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One-pot synthesis of 2,4,5-trisubstituted imidazoles catalyzed by dicationic magnetic room temperature ionic liquid

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ABSTRACT

Regarding the green chemistry's goals, dicationic magnetic room temperature ionic liquid open up new avenue to introduce an amazing and efficient system for facilitating catalyst recovery in different organic reactions. Ability of this dicationic magnetic room temperature ionic liquid catalyst in the one-pot three-components condensation reaction of benzil, aromatic aldehyde, and ammonium acetatate are also described. Utilization of easy reaction conditions, catalyst with high catalytic activity and good reusability, and simple magnetically work-up, makes this methodology as an interesting option for the synthesis of 2,4,5-trisubstituted imidazoles.

Keywords*: One-pot synthesis, 2,4,5-Trisubstituted imidazole, Dicationic magnetic ionic liquid, Solvent-free.*

1. Introduction

Green chemistry is a multi-faceted discipline that has been created as a contribution of chemistry to sustainable development, avoiding damage to the environment. Ionic liquids (ILs) are a new generation of chemicals that have a great potential for contributing to the greenness of chemical processes and developing new applications.

Recently, a new generation of magnetic ionic liquids (MILs) has been discovered which shows a strong response to magnetic field [1,2]. Magnetic ionic liquid is a kind of ionic liquid which is formed by organic cation and inorganic anion. It can be absorbed on the magnet, and has a certain magnetization in the presence of external magnetic field. In addition, magnetic ionic liquid can play as solvent, catalyst and template in organic synthesis, the resulting product is easy to separate and the structure of the product can be adjusted by an external magnetic field. Magnetic ionic liquid can be recycled and reused, and the catalytic activity of magnetic ionic liquid is not significantly reduced. [3-8].

These properties make magnetic ILs to have more advantages and potential application prospects than conventional ILs in terms of catalytic reactions, solvent effects and separation processes [9].

Recently, a lot of attention has been paid to synthesis of heterocyclic compounds. Among the various classes of heterocyclic compounds imidazole derivatives are the subject of considerable interest from both academic and industrial perspectives [10]. They have shown a broad spectrum of biological activities such as antimycobacterial [11], antidepressant [12] and antitumor [13] which has made them privileged structures in combinatorial drug discovery libraries [14]. Due to their wide range of applications, a variety of improved methods have been developed for the synthesis of imidazole derivatives such as $Yb(OPf)_3$ [15], $ZrCl_4$ [16], $NiCl_2$. $6H_2O$/ Al_2O_3 [17], silica sulfuric acid (SSA) [18], $[BMIm][H_2PO_4]$, [EMIM]OAc, $[HeMIM]BF_4$, $[HBIM]BF_4$, and phosphomolybdic acid [19-23]. By far, the most common method is the condensation of aromatic aldehyde with benzil and ammonium acetate in solvent free condition.

However, many of reported methods suffer from one or more limitations such as harsh conditions, unsatisfactory product yields, long reaction times, and critical product isolation procedures, use of volatile organic solvents and co-occurrence of several side products. Thus, the development of an alternate milder and safer method is highly demanding for synthesis of imidazole derivatives to overcome those limitations.

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In continuation of our work on the catalytic properties of magnetic ionic liquids [24], herein, we wish to report a simple, convenient and efficient method for the use of dicationic magnetic room temperature ionic liquid (DMRTIL) as catalyst for the synthesis of 2,4,5-triaryl-1H-imidazoles. Furthermore, to the best of our knowledge, there is no report on the use of magnetic ionic liquid catalysts in the synthesis of substituted imidazoles.

2. Experimental

2.1. General

All starting chemicals (AR grade) were purchased from commercial suppliers and some chemicals were further purified by recrystallization or distillation. Melting points were measured on an Electro thermal 9100 apparatus and are uncorrected. ^{1}H & $^{13}CNMR$ spectra were recorded on a FT-NMR Bruker Avance Ultra Shield Spectrometer at 400.13 and 100.62 MHz in $CDCl_3$ as a solvent and chemical shift values are recorded in units δ (ppm) relative to tetramethylsilane (Me_4Si) as an internal standard. IR spectra were recorded on a BOMEM MB-Series 1988 FT-IR spectrometer. Thermal decomposition temperatures were measured using thermogravimetry analysis (TGA, model: TGA-50, shimadzu) with a heating rate of 10 °C/min. Melting points were measured using a capillary melting point apparatus (Buchi B-540) with a heating rate of 10 °C/min. Visible absorption spectra were recorded on a Nicolet Eco 300 UV-Vis spectrometer in acetonitrile(0.1 M, 500 –800 nm). Aldehydes, benzil, anhydrous $FeCl_3$ and 1-methyl imimdazole were purchased from Merck company in high purity. Products were characterized by comparison of their physical and spectroscopic data with those of known samples. The purity of products and reaction monitoring were accomplished by TLC on silica gel Poly Gram SILG/UV 254 plates**.**

2.2. General procedure for the preparation of $[C_4(mim)_2](Cl)_2$

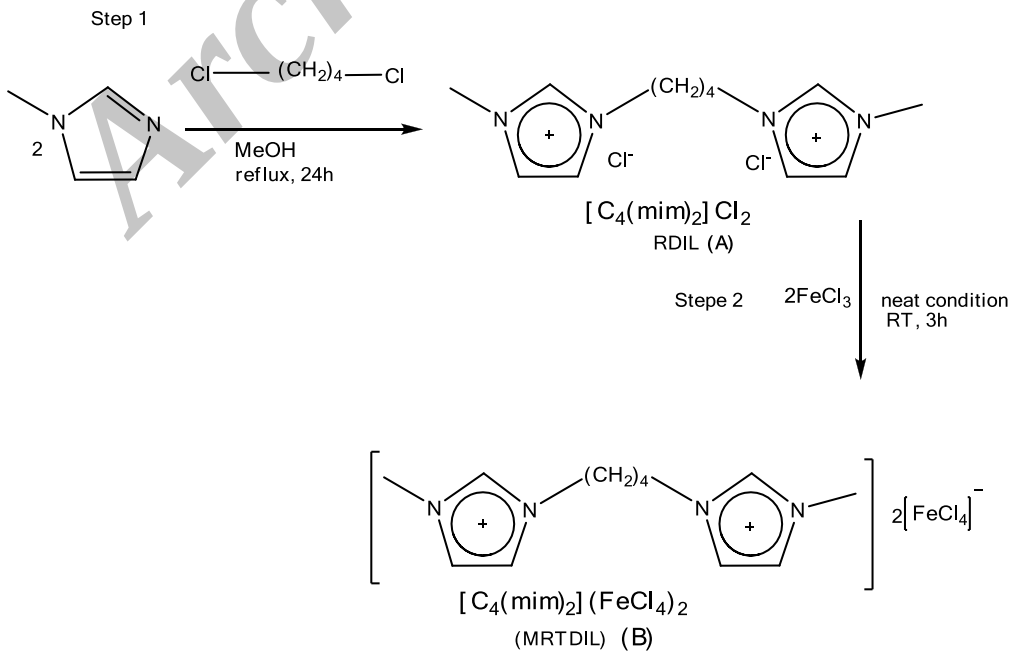
1,4-Dicholorobutane (1 mmol) was reacted with 1-methylimidazole (2 mmol), respectively, stirred in methanol, refluxed for 24 h, and then precipitated from ethyl acetate to obtain the required product (white solid 1a, yield 94%) [24, 25].

2.3. General procedure for the preparation of $[C_4(mim)_2](FeCl_4)_2$ as a magnetic room temperature dicationic ionic liquid.

$[C_4(mim)_2](FeCl_4)_2$, was prepared by mixing crystal powder of $[C_4(mim)_2](Cl)_2$ (1 mmol) with anhydrous $FeCl_3$ (2 mmol) at room temperature for 3h, a dark brown liquid was obtained (Scheme 1). The obtained $[C_4(mim)_2](FeCl_4)_2$ was extracted with small amount of ethyl acetate. The solvent was evaporated and resulting clear brown liquid was dried in vacuum oven at 60°C for 24h. The $[C_4(mim)_2](FeCl_4)_2$ was obtained in high yield.

2.4. General procedure for the synthesis of trisubstitutedimidazoles

At room temperature benzil (1 mmol), aromatic aldehyde (1 mmol), ammonium acetatate (3 mmol) were added to DMRTIL (20 mol %) in the test tube. The resulted mixture was stirred completely with a glass bar and then was heated at 100°C for an appropriate time.



Scheme 1. Synthesis of $[C_4(mim)_2](FeCl_4)_2$ as a magnetic room temperature dicationic ionic liuquid.

The progress of reaction was monitored by TLC. After completion of the reaction (TLC), the mixture was cooled to room temperature and washed with cooled water. The solid product was purified by crystallization from aqueous EtOH to afford products 4a-j. The aqueous phase was concentrated; the catalyst was separated using an external magnetic field. The residue catalyst was washed with a mixed of ethyl ether and deionized water and dried in a vacuum oven at 60°C for overnight. The [pbmim] $(FeCl_4)_2$ was successfully reused for fourth cycles without significant decline of activity.

Selected spectral data

2,4,5-Triphenyl-1H-imidazole **(4a)**: m.p. 270–272°C. FT-IR (KBr, cm^{-1}): 3424 (NH), 2993, 2470, 1636 (C=C), 1510 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 11.7 (s, 1H, NH), 7.1–7.9 (m, 15H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ (ppm) = 146.0, 136.0, 135.0, 130.8, 130.0, 129.0, 128.7, 128.3, 127.5, 127.0, 125.0.

2-(4-Nitrophenyl)-4,5-diphenyl-1*H*-imidazole **(4g):** m.p. 240–242°C. FT-IR (KBr, cm^{-1}): 3421(NH), 2928, 1596 (C=N), 1515, 856; ^{1}HNMR (400MHz, $CDCl_3$): δ (ppm) = 10.7 (s. br., NH), 7.1-7.78 (m, 12), 8.49 (d, J=7.8 Hz, 2H), 7.2-7.6; ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) = 148.0, 147.4, 145.6, 137.8, 134.7, 131.4, 131.0, 130.3, 129.6, 128.5, 126.8, 126.6, 124.0.

2-(2,4-Dimethoxyphenyl)-4,5-diphenyl-1*H*-imidazole **(4c):** m.p. 250-252°C. FT-IR (KBr, cm^{-1}): 3413 (NH), 2928, 1596 (C=N). ^{1}H NMR ($CDCl_3$): δ (ppm) = 10.34 (1H, s), 6.6-8.4(13H, m, Ar), 4.03 (3H, s), 3.9 (3H, s) ppm. ^{13}CNMR ($CDCl_3$): δ (ppm) = 161.0, 156.0, 144.0, 137.0, 135.0, 131.0, 129.3, 128.8, 128.2, 127.8, 127.6, 127.4, 126.7, 125.9, 111.6, 105.0, 98.8, 55.5.

3. Results and Discussion

The magnetic dicationic ionic liquid as a catalyst was synthesized according to our previously reported studies [24,25]. Scheme 1 illustrates the synthetic route for the preparation of DMRTIL synthesized and characterized in this study.

Due to the paramagnetic nature of the1,4'-(butane-1,4-diyl) bis(3-methylimidazolium) bis-[tetrachloro-ferrate(III)] (B), $[C_4(mim)_2]$ $(FeCl_4)_2$, nuclear magnetic resonance technique could not be used to confirm its structure. Instead, UV spectra was used to characterize the $[C_4(mim)_2](FeCl_4)_2$ structure. As previously reported in the literature [26], the typical three absorption bands of $FeCl_4^-$ can be observed at around 533, 615 and 688 nm. The UV spectrum is shown in Fig. 1. $[C_4(mim)_2](FeCl_4)_2$ spectra exhibited absorption bands in the visible region at 534, 620 and 680 nm which are characteristic for the $FeCl_4^-$ anion.

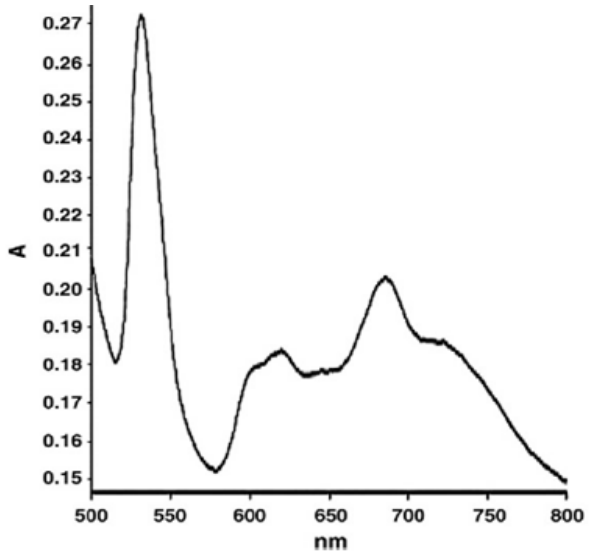


Fig. 1. Visible absorption spectrum of DMRTIL.

The thermal gravity analysis curve of catalyst under a nitrogen atmosphere at a heating rate of 10°C min^{-1} is shown in Fig. 2. There were three main steps of weight loss, and the decomposition events took place at 210°C, 319°C and 547°C. On the base of weight changes, the first process was attributed to the loss of 1-methylimidazole (found 12.30% calc. 13.98%). The second event corresponded to the loss of 1-methyyl-3-buyl imimdazole (found 19% calc. 22.4%). The weight loss (about 29.90%) during 400°C to 800°C was attributed to the decomposition of $FeCl_3$ and the loss of chlorine is shown in Fig. 2. According to the differential scanning calorimeter (DSC) result (data not shown), a major endothermic peak at 285 K was observed, which could be assigned to the melting point of $[C_4(mim)_2](FeCl_4)_2$.

The magnetic properties of DMRTIL were investigated by using MPMS SQUID system at 298 K (Fig. 3).

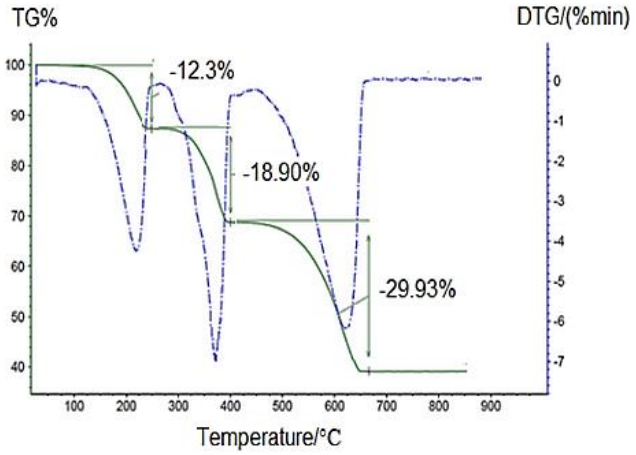


Fig. 2. TGA curve of DMRTIL.

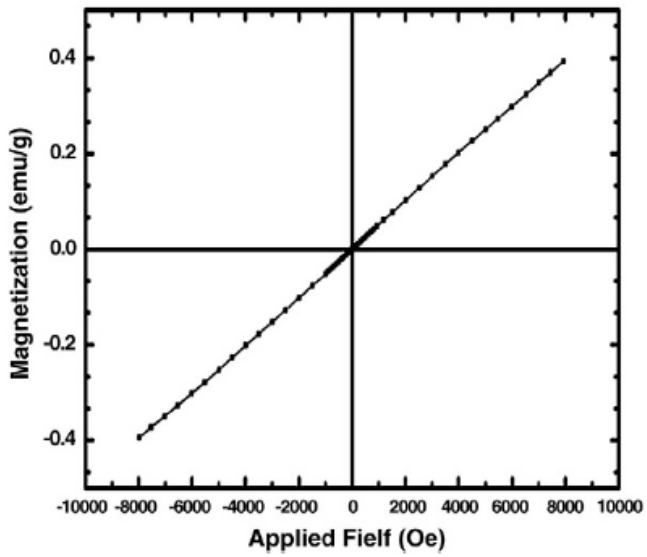


Fig. 3. Magnetic susceptibility of $[C_4(mim)_2](FeCl_4)_2$.

A 0.054 g of DMRTIL was contained in a pharmaceutical cellulose capsule and set at the tip of optical fiber rod for SQUID. The field dependence of magnetic moment of DMRTIL was measured in the range of -10,000 to 10,000 Oe, and it showed a paramagnetic linear response similar to iron (III) chloride. From M vs. H curves, the magnetization value for DMRTIL at the same field was found to be 0.4 emu Oe g^{-1}, lower than of $FeCl_3$ (0.7 emu Oe g^{-1}). Magnetic susceptibility of IL is reduced due to the presence of alkyl groups in the structure of IL. Initial experiments shows the response to the external magnetic field of the mixture of DMRTIL and water. Therefore, the magnetic catalyst could be easily isolated from the reaction mixture by simple magnetic decantation and reused.

In order to be able to carry out preparation of imidazoles derivatives in a more efficient way minimizing the time, temperature and amount of catalyst, the reaction of benzil, ammonium acetatate and benzaldehyde was selected as model system to the effects of the catalyst at different reaction temperatures (25, 60, 80, 100 and 120°C and the different amount of catalyst (0, 10, 20, 30, and 40% mol) were investigated. The results are summarized in Table 1. As shown in Table 1, the reaction using 20% mol of DMRTIL at 100°C proceeded in highest yield. Further increase in temperature to, 120°C had little effect on the rate of reaction. Therefore, we kept the reaction temperature at 100°C as optimal temperature.

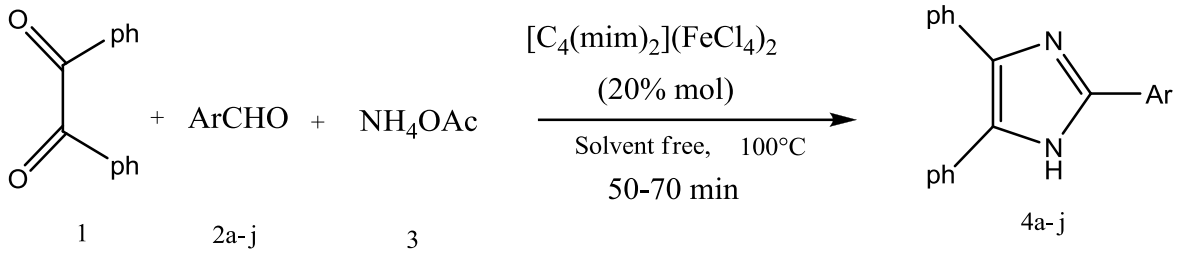
According to Table 1, this reaction was carried out without catalyst under solvent-free conditions in order to establish the effectiveness of the catalyst. It was found that imidazoles derivatives were not made after 120 min of heating. The best results were obtained with 1:3:1 ratio of benzaldehyde, ammonium acetatate, benzil and 20% mol of DMRTIL after 50 min at 100 °C.

Subsequently, with optimal conditions in hand, 1:3:1 molar ratios of benzaldehyde, ammonium acetatate, benzil and 20 mol% of DMRTIL at 100 °C under solvent-free conditions, the generality and synthetic scope of this coupling protocol were demonstrated by synthesizing a series of imidazoles derivatives (Table 2, Scheme 2).

Table 1. Optimization conditions for the synthesis of 2,4,5-triphenyl -1H-imidazole (4a[a]).

Temperature/°C	MRTDIL (mol %)	Time (min)	Yield (%)
25	20	120	10
60	20	120	50
80	20	120	70
100	20	50	90
120	20	50	91
100	0	120	5
100	10	120	45
100	30	50	91
100	40	50	91

[a]The molar ratio of benzaldehyde, benzil, and ammonium acetatate 1:1:3 respectively.



Scheme 2. Synthesis of 2,4,5-trisubstituted imidazoles catalyzed by $[pbmim](FeCl_4)_2$.

Gratifyingly, a wide range of aromatic aldehydes (carrying both electron releasing and electron withdrawing substituents in the ortho, meta, and para positions) were well tolerated under the optimized reaction conditions. The time taken for complete conversion (monitored by TLC) and the isolated yields are recorded in Table 2. The desired pure products were characterized by comparison of their physical data (melting points, FT-IR, ^1H and ^{13}C NMR) with those of known compounds.

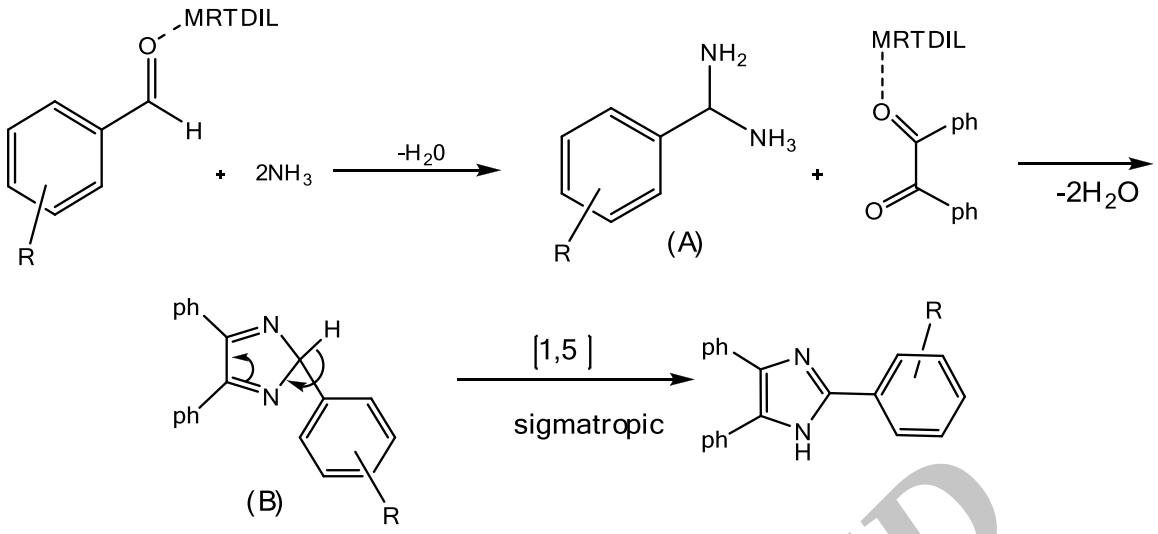
As shown in Scheme 3, it may be proposed that the $[C_4(mim)_2](FeCl_4)_2$ catalyst the formation of diamine intermediate [A] by increasing the electrophilicity of the carbonyl group of the aldehyde. Intermediate [A], in the presence of $[C_4(mim)_2](FeCl_4)_2$, condenses with benzyl to form intermediate [B], which in turn rearranges to trisubstituted imidazole by hydrogen shift. The success of the above reactions prompted us to investigate the recyclability of catalyst. We carried out our study by using the reaction benzil, benzaldehyde and ammonium acetate and under optimal conditions as a model study. After completion of the reaction (the progress of the reaction was monitored by TLC), the mixture was cooled to room temperature and the precipitated product was separated by filtration; then washed with water and dried. The aqueous phase was concentrated; the catalyst was separated using an external magnetic field (Fig. 3). The residue catalyst was washed with a mixed of ethyl ether and deionized water and dried in a vacuum oven at 60°C for overnight and reused in the next run. The catalyst could be reused for fourth times without significant decrease in catalytic activity (Fig. 4).

All the products were fully characterized by spectroscopic data and their melting points are compared with reported values. In conclusion, a one-pot, multicomponent methodology has been developed for the synthesis of 2,4,5-trisubstituted imidazoles catalyzed by $[C_4(mim)_2](FeCl_4)_2$ in high yields.

Table 2. Synthesis of 2,4,5-trisubstituted imidazoles catalyzed by $[C_4(mim)_2](FeCl_4)_2$ under solvent free conditions

Entry	Ar	Product	Time (min)	Yield[a] (%)	m.p (°C)	Ref.
1	C_6H_5	4a	50	90	270-272	[31]
2	4-CH_3-C_6H_4	4b	60	89	240-242	[31]
3	2,4-$(OCH_3)_2$-C_6H_3	4c	70	88	250-252	[32]
4	4-Cl-C_6H_4	4d	60	89	254-256	[31]
5	2-Cl-C_6H_4	4e	70	88	185-188	[31]
6	3-NO_2-C_6H_4	4f	70	90	196-199	[32]
7	4-NO_2-C_6H_4	4g	60	88	240-242	[33]
8	4-F-C_6H_4	4h	60	90	260-262	[31]
9	4-Br-C_6H_4	4i	60	90	235-238	[32]
10	2-NO_2-C_6H_4	4j	70	88	220-222	[30]

[a]Isolated yield after recrystallization.



Scheme 3. Plausible mechanism for the formation of 2,4,5-trisubstituted imidazoles.

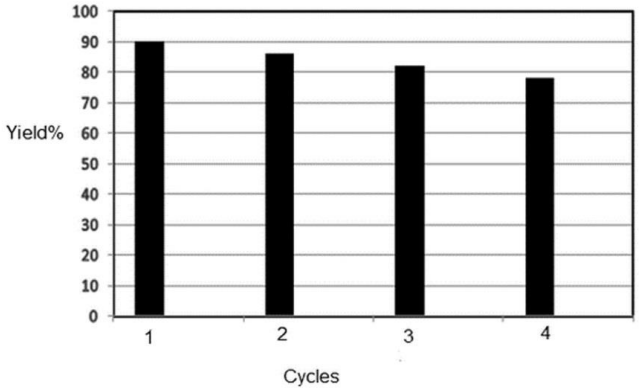


Fig. 4. Recyclability of the catalyst.

$[C_4(mim)_2](FeCl_4)_2$can replace the ILs and other homogeneous catalysts with reasonable recovery and reusability and therefore it is suitable for industrial applications.

The efficiency of DMRTIL (time, yield, reaction conditions) was compared with the efficiencies of other catalysts used in synthesis of 2,4,5,-trisubstituted imidazoles, the results are presented in Table 3. It is clear that the presented method is simpler, more efficient and less time consuming compared with other methods.

4. Conclusions

In conclusion, we have successfully developed a simple and green catalytic procedure for the efficient synthesis of 2, 4, 5, - trisubstituted imidazoles using DMRTIL and under mild reaction conditions. DMRTIL can replace the ILs and other homogeneous catalysts with reasonable recovery and reusability and therefore it is suitable for industrial applications.

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Table 3. Comparison of the synthesis of **4a** using different catalysts

Entry	Catalyst	Conditions	Time (min)	Yield	Ref.
1	$InCl_3.H_2O$	CH_3OH/R.T	492	76	[27]
2	KH_2PO_4	Reflux/EtOH	60	89	[28]
3	$Yb(OPf)_3$	$C_{10}F_{18}$/80 °C	360	80	[15]
4	$Zr(CH_3COO)_4$	EtOH/Reflux	120	95	[29]
5	L-Proline	CH_3OH/60 °C	540	87	[30]
6	$NiCl_2.6H_2O/Al_2O_3$	EtOH/Reflux	90	89	[17]
7	[BMIm][H2PO4]	MW, 130 w	4	94	[22]
8	[EMIM]OAc	EtOH/Ultrasond/r.t.	45	87	[19]
9	$[HeMIM]BF_4$	MW	2	93	[20]
10	$[HBIM]BF_4$	Solvent-free/100 °C	25	93	[21]
11	$[C_4(mim)_2](FeCl_4)_2$	Solvent-free/100 °C	60	90	This work

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