NO_2$, 4-$NH_2$

**Scheme 74.**

### 2.16. Acridines

Acridines are well known compounds because of their pharmacological profile as calcium channel modulators [158]. There are many methods for their synthesis carried out from aldehydes, dimedone, and ammonium acetate under a number of conditions, including by traditional heating in molecular solvents [159], by using tetraethyl-*n*-butylammoniumcarbonate (TEBAC) in water as a catalysts [160], or by using microwave irradiation [161]. In recent years, synthesis of acridine derivatives was achieved from various starting materials using ionic liquids reported by several researchers.

Zhong *et al.* have first reported [162] an efficient and green synthesis of 9-arylpolyhydroacridines **146**, through the three-component reaction of aromatic aldehydes **43**, 5,5-dimethyl-1,3-cyclohexanedione **144**, and ammonium acetate **145**, using ionic liquid, [Bmim]$BF_4$ (Scheme **72**). Ionic liquid was recovered, and reused three times with no appreciable decrease in yield.

Later on, Yadav and coworkers have reported [163] an efficient and green protocol for the synthesis of 1,2,3,4,4a,9,9a,10-octahydroacridine derivatives **149** and **150,** through the intramolecular hetero-Diels-Alder (4+2) of 2-azadienes derived *in situ* from aryl amines **148** and I-(+)-citronellal/3-methylcitronellal **147** using moisture stable ionic liquid *i.e.* [Bmim]$BF_4$ at room temperature (Scheme **73**).

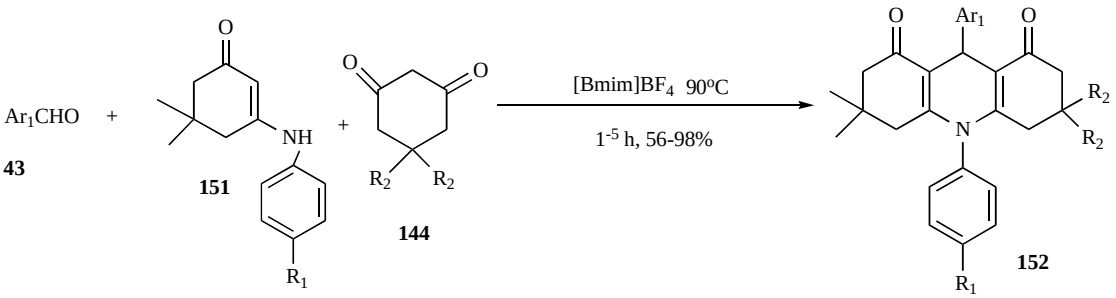
Later on, Lenardao *et al*. have reported [164] an efficient and green synthesis of octahydroacridines in high yields through the hetero-Diels-Alder cyclization of aryl imines derived from citronellal, using freshly prepared selenium and tellurium based ionic liquids (Scheme **74**). The ionic liquids used in this reaction are phenylbutylethyl- -selenonium tetrafluroborate or phenylbutylethyl telluronium tetraflouroborate to afford the desired products in high yields.

Wang *et al*. have also reported [165] an efficient and green synthesis of 9,10-diaryl acridine-1,8-diones **152**, and indenoquinolines derivatives **155** were accomplished through the reaction of 3-anilino 5,5-dimethyl cyclohex-2-enones **151**, aryl aldehydes **43**, and 1,3-dicarbonyl compounds **144**, using [Bmim]$BF_4$ as an ionic liquid (Scheme **75** & Scheme **76**).

Recently, Dabiri group have reported [166] an efficient and green protocol for the synthesis of 1,8-dioxo-decahydro-acridine derivatives **152**, through the reaction of 5,5-dimethyl-1,3-cyclohexane dione **144**, aromatic aldehydes **43**, and primary amines **10**, using [Hmim]TFA ionic liquid at 80°C (Scheme **77**).

### 2.17. Pyrimidines and Pyrimidinones

3,4-Dihydropyrimidine-2-(1*H*)-ones (DHPMs) and their derivatives are pharmacologically important compounds because of their promising biological activities, including antiviral, antibacterial, antitumor, and antihypertensive agents, $\alpha_{1a}$ adrenergic antagonists, and neuropeptide-Y antagonists, and furthermore, these compounds have emerged as the integral backbones of several calcium channel blockers [167]. Some marine alkaloids containing the dihydropyrimidinone core unit show interesting biological properties such

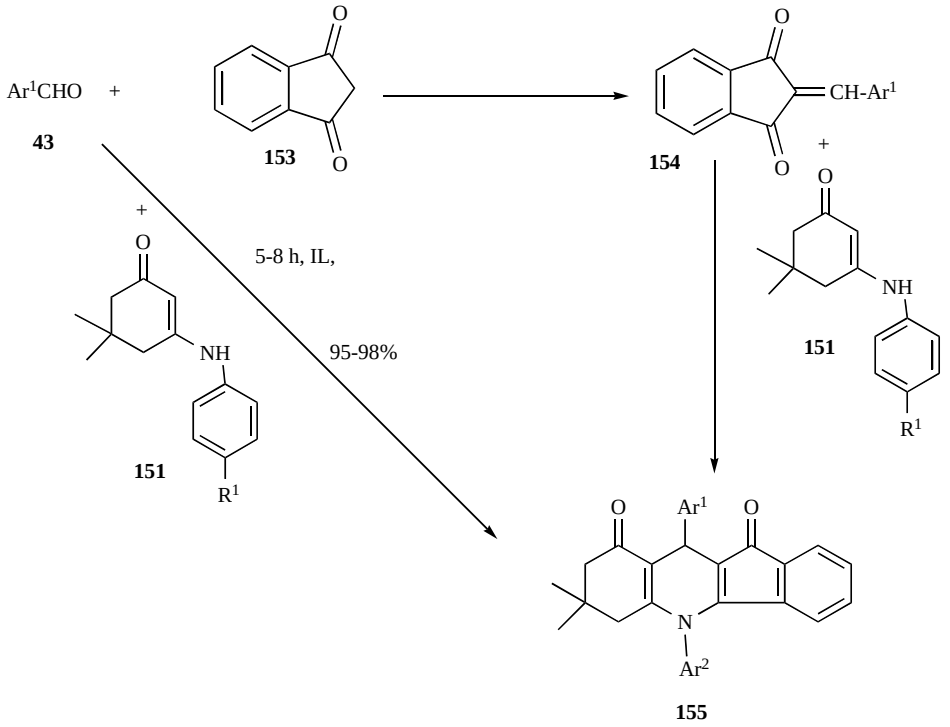



$Ar_1$ = 4-Tol, 4-Br-Ph, 3,4-$Cl_2$-Ph, 3-$NO_2$-Ph, 4-Cl-Ph,2-Cl-Ph, 4-F-Ph, 3,4-$Me_2$-Ph,

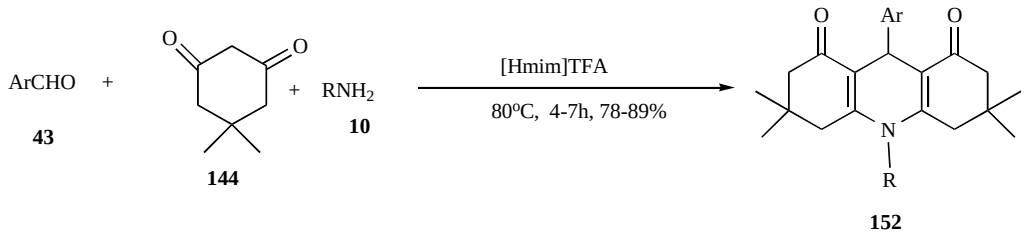
$R_1$ = Me, H, F, Cl, Br, I, $NO_2$,

$R_2$ = Me, H

**Scheme 75.**



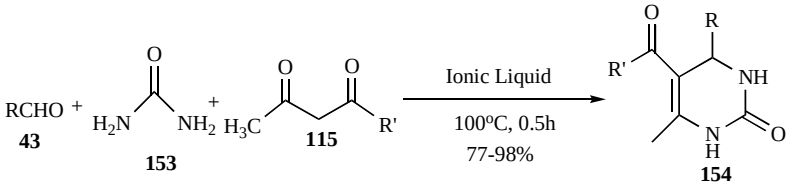

**Scheme 76.**




**Scheme 77.**

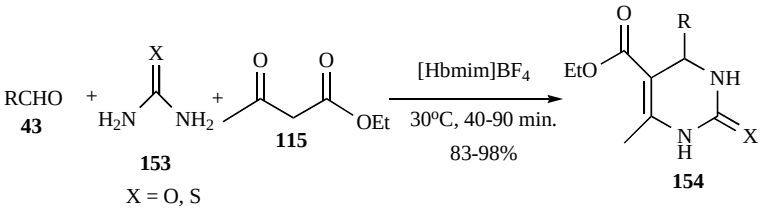
as batzelladine alkaloids have been found to be potent HIV gp-120-$CD_4$ inhibitors [168]. The most simple and straight forward procedure reported by Biginelli more than 100 years ago [169] involves the three-component acid catalyzed condensation in one-pot, but this reaction suffers from the harsh conditions, longer reaction times and frequently low yields. Recently, many methods for preparing these compounds have been developed to improve and modify this reaction by microwave and ultrasound irradiation and by using Lewis acids as well as Bronsted acid promoters [170]. In recent years, many researchers have directed their efforts for the synthesis of these derivatives using variety of ionic liquids.

Peng and Deng have first reported [171] an efficient and green synthesis of substituted 3,4-dihydropyrimidine-2-(1*H*)-ones **154**, through a one-pot, three-component Biginelli condensation of aryl




R = Ph, 4-MeO-Ph, 4-Cl-Ph,
4-$NO_2$-Ph, $C_5H_{11}$,
R' = OEt, Me

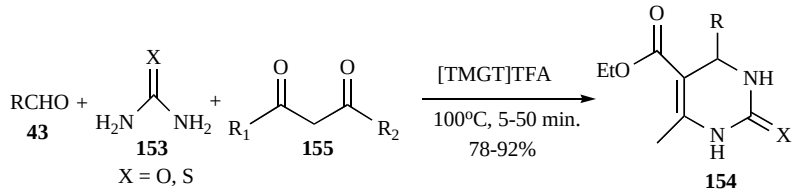
**Scheme 78.**




X = O, S

R = Ph, 4-$NO_2$-Ph, 4-$CH_3$-Ph, 2-F-Ph, 2Br-Ph, 4-MeO-Ph,
3-MeO-Ph, CH=CH-Ph, 2-Pyridyl, 2-Furyl, *n*-$C_9H_{19}$, 3,4,5-Trimethoxy-Ph

**Scheme 79.**



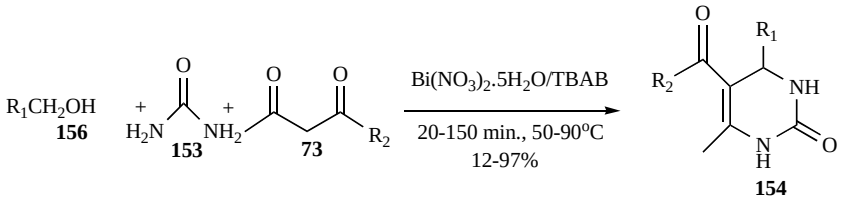

X = O, S

$R_1$ = OEt, OMe, Me

$R_2$ = Me

R = Ph, 4-$NO_2$-Ph, 4-$CH_3$-Ph, 2Br-Ph, 4-Br-Ph, 4-MeO-Ph,
3-MeO-Ph, $CH_3$,$C_3H_7$, 2-Me-Ph, 2-MeO-Ph, 3-Cl-Ph, 4-Cl-Ph

**Scheme 80.**




$R_1$ = Ph, 4-MeO-Ph, 3-MeO-Ph, 4-OH-Ph, 2-OH-Ph,
3-OH-Ph, 4-F-Ph, 4-Cl-Ph, 2-Cl-Ph, 2-Br-Ph, 2,4-$Cl_2$-Ph,
2-Furyl, 2-thiophenyl, Methlenedioxy-Ph, *n*-$C_5H_{11}$, *n*-$C_6H_{13}$
$R_2$ = OEt, OMe, Me

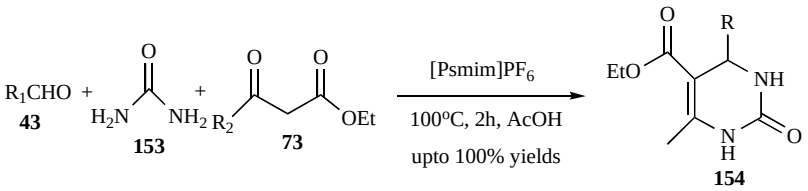
**Scheme 81.**

aldehydes **43**, urea **153,** and an active methylene compound using room temperature ionic liquids such as [Bmim]$BF_4$ or [Bmim]$PF_6$ (Scheme **78**).

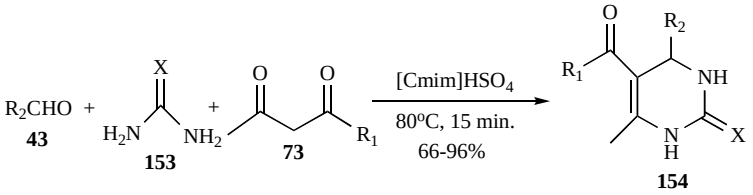
Later on, Srinivasan and coworkers have reported [172] an efficient and green protocol for the synthesis of 3,4-dihydropyrimidine-2(1*H*)-ones **154**, through the reaction between aromatic or aliphatic aldehydes **43**, with ethylacetoacetate **115**, and urea **153** using variety of Bronsted–acidic ionic liquids, out of which [Hbmim]$BF_4$ was found to be best in affording good excellent yields of the desired products (Scheme **79**).

Later on, Shaabani *et al.* have reported [173] an improved and green protocol for the synthesis of substituted-3,4-dihydropyrimidine-2-(1*H*)-ones **154,** through the reaction of an aldehyde **43**, an active methylene compound **155** and urea **153**, using 1,1,3,3-tetramethylguanidenium trifluoroacetate, [TMGT] TFA as a room temperature ionic liquid (Scheme **80**).

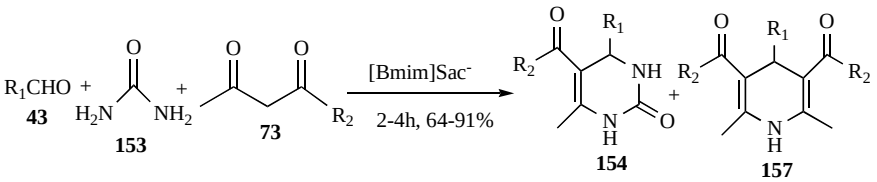
A modification of Biginelli reaction through using a primary alcohol **156** (which undergoes oxidation) instead of an aldehyde, was reported by Khosropour and coworkers [174]. They have synthesized substituted 3,4-dihydropyrimidine-2-(1*H*)-ones (DHPMs) **154,** through the reaction of primary alcohols **156**, with *β*-dicarbonyl compounds **73**, and urea **153** promoted by $Bi(NO_3)_3.5H_2O$ using ionic liquid, tetra-*n*-butylammonium bromide [TBAB] (Scheme **81**).




**Scheme 82.**

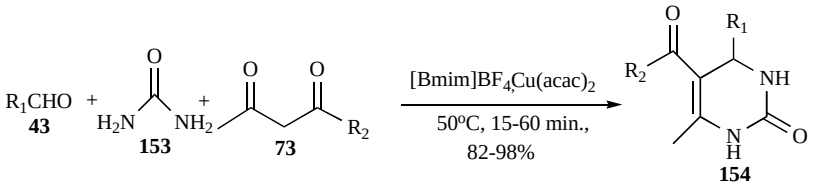



**Scheme 83.**




$R_1$ = Ph, 4-F-Ph, 4-Cl-Ph, 4-MeO-Ph, 4-$NO_2$-Ph,
= 4-$NMe_2$-Ph, 4-OH-Ph, 2-F-Ph, 2-Cl-Ph, 2-MeO-Ph, 2-Furyl
$R_2$ = OEt, Me

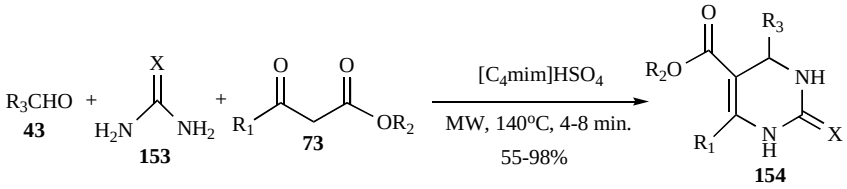
**Scheme 84.**




$R_1$ = Ph, 4-Cl-Ph, 4-Me-Ph, 4-MeO-Ph, 4-$NO_2$- Ph, 2,6-$Cl_2$-Ph, 4-$Me_2N$-Ph, 2-Pyridyl, 2-Furyl, *n*-$C_3H_7$, $Me_2CH$, *n*-$C_4H_9$, 2-Cl-Ph,

$R_2$ = OEt, Me, OMe

**Scheme 85.**




**Scheme 86.**

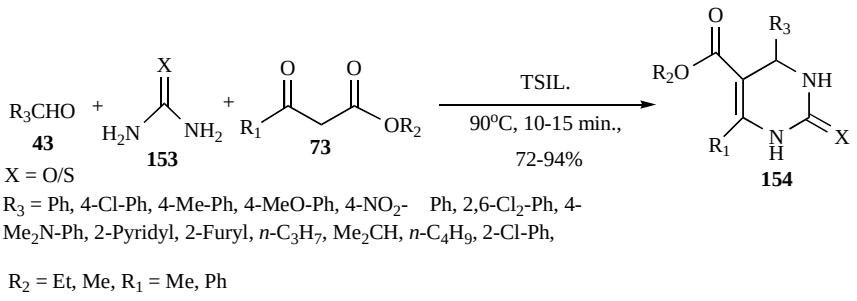
A further modification for the synthesis of substituted 3,4-dihydropyrimidine-2-(1*H*)-ones (DHPMs) **154**, through the Biginelli reaction using polymer supported reusable room temperature ionic liquid [Psmim]$PF_6$ was studied by Wang and coworkers [175] (Scheme **82**).

Recently, Zheng and coworkers have also reported [176] a further modification of Biginelli reaction which involves reaction of an aldehyde **43**, *β*-keto compound **73**, and urea/thiourea **153**, using Bronsted acid ionic liquid, 3-carboxymethyl-1-methyl imidazolium bisulphate [Cmim]$HSO_4$ afforded 3,4-dihydropyrimidine-2-(1*H*)-ones **154** in good to excellent yields (Scheme **83**).

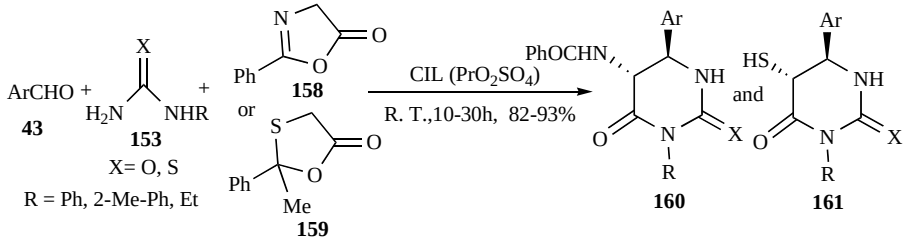
Later on, Li *et al*. have reported [177] a synthesis of 1,4-dihydropyridones (Hantzch product, **157**) and 3,4-dihydropyrimidones (Biginelli product, **154**) through a one-pot reaction of aldehydes **43**, *β*-dicarbonyl compound **73,** and urea **153**, using 1-*n*-butyl-3-methylimidazolium saccharinate [Bmim]Sac as an ionic liquid (Scheme **84**).

Jain and coworkers have recently reported [178] an efficient and green synthesis of 3,4-dihydropyrimidines **154**, through a one-pot cyclo-condensation reaction of an aldehyde **43**, *β*-carbonyl compound **73**, and urea **153** using [Bmim]$BF_4$ immobilized on $Cu(acac)_2$ as recyclable catalytic system (Scheme **85**).

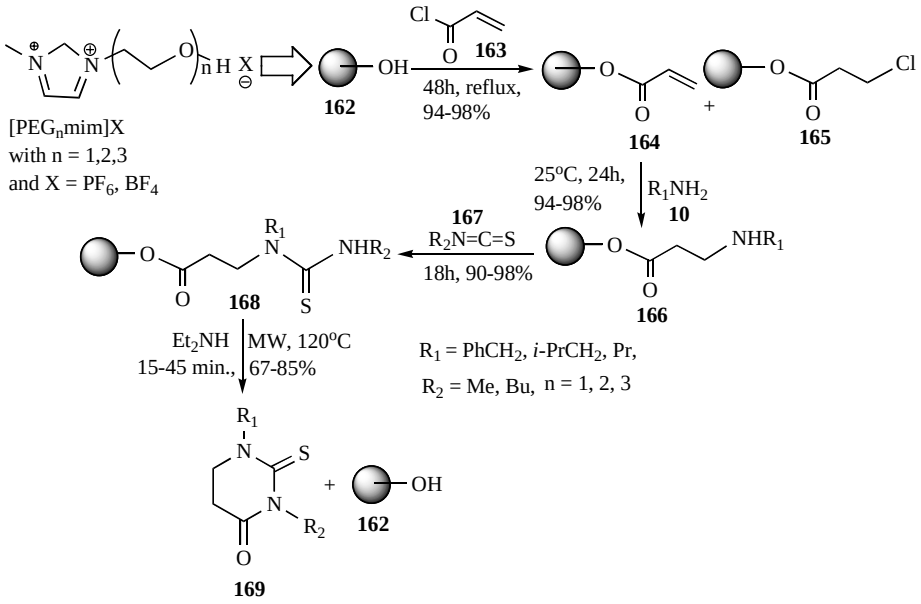
Arfan *et al.* have also recently reported [179] a simple and effective one-pot synthesis of 3,4-dihydropyrimidine-2H(*1H*)-one derivatives **154,** through the Biginelli reaction of substituted aromatic and heterocyclic aldehydes **43**, methyl acetoacetate **73**, and




**Scheme 87.**




**Scheme 88.**




**Scheme 89.**

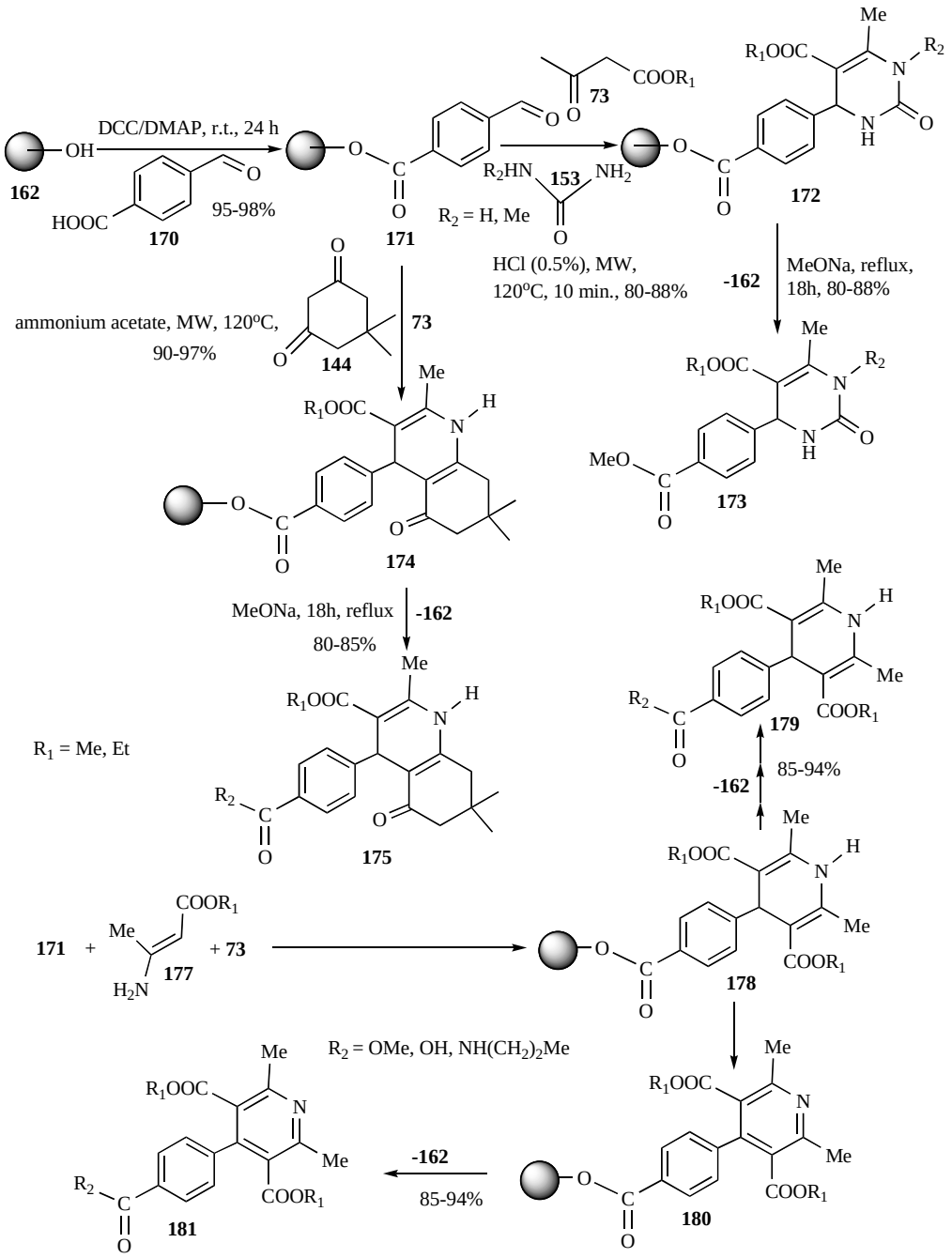
urea/thiourea **153** in presence of 10% of an task specific ionic liquid $[C_4mim]HSO_4$ as a catalyst (Scheme **86**).

Recently, Dong group have also reported [180] an efficient and green protocol for the synthesis of 3,4-dihydropyrimidine-2(*1H*)-ones **154,** *via* Biginelli reaction through the corresponding aldehydes **43**, *β*-ketodicarbonyl compound **73,** and urea **153** using cheap and reusable task-specific ionic liquids having an alkane sulfonic acid group in an acyclic trialkylammonium cation as catalyst (Scheme **87**).

Recently, Yadav *et al.* have reported [181] an efficient and green protocol for the synthesis of 5-amino-/mercaptoperhydropyrimidines **160** & **161** enantio and diastereoselectively through the Biginelli reaction using 2-phenyl-1,3-oxazo-5-one/2-methyl-2-phenyl-1,3-oxathiolan-5-one **158**/**159**, with aromatic aldehydes **43**, and urea/thiourea **153**, using a chiral ionic liquid, *i.e.* CIL (Scheme **88**).

Synthesis of substituted dihydropyrimidones through ionic liquid organic phase synthesis (IoLiPOS) using polymer supported ionic liquids has also been reported in recent years. Thus, Bazureau *et al.* have first reported [182] the synthesis of 2-thioxotetrahydropyrimidin-4-(1*H*)-ones **169**, through a series of reactions using polyethyleneglycol ionic liquid. Treatment of starting poly-(ethyleneglycol)-ionic liquid phases (PEGn-ILPs) **162**, with acryloyl chloride **163**, afforded a series of (PEGn)-ILPs bound acrylate **164** in quantitative yields. Michael addition of aliphatic amines **10** to the $PEG_1$-ILPs **164** allowed the preparation of *β*-aminoesters **166** in high yields. Addition of alkyl isocyanates **167** to **166** gave the corresponding thioureido esters **168**, which upon cyclization-cleavage under microwave/solventless strategy afforded the desired 2-thiooxotetrahydropyrimidin-4(1*H*)-ones **169** (Scheme **89**).

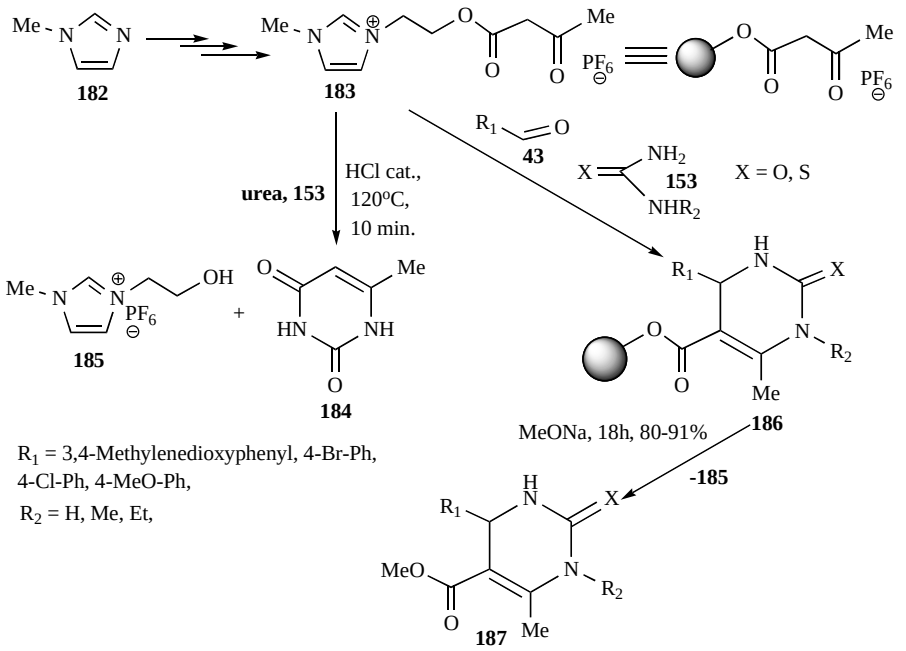
Bazureau group have further extended [183] the synthesis of Hantzsh 1,4-dihyropyridines **175**/**179,** and Biginelli 3,4-



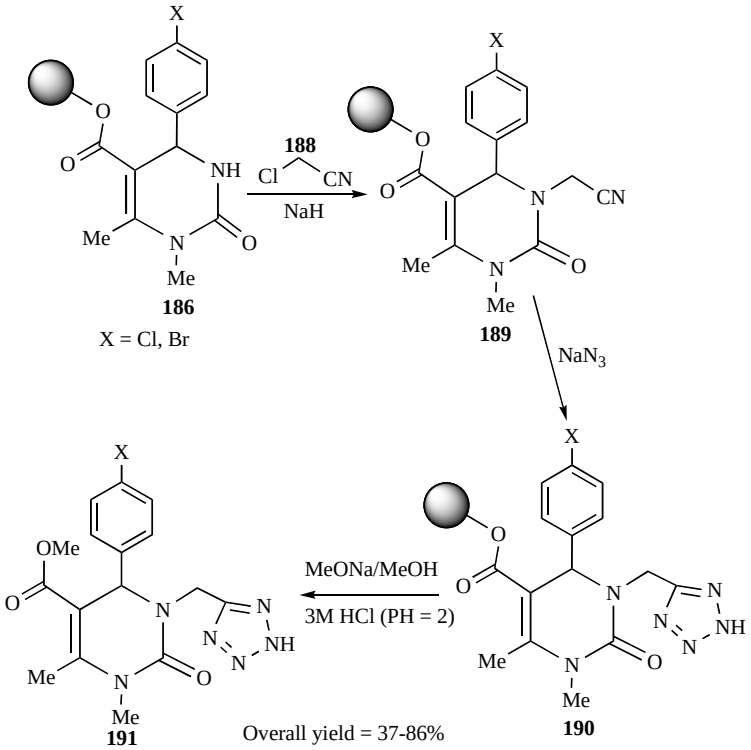

**Scheme 90.**

dihydropyrimidin-2 (1*H*)-ones **173**, using--same poly-(ethyleneglycol)-ionic liquid phases (PEGn-ILPs) **162** through ionic liquid phase technology (Scheme 90). Initially the compound **162** was esterified with 4-formylbenzoic acid **170** to afford compound **171**, which undergoes Biginelli reaction with ketoester **73,** and urea **153** afforded ionic liquid phase compound 3,4-dihydropyimidine derivative **172,** which undergoes base catalyzed treatment to afford free 3,4-dihydroprimidin-2(1*H*)-ones derivative **173**. For the synthesis of Hantzsch 1,4-dihydropyridine derivatives **175** and **179**, two reaction pathways have been reported by these workers. In first pathway, compound **171** undergoes three-component condensation reaction with diketone **144**, *β*-ketoester **73**, and ammonium acetate to afford the-corresponding supported 1,4-dihydropyrimidine derivative **174,** which upon treatment with base afforded desired 1,4-DHP compound **171** undergoes three-component condensation reaction with diketone **144**, *β*-ketoester **73**, and ammonium acetate to afford the corresponding supported 1,4-dihydropyrimidine derivative **174,** which upon treatment with base afforded desired 1,4-DHP compound **175**. In the second pathway, compound **171** undergoes three-component Hantzsch reaction with a *β*-ketoester **73**, and aminocrotonate **177** afforded the ILP-supported 1,4-DHP compound **178**, which upon treatment with a base afforded free DHP-compound **179.** Compound **178** undergoes DDQ oxidation to afford ILP-supported tetra-substituted pyridine derivative **180**, which upon treatment with base afforded compound **181** (Scheme **90**).

Recently, Bazureau *et al.* have further reported [184] the efficient and green synthesis of 3,4-dihydropyrimidine-2(1H)-ones **187**, through the three-component Biginelli reaction using ionic liquid phase bound acetoacetate **183**, urea/thiourea **153**, and an aldehyde **43**. Initially they have synthesized the ionic liquid bound




**Scheme 91.**



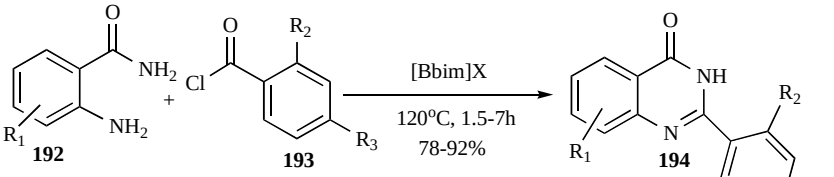

**Scheme 92.**

acetoacetate in --three-steps starting from *N*-methyl imidazole **182** (Scheme **91**). They have also synthesized 6-methyl pyrimidin-2,4-dione **184**, through acid catalyzed three-component coupling reaction of **183** with **153** at 120°C.

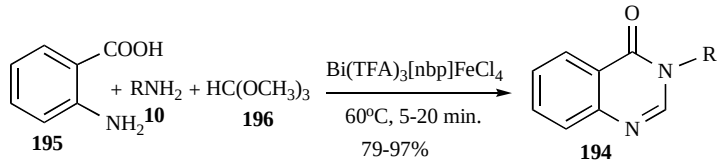
Recently, Bazureau group have also demonstrated [185] synthesis of 3,4-dihydropyrimidine-2(1*H*)-ones bearing a tetrazole functionality at *N*-3 position **191**, using ionic liquid phase organic synthesis, through the reaction of his previously synthesized ILP bound 3,4-dihydropyrimidine-2(*1H*)-ones **186** with chloroacetonitrile **188** using sodium hydride afforded compound **189**. Which upon treatment with sodium-azide using Click Chemistry afforded ILP bound tetrazole derivative **190**, further treatment with base afforded desired compound **191**(Scheme **92**).

### 2.18. Quinazolines and Quinazolinones

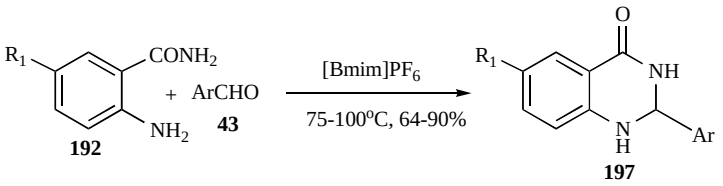
The quinazoline ring system is one of the most frequently encountered heterocycles in medicinal chemistry, present in many biologically active natural and synthetic compounds [186]. Several quinazoline and quinazolinone derivatives have been synthesized as potential anti-microbial [187], anticancer [188], anti-malarial [189],



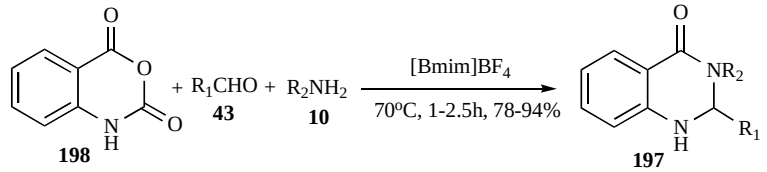

**Scheme 93.**




**Scheme 94.**




**Scheme 95.**




**Scheme 96.**

anti-inflammatory [190], anti-diabetic [191], anticonvulsant [192] agents. In addition more than 40 alkaloids comprising the 4(*3H*)-quinazolinone moiety have been isolated from the natural sources, which have displayed interesting biological properties such as anti-malarial activity, biofungicide, and diuretic properties [193-195].

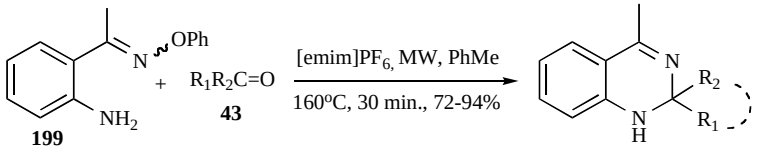
In view of the importance of quinazolines and their derivatives, a variety of preparatory methods have been reported in literature. The main synthetic routes to such compounds using 2-aminobenzoic acid or its derivatives [196], and 2-aminobenzonitrile [197] as starting materials. In addition, quinazolinones were also synthesized through reaction of isatoic anhydride with benzamide [198], by intra-molecular *aza*-Wittig reaction [199], by thermolysis of anil at 300°C [200] and two-step reaction from benzoyl chloride and 2-aminobenzamide [201]. Furthermore, quinazolinones have also been prepared from 2-aminobenzamide and sodium hydroxide [202], through the solid phase synthesis using variety of Lewis acids [203, 204], by microwave [205] and by using various transition metals such as Cu, Ru, Pt, and Pd complexes [206, 207]. In recent years, ionic liquids have received much attention for the synthesis of these compounds and many researchers have directed their efforts to the syntheses of these compounds using variety of ionic liquids.

Potewar and coworkers have first reported [208] an efficient, green one-pot synthesis of 2-aryl-4(*3H*)-quinazolines **194**, through the reaction of 2-amino benzamides **192**, with substituted benzoyl chlorides **193** using room temperature ionic liquids mainly 1,3-di-*n*-butylimidazolium salts [Bbim]X with varying anions (*i.e.* X = Br, Cl, $BF_4$, $PF_6$, $ClO_4$) (Scheme **93**). Out of various ionic liquids used [Bbim]Br was found to be best in affording good yields of the desired product.

Later on, Khosropour and coworkers have demonstrated [209] an efficient and green synthesis of 4(3*H*)-quinazolinones **194**, through one-pot condensation of anthranilic acid **195**, trimethylorthoformate **196**, and primary amines **10**, in presence of 5 mol% of $Bi(TFA)_3$ immobilized on [nbp][$FeCl_4$] as a room temperature ionic liquid (Scheme **94**).

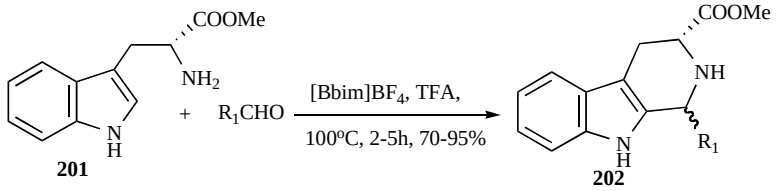
Later on, Chen group have demonstrated [210] an eco-friendly and efficient synthesis of 2,3-dihydro quinazoline-4(*1H*)-ones **197**, through the direct cyclo-condensation of anthranilamides **192**, with aldehydes **43**, using room temperature ionic liquid [Bmim]$PF_6$ (Scheme **95**).

Recently, Dabiri *et al*. have reported [211] an eco-friendly and efficient synthesis of 2,3-dihydro-quinazolin-4(*1H*)-ones **197**, through reaction of isatoic anhydride **198**, a primary amine **10** or ammonium acetate and different aromatic aldehydes **43**, using [Bmim]$BF_4$ (Scheme **96**).



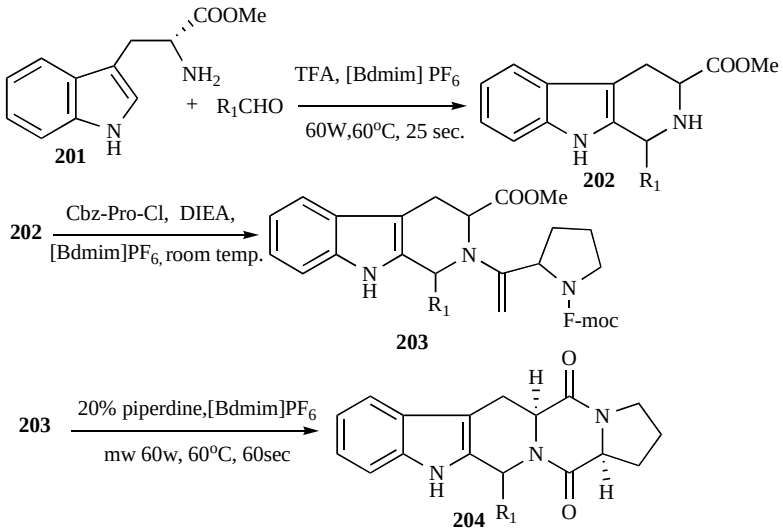

Carbonyl compounds = cyclohexanone, PhCHO, $PhCH_2CH_2CHO$, *n*-pentanal, 1-penten-5-al

**Scheme 97.**




$R_1$ = Ph, 3-$OCH_2$-4-O-Ph, 2-F-Ph, 2-Cl-Ph,
= 2-$NO_2$-Ph, 4-F-Ph, 4-Cl-Ph, 4-$NO_2$-Ph, 4-MeO-Ph

**Scheme 98.**




**Scheme 99.**

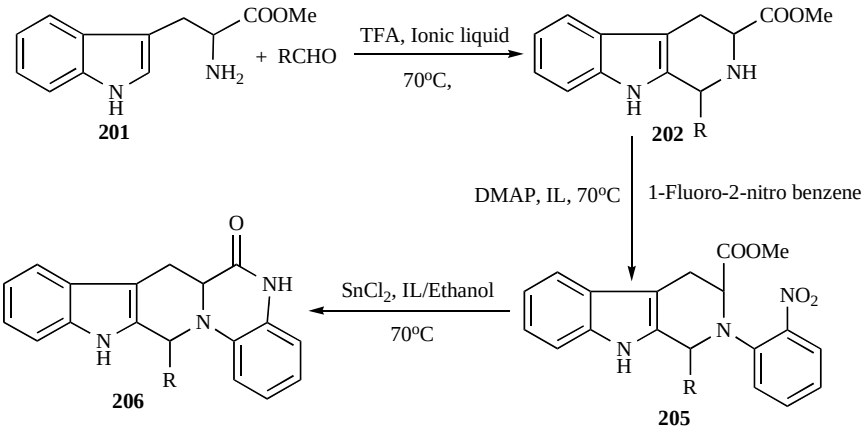
Recently, Walton and coworkers have reported [212] efficient and green synthesis of 1,2-dihydro-quinazolines **200**, through the reaction of 2-aminoacetophenone-*o*-phenyl-oxime **199**, with diverse series of carbonyl compounds (aldehydes and ketones) **43**, under microwave irradiation using 1-ethyl-3-methyl-1H-imidazol-3-ium hexaflourophosphate $[Emim]PF_6$ as ionic liquid (Scheme **97**).

### 2.19. Carbolines

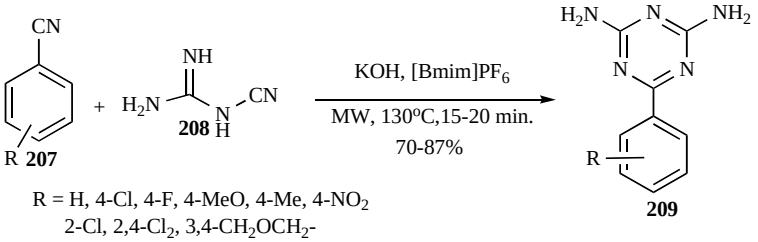
The *β*-carboline core is great of interest, being an important pharmacophore in numerous biologically active compounds [213]. Furthermore, tetrahydro-*β*-carboline- diketopiperazines and tetrahydro-*β*-carboline quinoxalinones skeleton present in many biologically active indole alkaloids [214, 215] and have displayed a wide spectrum of biological activities such as anti-HIV agents, antihypertensives, anti-thrombic, and ligands for a number of protein receptors [216]. Although, methods for the syntheses of tetrahydro-*β*-carbolinediketopiperazines, and tetrahydro-*β*-carbolinequinoxalinones ring systems were achieved [217, 218], through the Pictet-Spengler reaction commonly used for the synthesis of tetrahydro-*β*-carbolines [214]. In recent years, ionic liquids have attracted much attention for the syntheses of substituted tetrahydro-*β*-carbolines, tetrahydro-*β*-carbolinediketopiperazines, and tetrahydro-*β*-carbolinequinoxalinones.

Joshi and coworkers have first reported [219] efficient, and green synthesis of 1,3-disubstituted 1,2,3,4-tetrahydro-*β*-carbolines **202**, through the Pictet-Spengler condensation of D-tryptophan methyl ester **201**, and benzaldehyde **43**, in different imidazolium-based ionic liquids in the presence of TFA as an acid catalyst (Scheme **98**). Out of various imidazolium based ionic liquids were used, [Bbim] $BF_4$ was found to be best in affording good yields of desired products.

Yen and Chu have first reported [220] an efficient and green protocol for the synthesis of tetrahyro-*β*-carboline-diketopiprazines **204**, starting from tryptophan methyl ester **201**, using ionic liquid $[Bdmim]PF_6$ in presence of microwave heating (Scheme **99**). Initially, compound **201** was converted into substituted 1,2,3,4-tetrahydro-*β*-carbolines **202,** through the Pictet-Spengler condensation using an aldehyde **43**, and given ionic liquid $[Bdmim]PF_6$, under microwave heating. Compound **202** was further treated with Fmoc-protected prolinoyl chloride (Cbz-Pro-Cl) using same ionic liquid, afforded protected substituted tetrahydro-*β*-carboline compound **203,** which on further treatment with a base using same ionic

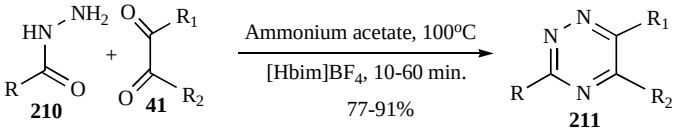



**Scheme 100.**




R = H, 4-Cl, 4-F, 4-MeO, 4-Me, 4-$NO_2$
2-Cl, 2,4-$Cl_2$, 3,4-$CH_2OCH_2$-

**Scheme 101.**




R = Ph, 4-$NH_2$-Ph-. 4-Me-Ph-, 3-MeO-Ph, 4-Cl-Ph-, 2-Cl-Ph-
$R_1$ = $R_2$ = Ph, 4-Me-Ph, 4-MeO-Ph

**Scheme 102.**

liquid, under microwave conditions afforded desired compound **204**.

Later on, Chu group have further demonstrated [221] an efficient and green protocol for the synthesis of fused tetrahydro-*β*-carboline quinazolinones **206**, starting from tryptophan methyl ester **201**, using 1-*n*-butyl-2,3-dimethyl imidazolium--*bis*(triflurometh sulfonyl)-imide [Bdmim]$Tf_2N$, and 1-*n*-butyl-2,3-dimethyl imidazolium perflurobutyro sulfonate [Bdmim]$PFBuSO_3$ ionic liquids (Scheme **100**). The synthesis of target compound was achieved through the Pictet-Spengler condensation using an aldehyde with ester compound **201** afforded compound **202**, which upon further treatment with 2-fluoro-2-nitrobenzene using DMAP afforded compound **205**. Compound **205** undergoes reductive condensation afforded compound **206**. Both of the ionic liquids were tried to accomplish each transformation afforded good yields in each step. The overall isolated yields for this three-step synthesis of tetrahydro-*β*-carboline-quinoxalinones were 34-55%.

### 2.20. Triazines

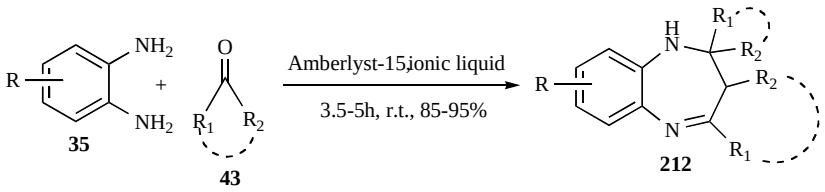
Substituted triazines are a class of attractive compounds in the modern chemical industry [222]. They are widely employed as flame-retardant additives in common resins or pivotal structural units in fire-resistant polymers. Chemically modified 6-aryl-2,4-diaminotriazines have also been reported as new ligands with potential multi-coordination models [223], cross linkers in coatings, vermin-repellent microcapsules with slow-release potentially, corrosion-resistant agents on metal surfaces, and candidates for anti-ulcerous [224] and allergy-inhibiting drugs. The synthesis of 6-aryl-2,4-diaminotriazines typically involves the condensation of aryl nitriles with dicyandiamide in an alcohol solution in the presence of a strong base [225, 226]. Unfortunately, these transformations have traditionally suffered from long reaction time, for example, 24h at 140°C with yields between 53-75% [225]. In recent years, ionic liquids have received much attention and thus researchers have directed their efforts for the synthesis of triazines using ionic liquids.

Peng and Song have reported [227] an efficient and green approach for the synthesis of 6-aryl-2,4-diamino-1,3,5-triazines **209**, through the reaction of corresponding variety of aryl-nitriles **207**, with dicyanodiamides **208**, using ionic liquid [Bmim]$PF_6$ under computer controlled microwave irradiation (Scheme **101**).

Recently, Srinivasan and coworkers have demonstrated [228] an efficient and green synthesis of 3,5,6-trisubstituted-1,2,4-triazines **211**, through the reaction between acid hydrazides **210**, 1,2-diketones **41**, and ammonium acetate using Bronsted acidic ionic liquid [1-*n*-butyl-imidazolium tetraflouroborate [Hbim]$BF_4$ (Scheme **102**).

### 2.21. Diazepines

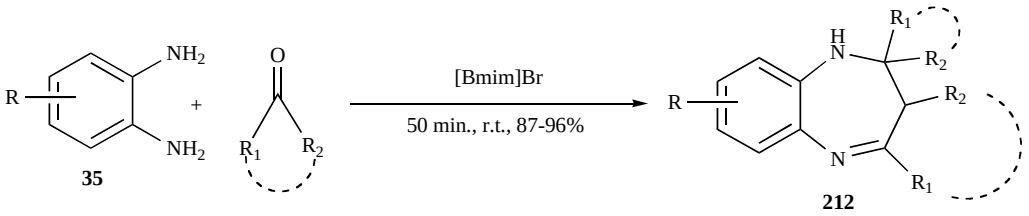
Diazepines are an important class of pharmacologically active compounds finding applications as anti-convulsant, anti-anxiety, sedative, anti-depressive, transquilizing, anti-inflammatory, anti-feedant, anti-bacterial, and analgesic agents [229, 230]. In addition, benzodiazepine derivatives are also used in industry as dyes for acrylic fibers in photography. Moreover, they are key intermediates for the preparation of other fused ring compounds such as triazolo




**35** **43** **212**

R = H, Me, PhCO
Ketones ($R_1$& $R_2$): MeCOMe, PhCOMe, MeCOEt, EtCOEt, cyclopentanone, cyclohexanone

**Scheme 103.**

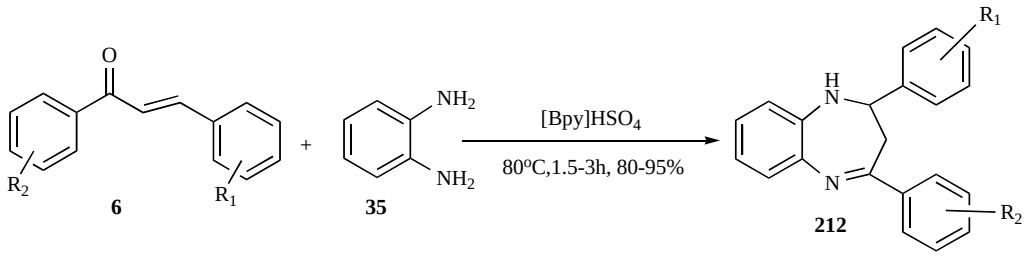



**35** **212**

R = H, Me, PhCO

Ketones ($R_1$& $R_2$): MeCOMe, PhCOMe, MeCOEt, EtCOEt, cyclopentanone, cyclohexanone

**Scheme 104.**




**6** **35** **212**

$R_1$ = $R_2$ = Ph, 4-Me-Ph, 4-$NO_2$Ph, 3,4-$Cl_2$-Ph, 4-MeO-Ph, 4-Br-Ph,

**Scheme 105.**

[231], oxazino [232], oxadiazolo [233], and furanobenzodiazepines [234].

1,5-Benzodiazepines have commonly been synthesized by the reaction of *o*-phenylenediamine with *α,β*-unsaturated carbonyl compounds, *β*-haloketones or ketones. There are many methods for the preparation of 1,5-benzodiazepines in the literature, including $BF_3$-etherate [235], $NaBH_4$ [236], polyphosphoric acid or $SiO_2$ [237], $Yb(OTf)_3$ [238], $MgO/POCl_3$ [239] $Al_2O_3/P_2O_5$ or acetic acid under microwave irradiation [240] $TiCl_4$/Sm/THF system [241], sulfated zirconia [242], silica gel [243], and $CeCl_3$/NaI/silica gel [244]. Many of these methods suffer from limitations such as requiring harsh reaction conditions, expensive reagents, high catalyst loading, corrosive reagents, or toxic ions, low to moderate yields and occurrence of several side reactions. In recent years, many researchers have directed their efforts for the syntheses of 1,5-benzodiazepines using ionic liquids.

Yadav group have first demonstrated [245] an efficient and green protocol for the synthesis of 1,5-benzodiazepines **212**, through the condensation of a variety of *o*-phenylene-diamines **35**, with a series of diverse acyclic/cyclic ketones **43**, catalyzed by acidic resin Amberlyst-15 immobilized in the air and moisture-stable ionic liquids *i.e.* $[Bmim]PF_6$ and $[Bmim]BF_4$ respectively (Scheme **103**). Among these ionic liquids used, $[Bmim]BF_4$ was found to be best in terms of yields and reaction rates.

Later on, Srinivasan *et al.* have reported [246] an improved and efficient synthesis of 1,5-benzodiazepine derivatives **212**, through the condensation reaction of *o*-phenlenediamines **35**, with both cyclic and acyclic ketones **43**, using [Bmim]Br as an ionic liquid (Scheme **104**).

Recently, Du and coworkers have reported [247] an efficient and green synthesis of 1,5-benzodiazepines **212**, through the reaction of *o*-phenylenediamines **35**, with variety of chalcones **6**, using 1-*n*-butyl pyridinium-hydrogen sulphate, $[Bpy]HSO_4$ as an acidic ionic liquid (Scheme **105**).

## 3. CONCLUSIONS

The unique properties of ionic liquids make them an interesting class of green reaction media which have frequently been used for variety of reactions in organic synthesis. Heterocycles are the major classes of bioactive compounds, many of them have already been approved drugs by FDA for various kinds of harmful diseases. The easy, economic, simple and efficient protocols for the synthesis of structurally diverse nitrogen heterocycles using variety of structurally diverse ionic liquids have been comprehensively studied. Present review covered all the reports for the synthesis of nitrogen heterocycles from beginning to the recent reports using variety of ionic liquids. I hope this review will provide first hand information to medicinal and organic chemists for further exploration of the drug discovery synthesis.

## 4. ACKNOWLEDGEMENTS

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## 5. LIST OF ABBREVIATIONS (FOR IONIC LIQUIDS)

[Bmim]$BF_4$ = 1-*n*-Butyl-3-methylimidazolium tetrafluoroborate

[Bmim]$PF_6$ = 1-*n*-Butyl-3-methylimidazolium hexaflourophosphate

[Bmim]F = 1-*n*-Butyl-3-methylimidazolium fluoride

[Bmim]Cl = 1-*n*-Butyl-3-methylimidazolium chloride

[Bmim]Br = 1-*n*-Butyl-3-methylimidazolium bromide

[Bmim]I = 1-*n*-Butyl-3-methylimidazolium iodide

[Bmim]OH = 1-*n*-Butyl-3-methylimidazolium hydroxide

[Bmim]$HSO_4$ = 1-*n*-Butyl-3-methylimidazolium hydrogen sulfate

[Bmim]$H_2PO_4$ = 1-*n*-Butyl-3-methylimidazolium biphosphate

[Bmim]$Br_3$ = 1-*n*-Butyl-3-methylimidazolium tribromide

[Bmim]$ClO_4$ = 1-*n*-Butyl-3-methylimidazolium perchlorate

[Bmim]SCN = 1-*n*-Butyl-3-methylimidazolium thiocyanide

[Bmim]SPh = 1-*n*-Butyl-3-methylimidazolium thiophenyl

[Bmim]$SO_3CF_3$ = 1-*n*-Butyl-3-methylimidazolium fluorosulfonate

[Bmim]$PF_3(C_2F_5)_3$= 1-*n*-Butyl-3-methylimidazolium hydroxide

[Bmim]TFA = 1-*n*-Butyl-3-methylimidazolium trifluoroacetate

[Bmim]OTf = 1-*n*-Butyl-3-methylimidazolium triflate

[Bmim]$NTf_2$ = 1-*n*-Butyl-3-methylimidazolium *bis*(trifluoromethyl sulfonyl) iodide

[Bmim]Sac = 1-*n*-Butyl-3-methylimidazolium saccharinate

[Bmim]$ZnCl_2$ = 1-*n*-Butyl-3-methylimidazolium zinc chloride

[Bbim]Cl = 1,3-Di-*n*-butylimidazolium chloride

[Bbim]Br = 1,3-Di-*n*-butylimidazolium bromide

[Bbim]I = 1,3-Di-*n*-butylimidazolium iodide

[Bbim]$PF_6$ = 1,3-Di-*n*-butylimidazolium tetrafluorophosphate

[Bbim]$BF_4$ = 1,3-Di-*n*-butylimidazolium tetrafluoroborate

[Bbim]$ClO_4$ = 1,3-Di-*n*-butylimidazolium perchlorate

[Bbim]$PFBuSO_3$ = 1-*n*-Butyl-2,3-dimethylimidazolium perflourobutyl sulfonate

[Bdim]$Tf_2N$ = 1-*n*-Butyl-3-methylimidazolium *bis*(trifluoromethylsulfonyl)amide

[Bpy]$BF_4$ = 1-*n*-Butyl-pyridinium tetrafluoroborate

[Bpy]$HSO_4$ = 1-*n*-Butyl pyridinium hydrogen sulfate

[Emim]$PF_6$ = 1-Ethyl-3-methyl-1*H*-imidazol-3-ium hexafluorophosphate

[Emim]$BF_4$ = 1-Ethyl-3-methyl-1*H*-imidazol-3-ium tetrafluoroborate

[Hbim]$BF_4$ = 1-*n*-Butyl imidazolium tetrafluoroborte

[Hbim]$PF_6$ = 1-*n*-Butyl imidazolium tetrafluorophosphate

[Hbim]Cl = 1-*n*-Butyl imidazolium chloride

[Hbim]Br = 1-*n*-Butyl imidazolium bromide

[Hbim]$ClO_4$ = 1-*n*-Butyl imidazolium perchlorate

[Hbim]TFA = 1-*n*-Butyl imidazolium trifluoroacetate

[Hbim]OTf = 1-*n*-Butyl imidazolium triflate

[Hbim]$NO_3$ = 1-*n*-Butyl imidazolium nitrate

[Hbim]$H_2PO_4$ = 1-*n*-Butyl imidazolium biphosphate

[Hmim]$BF_4$ = 1-Methyl imidazoilum tetrafluoroborate

[Hmim]$PF_6$ = 1-Methyl imidazolium hexafluorophaophate

[Hmim]TFA = 1-Methyl imidazoilum trifluoroacetate

[Hmim]$NO_3$ = 1-Methyl imidazoilum nitrate

[Hmim]OTf = 1-Methyl imidazoilum triflate

[Hmim]$H_2PO_4$ = 1-Methyl imidazoilum biphosphate

[Hemim]$BF_4$ = 1-Methyl-3-heptyl imidazolium tetrafluoroborate

[Hydemim]$PF_6$ = 1-(2-Hydroxyethyl)-3-methyl imidazolium hexafluorophosphate

[NbuPy]$BF_4$ = *n*-Butylpyridinium tetrafluoroborate

[Tmba]$NF_2$ = *N*-Trimethyl-*n*-butylammonium *bis*-(trifluoromethyl sulfonyl)-imide

[Bmp]$NF_2$ = 1-*n*-Butyl-1-methylpyrodinium *bis*-(trifluoromethyl sulfonyl)-imide.

[$C_4$mim]$HSO_4$ = 1-*n*-Butyl-3-methylimidazolium hydrogensulfate

[Cmim]$HSO_4$ = 3-Carboxymethyl-1-methylimidazolium bisulfate

[Pmim]Br = 1-Methyl-3-propylimidazolium bromide

[Pmim]$BF_4$ = 1-Methyl-3-propylimidazolium tetrafluoroborate

[Pmim]$PF_6$ = 1-Methyl-3-propylimidazolium hexaflourophosphate

[nbp]$FeCl_4$ = *n*-Butylpyridinium tetrachloroferrate

[TMGT]TFA = 1,1,3,3-*N*,*N*,*N'*,*N'*-Tetramethyl guanidinium trifluoborate

[Edu]$SO_3CF_3$ = 8-Ethyl-1,8-diazabicyclo[5,4,0]-7-undecinium trifluoromethane sulfonate

[TBAI] = Tetra-*n*-butylammnoium iodide

[TBAB] = Tetra-*n*-butyl ammonium bromide

[Tmba]$NTf_2$ = Trimethylbutylammonium triflimide.

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