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RAPID COMMUNICATION

Transition metal containing ionic liquid-assisted one-pot synthesis of pyrazoles at room temperature

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Abstract. The feasible and one of the green ways to synthesize organic compounds especially pyrazole and its derivatives are systematically presented. The one-pot synthesis of pyrazole was achieved by condensation of various hydrazines and 1,3-diketone derivatives at room temperature using transition metal-based ionic liquids. Herein, the unique combination of Fe(III) with ionic liquid is explored and utilized as an efficient homogeneous catalyst for the synthesis of pyrazole and its derivatives. The homogenous catalyst thus synthesised was re-used up to the fourth cycle (with 90%, 88%, 84%, 78% yields respectively).

Keywords. 1,3-Diketone; hydrazine; green chemistry; pyrazole; transition metal; paramagnetic ionic liquids.

1. Introduction

In organic synthesis, various toxic solvents and expensive catalysts prepared by tedious multistep reactions are generally used. To eliminate the hazards associated with routine organic synthesis we propose here a simple method to synthesize organic compounds keeping the principles of green chemistry on top priority. The use of ionic liquids (ILs) as catalyst or solvent is a part of the hazard-free chemical process, which has been used extensively in research fields. Thus, ILs gain escalating attention for their expansive range of applications as prospective replacements for volatile organic solvents.[1–3] The physicochemical properties of ILs have been well-studied. Different noteworthy ILs have been developed by means of appropriate exchange of cations and anions.[4,5] ILs have achieved special attention as a potential green solvent because they have remarkable physiological properties including a broad range of solubility, very low volatility, inflammability, excellent thermal stability, non-corrosive towards metals and good conductivity.[6–11] Because of the adjustable physical properties, ionic liquids have been used in various organic transformations including pyrazole synthesis.[12–16] The judicial choice of counterion in ionic liquids makes them green and more suitable as catalyst or solvent or both for many organic processes, as they increase the optimum possibility such as homogenous distribution of reactants, controllable product formation, jump in reactivity or rate of reaction, ease of product isolation and recycling.[17]

The ionic liquids with metal ion are a new subclass of task-specific ionic liquids since they have both magnetic and catalytic property. Most of the metal-based ionic liquids have been reported earlier with transition metal ion (M^{n+}) with various counter ions including halides (X^-), SCN^-, Tf_2N^- ions, etc.[18] Metal ion as a counterpart of the ionic liquid provides superior catalytic media due to the elevated effectual concentrations of metal ions

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and their Lewis acidic nature.[19–24] The presence of such high effective transition metal ion concentrations in this kind of ILs also termed as paramagnetic liquids, does not alter the properties of ILs such as low volatility, hydrophilicity, electrical conductivity, etc.

There are numerous reports from various research groups describing metal-based ionic liquids including transition metals such as $[Al_xCl_y]^-$, $[FeCl_4]^-$, $[MnCl_4]^{2-}$ $[CuCl_4]^{2-}$, $[NiCl_4]^{2-}$, $[PdCl_4]^{2-}$, etc.[25,26] Most of reported imidazolium-based transition metal ILs are solid at room temperature, except $[FeCl_4]^-$ salts which are liquid at room temperature due to its tetrahedral lattice breaking structure. In continuation of our interest in exploring the green and feasible synthetic route for various organic transformation, in this manuscript, we have used paramagnetic anion $[FeCl_4]^-$ bearing ionic liquid as an efficient catalyst for pyrazole synthesis.

Due to the medicinal importance, pyrazole core gains immense significance in the pharmacological industry for drug design such as anticancer, antibacterial, antimicrobial, antifungal, etc.[27–30] Because of the presence of lone pairs in the nitrogen atoms, pyrazole moiety itself acts as ligands for catalysis.[31–33] Pyrazole is also known to act as a precursor of agro-based chemicals as pesticides, herbicides, fungicides, etc.[34–36] Pyrazole moieties also have some other applications in industrial and material sciences such as ultraviolet stabilizer,[37] optical brighteners,[38] selective fluorescence sensors,[39] luminescent complexes, etc.[40,41] Among various procedures for the synthesis of pyrazoles, the condensation of hydrazine derivatives with 1,3-diketones is a widely utilized technique[42,43] over other reaction procedures which are associated with several disadvantages such as prolong reaction time, elevated temperature, use of costly ligands, multistep preparation of the substrate, formation of tautomers and conformers, etc.[44–47] In addition, the formation of numerous regioisomeric mixtures of pyrazoles was frequent while carrying out the synthesis making the system more cumbersome.[48,49] Literature reports reveal the use of several kinds of homogeneous catalysts,[50,51] heterogeneous catalysts,[52–54] different metal sources,[55,56] micellar catalyst,[57] nano ionic liquids,[58] enzymatic catalyst,[59] etc., for the synthesis of pyrazole through different reaction routes such as ultrasound,[60] microwave,[61] neat,[62] using different substrates, etc.

2. Experimental

All reagents and solvents were purchased from Sigma Aldrich, Merck and Alfa Aesar and used without further purification unless otherwise stated. All reported yields are isolated yields. Pyrazole synthesis was performed on oven-dried glassware at open air. ^1H and ^{13}C NMR spectra were recorded on 200 MHz and 50 MHz or 500 MHz and 125 MHz spectrometers at room temperature. Chemical shifts are reported in parts per million (ppm, δ). Column chromatography was performed on silica gel (120–230 mesh). Thin-layer chromatography (TLC) was carried out using aluminium sheets pre-coated with silica gel $60F_{254}$ (Merck) and was visualized under 254 nm UV light.

2.1 *Procedures*

2.1a *Synthesis and characterization of catalysts*: The transition metal-based ionic liquids, $[C_4mim]_2[MnCl_4]$ and $[C_4mim][FeCl_4]$ were synthesized according to reported literature. These ionic liquids were characterized by using different analytical techniques such as ESI-MS, DSC and TGA, UV and Raman spectra for anion, ICP-OES data for percentage metal content.

2.1b *Synthesis of transition metal-based ionic liquids*: The synthesis of transition metal-based ionic liquids is carried out according to previously reported procedure.[23,63,64]

(i) $[C_4mim][FeCl_4]$: To synthesize the $[C_4mim][FeCl_4]$, 1-butyl-3-methyl imidazolium chloride ($[C_4mim]Cl$) (5g, 28.63 mmol) and ferric chloride hexahydrate ($FeCl_3.6H_2O$) (8.5 g, 31.89 mmol) were taken in 100 mL round bottom flask with 1:1.1 molar ratio in methanol. The reaction mixture was refluxed for 24 h. After completion of the reaction, the solvent was removed from the product using rotary evaporator. The product was washed with a little amount of MQ water to remove unreacted $FeCl_3$. The dark brown product was again dried using rotary evaporator and stored in a vacuum oven. Mass analysis was done in MicroMass Q-TOF instrument using methanol as solvent. Observed Mass Spectral data: ESI^+ m/z for $[C_4mim]^+$ = 139.23, 140.23, ESI^- m/z for $[FeCl_4]^-$ = 195.91, 197.57 (100%) and 199.91. Percentage of Fe content in the IL was determined by ICP-OES (Inductively Coupled Plasma-Optical Emission Spectroscopy) analysis in Perkin Elmer ICP optima 2000 DV ICP-OES analyzer and it was found that Fe content in $[C_4mim][FeCl_4]$ is 14%.

(ii) $[C_4mim]_2[MnCl_4]$: For $[C_4mim]_2[MnCl_4]$, 1-butyl-3-methyl imidazolium chloride ($[C_4mim]Cl$) (5g, 28.63 mmol) and manganese chloride tetrahydrate ($MnCl_2.4H_2O$) (2.7 g, 13.63 mmol) were taken in 100 mL round bottom flask with 2.1:1 molar ratio in methanol. The reaction mixture was refluxed for 24 h. After completion of the reaction, the solvent was removed from the product using rotary evaporator. The product was washed with isopropyl alcohol to remove unreacted $[C_4mim]Cl$. The faint yellow-green coloured product was again dried using rotary evaporator and stored in a vacuum oven. Mass analysis was done in MicroMass Q-TOF instrument using methanol as a solvent. Observed Mass Spectral data: ESI^+ m/z for $[C_4mim]^+$ = 139.24, 140.25, ESI^- m/z for $[MnCl_4]^-$ = 195.59, 196.02

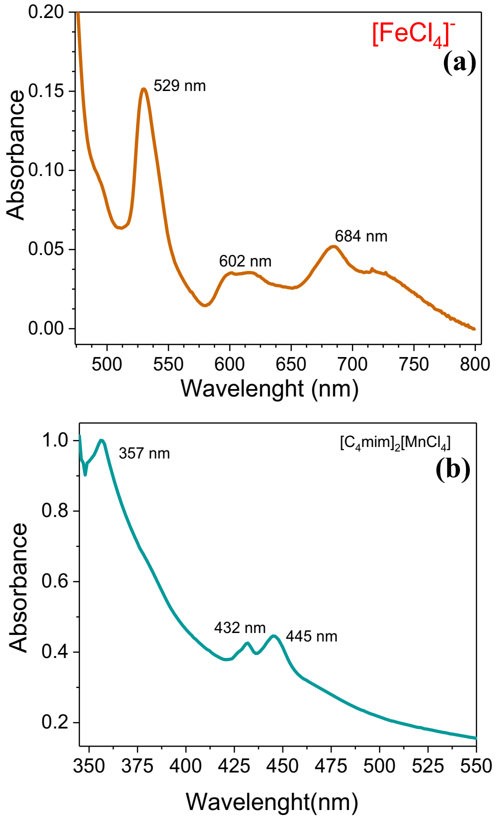


Figure 1. UV-Visible spectroscopy of the ionic liquid for (a) $[FeCl_4]^-$ anion and (b) $[MnCl_4]^-$.

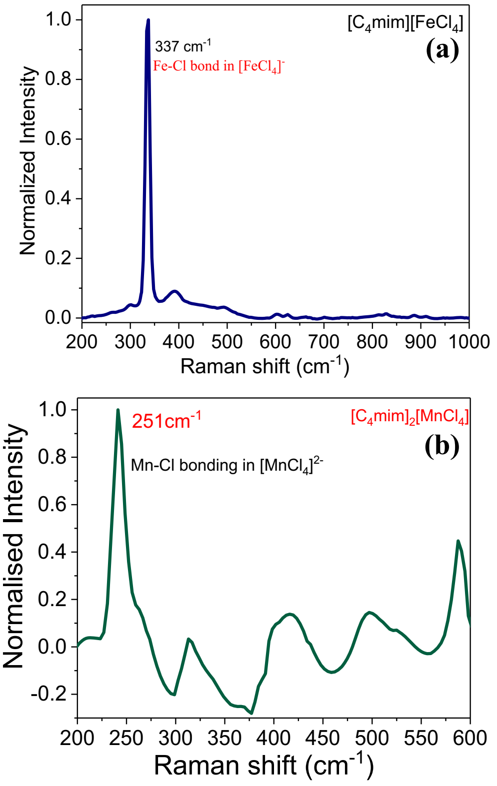


Figure 2. Raman spectra of the ionic liquids (a) [C$_4$mim][FeCl$_4$] and (b) [C$_4$mim]$_2$[MnCl$_4$].

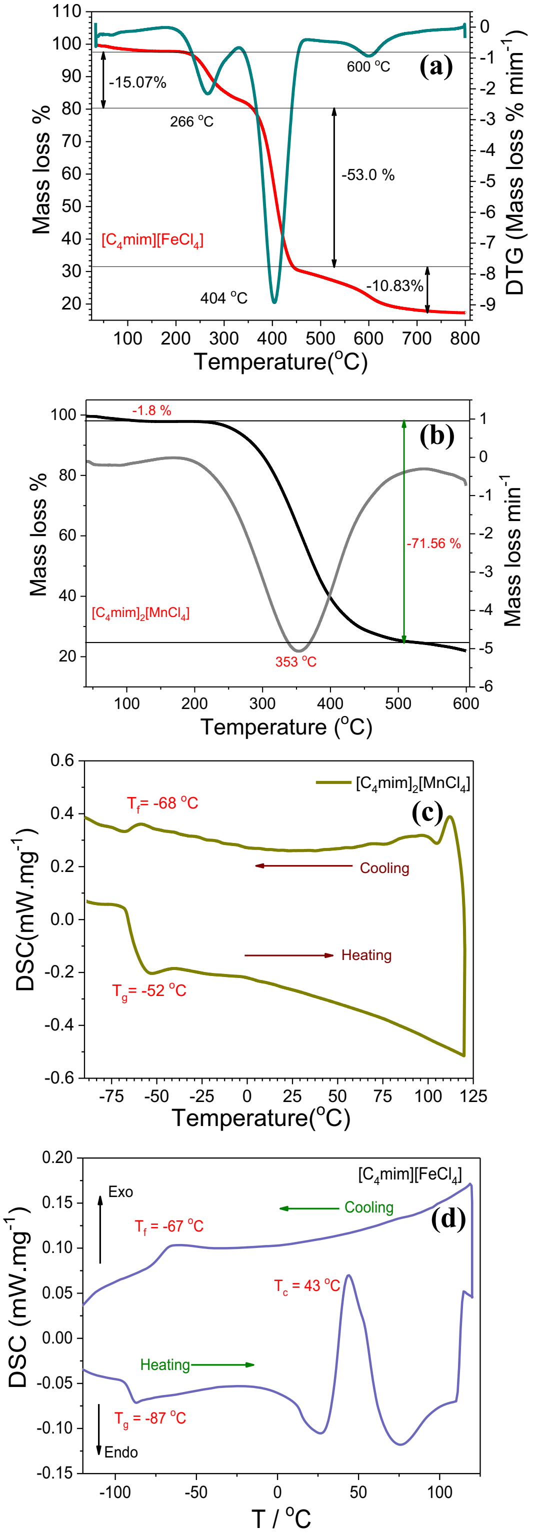


Figure 3. TGA of (a) [C$_4$mim][FeCl$_4$] (b) [C$_4$mim]$_2$[MnCl$_4$] and DSC of (c) [C$_4$mim][FeCl$_4$] and (d) [C$_4$mim]$_2$[MnCl$_4$] ILs.

(100%), 196.04. The percentage of metal content in IL was determined by ICP-OES analysis and it was found that Mn content in [C$_4$mim]$_2$[MnCl$_4$] is 12%.

2.2 *Characterization of the transition metal-based ionic liquids*

2.2a *UV and Raman spectra for [MCl_4] anion:* Structure elucidation of paramagnetic anions has been verified with UV-3600 Shimadzu UV-Vis-NIR absorption spectroscopy with quartz cuvette of 1 cm path length in the acetonitrile and LabRAM HR Evolutions (Horiba Jobin Yvon) Raman Spectroscopy. In Figure 1 (**a**), the characteristic bands for tetrachloroferrate(III) ($[FeCl_4]^{-)}$ anion has appeared in a range of 450 to 700 nm. The characteristic peaks have appeared at 529, 602 and 684 nm were due to $^6A_1 \rightarrow {}^4T_2$, $^6A_1 \rightarrow {}^4A_2$, and $^6A_1 \rightarrow {}^4T_2$ transition respectively.[65]

Similarly, in Figure 1 (**b**), the characteristic bands for tetrachloromanganate(II) ($[MnCl_4]^{2-}$) anion have appeared in a range of 300 to 600 nm. The Mn (II) based ionic liquid shows one peak at 357 nm which is due to the transition from $^6A_1 \rightarrow {}^4E(D)$. The second weak band has appeared at 432 nm is due to $^6A_1 \rightarrow {}^4A$, and just next to its peak at 445 nm is related to $^6A_1 \rightarrow {}^4T_2$ transitions of a tetrahedral $[MnCl_4]^{2-}$.[66]

Further, the structures of $[FeCl_4]^-$ and $[MnCl_4]^{2-}$ anions have been verified from Raman spectra shown in Figure 2 (**a–b**). The characteristic band has appeared at 337 cm^{-1} due to total symmetric vibration (A_1) mode in Fe-Cl bond.[67,68] It is observed from the Raman spectrum of $[FeCl_4]^-$ (Figure 2 (**a**)) that there is no any additional intense peaks (except 337 cm^{-1}) which eliminates the possibility of formation of the dimer ($[Fe_2Cl_7]^-$). The characteristic band at 251 cm^{-1} has been assigned for symmetric vibration (A_1) mode in Mn-Cl bond in tetrahedral $[MnCl_4]^{2-}$ anion (Figure 2 (**b**)).[66]

2.2b *DSC and TGA:* Thermal behavior of ILs has been investigated by using NETZSCH DSC 204F1 Phonex 240-12-0239-L and NETZSCH TG 209 F1 Libra TGA 209F1D-0105-L instrument. DSC has been recorded with a rate of 10 °C min^{-1} from -100 to 120 °C while for TGA, the scan rate was 10 °C min^{-1} from 30 to 600 °C. Figures 3 (**a–b**) and Figures 3 (**c–d**) shows thermal properties of ILs using Thermal Gravimetric Analysis (TGA) and Differential Scanning Calorimeter (DSC) respectively. The DCS thermograms show its glass transition temperature (T_g) and all the synthesized ILs have their glass transition temperature below room temperature which fulfill the criteria of ionic liquids with magnetic properties.[69] Herein, we found that T_g (in °C) value for the ILs as follows, $[C_4mim][FeCl_4]$ = -87 °C and $[C_4mim]_2[MnCl_4]$ = −52 °C.[70] The degradation temperature (T_d) of ILs was measured from TGA and first change at initial state between 100° to 120 °C which indicates the hygroscopic nature of the ILs. Beyond this temperature, major mass loss was observed which correlates with the thermal degradation of the ILs.[71] Here found T_d value for, $[C_4mim][FeCl_4]$ = 266 °C, and $[C_4mim]_2[MnCl_4]$ = 353 °C.

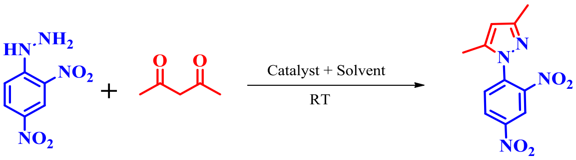
2.3 *Catalytic efficiency of ILs for pyrazole synthesis*

After the synthesis of these transition metal-based ionic liquids, we tried to show the practical importance and application of them in synthetic organic chemistry. Due to the Lewis acidic nature of these ILs, we used them for the synthesis of pyrazole moieties, which are available in many biologically active molecules and drug intermediates like Celebrex, Viagra, Fenpyroximate and Acomplia, etc.

2.4 *General reaction procedure for pyrazole synthesis*

In a round bottom flask, a mixture of hydrazine derivative (1 mmol) and 1,3-diketone (1.2 mmol) and $[C_4mim][FeCl_4]$ (1.5 mL) was added and then allowed to stir at room temperature for the given time period as mentioned in Table 2. The progress of the reaction was monitored by TLC. After completion of the reaction, it was extracted with ethyl

Table 1. Optimization of the catalytic system for the pyrazole synthesis.[a]



Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)
1	No Catalyst	Water	12	-
2[c]	$FeCl_3$	Water	8	30
3	Solvent itself as catalyst	$[C_4mim][BF_4]$	8	-
4	Solvent itself as catalyst	$[C_2mim][OH]$	8	-
5	Solvent itself as catalyst	$[C_4mim]_2[MnCl_4]$	8	50
6	Solvent itself as catalyst	$[C_4mim][FeCl_4]$	4	90

[a] Reaction condition: 2,4-dinitrophenylhydrazine (1 mmol), acetylacetone (1.2 mmol), catalyst + solvent (1.5 mL) at room temperature. [b] Isolated yield. [c] 10 mol% of $FeCl_3$ is used.

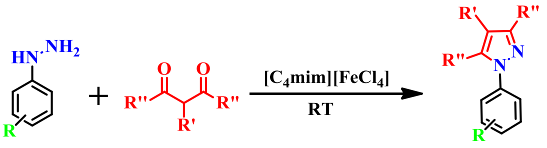
acetate (3 x 20 mL), washed with distilled water and brine solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified through silica gel column chromatography (15–20% EtOAc/hexane) to get the desired product.

3. Results and Discussion

For pyrazole synthesis, the reaction of 2,4-dinitrophenylhydrazine with acetylacetone was considered a model reaction (Table 1). Initially, the reaction was carried out in the presence of water without any catalyst; the reaction did not proceed at all even after 12 h (Table 1, entry 1). The reaction was also carried out in presence of neutral ionic liquid ([C_4mim][BF_4]) and basic ionic liquid, [C_2mim][OH] but the reaction did not afford any product even after 8 h indicating the necessity of the acidic condition (Table 1, entries 3, 4). Using a well-known Lewis acid, $FeCl_3$ the reaction devoted 30% yield of the product after 8 h (Table 1, entry 2). The use of transition metal-based ionic liquid [C_4mim]$_2$[$MnCl_4$] afforded 50% yields after 8 h (Table 1, entry 5) while the best results were obtained by using [C_4mim][$FeCl_4$] as the catalytic media affording 90% yields of the desired product at room temperature (Table 1, entry 6) and used for further studies.

With the optimized condition in hand (Table 1, entry 6), we turned our focus to extend the substrate scope of this simple condensation between functionalized hydrazines and 1,3-diketones (Table 2). It is noteworthy that electron-rich, electron-deficient and heteroatom hydrazines showed outstanding reactivity and equipped the desired products with greater yields

Table 2. Effect of the substituent on pyrazole synthesis.[a]



Entry	R	R′ Or R″	Time (h)	Yield[b] (%)
1	2,4-dinitro	$R' = H, R'' = CH_3$	4	90
2	H	$R' = H, R'' = CH_3$	3	95
3	4-CF_3	$R' = H, R'' = CH_3$	3	82
4	4-CN	$R' = H, R'' = CH_3$	4	85
5	4-Cl	$R' = H, R'' = CH_3$	3	88
6	Ph	$R' = Cl, R'' = CH_3$	4	78
7	4-Br	$R' = Cl, R'' = CH_3$	4	83
8	4-CH_3	$R' = Cl, R'' = CH_3$	3	74
9	4-CF_3	$R' = Cl, R'' = CH_3$	3.5	88
10	Ph	$R' = C_2H_5, R'' = CH_3$	3	78
11	4-Cl	$R' = Cl, R'' = CH_3$	4	72
12	Ph	$R' = CH_3, R'' = CH_3$	3	95
13	4-Br	$R' = CH_3, R'' = CH_3$	3	73
14	4-Br	$R' = C_2H_5, R'' = CH_3$	4	50
15	4-CH_3	$R' = CH_3, R'' = CH_3$	4	83
16	4-CH_3	$R' = C_2H_5, R'' = CH_3$	4	74
17	4-Cl	$R' = CH_3, R'' = CH_3$	3	86
18	4-CN	$R' = Cl, R'' = CH_3$	4	72
19	4-NO_2	$R' = H, R'' = CH_3$	4	50
20	4-CN	$R' = C_2H_5, R'' = CH_3$	4	68
21	4-Br	$R' = H, R'' = CH_3$	2	92
22	2-hydrazino pyridine	$R' = C_2H_5, R'' = CH_3$	3	90
23	4-CF_3	$R' = H, R'' = C_2H_5$	3	85
24	2-furoic hydrazide	$R' = H, R'' = C_2H_5$	3	94

[a] Reaction condition: Hydrazine derivative (1 mmol), 1,3-dicarbonyl derivative (1.2 mmol), [C_4mim][$FeCl_4$] (1.5 mL) at room temperature.

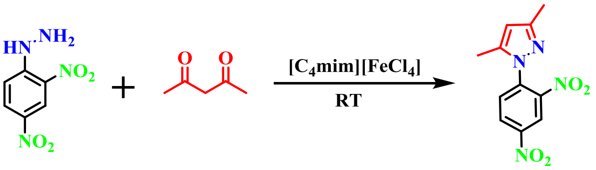
[b] Isolated yields.

at room temperature in shorter reaction times. (Table 2, entries 1–24).

In order to illustrate the practical appliances of this transition metal-based ionic liquid, it was very much essential to reuse and recycle this ionic liquid system (Table 3). The reaction of 2,4-dinitrophenylhydrazine with acetylacetone was carried out to check reusability and recyclability of the catalyst under optimal reaction condition. After the reaction, the catalyst can be separated easily due to its magnetic nature and solubility behavior. It was seen that the ionic liquid could be recovered easily since it is insoluble in organic solvents and reused up to three times for the pyrazole synthesis without loss of its activity (Table 3, entries 1–3). But after 3rd cycle, catalytic activity of the system goes on decreasing and it may be due to the small amount of loss of $FeCl_3$ attached to the ionic liquids in each batch which was confirmed from the ICP-OES analyses of the fresh and reused ionic liquid. We also found that the percentage of Fe was 14% in the fresh ionic liquid whereas it was 11% in reused $[C_4mim][FeCl_4]$ after the 4th cycle (Table 3, entry 4).

The ionic liquid does not undergo decomposition during continuous recycling and no structural changes were observed and it was confirmed by the Raman spectra and ICP-OES analysis of the reused ionic liquid. In the fresh ionic liquid, there was a peak at 337 cm^{-1} which is characteristic of total symmetric vibration (A_1) mode for Fe-Cl bond in $[FeCl_4]^-$ anion and after the fourth cycle, it was found at 334 cm^{-1} (Figure 4). Moreover, from the ICP-OES analysis, % of Fe was found to be 14% in the fresh ionic liquid whereas 11% Fe was available in reused $[C_4mim][FeCl_4]$ after the 4th cycle.

Table 3. Test of recyclability.[a]



Entry	Run	Time (h)	Yield[b] (%)
1	1st	4	90
2	2nd	4	88
3	3rd	4	84
4	4th	4	78

[a] Reaction Conditions: 2,4-dinitrophenylhydrazine (1 mmol), acetylacetone (1.2 mmol), $[C_4mim][FeCl_4]$ (1.5 mL) at room temperature.

[b] Isolated yields after column chromatography.

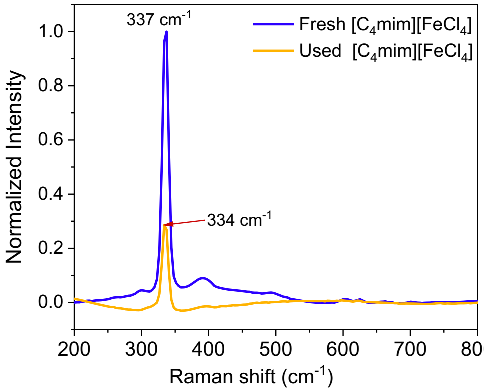
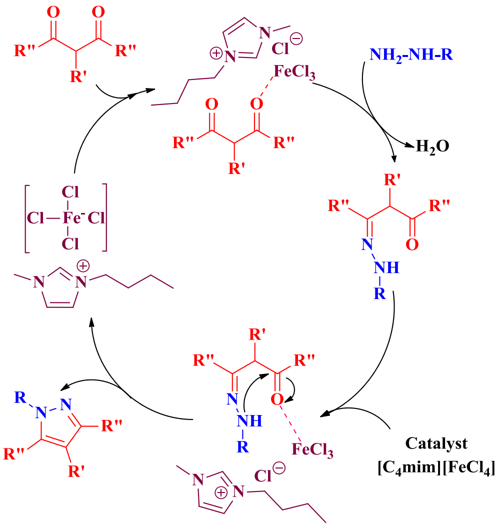


Figure 4. Raman spectra of the reused $[C_4mim][FeCl_4]$ after 4th cycles.

A plausible mechanism has been proposed after getting the experimental outcomes. Scheme 1 shows probable steps for the synthesis of substituted pyrazoles in presence of Fe containing ionic liquid. Initially, in equilibrium $[FeCl_4]^-$ breaks as the combination of $FeCl_3$ and Cl^- anion, and so formed $FeCl_3$ would act as a competent Lewis acid making an interaction with the lone pair of the oxygen atom of the acetylacetone molecule thereby increasing the electrophilicity of that carbon. Then the electrophilic centre is attracted by the basic nitrogen atom of hydrazine and subsequently rearranges to a hydrazone intermediate. The remaining carbonyl group of this hydrazone intermediate again follows similar steps and rearranges to pyrazole moiety followed by the loss of a water molecule. The reaction proceeds through the interaction of Lewis acidic Fe(III) ion and the nucleophilic oxygen atom of the 1,3-diketones and it was well-established by various research groups.[72–74]



Scheme 1. Plausible reaction mechanism.

Moreover, the other parts of the ionic liquid such as $[C_4mim]^+$ and Cl^- anion create a supportive environment in the reaction mechanism.

4. Conclusions

In conclusion, a facile, convenient and quick method for pyrazole synthesis was presented using metal-containing imidazole based ionic liquids. The $[C_4mim][FeCl_4]$ exhibits a dual role of solvent and catalyst for the synthesis of pyrazoles, with adequate yields in short reaction time at room temperature. The use of transition metal-based ionic liquid system can be considered as relatively less toxic, inexpensive, energy saving, efficient, non-corrosive and eliminates tedious catalyst synthesis steps.

Supplementary Information (SI)

The general experimental procedure, NMR and MS spectra for all compounds with full characterization are available as supplementary information at www.ias.ac.in/chemsci.

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