Chapter 1A

General review on target-oriented ionic liquid based systems in catalysis
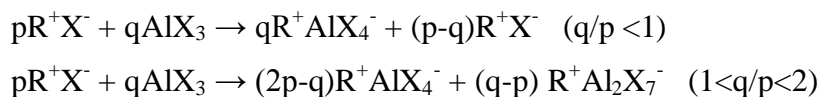
1B.1. Hallometallate ionic liquids

Ionic liquids containing complex metal halide anions were among the earliest developed room temperature ionic liquids (RTILs) obtained by mixing of different molar fractions of organic halide salts with corresponding metal halides. They are often termed as the first generation ILs. The unique characteristics of such families of ILs depend on the presence of various compositions of complex anionic equilibria of metal halide present and also on the nature of metal. Chloroaluminates (III) were the first group of chlorometallate ILs to draw significant attraction from the scientific community. The first ever chlorometallate dates back to 1972 reported by Parshall [1] that low melting tetraalkyl ammonium salts of $SnCl_3^-$ and $GeCl_3^-$ could be used as convenient solvents for homogeneous $PtCl_2$ catalyzed reactions of olefins such as hydrogenation, isomerization and hydroformylation. The pioneering work of Osteryoung [2], Hussey and Wilkes [3] examined this eutectic composition of chloroaluminate (III) ILs for development of lower temperature thermal batteries and also as homogeneous Lewis acid catalyst in Friedel-Craft reaction. The search for "water and air stable" halometallates ionic systems and their uses in various fields received continuous attention over the last two decades after the key review by Welton in 1999 [4] and the following works of Fuller et al. [5] , Wilkes and Zaworotko [6] and Bonhote et al. [7]. The industrial uses of Lewis acidic chloroaluminate(III) ILs in various processes were reviewed by Pletchkova and Seddon [8] who described the possible applications of these functional material in diverse fields bearing other halometallate systems. At present, this IL system covers the entire metallic region of the periodic table with variety of physicochemical properties. Diverse newer applications have been devised and given scope to improve over the existing technologies. These functional materials can play a key role in transformation of biomass to energy products [9], gas scrubbing processes [10], synthesis of new semiconductor materials [11], battery electrolytes [12], electroplating and polishing treatments [13], homogeneous and heterogeneous catalysis [14, 15] and also in controlled extraction and separation processes [16]. The dominating tricky key factor is the anion speciation. If it could be understood wisely, much control can be gained over the desired properties. Estager et al. [17] reviewed on halometallate ionic liquids which focus on various experimental techniques that can be applied to study and characterize the anion speciation in these

ionic liquids and also discussed the specialized applications of this class of IL in different fields.

1B.2. Acidity of chlorometallate ionic liquid systems

The composition of anionic speciation is the dominating factor for tuning of any physicochemical properties of chlorometallate ionic liquids such as viscosity, density, ionic conductivity, thermal stability, sensitivity towards moisture, acidity etc. [17]. The Lewis acidity of chlorometallates is a function of electron deficient nature (electrophilicity) of the metal and also the mole fraction of metal chloride with respect to the molar ratio of organic chloride salt. Both these factors determine the composition of anionic speciation in equilibrium state during reactions of the organic chloride with the metal chloride. Consequently, the Lewis acidity/basicity of chlorometallates depends on the constituent of anionic species which can be tuned by adjusting the molar ratio of both the components to a suitable level. For example, when an aluminum halide, AlX_3, is combined with an organic salt, R^+X^- the constituents of the resulting ionic liquid are determined by the molar ratio of these components, q/p, according to the following reactions, which proceed essentially to completion [18]:

$$pR^+X^- + qAlX_3 \rightarrow qR^+AlX_4^- + (p-q)R^+X^- \quad (q/p <1)$$
$$pR^+X^- + qAlX_3 \rightarrow (2p-q)R^+AlX_4^- + (q-p) R^+Al_2X_7^- \quad (1<q/p<2)$$

If q/p is less than 1, the melt is considered as basic since it contains halide ions that are not bound to aluminium. However, when the ratio is in between 1 and 2, the melt contains $R^+Al_2X_7^-$ as one of the principal constituent which is a halide acceptor and hence considered as acidic. Melts with $q/p=1$ were considered neutral due to presence of only $R^+AlX_4^-$ species. Therefore, it is of utmost concern to understand the complex speciation and after that careful assignment should be done.

For designing of efficient Lewis acidic chlorometallates, one must consider the electron deficient state of metal cation and also availability of its LUMO. Based on the Lewis acidic strength of metal chlorides, different chlorometallate ILs were synthesized for acid catalyzed organic reactions [19-24]. For example, chlorozincate(II) ionic systems are weaker in acidic properties as compared to the chloroaluminate(III) ionic systems [25]. The speciation of neutral chlorozincate(II) anion is $[ZnCl_4]^-$ at $\chi_{ZnCl_2}=0.33$ in contrast to the neutral chloroaluminate(III) anions $[AlCl_4]^-$ or $[Al_2Cl_7]^-$ at $\chi_{AlCl_3}=0.5$.

All compositions of the chlorozincate (II) with χ_{ZnCl_2}>0.33 are Lewis acidic and contain oligomeric $[Zn_xCl_{(2x+2)}]^{2-}$ species. The mild Lewis acidity of In(III) centre is also responsible for moderate Lewis acidity of chloroindate(III) ionic liquids with neutral anionic speciation $[InCl_6]^{3-}$ at mole fraction=0.25 [20]. The water tolerant capacity of chloroferrate (III) ionic liquids gives lots of scope for designing of strong Lewis acidic ionic systems for efficient application as industrial catalysts in spite of the limited capacity to form the most acidic dimeric $[Fe_2Cl_7]^-$ anions in homogeneous composition [26, 27].

1B.3. Stability of chlorometallate ionic liquids in water

Chlorometallate ionic liquids are quite sensitive to water. They undergo rapid hydrolysis and hydration reactions [28]. These reactions would change their chemical compositions and physicochemical properties. For example, hydrolysis of chloroaluminate ionic liquid undergoes violent exothermic reaction and forms high energy Al-O bond. The strong Lewis acidity of chloroaluminate(III) ionic liquids provide greater tendency for reaction with trace amount of water. Studies on the hydrolysis products identified various oxo- and hydroxochloroaluminate (III) species in addition to hydrochloric acid (equation-1) [29].

$$2[AlCl_4]^- + H_2O \rightarrow [Al_2Cl_5O]^- + [HCl_2]^- + HCl \text{-------(1)}$$
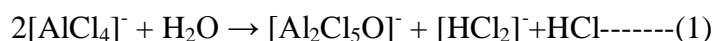
The Lewis acidity of chloroaluminate(III) ionic liquids are sufficient for utilization as industrial Lewis acid catalysts in dry atmosphere. For the acid catalyzed reactions influence of super acidic protons generated in the partial hydrolysis process carried out in chloroaluminate(III) media cannot be ruled out. The major industrial challenge of chloroaluminates(III) led to the development of chloroindate(III) and chlorozincate(II) salts as efficient moisture stable Lewis acid catalysts in open air [20, 30, 31] without dissociative hydrolysis process. The ionic salts of chloroindate(III) bind stoichiometric amount of water molecules through co-ordination to the metal center resulting changes in the composition of metal salts and also their properties without release of HCl. They can be used under anhydrous condition after drying in high vacuum or as hydrates in chemical reactions [17]. Some choline-based hydrated chlorometalltes were also employed as Lewis acid catalysts and in electrodeposition processes [32]. Two chlorocuprate (II) systems: $[C_2mim]Cl-CuCl_2$ and $[ch]Cl-CuCl_2-2H_2O$ generates various mole fractions of hydrated ionic salts by gradual replacement of

[CuCl$_4$]$^-$ anion of pure ionic liquid content (χ_{H_2O}=0.10) to chloroaquacuprate(II) complexes (χ_{H_2O}=0.95) and then complete hydrated cation of [Cu(H$_2$O)$_n$]$^{2+}$ where n=4-6 in dilute aqueous solution of ionic liquid [33, 34]. Abott et al. [35] synthesized an eutectic composition of choline-based hydrated chlorochromate(III) ionic liquid, [ch]Cl-CrCl$_3$.6H$_2$O, at mole fraction $\chi_{CrCl_3.6H_2O}$=0.67 that cannot be prepared from direct mixing of the corresponding reactants.

From literature, it is observed that hydrophobic nature of chlorometallte systems can be expected from selected metal chlorides based on Fe(III), Sn(II) or Pb(II) [36]. Although, the general practice to make a hydrophobic ionic liquid is the introduction of highly fluorinated anions such as [NTf$_2$]$^-$ or cations with long alkyl chains [37]. The most important contribution to understand this dual phase behavior was by Xie and Taubert who synthesized [C$_n$mim]Cl-FeCl$_3$ systems (n=4 or 12; χ_{FeCl_3}=0.5) from an exothermic reaction of [C$_n$mim]Cl and anhydrous FeCl$_3$ and also from endothermic reaction between [C$_n$mim]Cl and FeCl$_3$.6H$_2$O [36]. This ionic liquid-water mixture became one phase at lower temperature with lower ionic liquid ratios while they underwent phase separation upon heating and also with increasing amount of ionic liquids. The variation of phase separation was attributed to cohesive energy of water causing solvophobic immiscibility, long-rang coulombic forces as suggested by Debye-Huckel theory, competitive H-bonding between cation---anion and anion---HOH---anion etc. [38, 39]. Later on Estager et al. suggested that nephelauxetic effects may play a part in the hydrophobic behavior of tetrahedral [FeCl$_4$]$^-$ for increasing covalent character of Fe-Cl bearing lower partial negative on the chloride ions and thus decreases the ability of H-bonding with water [40].

1B.4. Sulfonic acid functionalized chlorometallate ionic liquid systems

It has always been interesting to develop new functionalized ionic liquids fit for different purposes. As already been explained in **Section 1A.3 of Chapter 1A**, the -SO$_3$H acid functionalized ionic liquid systems (SAFIL) serves the purpose of task specific ionic liquids at its best in different disciplines. In comparison with mineral acids such as HNO$_3$, H$_2$SO$_4$, HCl, they have Brönsted acidic -SO$_3$H sites for excellent solubility in water and thus perform as efficient reusable homogeneous catalyst in many acid-catalyzed organic reactions [41-43]. They appear to be greater candidate for

replacement of the above mentioned mineral acids as recyclable acidic catalyst due to fulfillment of all basic characteristics of ionic liquid properties [44]. Studies have been performed on incorporation of an acidic ionic liquid with a Lewis acid co-catalyst to enhance catalytic performance [45, 46]. This observation led to the conclusion that combination of Brönsted and Lewis acidic properties within an ionic liquid can impart new properties to the system. It is a well-established fact that Lewis acidic chloroaluminate salts become super acidic in presence of protons. Therefore, synthesis of ionic liquids with dual Brönsted-Lewis acidic sites may provide a route for generation of "water and air stable" bi-functionalized super acidic catalysts at atmospheric conditions.

Efforts have been put in past to design Brönsted-Lewis acidic catalyst systems by bubbling dried HCl gas into Lewis acidic ILs [47]. However these could be considered as mixtures not real Brönsted-Lewis acidic ILs and also use of HCl gas is very hazardous and the reuse process is difficult due to its highly volatile nature.

The latest comprehensive review on acidic ILs by Amarasekara describes a wide range of acidic ionic liquids including the references of specific N-alkylsulfonic group functionalized imidazolium, pyridinium, phosphonium and ammonium cations [44]. The review article on halometallate ionic liquids in 2014 excluded the literature of -SO_3H functionalized chlorometallate ionic systems based on imidazolium, pyridinium and ammonium cation as potential functional material [17]. Other literature reports have been found on different N-alkylsulfonic acid functionalized chlorometallate systems. However, no reports were found on direct N-sulfonic acid functionalized chlorometallate systems till 2015. Based on these literature data, we aimed to synthesize N-SO_3H functionalized imidazolium chlrometallates of transition metal chlorides of Fe(III), Zn(II) and Cu(I) as Brönsted-Lewis acidic solid material for further applications as reusable heterogeneous catalyst in the preparation of *bis*(indolyl)methane derivatives at mild condition.

In 2008, Liu [48] first prepared three members of -SO_3H functionalized chlorozincates: (3-sulfonic acid)-propyltriethylammonium chlorozincinates by treating a mixture of different mole fraction (mole fraction of $ZnCl_2$ = 0.5, 0.64, and 0.75) of zinc chloride with [HSO_3– $(CH_2)_3$–NEt_3][Cl] at 100 °C with vigorous stirring for 4h (**Scheme 1B.1**). The system was Brönsted-Lewis acidic if the mole fraction of

$ZnCl_2>0.5$, otherwise it only possessed Brönsted acidity. These IL systems were used as catalysts in the dimerization process of rosin. Among the different compositions synthesized, $[HSO_3–(CH_2)_3–NEt_3]Cl–ZnCl_2(x = 0.64)$ exhibited the best catalytic activity and recyclability up to fifth consecutive cycles. As explained by the authors, the reason behind this excellent stability might be the covalent bonding between the sulfonic acid group and the IL cation and also the inertness of $Zn_2Cl_5^-$ anion towards water or Brönsted acid.
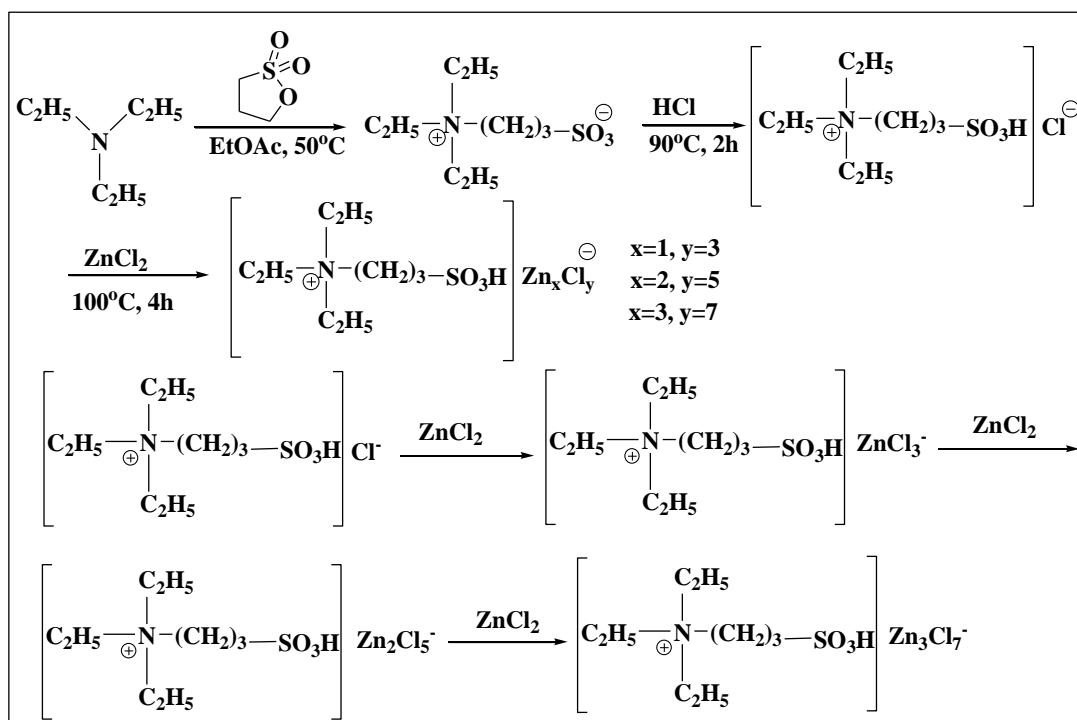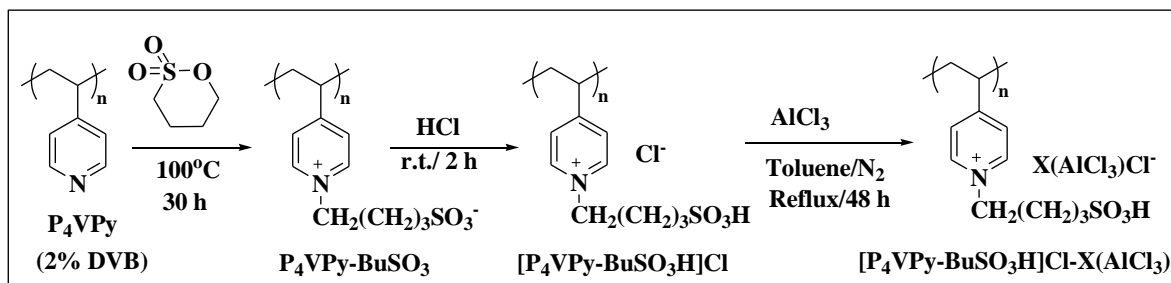

Scheme 1B.1: Synthesis of (3-sulfonic acid)-propyltriethylammonium chlorozincinates

The author extended the above methodology for formation of another Brönsted-Lewis acidic IL: 1-(3-sulfonic acid)-propyl-3-methylimidazole chlorozincinates ($[HO_3S-(CH_2)_3-mim]Cl-ZnCl_2$) with different mole fractions of $ZnCl_2$ [49]. The catalytic efficiencies of these ILs were again evaluated for the rosin dimerization reaction. The IL with mole fraction of $ZnCl_2 = 0.64$ gave the best catalytic performance under the optimized reaction conditions. The IL also exhibited very good recyclability up to fifth consecutive cycle.

Boroujeni and Ghasemi [50] synthesized a poly(4-vinylpyridine)-supported chloroaluminate ionic liquid: $[P4VPy-BuSO_3H]Cl-X(AlCl_3)$ (**Scheme 1B.2**) and investigated it as highly efficient heterogeneous catalytic system for the synthesis of

biscoumarins by two-component one-pot domino Knoevenagel-type condensation/Michael reaction between various aliphatic and aromatic aldehydes with 4-hydroxycoumarin. The major advantages of this route were clean protocol, short reaction time, simple work-up, easy preparation and handling of the catalyst system.

Scheme 1B.2: Synthesis of poly(4-vinylpyridine)-supported chloroaluminate ionic liquid: [P4VPy-BuSO$_3$H]Cl-X(AlCl$_3$)

The ammonium based sulfonic acid functionalized chloroironinate ionic liquid: 3–sulfonic acid)–propyltriethylammoniumchloroironinate [HO$_3$S-(CH$_2$)$_3$-NEt$_3$]Cl-[FeCl$_3$]$_x$ (χ_{FeCl_3}=0.67) (**Scheme 1B.3**) was developed as reusable acid catalyst by Liu [51] for esterification reaction. The synergistic effect of the Lewis and Brönsted acidic sites of the catalyst system enhanced its performance towards the esterification reaction. The IL was reusable up to sixth consecutive cycle.
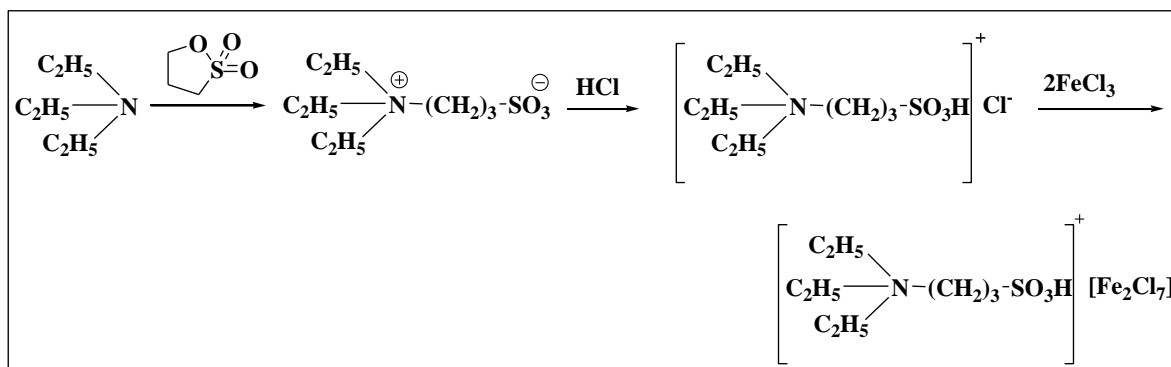
Scheme 1B.3: Synthesis of 3-sulfonic acid)–propyltriethylammoniumchloroironinate [HO$_3$S–(CH$_2$)$_3$–NEt$_3$]Cl–[FeCl$_3$]$_x$

In the same year, Liu [52] synthesized -SO$_3$H bearing chlorochrominate IL: (3-sulfonicacid)-propyl-triethylammoniumchlorochrominate [HO$_3$S-(CH$_2$)$_3$-NEt$_3$]Cl-CrCl$_2$ (χ_{CrCl_2} = 0.55) (**Fig. 1B.1**) and employed it as reusable catalyst for dehydration of fructose to 5-hydroxymethylfurfural (HMF). A maximum of 93.4% yield of HMF was

obtained under optimized reaction conditions and the IL was reusable up to five times without appreciable loss in activity.
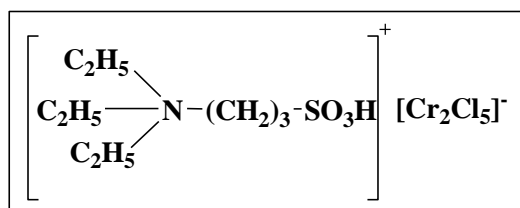
$$\left[\begin{array}{c} C_2H_5 \\ C_2H_5 \longrightarrow N - (CH_2)_3 - SO_3H \\ C_2H_5 \end{array}\right]^+ [Cr_2Cl_5]^-$$

Fig. 1B.1: Structure of (3-sulfonic acid)-propyl-triethylammonium chlorochrominate [HO$_3$S-(CH$_2$)$_3$-NEt$_3$]Cl-CrCl$_2$

The same group also explored the use of (3-sulfonic acid)-propyltriethylammonium chlorozincinate [HO$_3$SC$_3$NEt$_3$]Cl-ZnCl$_2$ (molar fraction of ZnCl$_2$, $\chi = 0.83$) (**Fig. 1B.2**) as an efficient catalyst for alkylation reactions of isobutene [53]. Under optimum reaction conditions, 100% conversion of isobutene with 91.7% selectivity towards C$_8$-alkylated products was obtained. The IL was reusable up to tenth consecutive cycles.
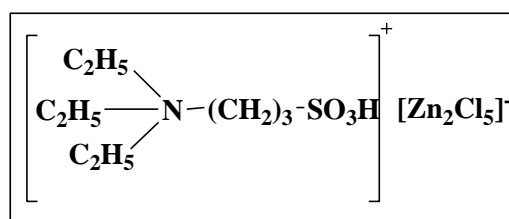
$$\left[\begin{array}{c} C_2H_5 \\ C_2H_5 \longrightarrow N - (CH_2)_3 - SO_3H \\ C_2H_5 \end{array}\right]^+ [Zn_2Cl_5]^-$$

Fig. 1B.2: Structure of (3-sulfonic acid)-propyltriethylammonium chlorozincinate [HO$_3$SC$_3$NEt$_3$]Cl-ZnCl$_2$

The objective of this chapter was to synthesize three new catalytic frameworks of 3-methyl-1-sulfonic acid imidazolium transition metal chlorides [Msim][X] ionic salts as solid acids with dual acidic sites, where X = [FeCl$_4$]$^-$, [Zn$_2$Cl$_6$]$^{2-}$, [CuCl$_2$]$^-$: a series of 3-methyl-1-sulfonic acid imidazolium transition metal chlorides. The catalytic efficiency of these solid acids were evaluated in the synthesis of various *bis*(indolyl)methane derivatives at ambient conditions using the reaction of indole with different aromatic aldehydes.

1B.5. Importance of *bis*(indolyl)methane (BIM) derivatives

Indole and their derivatives are well known as valuable heterocyclic compounds in organic synthesis which have versatile biological activities and are widely present in various biologically active natural products [54-56]. *Bis*(indolyl)methanes (BIM) are a class of compounds with variety of pharmacological properties and their chemistry has been reviewed by Shiri [57]. These compounds have many applications in material sciences, agrochemicals, and pharmaceuticals sciences [58]. It works as intercellular signal molecule in bacteria to regulates various aspects of bacterial physiology, including spore formation, plasmid stability, and resistance to drugs, biofilm formation, and virulence [59]. Studies have displayed their role for promoting beneficial estrogen metabolism in men and women [60], induce apoptosis in human cancer cell [61], inhibit bladder cancer growth [62], and prevent renal cell carcinoma growth [63], inhibitory activity on lung cancer cells [64], and active against colon cancer [65]. Some of these derivatives possess broad range of pharmacological values including antibiotic [66] and antibacterial activities [67], analgesic and anti-inflammatory activities [68], exhibit antimicrobial and antifungal activities [69], serve as cytodifferentiating agents [70], act as antileishmanial agent [71], exhibit topoisomerase IIα catalytic inhibition [72], inhibitors of the platelet-derived growth factor receptor kinase [73], active against phenobarbital-induced hepatic CYP mRNA expression [74] etc. In addition, they can be applied as chemotherapeutic agents against tumors [75] and also used for determination of trace amount of heavy metal ions via complexation reactions [76]. Due to these versatile applications and attractive possibilities offered by the BIMs, there is a great interest in the synthesis of these compounds.

1B.6. Ionic liquid mediated/catalyzed synthesis of *bis*(indolyl)methanes (BIMs)

Bis(indolyl)methane derivatives are generally prepared from the acid catalyzed electrophilic substitution of indoles with various aldehydes and ketones through in *situ* formation of azafulvenium salts as reaction intermediate. A variety of Brönsted or Lewis acidic catalytic systems have been utilized in recent years in solution or solvent-free conditions in presence of various energy sources such as thermal, mechanical or microwave energies. Some examples of such catalysts are protic acids [77], NH_4Cl [78],

trichloro-1, 3, 5-triazine [79], transition metal complexes [80], I_2 [81], NBS [82], $KHSO_4$ [83], CAN [84], hexamethylenetetramine-bromine [85], $Sc(OTf)_3$ [86], $InCl_3$ [87], microwave assisted Lewis acids ($BiCl_3$, $FeCl_3$, $InCl_3$, $CoCl_2$, $ZnCl_2$) [88], $H_3PW_{12}O_{40}$ [89], $La(NO_3)_3.6H_2O$ [90], and $Fe(DS)_3$ [91]. TiO_2 [92], $LiClO_4$ [93], $NaBF_4$ [94], Ph_3CCl [95], metal hydrogen sulfates [96] etc. Most of them lost their catalytic activities during aqueous work-up step because of moisture sensitivity in spite of good catalytic activity for the formation of desired product. The Lewis acid catalyzed reactions require more than stoichiometric amount of catalyst as they are trapped/deactivated by indole-N during the reaction [97]. Several modified acidic catalysts have been developed in the form of heterogeneous catalysts [98-101], use of acidic ionic liquids [102], Lewis acids/ionic liquids [103] till date to eliminate other limitations of the above mentioned catalytic systems such as longer reaction time, non-recyclability of catalysts, high reaction temperature, use of volatile organic solvent, corrosive nature of catalysts which eventually leads as toxic chemical wastes to the environment.

From this point of view, the designing and evaluation of various ILs have shown themselves as environmentally benign dual solvent/catalyst systems for the preparation of BIM at different reaction conditions. In this section we have included the literature review of ILs catalyzed/mediated synthesis of *bis*(indolyl)methane derivatives till 2015.

The ILs mediated *bis*(indolyl)methanes synthesis was first studied by Yadav et al. [102] involving the two component reaction of variety of aldehydes (or ketones)with indoles using recyclable hydrophilic 1-butyl-3-methylimidazolium tetrafluoroborate [bmim][BF_4] or hydrophobic 1-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF_6] ionic liquids at room temperature stirring. They produced 80-93% of products during 3-7.5 hour in which electron deficient aromatic aldehydes required more reaction time as compared to other aliphatic or electron rich aromatic aldehydes **(Scheme 1B.4).**

R = H, 5-OMe, 5-Br

R' & R'' = H, alkyl, aryl
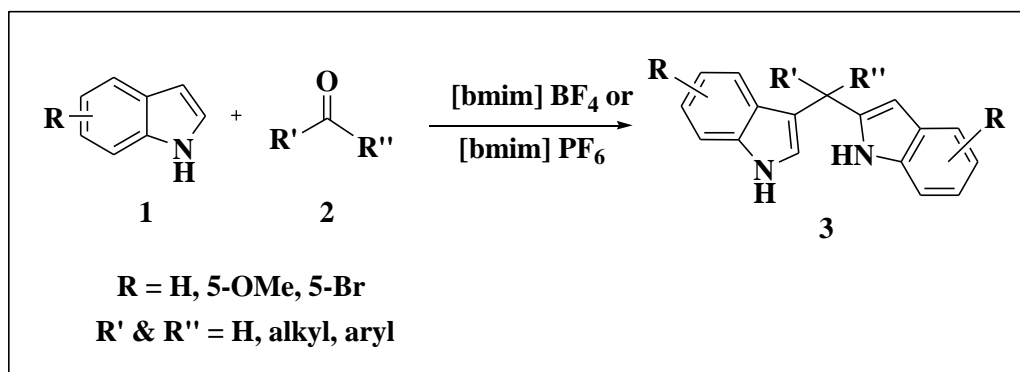
Scheme 1B.4: Synthesis of *Bis*(indolyl)methanes catalyzed by ionic liquids

In the year 2003, Ji et al. [103] studied this same reaction at room temperature in six ILs as reaction medium namely [bmim][PF$_6$], [hmim][PF$_6$], [omim][PF$_6$], [dmim][PF$_6$], [bmim][BF$_4$] and [hmim][Cl] (**Fig. 1B.3**) using 5 mol% of the Lewis acids catalysts such as In(OTf)$_3$, YbCl$_3$, InCl$_3$, BiCl$_3$, and ZnCl$_2$ for different reaction time. The reaction was optimized with 5 mol% of In(OTf)$_3$ catalyst in [omim][PF$_6$] ionic liquid for 15-75 min reaction starting from aliphatic and aromatic aldehydes with moderate to excellent yields of the indole derivatives (70-95%). However the recyclability profile of this catalytic system gradually deteriorated in the second and third cycles.
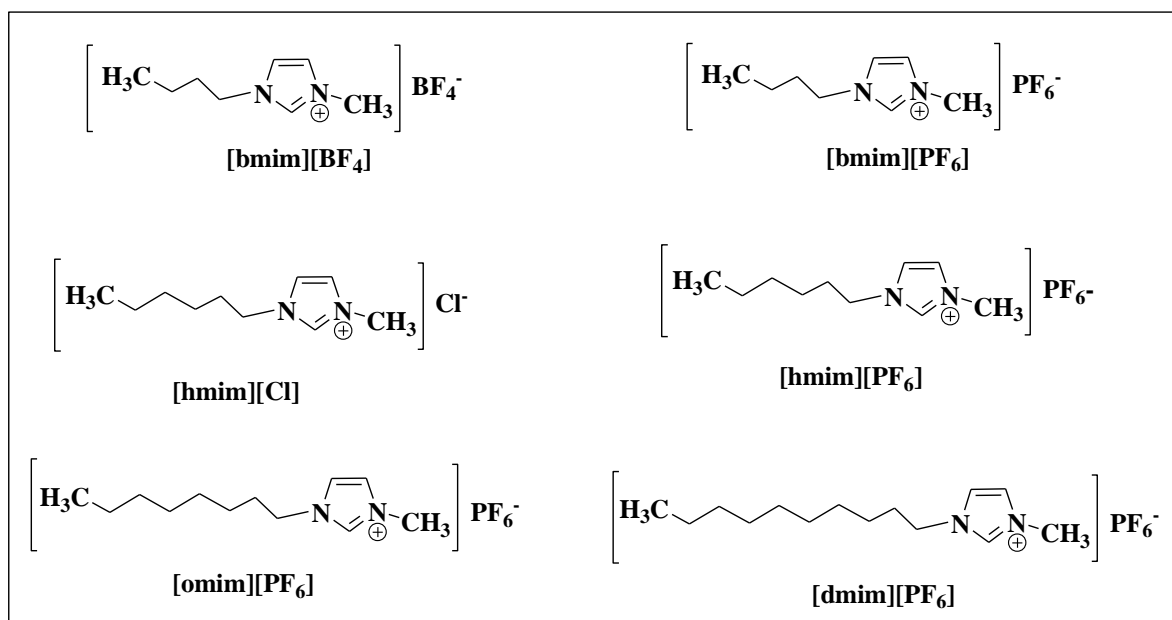

Fig. 1B.3: ILs used by Ji et al.

They also performed similar types of observation in 2004 for 5 mol% of FeCl$_3$.6H$_2$O catalyst in presence of seven different imidazolium ILs (**Fig. 1B.4**) such as

[bmim][PF$_6$], [hmim][PF$_6$], [omim][PF$_6$], [dmim][PF$_6$], [hmim][BF$_4$], [omim][BF$_4$] and [bmim][Cl] as reaction medium at ambient temperature for the electrophilic substitution of indole with various aldehydes [104]. Among the different combinations of IL and Fe(III) salt used, FeCl$_3$.6H$_2$O/[Omim][PF$_6$] system efficiently catalyzes the reactions with a good recyclability profile.
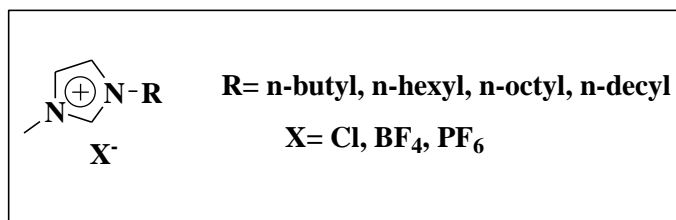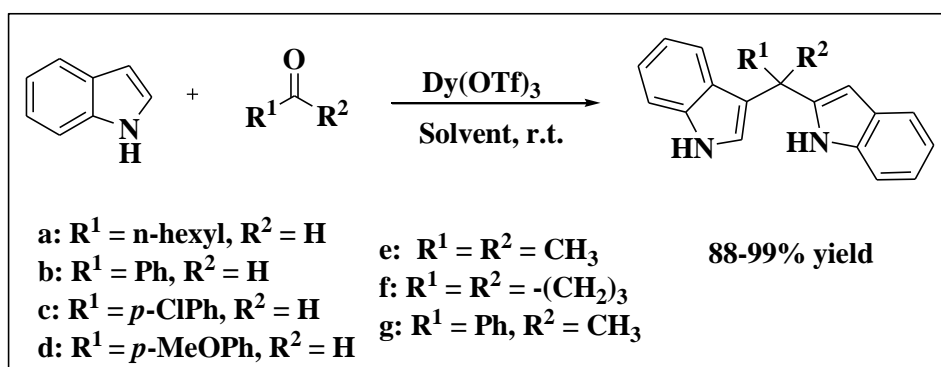

R= n-butyl, n-hexyl, n-octyl, n-decyl

X= Cl, BF$_4$, PF$_6$

Fig. 1B.4: Struture of imidazolium ILs

Mi et al. [105] used 2-5 mol% of Dy(OTf)$_3$ immobilized three ionic liquids [Bmim][BF$_4$], [Bmim][PF$_6$] and [bupy][BF$_4$] as efficient reusable catalytic systems for the reactions of indole with aldehydes/ketones at room temperature during 1-24 hour reaction time to form 88-99% of product (**Scheme 1B.5**). Reactions performed in ILs were found to be superior to the reactions carried out in aqueous medium both in terms of reaction time and percentage yields. Though the catalytic system was demonstrated to be a mild and efficient catalytic one, the cost of lanthanide triflate is of great concern.

a: R^1 = n-hexyl, R^2 = H
b: R^1 = Ph, R^2 = H
c: R^1 = p-ClPh, R^2 = H
d: R^1 = p-MeOPh, R^2 = H

e: R^1 = R^2 = CH$_3$
f: R^1 = R^2 = -(CH$_2$)$_3$
g: R^1 = Ph, R^2 = CH$_3$

88-99% yield

Scheme 1B.5: Dy(OTf)$_3$ catalyzed reactions of indole with aldehydes/ketones.

Gu et al. [106] investigated two acidic ILs catalysts [acmim][Cl] and [hmim][HSO$_4$] (**Fig. 1B.5**] for the electrophilic substitution of indole with variety of aldehydes in different organic solvents such as MeCN, THF, DMF, CH$_2$Cl$_2$ and EtOH at ambient temperature. They found 5 mol% of [hmim][HSO$_4$] ionic liquid in EtOH as optimized amount of catalyst with large number of electron-withdrawing/donating

group substituted aromatic aldehydes to generate excellent yields of *bis*(indolyl)methanes (80-99%) for 1-8 hour reaction.
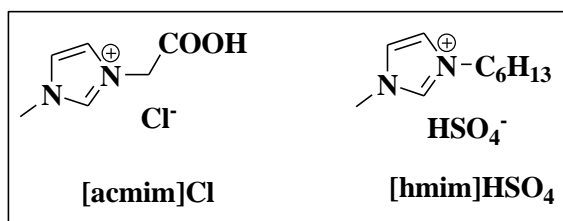

Fig. 1B.5: Structure of acidic ILs

They have shown that [hmim][HSO_4]/EtOH catalytic system could be reused up to five consecutive cycles with significant activity.

Hagiwara et al. [107] utilized an organo-catalytic procedure involving various acidic ILs grafted on silica gel (ILIS-SO_2Cl) (**Fig. 1B.6**) in solution of organic solvents like MeCN, EtOH and water for the preparation of *bis*(indolyl)methanes at mild temperature. The reaction afforded moderate to excellent results (64-98%) in acetonitrile for aromatic/aliphatic aldehydes during 1.5 to 19 hour reaction by 0.1 equivalent of ILIS-SO_2Cl catalyst which were the best results than Brønsted acidic ionic liquids, ILIS-SO_3H. The catalyst ILIS-SO_2Cl was reused four times in 93% average yield.
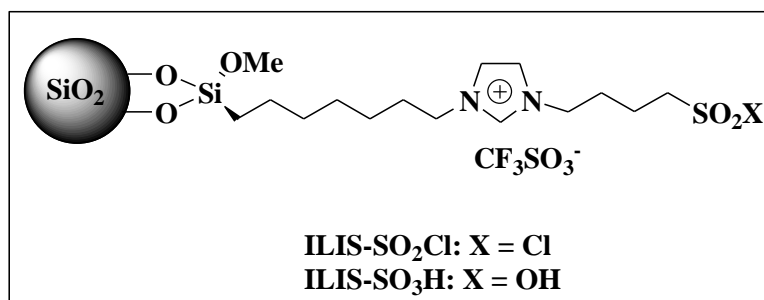

Fig. 1B.6: Structure of Silica supported acidic IL

Dabiri et al. [108] tested a model reaction of 4-chlorobenzaldehyde with indole at room temperature stirring in six different ILs viz. [Hmim][Tfa], [Hmim][HSO_4] [Hmim][OTs], [bmim][Br], [bmim][PF_6], [bmim][BF_4]. Among these, [Hmim][HSO_4] exhibited the best catalytic performance with a number of aliphatic, aromatic and heterocyclic aldehydes within 10-30 min reaction to produce excellent yields (82-94% yields).

Chakraborty et al. [109] explored the catalytic efficiency of room temperature ionic liquids derived from butylmethylimidazolium cation with different counter anions to afford *bis*(indolyl)methanes in neat at room temperature using 5 mol% of each catalyst. Among the various tested ionic liquids, they found the following order in case of catalytic efficiency: [bmim][MeSO$_4$]> [bmim][HSO$_4$] ~[bmim][MeSO$_3$]>> [bmim][BF$_4$]>[bmim][Br]>[bmim][NTf$_2$]~[bmim][PF$_6$]>[bmim][N(CN)$_2$]~[bmim][ClO$_4$]~[bmim][HCO$_2$]>[bmim][N$_3$]>[bmim][OAc]. They devised the ambiphilic role of the [bmim][MeSO$_4$] in catalyzing the reaction through a mechanistic model. The most reactive IL was recyclable up to three times.

Sadaphal et al. [110] conducted a microwave assisted efficient preparation method of the *bis*(indolyl)methanes of substituted aryl/heterocyclic aldehydes in recyclable 1-benzyl-3-methylimidazolium hydrogen sulphate ([bnmim][HSO$_4$]) ionic liquid under 450W microwave power within short reaction time (5-19 min) (**Fig. 1B.7**).

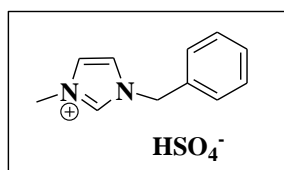**Fig. 1B.7**: Structure of 1-benzyl-3-methyl imidazolium hydrogen sulfate [bnmim][HSO$_4$]

Veisi et al. [111] introduced another catalytic system based on benzyl tributylammonium chloride-FeCl$_3$ ([BTBAC]Cl-FeCl$_3$) (**Fig. 1B.8**) under solvent-free thermal method at 60 °C with aldehydes and ketones for 8-30 min to get higher yields of the *bis*(indolyl) derivatives. This catalytic system was found to be highly chemoselective for arylaldehydes in the presence of aliphatic aldehydes and ketones.
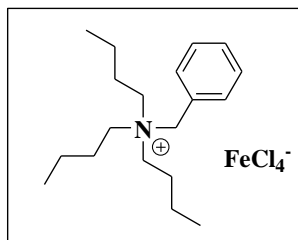

Fig. 1B.8: Structure of benzyl tributylammonium chloride-FeCl$_3$ system

Another efficient recyclable catalyst $Cu_{1.5}PMo_{12}O_{40}$ in molten tetraethylammonium chloride was reported by Seyedi et al. [112] for the reactions of aldehydes/aliphatic ketones/aryl ketones with indole at 100 °C within 5 min to 2 hour reaction to generate 71-95% of product. The aryl ketones require longer reaction time as compared to the aliphatic ketones.

The catalytic activity of $N-SO_3H$ based task-specific IL 3-methyl-1-sulfonic acid imidazolium chloride [Msim][Cl] was examined by Zolfigol et al. [113] using various types of aldehydes and ketones including heteroaldehydes in neat condition at ambient temperature in presence of 25 mol% of catalyst to get excellent results for 10-90 seconds (**Fig. 1B.9**). The non-recyclability of the catalyst is one of the major limitations although it was efficient, simple and cheaper in cost.
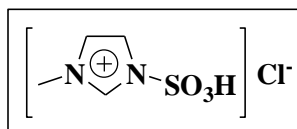

Fig. 1B.9: Structure of 3-methyl-1-sulfonic acid imidazolium chloride [Msim][Cl]

Again, Rajendran et al. [114] investigated 30 mol% of acidic $[Et_3NH][HSO_4]$ ionic liquid as efficient catalyst for the reactions of aromatic aldehydes with indole at 80 °C within 25-40 min reaction without any solvent. This inexpensive catalyst could be reused for more than five cycles without any significant loss in activity.

Liu et al. [115] also added another pyridinium based Brönsted acidic ionic liquid catalyst $[PyNCH_2CO_2H][HSO_4]$ for the condensation of indole with various 4-formylpyrazoles to afford the corresponding *bis*(indolyl)methane containing pyrazole (**Scheme 1B.6**) under solvent free condition at 80 °C. This protocol offered excellent yields within short period of time.
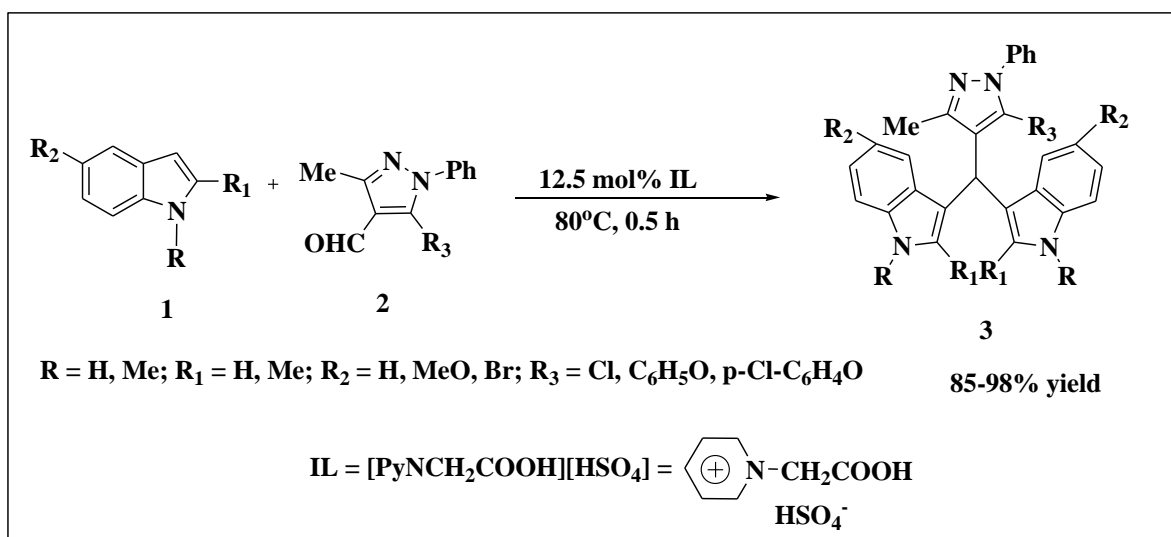
Scheme 1B.6: Synthesis of pyrazole containing *bis*(indolyl)methane derivatives catalyzed by acidic IL

The phosphonium based multi-SO_3H group (**Fig. 1B.10**) containing IL catalyst was introduced by Vahdat et al. [116] in aqueous solution at room temperature stirring using 1 mol% of catalyst with various aldehydes and ketones for 1-25 min reaction. This catalytic system showed chemo selectivity towards benzaldehyde in a mixture with acetophenone. Along with that, the catalytic system could be reused up to six cycles without appreciable loss in activity.
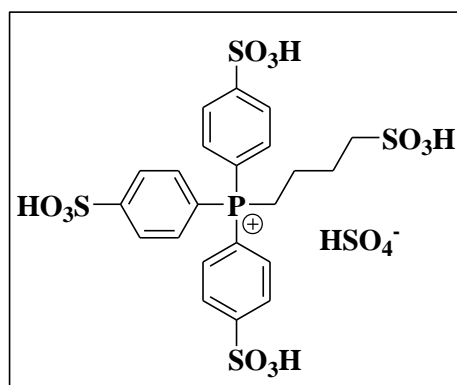
Fig. 1B.10: Structure of phosphonium based multi-SO_3H IL

Zhang et al. [117] also prepared a novel series of *bis*(indolyl)methanes containing 1, 2, 3-triazolyl moiety using the already mentioned Brönsted acidic IL [$PyNCH_2CO_2H$][HSO_4] by Liu et al. (2011) [115] at 80 °C in 0.5 hour. They explored the scope of this method in a wide variety of substituted indoles and 4-formyl-1, 2, 3-triazole and products were obtained in good to excellent yields (**Scheme 1B.7**).
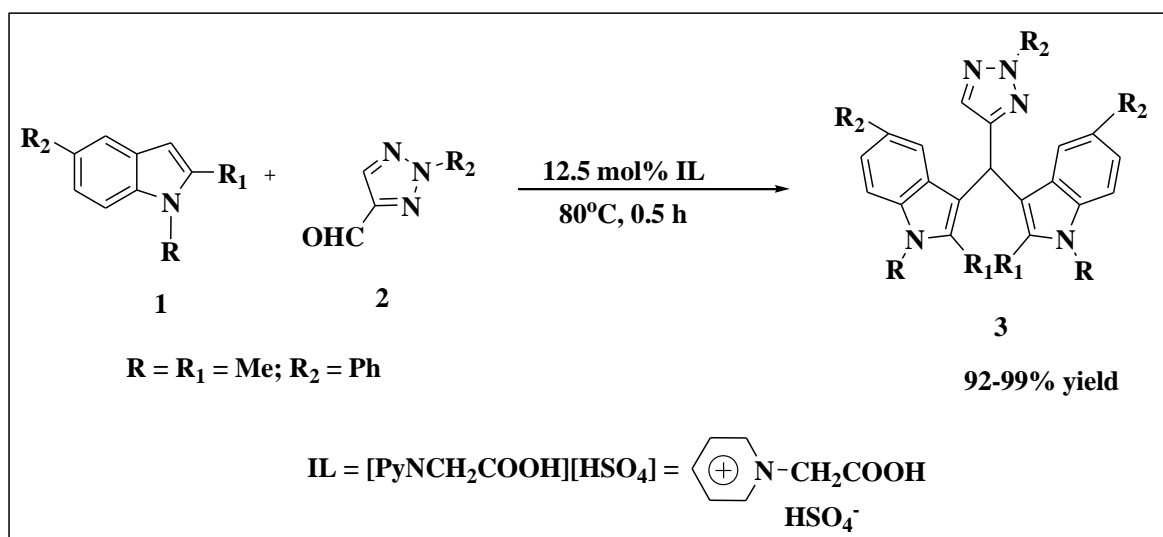
Scheme 1B.7: Synthesis of *bis*(indolyl)methanes containing 1,2,3-triazolyl moiety

Kalantari et al. [118] explored acidic IL triethyl ammonium dihydrogen phosphate [Et$_3$NH][H$_2$PO$_4$] as efficient catalyst for the same reaction of aryl aldehydes with indole at 100 °C for 5-30 min reaction to form 84-98% of yields of bis(indolyl)methanes. The author did not mention anything about the recyclability of the catalytic system.

Das et al. [119] published another work about the synthesis of aryl/aryl(3,3'-bis-3-methylindolyl)methanes and aryl(bis-3,3'-indolyl)methanes in presenc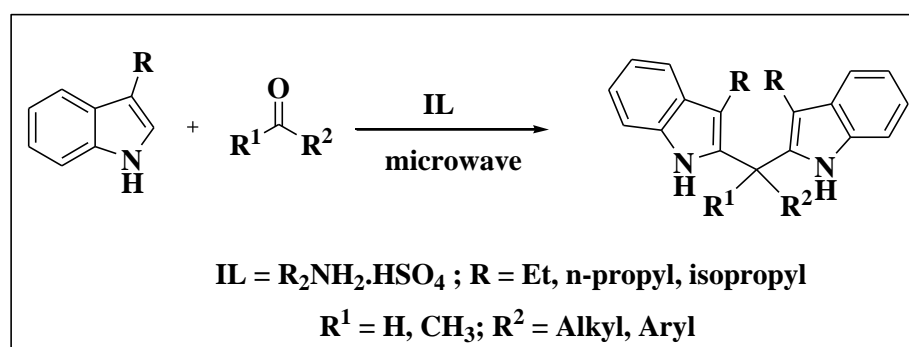e of reusable acidic ILs catalysts derived from secondary amine based ILs (**Scheme 1B.8**) under microwave irradiation (560W) in ethanol for shorter reaction time to get excellent results.

Scheme 1B.8: Synthesis of alkyl/aryl(3, 3'-bis-3-methylindolyl)methanes and aryl(bis-3,3'-indolyl)methanes catalyzed by acidic IL

Vahdat et al. [120] demonstrated two non-conventional heteropolyanion-based ionic liquids systems (**Fig. 1B.11**) as reusable sold acidic catalysts in water with a variety of aldehydes and carbonyl compounds in presence of 1 mol% of catalyst at room temperature within less reaction period. They produced higher yields of the indole derivatives and also can be recycled for six consecutive runs.
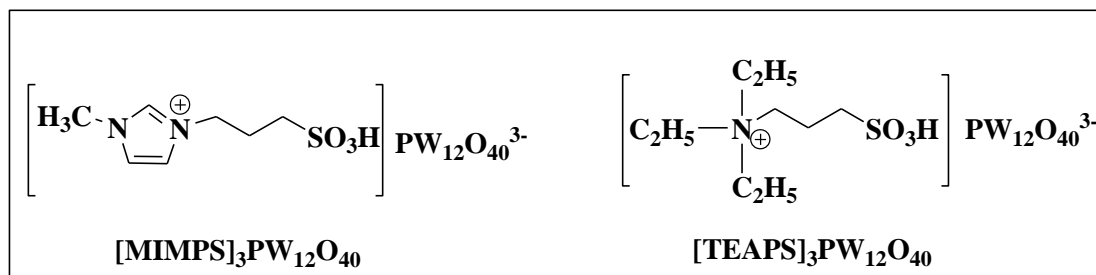
Fig. 1B.11: Structure of heteropolyanion based IL systems

Gupta et al. [121] used sulfuric acid in methanol as efficient catalyst in molten *N*-butyl-pyridinium bromide as medium for the same synthesis at moderate experimental conditions of temperature and ambient pressure for 15 min reaction.

Mulla et al. [122] performed the synthesis of *bis*(indolyl)methane in excellent yields using ethyl ammonium nitrate (EAN) as reusable ionic liquid at room temperature (**Scheme 1B.9**) for 1-10 min. The protocol involves an electrophilic substitution reaction of indoles with several aldehydes.
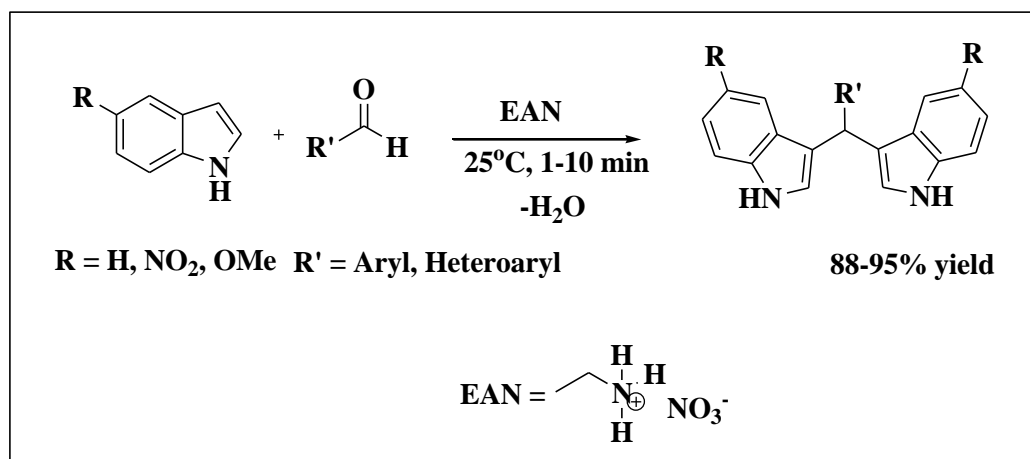
Scheme 1B.9: Synthesis of *bis*(indolyl)methane derivatives mediated by EAN

Zare et al. [123] synthesized a large number of *bis*(indolyl)methanes from the reactions mixture of indole /or 2-methyl indoles with aldehydes and ketones in presence of 25 mol% of -SO_3H functionalized IL catalyst [Et_3NSO_3H][Cl] at room temperature

solvent-free grinding method for 3-15 min to produce 79-98 % of product. During work-up step, addition of water to the reaction mixture followed by treatment with NaOH converted the IL to Et$_3$N and Na$_2$SO$_4$. The Et$_3$N was recovered from the dichloromethane extract and then again reconverted to the initial IL by reaction with ClSO$_3$H (**Scheme 1B.10**).

$$Et_3N \ + \ ClSO_3H \ \xrightarrow{\ CH_2Cl_2\ } \ [Et_3NSO_3H]Cl$$
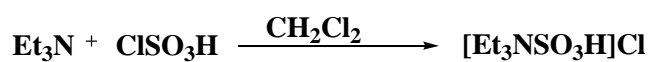
Scheme 1B.10: IL prepared by Zare et al.

Khazaei et al. [124] employed three tributyl(carboxymethyl)phosphonium halide (**Scheme 1B.11**) as task-specific catalysts for the preparation of *bis*(indolyl)methane derivatives of substituted aryl aldehydes using mortar and pestle at mild condition. Out of the three, tributyl(carboxymethyl)phosphonium bromide acted as highly efficient, homogeneous and green catalyst utilizing 25 mol% of the catalyst within short time.
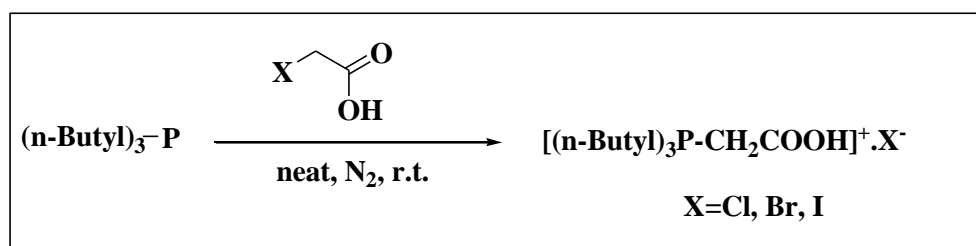
Scheme 1B.11: Preparation of phosphonium ionic liquids

Moosavi-Zare et al. [125] employed 20 mol% of 1-carboxymethyl-3-methylimidazolium chloride {[cmmim]Cl} (**Fig. 1B.12**) as reusable homogeneous catalyst for the preparation indole with aryl aldehydes under solvent-free grinding method ambient temperature for 8-15 min reaction to generate 87-98% of product.

Fig. 1B.12: Structure of 1-carboxymethyl-3-methylimidazolium chloride {[cmmim]Cl} IL

Ying et al. [126] prepared four novel multiple-acidic ILs based on triethanolamine (TEOA) (**Scheme 1B.12**) and examined their cataly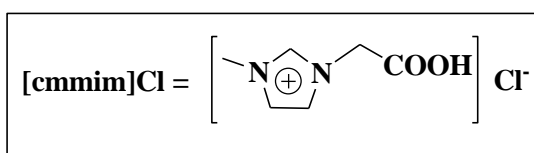tic activity under solvent-free condition at room temperature to synthesize *bis*(indolyl)methanes. They found 10 mol% of [TEOA][HSO$_4$] as the best optimized amount of the reactive IL catalyst for reactions of various aldehydes/ketones with indole/substituted indole to afford 70-99% yields within 2-30 min. This IL was recycled for five times with only a slight decrease in catalytic activity.

From the above discussion, we didn't find any literature on use of Brönsted-Lewis acidic chlorometallates IL as catalysts for the preparation of BIMs up to 2015. At the very outset of this chapter, we have discussed about the different N-SO$_3$H functionalized chlorometallate IL systems synthesized so far and their various advantageous properties. In this regard, we have decided to develop three new catalytic frameworks of 3-methyl-1-sulfonic acid imidazolium chlorometallate ILs and explored the catalytic efficiencies of these newly synthesized systems for development of *bis*(indolyl)methane derivatives.
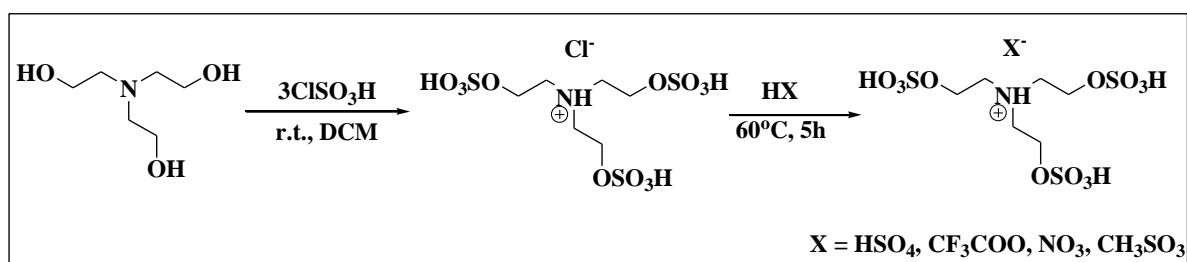
Scheme 1B.12: Synthesis of [TEOA][X] ILs

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Chapter 1B

Literature on halometallate ionic salts and ionic liquid catalyzed synthesis of bis(indolyl)methanes

1C.1. Results and discussion

In this chapter, three new solid Brönsted-Lewis acidic catalysts of 3-methyl-1-sulfonic acid imidazolium metal chlorides ([Msim][X], where X = $FeCl_4$, $CuCl_2$, $Zn_2Cl_6^{2-}$) were prepared and characterized via FT-IR, ^1H NMR, ^{13}C NMR, Raman, TGA, SEM-EDX, BET, AAS, UV-Vis spectroscopy and elemental analysis. The catalytic efficiencies of these solid catalytic systems were explored for the synthesis of *bis*(indolyl)methane derivatives under ambient condition. All the synthesized products were characterized via FT-IR, ^1H NMR, ^{13}C NMR and melting point determination.

Synthesis and characterization of 3-methyl-1-sulfonic acid imidazolium transition metal chlorides

To fulfill the above mentioned objective, three new ionic salts of 3-methyl-1-sulfonic acid imidazolium metal chlorides (**2a**, **2b** & **2c**) were synthesized from the 1:1 reaction mixture of 3-methyl-1-sulfonic acid imidazolium chloride (**1**) and three transition metal chlorides namely, $FeCl_3$, $ZnCl_2$ and CuCl at 60 °C in an inert atmosphere for 2 h stirring according to **Scheme 1C.1**.
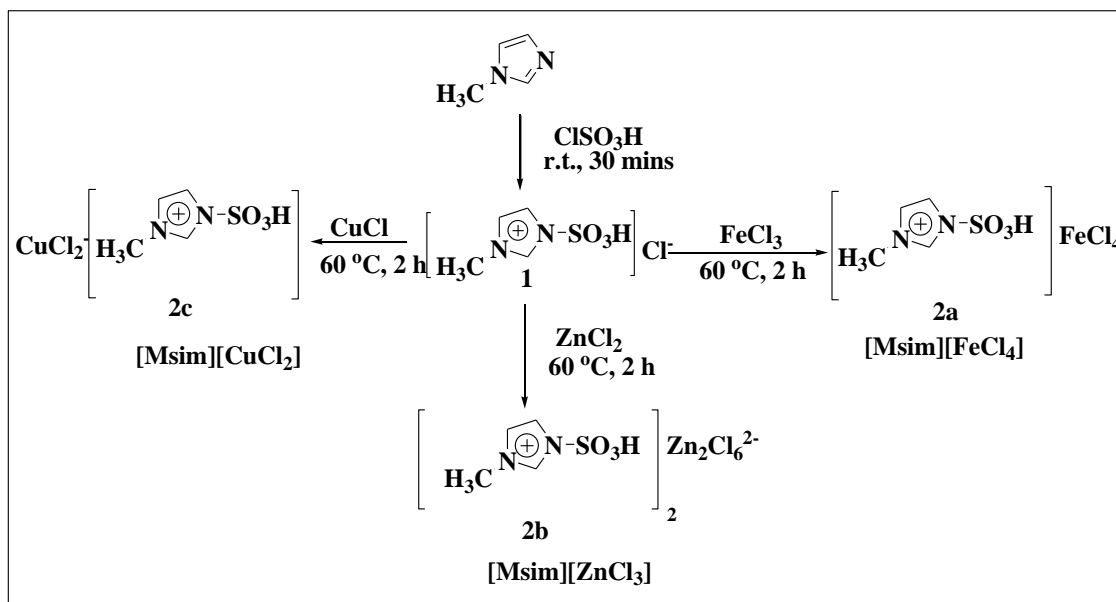
Scheme 1C.1: Synthesis of 3-methyl-1-sulfonic acid imidazolium metal chlorides

Characterization of the synthesized ionic salts

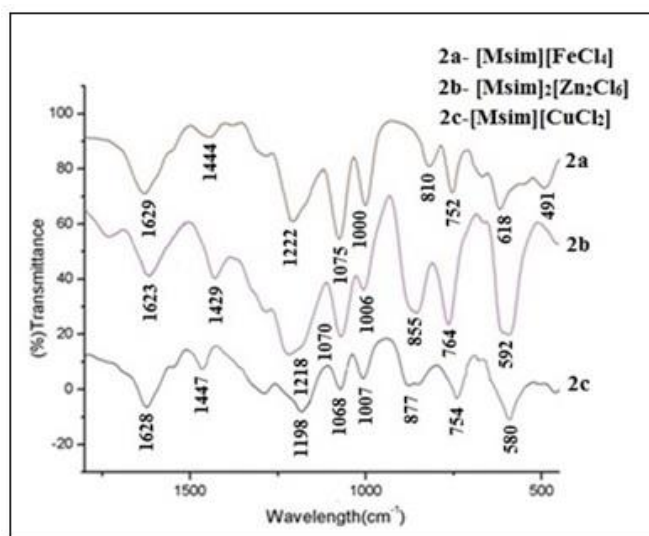*Preliminary spectral analysis*

Fig. 1C.1: FT-IR spectra of the ionic salts

The FT-IR spectral analysis of the three ionic salts is presented in **Fig. 1C.1**. The O-H stretching vibration corresponding to the -SO$_3$H group was observed at 3450-3000 cm^{-1}. A peak at 1629-1623 cm^{-1} was observed due to -C=N- stretching vibrations. The band obtained at 1447-1429 cm^{-1} can be correlated to the out of phase bending vibrations of C-H bonds of methyl group [1]. The presence of the -SO$_3$H groups in the ionic salts was confirmed from the presence of characteristic strong FT-IR absorptions at 1222-1198, 1075-1068 and 618-580 cm^{-1} pertaining to the S-O symmetric and antisymmetric stretching and bending vibrations respectively. The incorporation of the -SO$_3$H group to the 1-methylimidazolium moiety could also be confirmed from the presence of N-S stretching and in plane ring bending vibrations in the region 877-810 cm^{-1}. The peak around 764-752 cm^{-1} can be correlated to the out-of-plane ring C-H bending vibration [2]. From the ^{1}H NMR spectra, the presence of -SO$_3$H proton can be confirmed from the singlet obtained in the range of 14.1-14.5 ppm for all three ionic salts. For **2b** & **2c**, ^{13}C NMR spectra confirmed the formation of these two ionic salts in conjunction with the ^{1}H NMR spectra. However, in case of **2a**, we were unable to get the ^{13}C NMR spectrum which might be due to very low concentration of the sample solution. Since the nature of **2a** is paramagnetic, we could not increase the concentration of sample solution in DMSO-d$_6$.
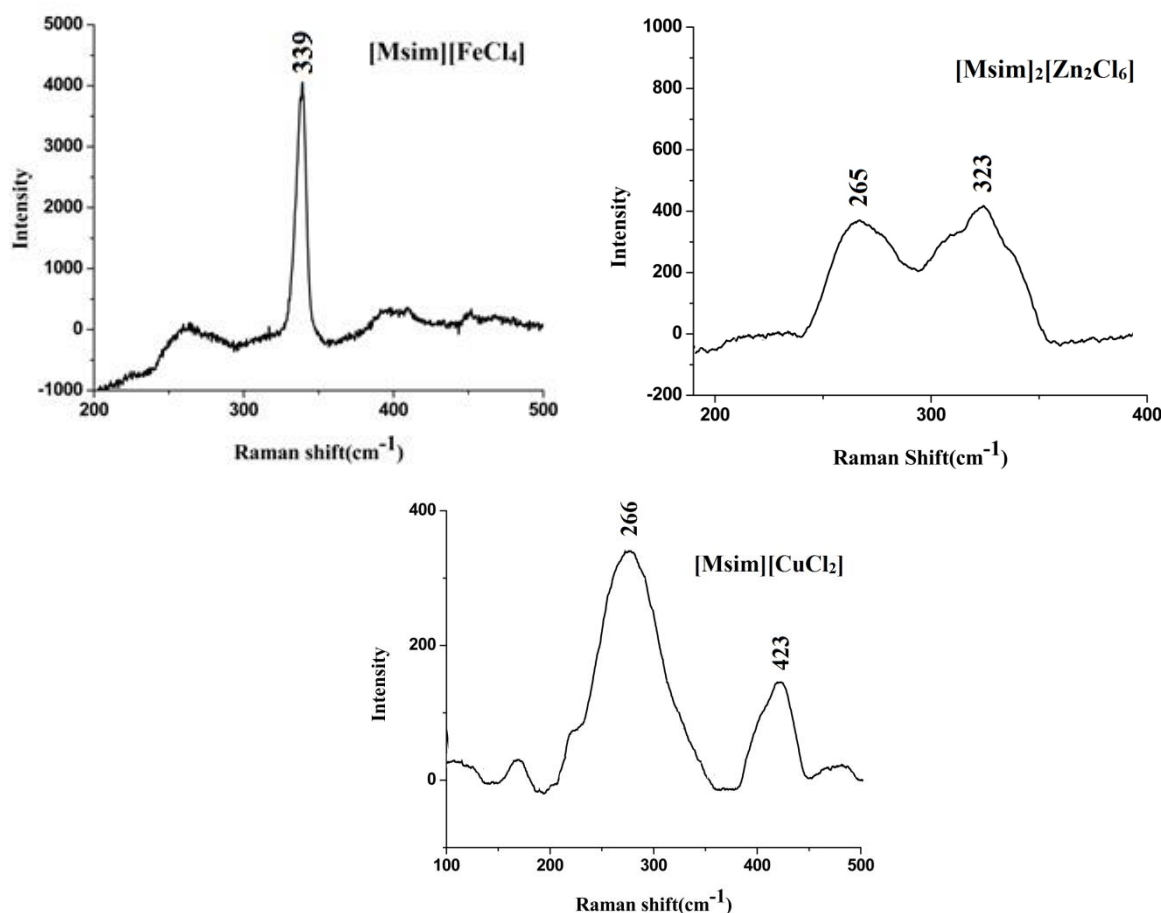
Raman analysis

Fig. 1C.2: Raman spectra of the ionic salts

The Raman spectra of the three ionic salts are presented in **Fig. 1C.2**. For [Msim][FeCl$_4$](**2a)**, the Raman spectrum displayed a strong peak at 339 cm^{-1} which coincided closely with the literature value of [FeCl$_4$]$^-$ complex [3]. The Raman spectra of [Msim]$_2$[Zn$_2$Cl$_6$] (**2b**) indicated two broad peaks at 265 & 323 cm^{-1} which could be assigned to a doubly charged [Zn$_2$Cl$_6$]$^{2-}$ anion as supported by literature data [4-7]. There was no experimental evidence found for the presence of [ZnCl$_3$]$^-$ anion either in the solid or liquid state. For [Msim][CuCl$_2$] (**2c**), two absorption peaks were obtained in the region 266-295 cm^{-1} and 423 cm^{-1} which can be assigned for the mixture of [CuCl$_2$]$^-$ with minor amount of [Cu$_2$Cl$_3$]$^-$ [8]. Literature survey supported the formation of [CuCl$_2$]$^-$ anion by the presence of two strong peaks at 300 cm^{-1} and 412 cm^{-1} pertaining to the symmetric and antisymmetric stretching respectively [9]. Presence of small amount of CuCl$_2$ along with starting CuCl might lead to the formation of [Cu$_2$Cl$_3$]$^-$ anion in this ionic salt.
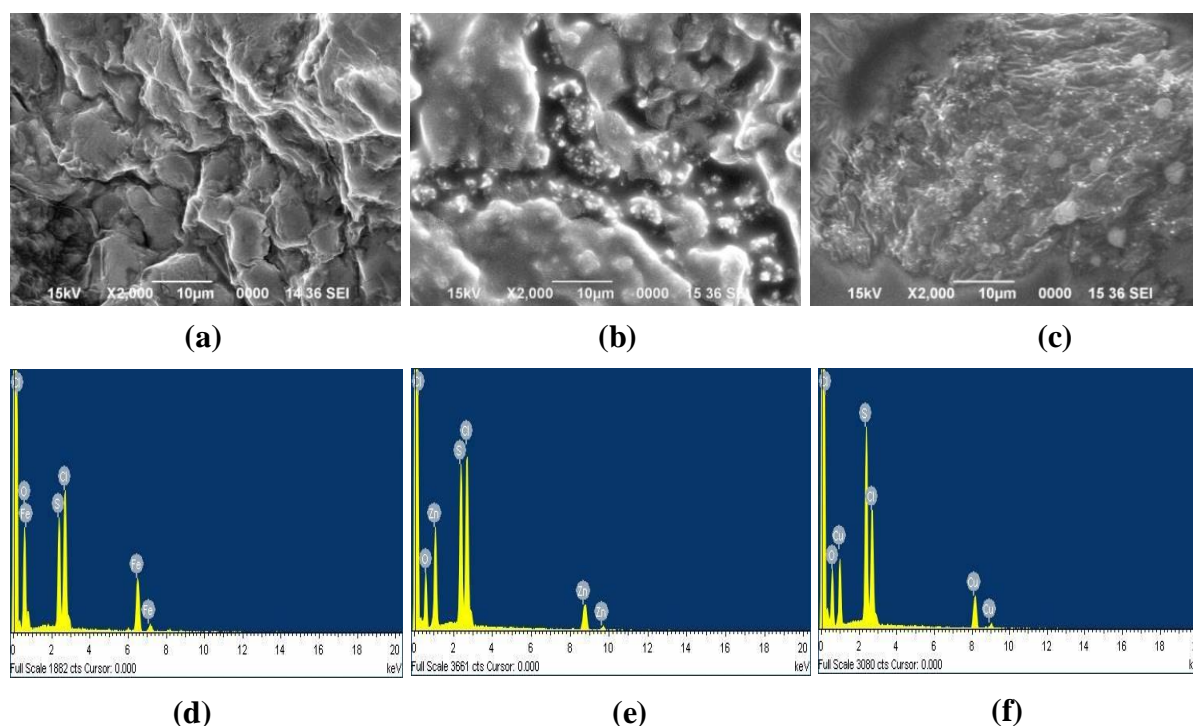
SEM-EDX analysis

Fig. 1C.3: SEM images [(**a**)-(**c**)] and EDX spectra of [(**d**)-(**f**)] of [Msim][FeCl$_4$], [Msim]$_2$[Zn$_2$Cl$_6$] and [Msim][CuCl$_2$]

SEM images of the three ionic salts are presented in **Fig. 1C.3**. The surfaces of the solid acids have no definite morphology and size. The SEM images of [Msim][FeCl$_4$] (**a**) depicted the surface to be a rough one. The SEM images of [Msim]$_2$[Zn$_2$Cl$_6$] (**b**) pointed the surface to be constituted of some aggregates rather than detached particles. For [Msim][CuCl$_2$] (**c**) the surface was more even than (**a**) and (**b**). In some parts, the ionic salt formed some spherical shaped clotting like structure. EDX analysis of the ionic salts confirmed the presence of respective constituent elements in each case devoid of any other impurities.

Thermo gravimetric analysis

Thermal stability of the three ionic salts was assessed via thermo gravimetric analysis and results are presented in **Fig. 1C.4**. The TGA graph of [Msim][FeCl$_4$] suggested three step weight loss for this ionic salt. Initial 13% weight loss below 100 °C may be attributed to the loss of physisorbed water. The 2nd and 3rd weight loss steps are observed in the temperature range of 115-150 °C and 150-346 °C respectively. The

TGA curve of [Msim]$_2$[Zn$_2$Cl$_6$] and [Msim][CuCl$_2$] witnessed very small weight loss below 100 °C due to negligible amount absorbed moisture. The [Msim][CuCl$_2$] displayed thermal stability up to 376 °C. Among the three synthesized ionic salts, the highest thermal stability was observed up to 444 °C for [Msim]$_2$[Zn$_2$Cl$_6$].

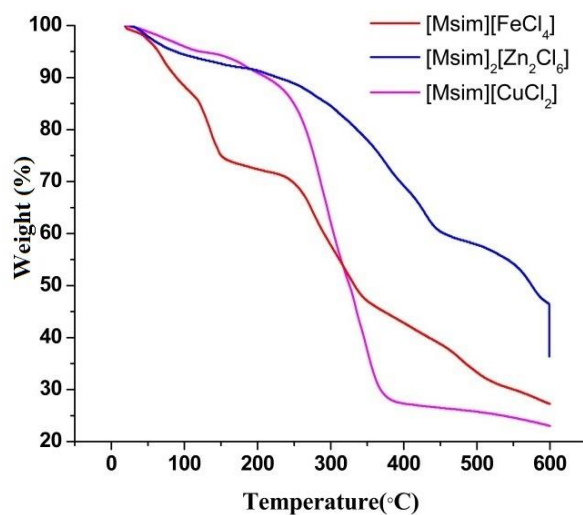**Fig. 1C.4**: TGA graphs of the three ionic salts

Powder X-Ray diffraction analysis

The powder XRD pattern for [Msim]$_2$[Zn$_2$Cl$_6$] (**2b**) and [Msim][CuCl$_2$] (**2c**) are presented in **Fig. 1C.5**. For **2b**, diffraction peaks centered at 2θ = 26.1°, 29.1°, 35.6° & 41.2° characteristic of ZnCl$_2$ were obtained. It matched well the XRD database (JCPDS card no. 74-0517) and they could be assigned to (101), (103), (104) reflections respectively. The peaks lost their sharpness to extent due to loss of crystallinity of ZnCl$_2$ during the impregnation process. For **2c**, diffraction peaks at 2θ = 28.5° & 47.4° were obtained which may be attributed to the (111) & (220) reflection planes respectively and they can be attributed to the presence of crystalline CuCl (JCPDS 06-0334). Two additional peaks were obtained at 2θ = 25.1° & 26.8° which may be attributed to the presence of considerable amount of CuCl$_2$ in the starting CuCl. No significant losses in crystallinity were observed for the diffraction peaks of **2c** as compared to the standard chart for CuCl. Highly hygroscopic nature of [Msim][FeCl$_4$] (**2a**) posed a limitation to this ionic salt to generate accurate XRD data as shown by the TGA profile (**Fig. 1C.4).**
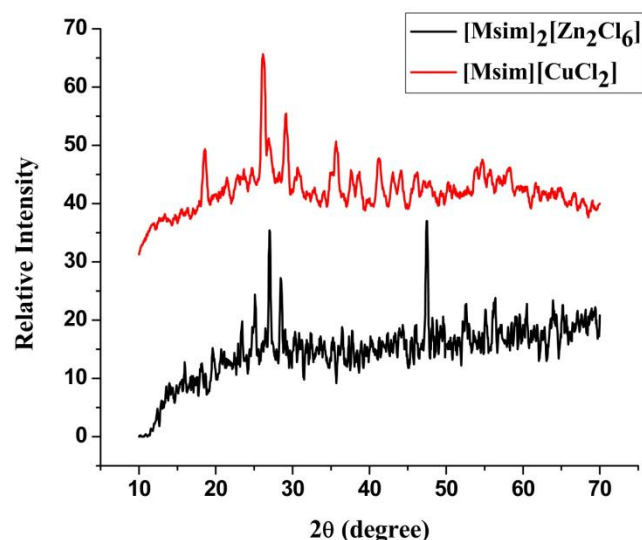
Fig. 1C.5: Powder XRD patterns of [Msim]$_2$[Zn$_2$Cl$_6$] and [Msim][CuCl$_2$]

Atomic absorption spectroscopy analysis

AAS analysis was carried out to quantify the metal content of the three ionic salts. Results are presented in **Table 1C.1**. For each of the three salts, 10 ppm solution in water were prepared and subjected to the analysis. The obtained results were found to match the starting metal content and ensured the 1:1 ratio for the [Msim]Cl and the respective metal chlorides.

Table 1C.1: Atomic absorption analysis of the three ionic salts

| Entry	Sample name	Molecular weight (g/mol)	Atomic weight of the metal (g/mol)	Amount of the metal (mg/L)	
				Experimental	Calculated
1.	[Msim][FeCl$_4$]	360.98	55.85	1.56	1.54
2.	[Msim][CuCl$_2$]	296.50	63.50	2.18	2.14
3.	[Msim]$_2$[Zn$_2$Cl$_6$]	335.01	65.38	1.96	1.95

BET analysis

The N$_2$ absorption-desorption measurement was carried out only for **2a**. The surface area obtained for **2a** was negligible. It may be attributed to the non-porous nature of the ionic salt. The SEM image of **2a** also supports the fact.

Quantitative Brönsted acidity determination by Hammett function

The Hammett plot for the three ionic salts was determined on an UV-Vis spectrophotometer using p-nitroaniline as the basic indicator [10-11]. It is presented in **Fig. 1C.6**. It is age old theory to determine the Brönsted acidity of a compound where basic indicator is used to trap the acidic proton. The absorbance of the indicator [I] in ionic salt solutions goes on decreasing as the acidity of the salts increases. The protonated form of the indicator $[HI]^+$ did not appear in the spectrum due to its low molar absorptivity. The Hammett functions for the ionic salts were determined from the absorption differences using the equation (1):

$$H^0 = pK(I)aq + \log [I]/[IH]^+ ----------(1)$$

Where pK(I)aq is the pKa value of the p-nitroaniline indicator in aqueous solution. For determination of the Hammett function, procedure required the mixing of equal amount of 4-nitroaniline solution (5 mg/L, pKa＝0.99) and catalyst (5 mmol/L) in ethanol solution. The indicator displayed maximum absorbance at 378 nm in ethanol. The Hammett plot expressed the following decreasing Brönsted acidity order for the three ionic salts against their observed H^0 values (**Table 1C.2):**

$$[Msim][FeCl_4] > [Msim]_2[Zn_2Cl_6] > [Msim][CuCl_2]$$
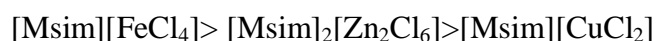
The presence of dual acidic sites in these ionic salts makes them more suitable to perform as highly efficient heterogeneous catalyst in organic transformations.
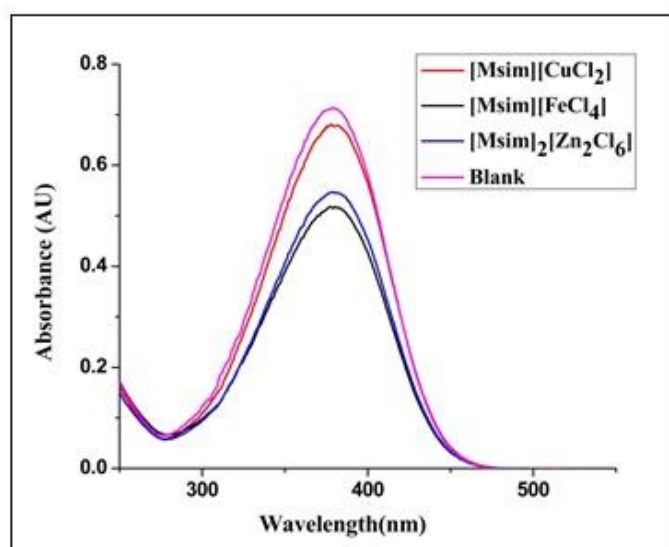

Fig. 1C.6: Hammett plot for the three ionic salts

Table 1C.2: Calculation of Hammett Function of the three catalyat

Entry	IL[a]	A_{max}	[I]%	[IH]%	H^o
1	Blank	0.714	100	0	-
2	[Msim][CuCl$_2$]	0.680	95.2	4.8	2.29
3	[Msim][Zn$_2$Cl$_6$]	0.546	76.5	23.5	1.50
4	[Msim][FeCl$_4$]	0.515	72.1	27.9	1.40

[a]p-nitroaniline

Evaluation of catalytic performances of the ionic salts

The synthesized ionic salts were fully characterized via various analytical tools. Then, we investigated the catalytic activity of these salts as reusable heterogeneous acid catalysts for the synthesis of *bis*(indolyl)methanes in a typical reaction procedure utilizing 1 mmol of indole and 0.5 mmol of aromatic aldehyde in dichloromethane (1 mL) at room temperature stirring. The catalytic activity of the salts was found to correlate well with the acidity order determined from the Hammett plot under the optimized reaction conditions. The catalysts could be recovered as solid residue at the end of the reaction after extraction of the reaction mixture with dichloromethane. The filtrate was evaporated and the solid residue was recrystallized from ethanol to get analytically pure product.

To obtain the best reaction condition, we studied the effect different polar and non-polar solvents as well as catalyst amount in the model reaction of indole and benzaldehyde according to **Scheme 1C.2**. The optimization results are summarized in **Table 1C.3**.
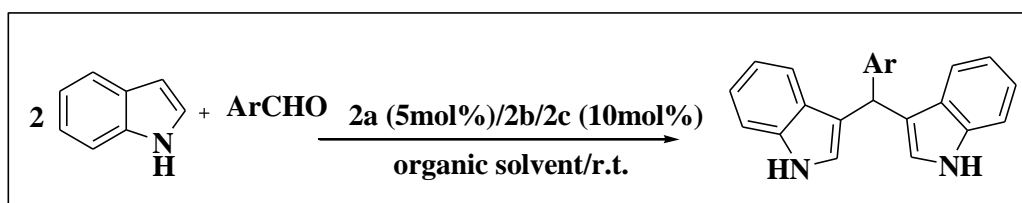

Scheme 1C.2: Optimization for best solvent and catalyst amount

Table 1C.3: Optimization of the solid acid catalysts amount for the preparation of bis(indolyl)methane derivatives at room temperature

Entry	Ionic salts	Amount (mol%)	Time(mins)	Yield(%)[a] 5a	TON/TOF(h^{-1})[b]
1.	[Msim][FeCl$_4$]	50/25/10/5	3/5/10/15	98	19.6/78.4
2.	[Msim][ZnCl$_3$]	50/25/10/5	15/30/60/75	97	9.7/9.7
3.	[Msim][CuCl$_2$]	50/25/10	30/45/75	97	9.7/7.8

[a]Using 2 mmol of indole and 1mmol of benzaldehyde in dichloromethane; [b]Turnover number (TON) = (molar amount of product)/(molar amount of catalyst). Turnover frequency (TOF) = TON/ (time in h) which were calculated only for the optimized conditions.

From **Table 1C.3**, it was observed that only 5 mol% of the more acidic [Msim][FeCl$_4$] catalyst was sufficient to produce 98% of product **5a** in 15 min under mild condition (**Table 1C.3**, entry 1). For the less acidic [Msim]$_2$[Zn$_2$Cl$_6$] and [Msim][CuCl$_2$] 10 mol% of catalysts was required to give excellent yields during 60-75 min reaction time (**Table 1C.3**, entries 2-3). The higher TON/TOF of **2a** under optimized conditions distinctly expressed the superior catalytic behaviour of **2a** for the synthesis of *bis*(indolyl)methane derivative **5a** (**Table 1C.3**, entry 1) under the optimized reaction condition.

We have also studied the effect of different polar (EtOH, CH$_3$CN, EtOAc) and non-polar (CHCl$_3$, CH$_2$Cl$_2$) solvents on the activity of [Msim][FeCl$_4$] in the model reaction. The reactions were performed at ambient temperature using 5 mol% of this catalyst. All the reaction proceeded well with 97-98% conversion in CH$_2$Cl$_2$, CH$_3$CN, CHCl$_3$ and EtOAc within 10-15 min. However, in case of EtOH, only 60% conversion was achieved. This might be attributed to the possible breakdown of the catalytic system in EtOH. By considering the environmental risk, disposal issues and time frame, we selected EtOAc as the best solvent for carrying out the reactions with the optimized amount of the catalysts. Also keeping in mind the higher hygroscopic nature of the catalytic systems, use of dry solvents is highly recommended as it may improve the activity and lifetime of the systems. Subsequently, we extended the optimized reaction conditions (**Table 1C.4**) towards the reactions of various aromatic aldehydes with

indole for the synthesis of respective *bis*(indolyl)methane derivatives (**Scheme 1C.3**).

Where X = electron withdrawing or donating groups
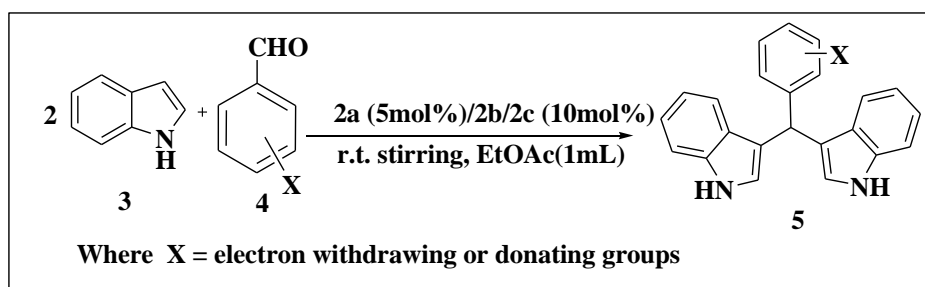
Scheme 1C.3: Synthesis of *bis*(indolyl)methane derivatives catalysed by the ionic salts

Table 1C.4: Synthesis of b*is*(indolyl)methane derivatives **5** using the solid acid catalysts

Entry	Aldehydes	Time(method)[a] (min)	Yield(%)[a]	M.P.(°C) Found	M.P.(°C) Reported
1.	C_6H_5 **4a**	15[A]/60[B]/75[C]	98/97/97 **5a**	120.3	124-126 [12]
2.	4-OMe **4b**	10[A]/20[B]/40[C]	97/97/96 **5b**	185.2	195 [13]
3.	4-NO$_2$ **4c**	20[A]/30[B]/45[C]	97/96/96 **5c**	242.4	245–246 [12]
4.	4-Cl **4d**	20[A]/30[B]/50[C]	98/97/97 **5d**	90	87–89 [13]
5.	C_6H_5-CH=CH- **4e**	10[A]/15[B]/40[C]	97/96/95 **5e**	95	94–96 [12]
6.	2-naphthaldehyde **4f**	30[A]/60[B]/90[C]	98/97/95 **5f**	228	227-229 [13]
7.	4-CH$_3$ **4g**	10[A]/15[B]/30[C]	97/96/94 5g	99	96–98 [12]

[a]Methods: [A] Using 5 mol % of **2a** as catalyst; [B] Using 10 mol % of **2b** as catalyst; [C] Using10 mol% of **2c** as catalyst

The results of **Table 1C.4** clearly represented the higher catalytic activity of these Brönsted-Lewis acidic sites containing solid acids. **Table 1C.5** includes the results of various reported methods [14-20] with the present procedure for comparisons in terms of reaction condition, recyclability of catalyst, time and yield for the synthesis of *bis*(indolyl)methanes **5a**. As it is evident from the **Table 1C.5** that [Msim][X⁻] were found to be effective catalysts for the synthesis of *bis*(indolyl)methanes.

Table 1C.5: Results of bis(indolyl)methane synthesis using different catalysts and reaction conditions

Entry	Catalyst	Conditions	Time (h)	Yield (%)	Recycla-bility[a]	Ref.
1.	Polyindole salt (20 wt.%)	Methanol/r.t.	3	98	Y	[14]
2.	[Et₃NH][H₂PO₄] (0.4 g)	[Et₃NH][H₂PO₄]/ 100 °C	10 min	97	N	[15]
3.	Al(HSO₄)₃ (0.636 g)	Ethanol/ r.t.	2.5	92	N	[16]
4.	Fe(DS)₃ (Ferric Dodecyl Sulfonate) (1 mol%)	H₂O/r.t.	6	90	N	[17]
5.	CuBr₂ (10 mol%)	MeCN/r.t.	30 min	94	N	[18]
6.	FeCl₃.6H₂O (5 mol%)	[omim][PF₆]/r.t.	1.5	98	Y	[19]
7.	SBA-15/SO₃H (70%)	CCl₄/70 °C	24	52	Y	[20]
8.	[Msim][FeCl₄] (5 mol%)/ [Msim][ZnCl₃ (10 mol%)/ [Msim][CuCl₂]	EtOAc/r.t.	15min/ 1/1.25	98/97/ 97	Y/Y/Y	Present method

	(10 mol%)					

[a]Y = Yes, N = No

Recycling of catalysts

The bar diagram presented in **Fig. 1C.7** expressed the reusability profile of the solid acids is for three consecutive runs for the reactions of indole (1 mmol) and benzaldehyde in ethylacetate solution. The catalytic systems could be reused for three consecutive cycles without reactivation. Needless to say, they retained significant catalytic activity up to third cycle of reaction. The FT-IR spectra of reused catalysts also displayed the already mentioned characteristics stretching vibrations of the fresh chlorometallates in **Fig. 1C.8.**
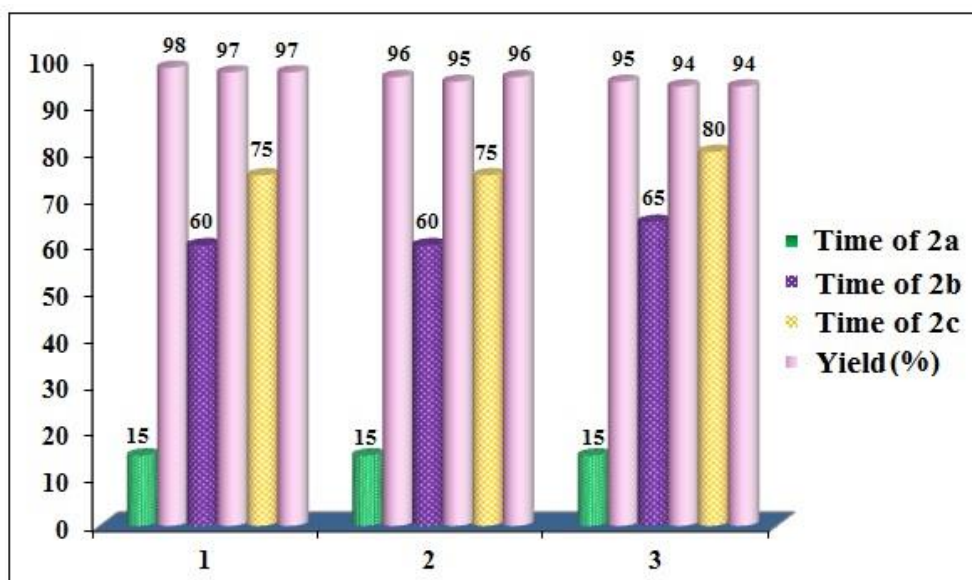
Fig. 1C.7: Recyclability profile of the solid acid catalysts
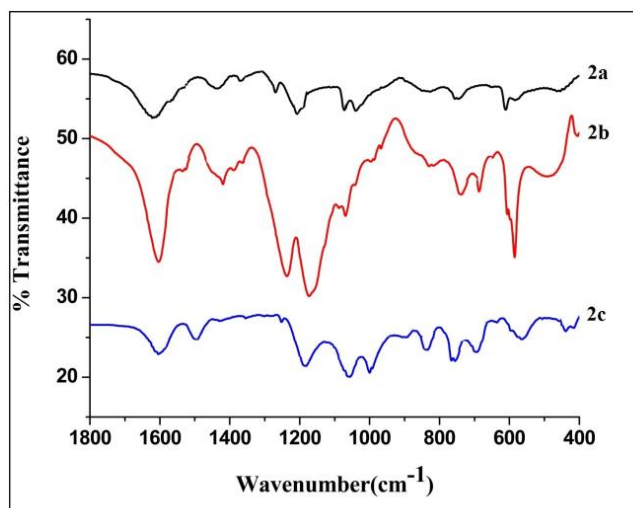
Fig. 1C.8: FT-IR spectra of reused catalysts

Plausible mechanism of the bis(indolyl)methane synthesis
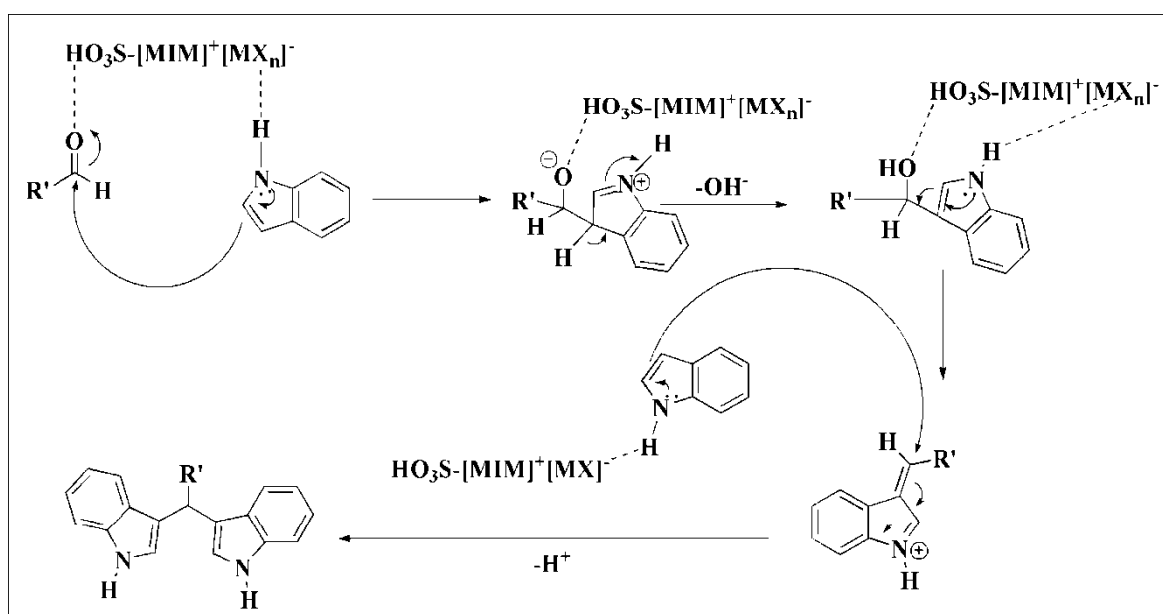
Scheme 1C.4: Mechanism for synthesis of bis(indolyl)methane derivatives

The plausible mechanism for the synthesis of *bis*(indolyl)methane derivatives is outlined in **Scheme 1C.4.** The Brönsted acidic site of the ionic salts activates the carbonyl carbon followed by double nucleophilic attack from the N-atom of the indole moiety. The Lewis acidic site of the ionic salts synergistically supports the formation of the final products.

1C.2. Conclusion

In concluding remark, we have developed a new class of solid acids of 3-methyl-1-sulfonic acid imidazolium transition metal chlorides as efficient heterogeneous catalytic system containing both Lewis and Brönsted acidic sites. The resulting catalysts were characterized in terms of composition, structure, thermal stability, and morphology. The efficiency of the newly synthesized catalysts was evaluated for the selective synthesis of *bis*(indolyl)methane derivatives in ethylacetate at ambient temperature within short time with excellent yields. The obvious advantages of these catalytic systems are high thermal stability, high catalytic activity, simple operating procedure coupled with easy work up, recyclability, and low cost. We believe that these green features will add supremacy to these Brönsted-Lewis acidic catalysts over the traditional ones in organic synthesis and will find extensive application in the catalysis field.

1C.3. Experimental

General remarks

All chemicals were purchased from different chemical suppliers and used as received without any further treatment. The ^{1}HNMR and ^{13}CNMR were recorded on a JEOL 400 MHz spectrometer (δ in ppm) in DMSO-d_6 and CDCl$_3$ solvents. Nicolet Impact-410 spectrometer was used to record FT-IR spectra. The Hammett plot of the solid acids was determined on an UV 2550 spectrophotometer using 4-nitroaniline as the basic indicator. The thermo gravimetric analysis of the three solid acids was performed on Shimadzu TGA 50. All elemental analyses were obtained from Perkin Elmer 20 analyzer. The scanning electron microscopy (SEM) analyses were carried out using a JEOL JSM-6390LV SEM, equipped with an Energy-Dispersive X-ray analyzer. The powder X-ray diffraction patterns were recorded on a Rigaku Multiflex instrument using a nickel-filtered CuKα (0.15418 nm) radiation source and scintillation counter detector. Melting points were recorded on a Buchi-545 apparatus. The laser micro-Raman spectroscopic measurement was conducted in a Horiba LabRAM HR spectrometer equipped with a He−Ne laser that has an excitation wavelength of 514.5 nm. The BET surface area of **2a** was measured in Quantachrome NovaWin apparatus. Atomic absorption analyses of the solid acids were performed on an AAS, model

Analyst 200, Thermo iCE 3000 series. The spectral data of known *bis*(indolyl)methanes (**5**) were compared with the literature data [12-20] .
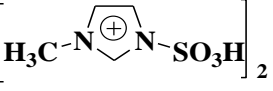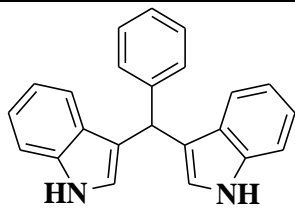
Synthesis of 3-methyl-1-sulfonic acid imidazolium metal chlorides [Msim][X], where

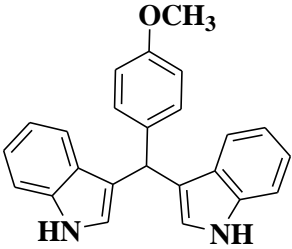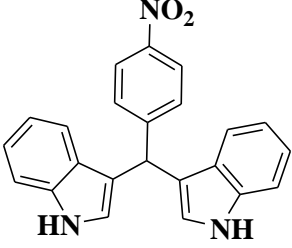***$X^- = [FeCl_4]^-$, $[Zn_2Cl_6]^-$, $[CuCl_2]^-$***
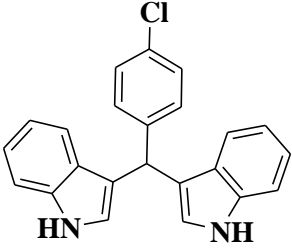
To a stirred solution of 1-methyl imidazole (10 mmol) in dry CH_2Cl_2 (30 mL), chlorosulfonic acid (10 mmol) was added drop wise over a period of 5 minutes at ice bath. The reaction mixture was stirred for another 45 minutes to make certain completion. After the reaction was over CH_2Cl_2 layer was decanted, the residue was washed with dry CH_2Cl_2 (3×20 mL) and dried under powerful vacuum to give 3-methyl-1-sulfonic acid imidazolium chloride [Msim]Cl as viscous pale yellow oil in 98% yield. Then the solid [Msim][X] acids were prepared by stirring equimolar amounts of 3-methyl-1-sulfonic acid imidazolium chloride and the respective metal chlorides ($FeCl_3$, $ZnCl_2$ and CuCl) in an oil bath at 60 °C under nitrogen atmosphere for 1 hour. The reaction mixture was stirred for an extra one hour to ensure complete impregnation of the metal halides over the basic moiety [Msim]Cl. The resultant solid residues were dried under powerful vacuum to get the respective [Msim][X] in 97-99 % yields and stored in vacuum desicator.
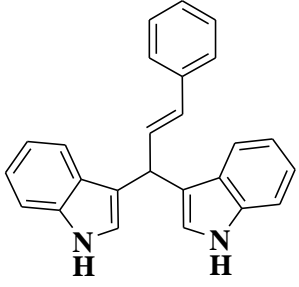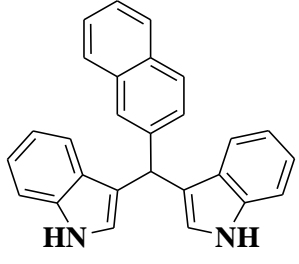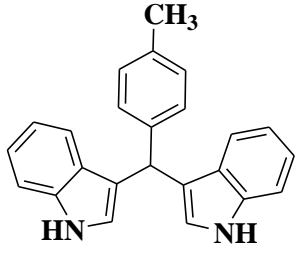
General procedure for the synthesis of bis(indolyl)methanes (5):

A mixture of aromatic aldehyde (1 mmol), indole (2 mmol) and the solid acid (5 or 10 mol%) in 1 mL of ethylacetate was magnetically stirred in a 50 mL round bottomed flask at room temperature fitted with a calcium chloride guard tube. The progress of the reaction was monitored by thin layer chromatography using petroleum ether and ethylacetate as solvent system. After completion of the reaction, the product was dissolved in ethylacetate and then filtered to collect the solid catalystfor recycling. The product was isolated from the solution by evaporation of the solvent. The crude product was recrystallized from aqueous ethanol to get analytically pure product.

1C.4. Spectral data of the ionic salts and the *bis*(indolyl)methane derivatives

Products	Spectral Data
$\left[H_3C-N\overset{\oplus}{\underset{}{}}N-SO_3H \right]$ FeCl$_4^-$	**[Msim][FeCl$_4$] 2a**: Green Solid, M.P.(°C) 129.8-130.5; FT-IR(KBr): 3354, 3283 ,2894, 2848, 1629, 1444, 1222, 1075, 1000, 810, 752, 618 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 14.5 (s, 1H), 8.91 (s, 1H), 7.56-7.53 (s, 2H), 3.74 (s, 3H); CHN analysis(%): C$_4$H$_7$O$_3$SN$_2$FeCl$_4$: Cal. C 13.30, H 1.93, N 7.76; Found C 13.27, H 2.08, N 7.74.
$\left[H_3C-N\overset{\oplus}{\underset{}{}}N-SO_3H \right]_2$ Zn$_2$Cl$_6^{2-}$	**[Msim]$_2$[Zn$_2$Cl$_6$] 2b**: Off White Solid, M.P.(°C): 131.5-132.2; FT-IR(KBr): 3427, 3327, 2894, 1729, 1623, 1429, 1218, 1070, 1006, 855, 764, 592 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 14.2 (s, 1H), 8.97 (s, 1H), 7.62 (s, 1H), 7.58 (s, 1H), 3.99 (s, 3H); ^{13}C NMR (DMSO-d$_6$, 100 MHz): δ 136.3, 123.7, 120.2, 39.7; CHN analysis(%): C$_4$H$_7$O$_3$SN$_2$Zn$_2$Cl$_6$: Cal. C 14.3, H 2.08, N 8.36; Found C 14.26, H 2.50, N 8.30.
$\left[H_3C-N\overset{\oplus}{\underset{}{}}N-SO_3H \right]$ CuCl$_2^-$	**[Msim][CuCl$_2$] 2c**: Dark brown Solid, M.P.(°C): 109.7-110.3; FT-IR(KBr): 3430, 3368, 2989, 1628, 1447, 1198, 1068, 1007, 877, 754, 580 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 14.1 (s, 1H), 8.84 (s, 1H), 7.49 (s, 2H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ 136.2, 123.7, 120.2, 36.1; CHN analysis(%): C$_4$H$_7$O$_3$SN$_2$CuCl$_2$: Cal. C 16.14, H 2.35, N 9.41; Found C 16.10, H 3.28, N 9.38.
 HN NH (**Table 1C.4**, entry 1)	*Bis*(**3-indolyl)phenylmethane 5a**: Dark brown solid, FT-IR(KBr): 3403, 3043,2379, 1602, 1450, 1337, 1215, 1086, 1008, 925, 800, 741 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.84 (s, 2H), 7.38 (d, *J* = 7.8 Hz, 2H), 7.34-7.12 (m, 9H), 6.98 (t, *J* = 7.3 Hz, 2H), 6.6 (s, 2H), 5.87 (s, 1H);^{13}C NMR (100 MHz, CDCl$_3$): δ 144, 136.7, 128.7, 128.2, 127, 126.1, 123.6, 121.8, 119.9, 119.7, 119.2, 111, 40.1; CHN analysis (%): C$_{23}$H$_{18}$N$_2$: Cal. C 85.72, H 5.58, N 8.68; Found C

	85.50, H 5.64, N 8.62.
OCH₃ (**Table 1C.4**, entry 2)	***Bis*(3-indolyl)(4-methoxyphenyl)methane 5b**: Brown solid, FT-IR(KBr): 3347, 3048, 2835, 2380, 1607, 1506, 1453, 1313, 1242, 1172, 1021, 926, 817, 740 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.88 (s, 2H), 7.38 (d, *J* = 7.8 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 2H), 7.14 (t, *J* = 7.8 Hz, 2H), 6.98 (t, *J* = 8.2 Hz, 2H), 6.81 (d, *J* = 6.9 Hz, 2H), 6.60 (s, 2H), 5.51 (s,1H), 3.73 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 157.9, 136.8, 136.4, 129.7, 127.2, 123.6, 121.9, 120.1, 120, 119.3, 113.7, 111.1, 55.2; CHN analysis(%): C₂₄H₂₁N₂O: Cal. C 81.59, H 5.94, N 7.92; Found C 81.5, H 6.01, N 7.90.
NO₂ (**Table 1C.4**, entry 3)	***Bis*(3-indolyl)(4-nitrophenyl)methane, 5c**: Brown solid, FT-IR(KBr): 3452, 3385, 3056, 2846, 1594, 1504, 1455, 1412, 1339, 1223, 1097, 1011, 806, 743 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.14 (d, *J* = 8.7 Hz, 2H), 8 (s, 2H), 7.52 (d, *J* = 8.7 Hz, 2H), 7.39 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 7.8Hz, 2H), 7.19 (t, *J* = 8.2 Hz, 2H), 7.02 (t, *J* = 8.2Hz, 2H), 6.69 (s, 2H), 5.99 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 151.8, 146.6, 136.7, 129.5, 126.7, 123.6, 122.3, 119.6, 119.5, 118.2, 111.2, 40.2; CHN analysis(%): C₂₃H₁₈N₃O₂: Cal. C 75.01, H 4.88, N 11.40; Found C 74.95, H 4.92, N 11.36.
Cl (**Table 1C.4**, entry 4)	***Bis*(3-indolyl)(4-chlorophenyl)methane 5d**: Pink solid, FT-IR(KBr): 3405, 3049, 2380, 1903, 1681, 1590, 1482, 1451, 1410, 1331, 1213, 1172, 1087, 1009, 926, 740 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.94 (s, 2H), 7.35 (d, *J* = 7.8 Hz, 4H), 7.25 (d, *J* = 7.8 Hz, 2H), 7.22-7.12 (m, 4H), 7.02-6.97 (m, 2H), 6.60 (s, 2H), 5.85 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 142.6, 136.8, 131.7, 130.1, 128.9, 128.4, 126.9, 123.7, 122.2, 119.9, 119.4, 119.3, 111.2, 39.7; CHN analysis(%): C₂₃H₁₈N₂Cl: Cal. C 77.20, H 5.07, N 7.83; Found C 77.13, H 5.10, N 7.80.

  (**Table 1C.4**, entry 5)	**3-((*E*)-1-(1*H*-indol-3-yl)-3-phenylallyl)-1*H*-indol** **5e:** Yellow solid: FT-IR(KBr): 3413, 3054, 2926, 2854, 1596, 1531, 1489, 1455, 1417, 1332, 1246, 1216, 1094, 965,748 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.56 (s, 2H), 7.43 (d, *J* = 8Hz, 2H), 7.28 (m, 3H), 7.13 (m, 2H), 7.04 (dd, 1H, *J$_{cis}$* = 7.2 Hz, *J$_{trans}$* = 15.6 Hz, Ph-CH=CH-), 7.00 (m, 2H), 6.93 (m, 2H), 6.81 (d, *J* = 7.6 Hz, 2H), 6.78 (d, *J* = 7.6 Hz, 2H), 6.45 (d, 1H, *J*$_{trans}$ = 15.6 Hz, Ph-CH=CH-), 5.23 (d, *J* = 7.2 Hz, 1H), ^{13}C NMR (100 MHz, CDCl$_3$): δ 138.8, 138.2, 134.2, 130.0, 129.3, 128.1, 127.7, 127.0, 123.5, 122.1, 120.3, 119.3, 118.6, 112.1, 38.6; CHN analysis(%): C$_{25}$H$_{20}$N$_2$: Cal. 86.17, H 5.79, N 8.04; Found C 86.14, H 5.83, N 8.05.
  (**Table 1C.4**, entry 6)	***Bis*(3-indolyl)(2-napthyl)methane 5f**: Orange solid, FT-IR(KBr): 3446, 1682, 1618, 1501, 1455, 1414, 1341, 1215, 1092, 1013, 905, 796, 743 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.36 (s, 2H), 8.01-7.88 (m, 2H), 7.77-7.68 (m, 3H), 7.51-7.49 (m, 3H), 7.41-7.32 (m, 2H), 7.16-7.10 (m, 3H), 6.99-6.95 (m, 2H), 6.65 (s, 2H), 6.04 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 141.6, 136.7, 133.6, 132.3, 129.1, 127.9, 127.7, 127.6, 127.2, 126.8, 125.7, 125.3, 123.8, 121.9, 119.9, 119.6, 119.3, 111.0, 40.3; CHN analysis(%): C$_{27}$H$_{20}$N$_2$: Cal. C 87.07, H 5.41, N 7.52; Found C 87.01, H 5.47, N 7.49.
  (**Table 1C.4**, entry 7)	***Bis*(3-indolyl)(4-methylphenyl)methane 5g**: Pale red solid, FT-IR(KBr): 3411, 3043, 2924, 1676, 1604, 1507, 1453, 1340, 1211, 1096, 743 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.86 (s, 2H), 7.39 (d, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 7.14 (t, *J* = 7.8 Hz, 2H), 7.07 (d, *J* = 7.8 Hz, 2H), 6.98 (t, *J* = 7.4 Hz, 2H), 6.61 (s, 2H), 5.83 (s, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 141.1, 136.8, 135.6, 129.9, 129.8, 129, 128.7, 127.2, 123.7, 121.9, 120.04, 119.9, 119.3, 111.2, 39.9,

	22.1; CHN analysis(%): $C_{24}H_{21}N_2$: Cal. C 85.43 H 6.27 N 8.30; Found C 85.39 H 6.33 N 8.27.

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Chapter 1C

Design of Brönsted-Lewis acidic solid catalytic systems of 3-methyl-1-sulfonic acid imidazolium transition metal chlorides and evaluation of their catalytic performances in preparation of bis(indolyl)methanes


Published with small modification

2A.1. Zeolites: Composition and Structure

Zeolites are micro porous crystalline aluminosilicates, composed of infinitely extending three dimensional networks of $[SiO_4]^{4-}$ and $[AlO_4]^{5-}$ tetrahedra linked to each other by sharing of oxygen atoms between two T elements of TO_4 unit (T= Si, Al) [1]. The presence of Al^{3+} cation in SiO_2 framework makes the framework negatively charged, and requires additional extra framework inorganic/organic cations within the structure to keep the overall zeolite framework neutral.

The definition of zeolite is given by Smith [2] as "A zeolite is a crystalline aluminosilicate with a tetrahedral framework structure enclosing cavities occupied by cation and water molecules, both of which have enough freedom of movement to permit cation exchange and reversible dehydration". The microporosity must be "open", and the framework must have enough stability to allow the transfer of materials between interior and exterior of the crystals.

The composition of zeolites can be written in terms of three components such as extra framework cations, TO_4 framework and sorbed water molecule as follows:

$$[M^{n+}]_{y/n} \cdot (SiO_2)_x (AlO_2)_y \cdot zH_2O$$
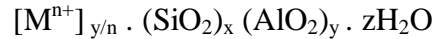
Here M^{n+} is the exchangeable extra framework cation and gives rise to variety of ion-change materials. The value of (x+y) indicates the total number of TO_4 per crystallographic unit cell. The x/y ratio of zeolite formulae is equivalent to the amount of Si/Al ratio per unit cell. The value of Si/Al lies in between 1 and ∞. The composition of zeolite structure is found to depend on the synthesis condition. Further post synthetic modifications have been developed for insertion of Si or Al into the framework [3]. The hydrothermal and hydrophobic properties of zeolites structure increases as the ratio of Si/Al increases.

The primary building unit (PBU) of all types of zeolites is tetrahedra of four oxygen anions surrounding a silicon and aluminium ion (**Fig. 2A.1**). These tetrahedra are so arranged that each of the four oxygen anions is shared in turn with another silica or alumina tetrahedra. Lowenstein proposed [4] that no two Al atoms are joined together via Al-O-Al bond involving the same oxygen atom within the zeolite framework. Each silicon has +4 charge balanced by four tetrahedral oxygen and therefore silica tetrahedra are electrically neutral. Each alumina tetrahedron has a residual charge of -1 as it

bonded to four oxygen anions. Hence, each of the alumina tetrahedra requires a +1 charge from a cation in the structure to maintain electrical neutrality. These cations are usually sodium in the zeolites as it is initially prepared, but they can be readily replaced by ion exchange method. The oxygen at each tetrahedral corner is connected with another tetrahedron in straight line with the formation of T-O-T bridge (**Fig. 2A.1).** These PBU's are combined to form the secondary building units (SBU's) of the zeolite framework (**Fig.2A.2**) with unique topology [5].
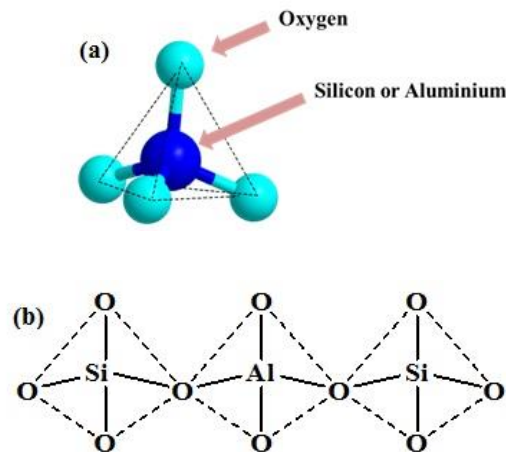
Fig. 2A.1: (a) Primary building unit of zeolite structures; (b) T-O-T bridge
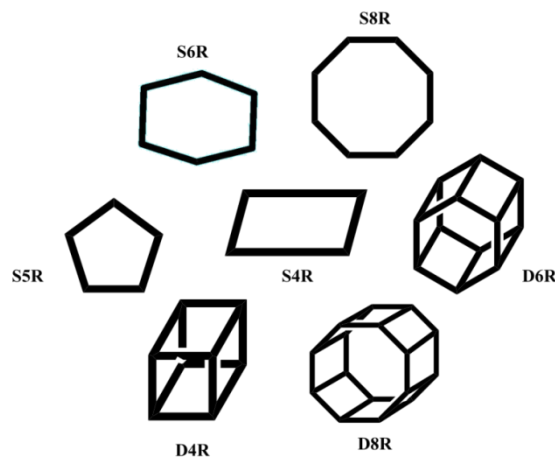
Fig. 2A.2: Secondary building unit of zeolite structures

As soon as SBU's are linked together, any geometrical shape like sodalite cage can be formed for the zeolite framework (**Fig.2A.3**). The SBU for each zeolite structure have been derived assuming that a zeolite network is composed entirely of one kind of unit. The wide variety of possible zeolite structures is the result of large numbers of ways in which the SBU can be linked to form various polyhedra. These polyhedra create networks of regular channels and cavities. The compositions of secondary building units

are different in different types of zeolites and within the zeolite structure; a unit cell always contains the same number of SBUs.
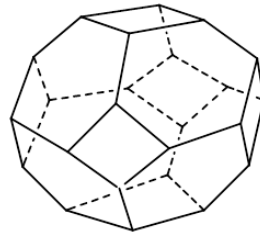
Fig. 2A.3: Sodalite cage structure (Tertiary building unit)

The truncated octahedron shapes of sodalite cage has 24 numbers of linked tetrahedra (T) and are further linked with distinct framework topology in different zeolites. Within the sodalite cage (also known β cage), they are interlinked through four and six membered rings.

The Structure Commission of the International Zeolite Association (IZA) assigns each zeolite framework with a three-letter mnemonic code based on the arrangement of SBUs (**Table 2A.1**) [6]. Some of the designations of SBUs structure types are FAU for the structure type of Faujasite zeolite, MFI for ZSM-5 zeolite, BEA for beta zeolite, MOR for mordenite type zeolites, LTA for zeolite A etc.

The microporous structures of zeolites depend on the size of oxygen ring that defines the pore size of the secondary building units. Therefore, it is necessary to give brief description of a zeolite structure in terms of specific pore opening and dimension of the channel system within the structure.

Table 2A.1: Examples of nanoporous aluminosilicates with their three letter IZA designation and description of the pore systems

System	Pore system
Sodalite family (SOD) (e.g. mineral and synthetic sodalities	3-dimensional; 6-ring channels
Zeolite A family (LTA) (e.g. zeolites A, ZK-4; no mineral analogue)	3-dimensional; 8-ring channels
Chabazites (CHA) (e.g. mineral chabasites, SSZ-13)	3-dimensional; 8-ring channels

ZSM-5 (MFI) (e.g. mineral murataite, silicalite	2-dimensional; 10-ring channels
Ferrierites (FER) (e.g. mineral and synthetic ferrierites	2-dimensional; 10 & 8-ring channels
Faujasites (FAU) (e.g. mineral faujasites, zeolites LSX, X, Y, US-Y	3-dimensional; 12-ring channels

2A.2. Classification of zeolites

Zeolites can be classified based on their morphological characteristics, chemical composition, effective pore diameter and natural occurrence.

Bragg [7] first made the classification based on morphological characteristics. According to this, zeolites are classified as fibrous, lamellar and those having framework structures. It was later modified by Meier and Barrer according to the SBU's present in them.

Zeolites are divided into three groups based on their pore size, number of tetrahedra and maximum free diameter within the pores (**Table 2A.2**) [8, 9].

Zeolites can also be classified into three classes according to their Si/Al ratio [10], namely:

- Zeolites with low Si/Al ratios (<5): e.g., Zeolite A, Zeolite X, Zeolite Y

- Zeolites with medium Si/Al ratios (5 to 10): e.g., Mordenite

- Zeolites with high Si/Al ratios (>10): e.g., ZSM-5

The thermal stability increases from about 700 °C in low silica zeolites to about 1300 °C in high silica zeolites.

Table 2A.2: Classification of zeolites

Type	No of tetrahedra	Pore diameter of framework (O) (Å)	Examples
Small pore size	8	Diameter (O) ≤ 4.5 Å	Zeolite A
Medium size	10	4.5 A <diameter (O) ≤ 6.5 Å	ZSM-5(pentasil

			type)
Large pore size	12	Diameter(O) > 6.5 Å	Zeolite Y(Faujasite type)

2A.3. Characteristic properties of zeolites

The properties of a zeolite are dependent on the topology of its framework, the size, shape and accessibility of its free channels, the location of charge and size of the cations within the framework, the presence of impurities, the ordering and local environment of T-atoms. They have a microporous crystalline framework and are more commonly known as molecular sieves. Zeolites have some interesting structural properties which can be listed as below:

(a) High hydrothermal and mechanical stability

(b) Defined porous structure lying in the range of common chemicals with high surface area: it gives rise to shape selectivity effect in adsorption process

(c) Tunable chemical composition: The constituent positive cations of zeolite framework are rather loosely held and can be exchanged for others in contact solution.

(d) High sorption capacity due to high porosity: It allows molecules of adsorptive as well as reactants, products or transition states of chemical reactions to be selectively excluded from access to and/or egress from the zeolite pores [11].

(e) Environment friendly.

(f) Recoverable and reusable.

These properties make zeolites attractive candidates for several purposes such as gas adsorption processes, development of heterogeneous catalytic systems, ion-exchange reactions etc. Zeolites are often preferred as support materials over other mesoporous materials without crystalline framework. Since a support material may sometimes exert structural effect brought about by its textural and active phase-linked effect, hence it must possess certain properties like porosity, surface area, dispersion, selectivity and of course activity. Zeolites in this context, successfully justify the requirements. The synergistic effect of the morphology, porosity of the zeolite structure

and catalytic ability of the supported phase results in to development of a heterogeneous catalyst with high thermal as well as chemical stability and activity.

2A.4. Structure of Y Zeolite

Zeolite Y has the faujasite framework structure with sodalite cages as the tertiary building units (TBU) (**Fig.2A. 3**). In this, the tetrahedra are linked to form cubo-octahedra or so-called β cage units. The β-cage has both four-membered and six-membered rings in its structure. Zeolite A is formed by bridging (not fusing) the four-membered rings. It does not occur in nature, but is industrially produced on a massive scale for its use in ion exchange, gas separation and drying processes. If the six-membered rings are bridged, then possibly the most important zeolite structure, zeolite X/Y is formed. Depending on the silica-to-alumina ratio of their framework, synthetic faujasite zeolites are divided into X and Y zeolites. The Si/Al ratios are 1-1.5 for the X zeolite and 1.5-3 for the Y zeolite. The unit cell of the faujasite type zeolites is cubic with a unit cell dimension of 25Å and it contains 192 silica and alumina tetrahedra. Each of the sodalite unit is connected to four other sodalite units by six bridging oxygen atoms connecting the hexagonal faces of two units to generate layers of sodalite units. The oxygen bridging unit is referred to as the hexagonal prism. The sodalite layers are also linked by hexagonal prisms in an ABC sequence to generate a tetrahedral array of sodalite having cubic symmetry and the same space group as diamond. This arrangement of sodalite units generates wide pores with free diameter of 7-8Å via the interlinking of 12 tetrahedra, which provides entrance in to larger supercages of 11-12Å diameter. The supercages are linked tetrahedrally via the 12 rings to form a highly porous framework structure [12]. Owing to the large microporous spaces, Zeolite Y (**Fig. 2A.4**) has the liberty to allow organic molecules to diffuse in and out easily from the framework. This property makes zeolite very useful for catalytic, ion-exchange and absorption purposes.
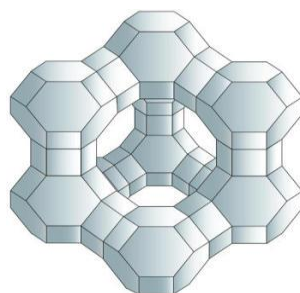

Fig. 2A.4: Cage structure of Y zeolite

2A.5. Dealumination of Y zeolite

The term "dealumination" refers to structural modification of zeolite frameworks with formation of extra framework aluminium species (EFAl) by chemical reactions resulting in deficiencies of framework Al lattice points [13]. The various important parameters of zeolite can be affected with variation of the ratio of framework Si/Al atoms within the zeolite structure using chemical and hydrothermal treatments. Mainly, this ratio exerts a strong influence on the physical properties such as maximum ion-exchange capacity, hydrothermal and thermal stability, hydrophobic properties, and generation of strong Brönsted-acidic sites which may determine the catalytic activity and selectivity of modified form of zeolite structure for a particular reaction. Since the low Si/Al ratios zeolite are unstable in acids or water at elevated temperatures, therefore zeolites with low aluminum content (high Si/Al ratio) are more favorable, especially when applied as catalysts [14-16]. The commercial synthesis of faujasite family (X & Y) cannot be directly obtained with the Si/Al ratios substantially higher than 3 [17]. Therefore, all catalytically relevant material must be prepared by post synthetic removal of framework Al that can increase the Si/Al ratio to thermally stable dealuminated zeolite. Generally, the dealumination process of zeolite framework can be divided into three categories such as (1) those involving removal of framework aluminium by chemical agents or by thermal dehydroxylation, (2) those in which in addition to the mere extraction of framework aluminium, framework vacancies are filled by intrinsic silicon and oxygen atoms migrating in the zeolite lattice by hydrothermal treatment and (3) those representing true substitution reactions of Al component of the framework and the dealuminating agent. Not all zeolites can preserve the integrity of the framework during dealumination process. The structural arrangement and stability of the framework may get compromised depending upon the severity of the conditions applied.

The first synthesis of Y-zeolite was reported by Breck [18] in 1964 and he observed that the change of X to Y modifications occurs at a critical characteristic value of Si/Al ratio at 1.5. Ruster et al. [19] in 2006 described another typical chemical behavior of the Y-zeolite sample that is dealumination by stream treatment. According to that observation, Y zeolite may be dealuminated in steam above the Si/Al ratio of 2.2 without destruction of its framework. At the same time, NaA and NaX zeolites get completely collapsed after any dealumination process. Different dealumination

techniques of Y-zeolites include acid extraction [20], isomorphous Al/Si substitution [21] and thermochemical treatment of NH_4Y [22]. The healing effects of NH_4Y in dry or wet air were also investigated by Ward in 1972 that led to structural features of dealuminated Y zeolites (DAY) [23]. The appearance of EFAl species brings a stabilizing effect on the zeolite framework with a more regular structure in the DAY zeolite [24]. The higher thermal stability of DAY samples were reasoned for removal of mineralizing effects of Na^+ ion on the destabilization of framework [25], preferential formation of Si-O-Si bonds as a results of dehydroxylation of intermediately formed hydroxyl nests [26] and also healing effects of Al defects with migration of H_4SiO_4 from the crystal surface [27]. Different types of defects such as sorption centers for gases or liquids are reorganized in the form of regular structure and thus the silica framework loses its sorption behavior with rising temperature [28]. The formation of secondary pore structure in DAY is one of the reasons for higher activity of the zeolite in high temperature catalytic process.

The dealumination process of Y-zeolite favors the formation of an ultra-stable Y-type zeolite (USY). It makes it so by drastically improving the thermal as well as chemical stability of the zeolite framework. Mild hydrothermal treatment of the faujasite type Y-zeolite usually triggers partial release of aluminium from the zeolite framework and results in to formation of extra-framework aluminium species. The oxoaluminum cations, such as AlO^+, $AlOH_2^+$, and $Al(OH)_2^+$, and some neutral species such as AlOOH and $Al(OH)_3$ are proposed to be the EFAl species. The presence of these EFAl species improves not only the thermal stability but also the catalytic activity of the dealuminated zeolite framework. This beneficial effect of EFAl species on the catalytic activity can be understood on the basis three hypotheses: (a) some EFAl species themselves serve as the Lewis acidic site; (b) their presence stabilizes the negative charges on the lattice after removal of the acidic protons; (c) there is synergistic effect between the EFAl species and the nearby Brönsted acidic sites thereby resulting in to formation of super acidic zeolite framework [29].

All these three hypotheses are the outcome of extensive studies by the researchers on the dealumination of Y-zeolite framework from time to time. Though these hypotheses are largely debated [30, 31], some researchers have proven their point based on sound experimental evidences as well as theoretical calculations [29]. The resulting super acidity of the dealuminated of Y-zeolite framework was also reasoned to

the interactions between protonic sites and polymeric oxoaluminium deposited in the zeolite voids [32] and can be very beneficial for promoting isomerization, cracking, hydrogen transfer in dealuminated HY framework as well as acid catalyzed organic conversions [33, 34].

2A.6. Use of zeolite as support material for immobilization of ionic liquids

The immobilization of ILs on to a solid support provides a simple way for reducing the amount of IL required for a given application, reducing accordingly the associated cost; simplifies their handling and separation process from the reaction mixture, and finally, significantly reduces the leaching of ILs to the environment [35]. Among various types of inorganic supports (e.g. alumina, silica, clay etc.), zeolites have some unique properties for efficient immobilization of ILs on their surfaces such as high surface area, well organized pore channels, excellent thermal stability, environmentally benign nature and high absorption towards organic compounds [36]. There are a few reports found in literature on the synthesis of zeolite supported ionic liquids and their use in different organic syntheses as heterogeneous catalyst. The supported IL material can manifest good thermal and water stability as compared to the parent IL. The immobilization of the ionic liquid can be achieved by different means, such as by covalent anchoring of the surface functional groups with the cation or anion of the ionic liquid or without covalent bonds in the form of supported liquid phases. In some cases up to minimal loading of 10%, small islands of the ionic liquid could form over the support material; while in cases of high loading complete coverage of the support surface occurred.

The heterogenization of acidic ionic liquids on solid supports offers several advantages as compared to the use of catalytically active ILs in homogeneous or heterogeneous phases. The number of accessible active sites of the catalyst may increase through immobilization and thus reduction in the amount of IL required for catalysis. The leaching problem of IL phase is completely eliminated in the covalent attachment mode. It is suitable for application in a continuous fixed bed reactor.

This section summarizes the literature for immobilization of ionic liquids on zeolite support and their utilization in organic synthesis as well as in other fields till 2016.

DeCastro et al. [37] prepared immobilized Lewis acidic ionic liquids (AL-ILs) in different ratios of 1-butyl-3-methyl-imidazolium chloride ([bmim]Cl) and $AlCl_3$ on SiO_2, Al_2O_3, TiO_2, ZrO_2 and H-BEA zeolite (Si/Al = 13.8) in order to prepare heterogeneous acidic catalysts for the alkylation of aromatic compounds with dodecene under continuous liquid-phase and continuous gas-phase batch methods. A comparison of catalytic activities of different supports expressed higher activity of silica-based supports in the alkylation reaction of benzene with dodecene. In this study, the zeolite based IL material was not selected for studying the alkylation reaction, since the zeolite structure significantly lost its crystallinity after immobilization of AL-IL. The shape-selective effects of pure beta-zeolite towards generation of 2-phenyl-dodecane product were lost in case of the AL-IL supported beta-zeolite under the same reaction condition.

Valkenberg et al. [38] prepared supported Lewis-acid catalysts for Friedel-Crafts reaction by immobilizing chloroaluminate ionic liquids in different porous materials such as silica, alumina, MCM-41, NaY zeolite, Nb_2O_5 and TiO_2. The ILs were added directly on to the porous support without use of any solvent. These materials containing ionic liquids in supported phase showed leaching of the IL components in liquid phase reactions. The major drawback of this method was observed in case of the structured support materials, namely zeolites and MCM-41. The structure of the supports was destroyed after immobilization of chloroaluminate ionic liquids as evidenced in PXRD analysis [39-41].

Pietschmann et al. [39] impregnated [EMIM$^+$][BF$_4^-$] over BEA zeolite and mesoporous silica by addition of zeolite powder (or silica powder) in to a solution of IL in methanol under continuous stirring for several hours. The solid materials were separated from the suspension by filtration and any excess of IL was removed by Soxhlet extraction.

Jin et al. [42] immobilized palladium acetate in thin ionic liquid layers on the mesopore wall of hierarchical MFI zeolite (**Scheme 2A.1**) and examined as heterogeneous catalyst for Suzuki coupling reaction in water. The catalyst exhibited very high activity in the coupling of various aryl bromides with aryl boronic acids in water with high stability. This catalyst could be recycled for four runs without significant loss in catalytic activity. Hierarchical MFI zeolite was proven to be a promising support for the supported ionic liquid catalysis.
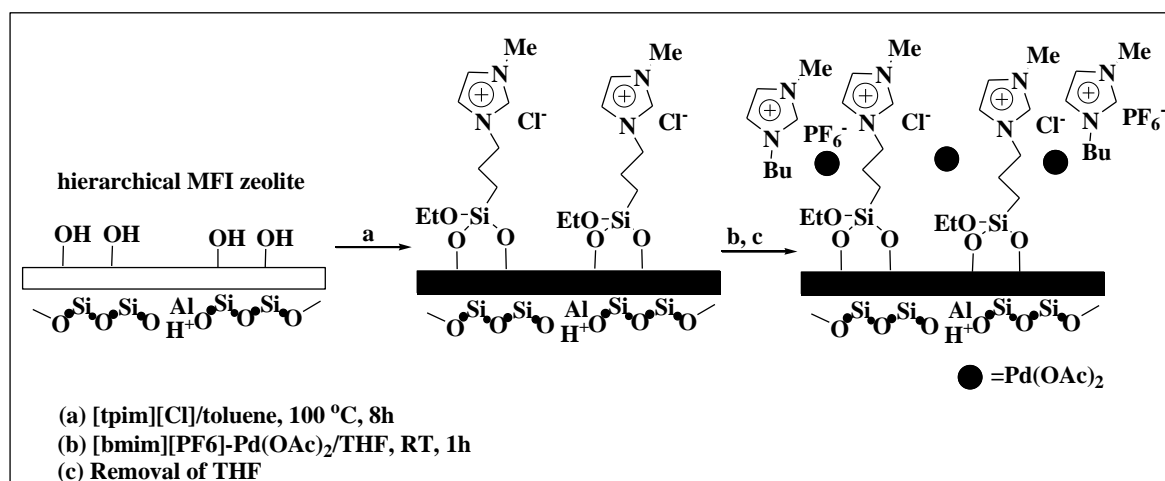
Scheme 2A.1: Synthesis of MFI-supported Pd(OAc)$_2$-ionic liquid

Ntais et al. [43] studied the synthesis of NaY zeolite-ionic liquid (H-3-methylimidazolium bis(trifluoromethanesulfonyl) imide) (HMITFSI) composites with a weight ratio of IL/Zeolite = 250 and the excess of IL was eliminated from the composite material by Soxhlet extraction. The prepared material was characterized via Powder XRD analysis and FT-Raman spectroscopy. The XRD patterns showed a redistribution of extra framework cations without loss in crystallinity of the zeolite structure. This study indicated encapsulation of HMITFSI in to the zeolite pores and that HMI$^+$ might have replaced part of the Na$^+$ in the zeolite structure. The FT-Raman spectra of the composite supported the presence of both the two ions of the ionic liquid even after 24 hours of Soxhlet extraction.

Ntais et al. [44] synthesized H-3-methylimidazolium bis(trifluoromethane sulfonyl)imide encapsulated NaY zeolite composites (TFSI)/NaY with six different weight ratios of IL/zeolite and studied their ion transport properties. The different properties of the resultant composites showed direct correlation of the loaded ionic liquid amount over the zeolite. The composites displayed lower water capacitance with increasing loading of IL because of reduction of the micro pore surface area. Likewise, the A.C. impedance measurement revealed that at dry condition, conductivity of the composites increased with loading and temperature. However, measurements at wet conditions revealed two different temperatures dependencies. At higher IL loading, the conductivity increased with increasing temperatures while the opposite was observed for lower IL loaded composites.

Eguizábal et al. [45] developed supported ammonium based ionic liquid systems (2-hydroxymethyl)trimethylammonium dimethyl phosphate (IL1) and N,N-dimethyl-N-(2-hydroxyethyl) ammonium bis(trifluoromethanesulfonyl) imide (IL2) with Y (FAU framework code) and beta (BEA framework code) type zeolites for evaluation of proton transfer conduction properties of the composites. These composites were used as raw materials in high temperature proton exchange membrane fuel cells (HTPEMFCs) (**Fig. 2A.5**). The encapsulation of ILs in the support was confirmed with the help of X-ray diffraction, N_2 physisorption, TGA analysis, ATR-FTIR, Raman spectroscopy and A.C. impedance measurement techniques. The conduction properties of the composites as a function of temperature and water partial pressure have been selected as analytical tool to define the best encapsulation procedure and hence to develop IL/Zeolite composites for proton exchange membrane fuel cell (PEMFC) applications.
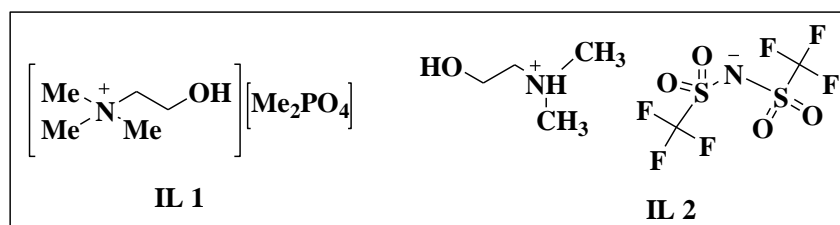
Fig. 2A.5: Structure of ammonium based ILs

Arya et al. [46] developed Brönsted-acidic catalyst systems by supporting Brönsted acidic ionic liquids 1-methylimidazolium tetrafluoroborate ionic [MIM][BF$_4$] over ZSM-5 zeolite. The catalytic efficiency of the synthesized Supported Ionic Liquid Phase (SILP) materials were examined for the preparation of spiro[indole-pyrido[3,2-e]thiazine] in water under ultrasonic irradiation (**Scheme 2A.2**). The reactions were also studied under conventional heating and microwave promoted conditions. The ultrasound-promoted method proved to be more efficient in terms of product yield. The recyclability of the catalytic system was tested under ultrasound-promoted reaction condition and it was found that the catalytic system could be easily recycled up to fifth consecutive cycles without any obvious loss in activity.
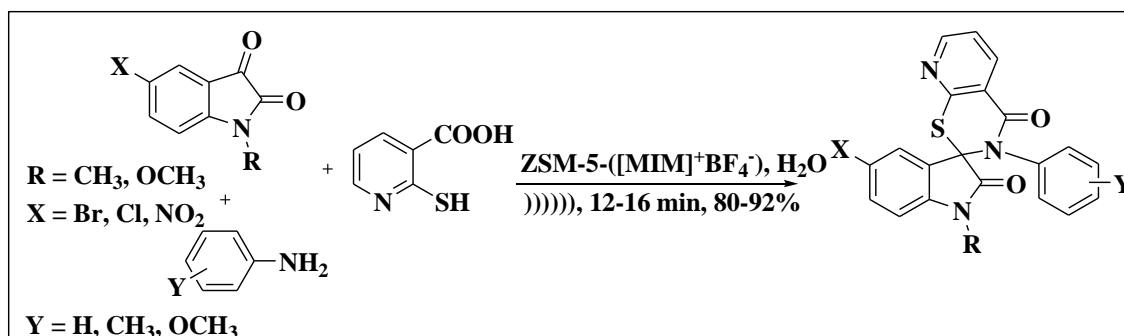
Scheme 2A.2: Synthesis of spiro[N-substituted indole-pyrido thiazines]

Arya and Prabhakar [47] encapsulated 10 mol % of various ionic liquids namely ([Bmim][BF$_4$], [Bmim][PF$_6$], [C$_8$mim][BF$_4$] and [C$_8$mim][PF$_6$]) within mesoporous ZSM-5 zeolite on the basis of organic-additive -instant seed technology method [48]. The catalytic activity of the synthesized systems was tested for the synthesis of spiro[pyrazolo[3,4-e]benzothiazepine] analogues in water within short reaction time (**Scheme 2A.3**). The recyclability profile of the [Bmim][BF$_4$] confined ZSM-5 zeolite system was checked and it was found to be successfully recycled for six consecutive cycles without any appreciable loss in catalytic activity.
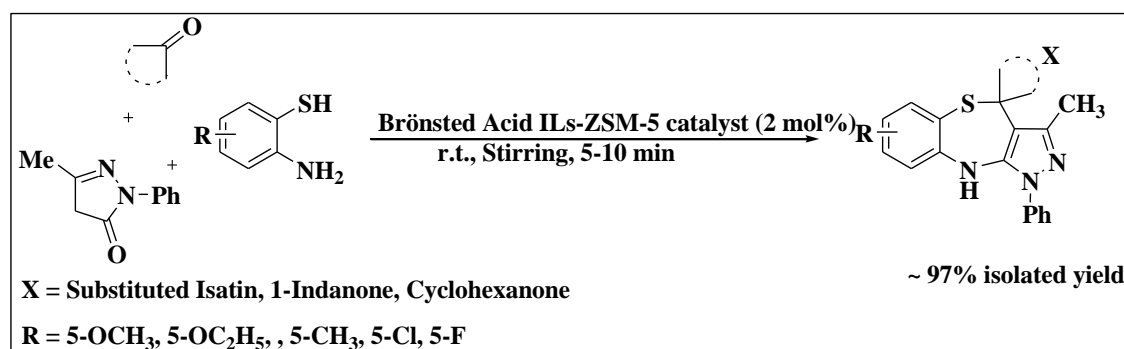
Scheme 2A.3: Synthesis of spiro [pyrazolo[3,4-e][1,5]benzothiazepaine] analogues

Noroozifar et al. constructed [49] a novel biosensor by incorporating modified nanosized natural zeolite and 3-hydroxypropanaminium acetate (HPAA) as a novel room temperature ionic liquid, supported on multiwalled carbon nanotube (MWCNTs) and employed for the simultaneous determination of dopamine (DA) and uric acid (UA).

Blanes et al. [50] introduced an approach for generation of three different zeolite families (BEA, MFI, and ANA) using 1-butyl-3-methyl imidazolium methane sulfonate [bmim][CH$_3$SO$_3$] as template. The use of TEOS (Tetraethyl orthosilicate) as a silicon source and [bmim][CH$_3$SO$_3$] as a templating agent results in IL/Na-ZSM-5 composite

with the IL remaining trapped within the zeolite structure. The encapsulated IL acquires a configuration where the longer alkyl chain of substituted imidazolium enters the secondary cages of the structure. The resulting ionic liquid-zeolite composite showed resistance towards high thermal treatment supporting either the chemical bonding through the imidazolium ring to the zeolite framework (bmim-BEA) or the entrapment of the IL into the resulting channels (bmim-MFI). The replacement of the silicon source by colloidal silica led to the formation of IL/BEA composite with IL playing the role of the charge compensation cation. The sole mordenite structure was obtained in absence of the IL.

Yu et al. [51] developed a ship-in-a-bottle strategy to prepare [APMIM]Br@NaY host-guest system for CO_2 capture from simulated flue gas. The host-guest system was prepared by in situ encapsulation of 1-aminopropyl-3-methylimidazolium bromide ([APMIM]Br) IL in the NaY supercages. The encapsulated ILs were found to be more stable than the bulk ILs. The excellent physicochemical properties and the CO_2 capture performance of the host-guest systems render great pledge for the future practice in the industrial CO_2 capture.

Li et al. [52] synthesized a heterogeneous mordenite (MOR) supported Brönsted acidic IL catalyst: BAIL@MOR via covalent anchoring of [CPES-BSIM]-[HSO$_4$] ionic liquid over mordenite zeolite (**Scheme 2A.4**). The covalent binding interactions of the BAIL [CPES-BSIM][HSO$_4$] was confirmed from the combined characterization results of XRD, FT-IR, SEM, TG-DTG and N_2 adsorption isotherm studies. The prepared material was investigated as efficient recyclable catalyst in the ketalization of cyclohexanone with 1, 2-propylene glycol and 1, 3-butylene glycol under mild reaction conditions. The conversion of the cyclohexanone showed positive dependence with the reaction temperature and catalyst loading in the presence of BAIL@MOR as catalyst. The catalyst witnessed a very good recyclability profile up to five consecutive cycles.
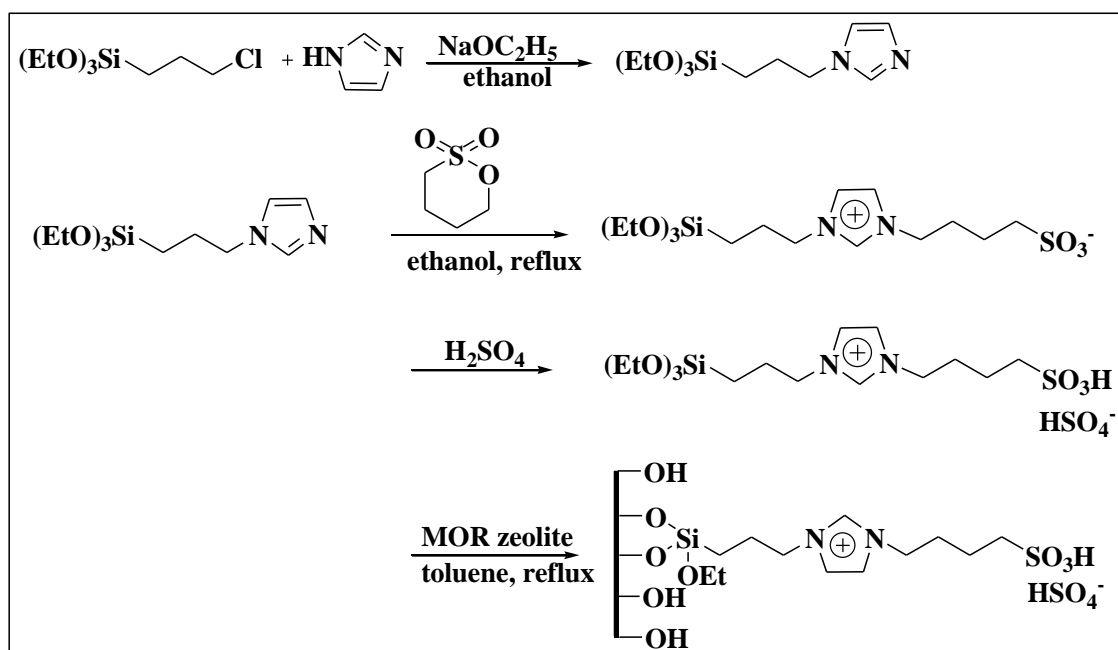
Scheme 2A.4: Route for the synthesis of catalyst BAIL@MOR

Losch et al. [53] explored the catalytic activity of [bmim][CH$_3$SO$_3$]/zeolite composites as heterogeneous catalyst in liquid phase toluene chlorination reactions. ILs/zeolites composites exhibited low toluene conversion at room temperature compared to the bare Na-zeolite. It may be reasoned to the restricted accessibility of the Na-zeolite pores in the presence of IL.

2A.7. Biginelli reaction: An introductory note

Biginelli is a kind of multicomponent reaction and it employs the easily accessible ethyl acetoacetate, aryl aldehyde and urea/thiourea to form the respective 3, 4-dihydropyrimidin-2(1H)-one (DHPM) derivatives. The reaction was named after Pietro Biginelli who had discovered it in 1893. He investigated the reaction of ethyl acetoacetate and urea in presence of benzaldehyde in EtOH under reflux conditions. The mechanism of Biginelli reaction has been a topic of much debate in various experimental and theoretical reports. As depicted in **Fig. 2A.6**, three main mechanisms involving the protonated intermediates have been proposed. The first mechanism which is called the iminium route, involves condensation between aldehyde and urea to give rise to an iminium intermediate, which further undergoes a nucleophilic addition with a β-keto ester resulting the DHPM. The second mechanism also termed as 'enamine route' is based on condensation between urea and β-keto ester leading to a protonated enamine intermediate, which subsequently reacts with aldehyde to form the DHPM. The

third mechanism involves a Knoevenagel type reaction mechanism. The reaction between aldehyde and β-keto ester results in the formation of a carbenium ion intermediate which further reaction with urea results the DHPM [54]. However, further studies confirmed the authentic route to be the iminium pathway [55-57].

After more than 100 years of long discovery, the reaction has still elicited due to diverse applications of the resulting product across therapeutic and pharmaceutical field. The traditional Biginelli reaction involves the use of strong acidic conditions to give the DHPMs. However, it suffers from low yield of the resulting product. The growing interest in DHPMs has surged interest in development of efficient routes and catalysts over the years. The search led to wide variations in reactions conditions. The use of different type of catalysts such as Brönsted/Lewis acidic, biocatalysts, heterogeneous catalysts, organocatalysts etc. was reviewed by Suresh and Sandhu in 2012 [58]. Recent developments also involved the use of environment friendly and easily recoverable nanocatalysts to carry out the Biginelli reaction [59-62]. The blooming of different green protocols on account of growing interest over development of safer chemistry such as use of solvent free conditions, microwave heating, sonochemistry, use of water/ethanol as the solvent, ionic liquids etc. over the decades has been reviewed by Panda and co-workers in 2012 [63]. A recent review by Nagarajaiah and co-workers (2016) summarizes the critical developments of this reaction in the realm of material chemistry, natural product synthesis and also the access provided by this reaction towards syntheses of chiral DHPMs [54].

Considering the facile synthetic access provided by this reaction towards the diverse heterocyclic systems, researchers are still in to it and the outcome is exciting research publications in peer-reviewed journals with variation in every possible manner.
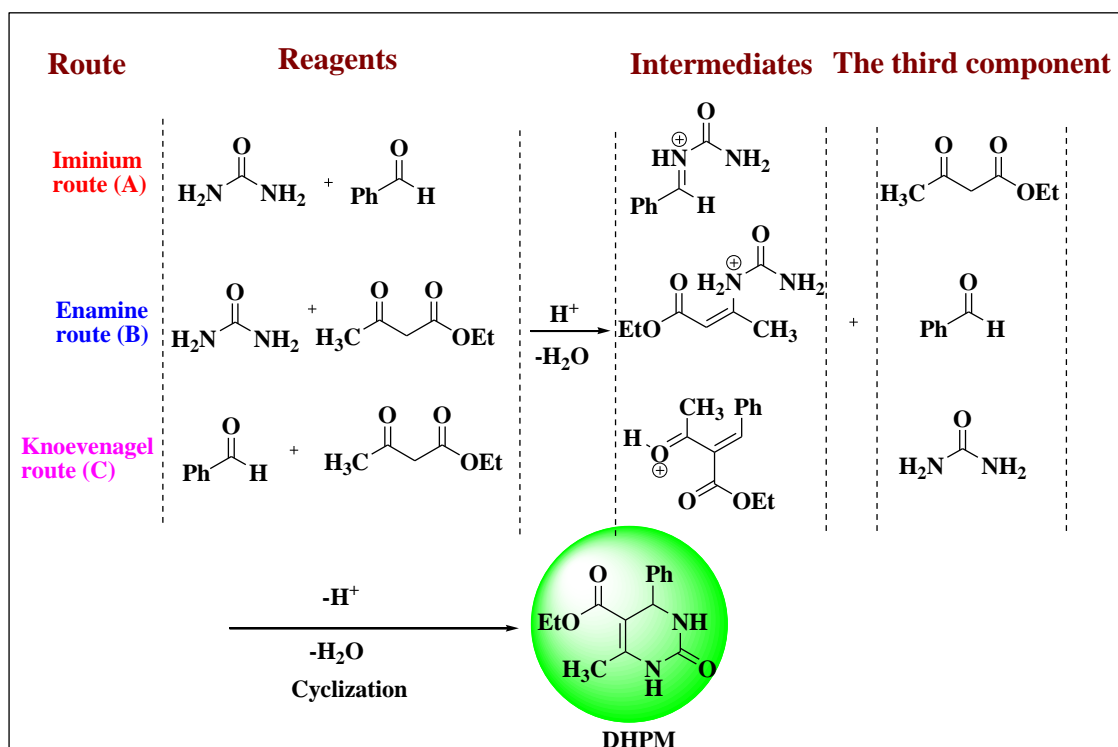
Fig. 2A.6: Mechanisms for Biginelli reaction

2A.8. Biological aspects of Biginelli 3, 4-dihydropyrimidinone (DHPM) derivatives

Biginelli DHPMs possess wide spectrum of interesting pharmaceutical and therapeutic activities. After Pietro Biginelli discovered the multicomponent route to the multifunctionalized dihydropyrimidinones in 1893, these partly reduced pyrimidines were largely ignored in the following decades and hence the biological activity of these compounds remained unexplored. For the first time in 1930, the wool protection activity of these scaffolds was patented [58]. Since the early 1980s, the interest in dihydropyrimidinones surged due to their apparent structural similarity to the well-known dihydropyridine calcium channel modulators of the Hantzsch type: nifepidine (**1**); the respective biginelli product being an aza-analogue (**2**) proved to be an effective orally active antihypertensive agent [64] (**Fig. 2A.7**).
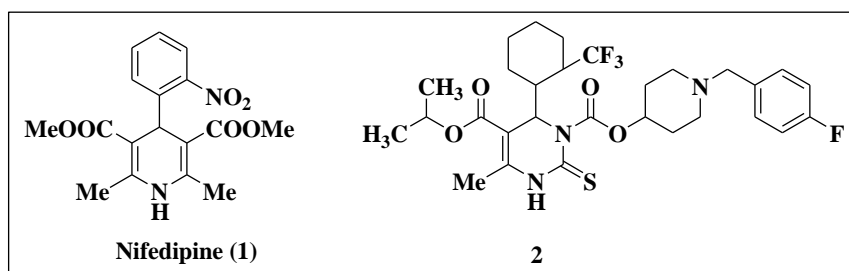
Fig. 2A.7: Structure of Nifedipine (**1**) and its biginelli analogue (**2**)

More recently, the interest has been shifted from DHPM calcium modulators to the development of other biologically active DHPM derivatives (**Fig. 2A.8**). DHPMs with annulated benzimidazole ring (**3**) showed potential potassium channel antagonists activity [65]. Also, Batzelladine A (**4**) derivative of DHPMs obtained from marine natural source have promising anti HIV activity [66]. Monastrol (**5**) was the first Biginelli compound which showed excellent anticancer activity [67]. Some other important pharamacological activities offered by DHPM derivatives are anti-epilepsy activity [68], anti-malarial activity [69], anti-microbial activity [70], anti-inflammatory activity [71], anti-tubercular activity [72] and anti-bacterial activity [73] etc. Additionally, some DHPMs are also developed as anti-oxidants [74], anti-filarial agents [75] and α-1A adrenergic receptor antagonists [76] in recent times. Apart from this, they are also employed as important agents for treating anxiety [77] and optic nerve dysfunction [78].
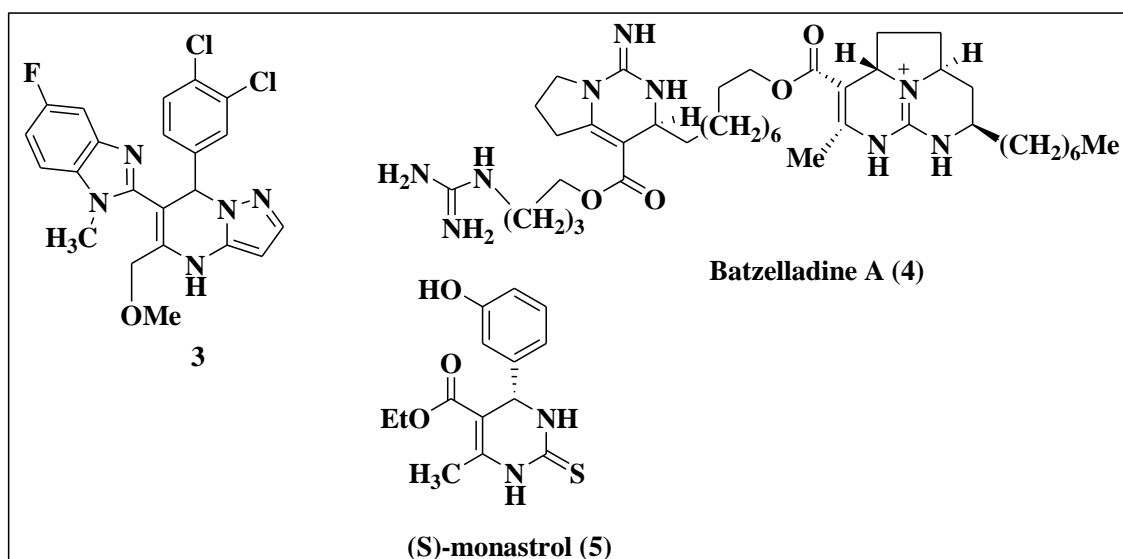
Fig. 2A.8: Structure of some important DHPM derivatives

These reasons led researchers to focus their attention on the synthesis of these compounds, to explore more and more functionalized DHPM derivatives and build up a rich library of potential agents suitable for different purposes.

The next section summarizes the literature on use of different heterogenized ionic liquid catalyst for development of 3, 4-dihydropyrimidinone derivatives over the years.

2A.9. Use of heterogenized ionic liquid catalysts for synthesis of 3, 4-dihydropyrimidinone derivatives via Biginelli reaction

In 2005, Wang et al. [79] studied the three-component Biginelli reaction of aromatic aldehyde, ethyl acetate and urea in glacial acetic acid at 100 °C using 3.5 mol% of polymer supported catalyst PsMimPF$_6$ (**Fig. 2A.9**) to afford the corresponding pyrimidine-5-carboxylates in yields up to 99% within 2 hour. The catalyst was prepared through immobilization of room temperature ionic liquids on polymer support which was reused at least five times with retention of original catalytic activity. Aliphatic aldehyde was not suited with this condition for the formation of Biginelli product.
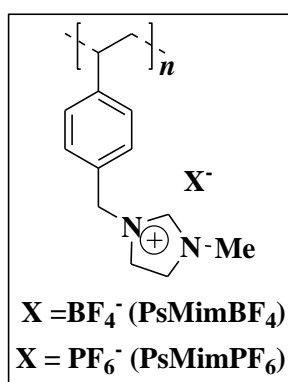
Fig. 2A.9: Structure of PsMimPF$_6$ and PsMimBF$_4$

The use of ionic liquid-functionalized SBA-15 (ILSBA-1) as catalyst in the Biginelli reaction was studied by Xu et al. [80] in three different solvents CH$_3$CN, EtOH and AcOH under reflux temperature according to the reaction **Scheme 2A.5**. It was observed that glacial AcOH was a better solvent with excellent isolated yield, and no precipitation was observed during reaction except for ILSBA-1. This catalytic system produced 59-95% yield of 3, 4-dihydropyrimidinone derivatives in presence of 1-5 mol % of catalyst within 3 hour reaction at 100 °C from various substituted aromatic

aldehydes. The ILSBA-1 catalyst was recycled for five times with good catalytic activities. The ionic liquid-functionalized SBA-15 (ILSBA-1) was prepared from MTESPImCl (1-Methyl-3-[(triethoxysilyl) propyl]imidazolium chloride) by following the reaction **Scheme 2A.6** [81].
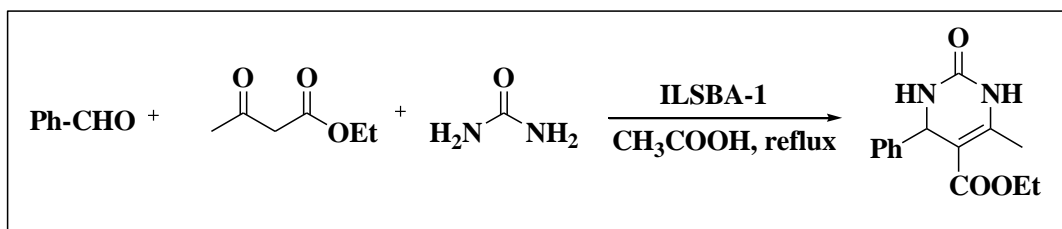
Scheme 2A.5: Synthesis of substituted tetrahydropyrimidine-5-carboxylates
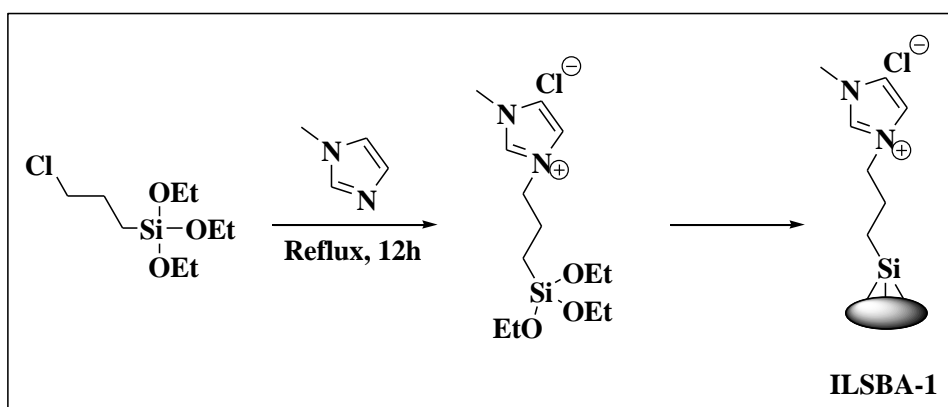
Scheme 2A.6: Synthetic route of MPImCl-SBA (ILSBA-1)

Kang et al. [82] reported the use of silica-supported sulfonic acid-functionalized ionic liquid (Si-[SbSipim][PF$_6$]) as heterogeneous recyclable catalyst for the multi-component synthesis of Biginelli products. The reactions were carried out under reflux condition in ethanol within 3.5-5 hour to form 80-94 % yields of DHPM derivatives starting from various substituted aromatic aldehydes (**Scheme 2A.7**). The catalyst could be easily separated from the reaction mixture and efficiently reused for six times. The supported catalyst was prepared according to **Scheme 2A.8** [83].

R = H, 2-OH, 3-NO₂, 3-OCH₃-4-OH, 4-CH₃, 4-OH, 4-F, 4-OCH₃, 4-Cl

R' = OCH₃, OCH₂CH₃
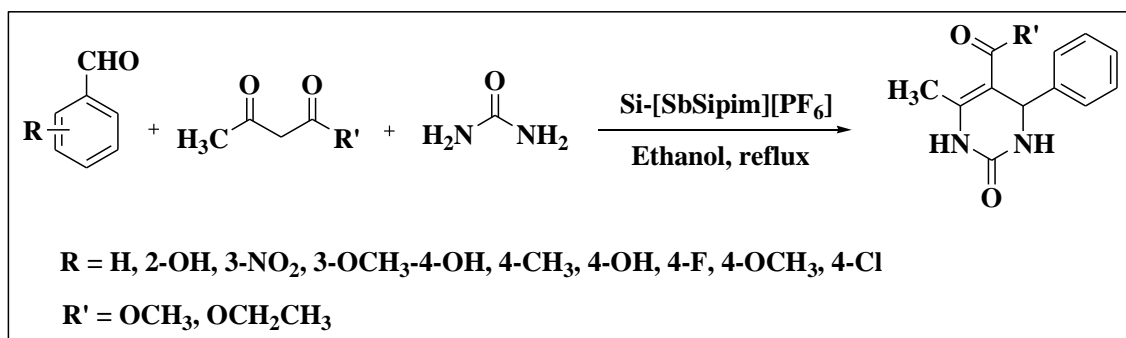
Scheme 2A.7: Synthesis of DHPM derivatives using Si-[SbSipim][PF₆] as catalyst

a: 3-chloropropyl trimethoxysilane, toluene, reflux, 72 h, N₂; b: imidazole, 24 h, reflux, N₂; trimethoxysilane, 15 min, r.t.; c: acetone, 1,4-butanesultone, 24 h, r.t.; d: acetonitrile, CF₃SO₃H, 12 h, r.t.; e: KPF₆, ethanol and water (v/v, 1:1), 24 h, r.t.
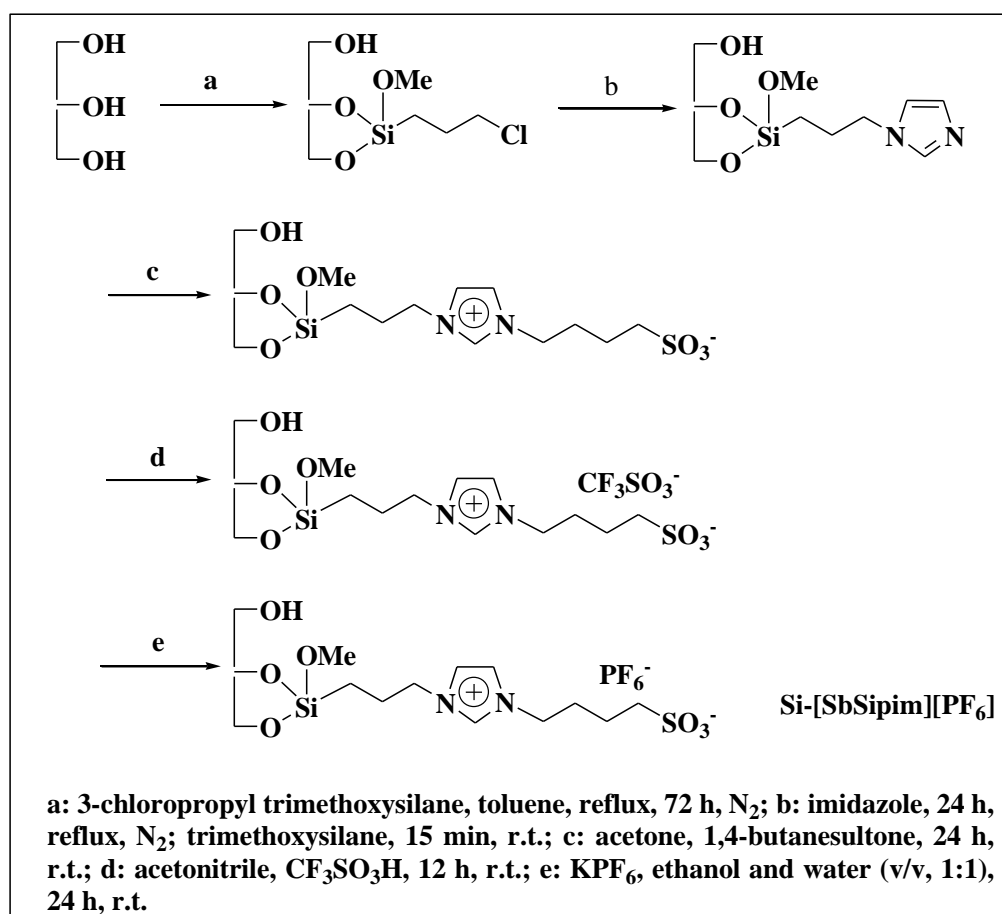
Scheme 2A.8: Synthetic route for Si-[SbSipim][PF₆]

Elhamifar and Shàbani [84] reported the catalytic application of manganese containing periodic mesoporous organosilica with ionic liquid framework (Mn@PMO-IL) in the synthesis of 3, 4-dihydropyrimidinones from the reaction of various aldehydes with urea and alkyl acetoacetates under solvent-free condition (**Scheme 2A.9**). The products were obtained within 45-120 min of duration in excellent yields with 0.6 mol% of catalyst at 75 °C. The catalyst was recovered and reused up to 14 times without significant loss in activity and selectivity.
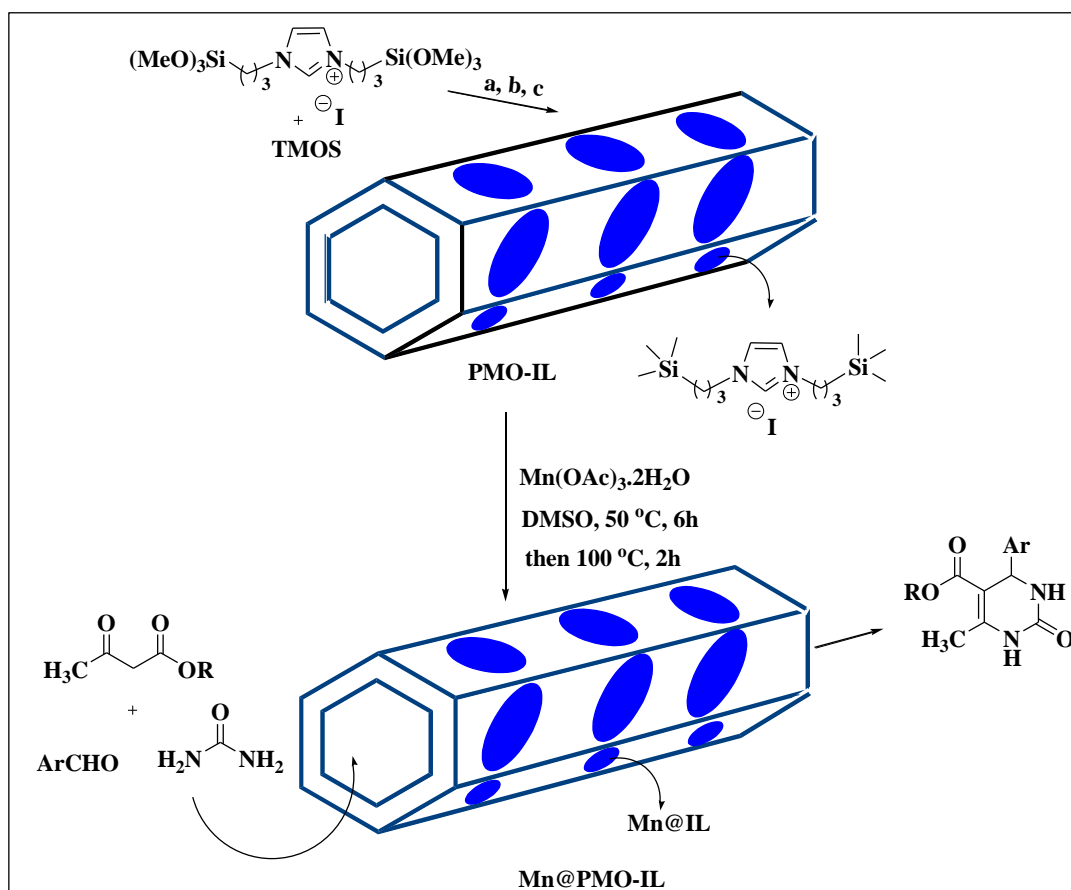
Scheme 2A.9: Synthesis of Mn@PMO-IL and its application in the synthesis of DHPMs: a) H_2O, HCl, (2M), P123, 40 °C, 24h; b) Static conditions, 100 °C; c) Soxhlet extraction of surfactant

In the same year, Elhamifar et al. synthesized novel copper-loaded ionic liquid-based periodic mesoporous organosilica (Cu@PMO-IL) nanoparticles (**Scheme 2A.10**) [85] and characterized the mesoporous structure of the Cu@PMO-IL material via transmission electron microscopy (TEM) and nitrogen adsorption-desorption analysis. The authors confirmed the presence of copper species in the material framework X-ray photoelectron spectroscopy (XPS) and elemental analysis (EA). The catalytic application of the Cu@PMO-IL nanocatalyst was examined in the Biginelli condensation of different aldehydes with urea and alkylacetoacetates under solvent-free conditions and at moderate temperature. Moreover, the stability, reactivity and reusability of the catalyst were found improved against the reaction conditions.

Scheme 2A.10: Synthesis of Cu@PMO-IL nanoparticles and their application in Biginelli reactions

Elhamifar and Nazari [86] in an another study described the use of iron containing Schiff base and ionic liquid based bifunctional periodic meso porous organosilica (Fe@SBIL-BPMO) (**Scheme 2A.11**) for the synthesis of 3, 4-dihydropyrimidinone/thione derivatives under solvent free reaction medium at 80 °C. The method showed high tolerance towards various aromatic electron withdrawing and electron donating group containing aldehydes. Aldehydes with electron donating substituents were converted to the desired products with high efficacy under the optimized reaction conditions. The synthesized nano-catalyst system showed high reactivity, durability as well as recyclability up to 15 consecutive cycles. TEM analysis of the recovered catalysts after fifth cycle confirmed the stability of the catalyst mesoporous framework.

Safari et al. [87] utilized acidic $[((EtO)_3Si)^3C_3C_1im][HSO_4]$ ionic liquid grafted on Fe_3O_4 magnetic nanoparticles as catalyst for the Biginelli synthesis of 3, 4-dihydropyrimidin-2(1H)-ones or -thiones (**Scheme 2A.12**) under solvent-free conditions at 100 °C with 90–98% yields within 20-35 min. Different aromatic and heteroaromatic aldehydes were worked efficiently under the reaction conditions to form the corresponding products. The catalyst could be recovered easily from the reaction mixture by using a simple bar magnet and recycled up to 8th cycle with slight decrease in activity for the model reaction of benzaldehyde, ethyl acetoacetate, and urea.

Scheme 2A.11: Synthesis of the Fe@SBIL-BPMO catalyst and its application in the synthesis of 3, 4-dihydropyrimidinones/thiones
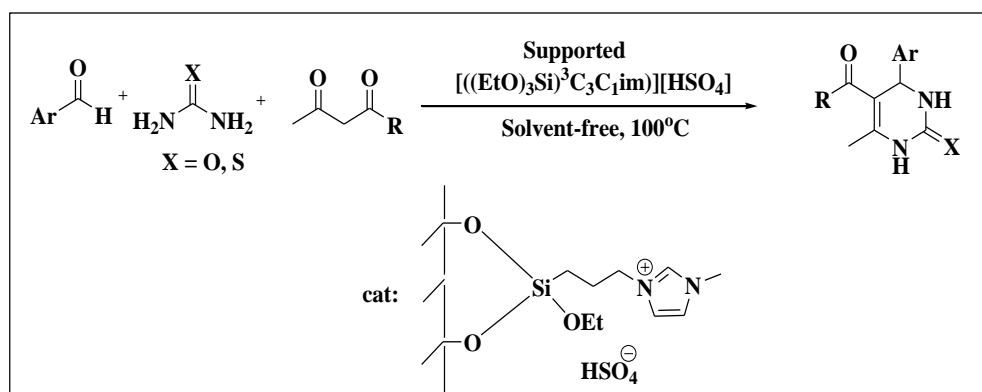
Scheme 2A.12: Synthesis of Biginelli 3,4-dihydropyrimidinones/thiones catalyzed by $[((EtO)_3Si)^3C_3C_1im][HSO_4]$ ionic liquid grafted on Fe_3O_4 magnetic nanoparticles

The literature review on various heterogenized ionic liquid systems highlights the progresses in this field over the years and encourages us to develop unique SILP systems using zeolite as the support. Also the review on use of different heterogeneous

ionic liquid systems in preparation of Biginelli 3, 4-dihydropyrimidinone derivatives signifies the superiority of these systems and uplifts the quest of researchers for such systems.

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