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Green synthesis of imidazole derivatives in a ternary deep eutectic solvent system

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Deep eutectic solvents (DESs) have gained recognition for their sustainable characteristics and demonstrated potential for various applications in chemical processes. Their biodegradability and recyclability make them an attractive alternative for sustainable chemistry. Herein, we investigated the application of novel ternary DES as a reaction medium and recyclable catalyst for one-pot, multicomponent synthesis of tri and tetra-substituted imidazole derivatives under mild conditions. A ternary DES composed of dimethyl urea, $SnCl_2$, and HCl was prepared using a simple method from readily available starting materials. The structural and chemical composition of this ternary DES was characterized using FT-IR and EDX spectroscopy. The synthesis of various substituted imidazoles using the ternary DES has resulted in good to excellent yields, with high-purity products, which were achieved in a relatively short reaction time. Ternary DES exhibited remarkable properties as a cost-effective and environmentally friendly dual solvent and catalyst. The prepared DES exhibits excellent recyclability, with no noticeable decline in its catalytic performance even after five consecutive runs.

Keywords Multicomponent reactions, Ternary DES, Imidazoles, Recyclable catalyst, Green chemistry

The utilization of multicomponent reactions (MCRs) has become increasingly valuable in the realms of medicinal and heterocyclic chemistry[1]. They are considered efficient synthetic strategies for the synthesis of various functionalized complex molecules in a time and cost-effective manner[2]. MCRs involve the combination of at least three reactants in a one-pot procedure, resulting in the formation of a new compound with excellent atom economy and high yields[3]. One of the key advantages of MCRs is their ability to streamline synthetic processes by allowing the simultaneous incorporation of multiple functional groups in a single step. This feature significantly reduces the number of synthetic steps, consequently saving time and resources. Additionally, MCRs offer high atom efficiency, as most of the starting materials are incorporated into the final product without generating significant waste[4]. The eco-friendly nature of MCRs has contributed to their growing popularity. MCRs align closely with the principles of green chemistry by minimizing the use of hazardous reagents and maximizing the utilization of reactants. They promote sustainability by reducing the environmental impact associated with traditional stepwise synthetic approaches[5].

The imidazole moiety has demonstrated its significance as a central core structure in a wide range of bioactive compounds, particularly those known for their antimicrobial and antifungal properties[6]. This versatile building block plays a pivotal role in the pharmacological profiles of numerous drugs and natural products[7]. The imidazole scaffold possesses unique chemical and structural characteristics that enable interactions with specific targets within biological systems[8]. By incorporating the imidazole moiety into molecular structures, researchers have successfully developed compounds with enhanced potency and efficacy in combating microbial and fungal infections. Numerous imidazole-based compounds have been verified as commercial antifungal drugs like miconazole, clotrimazole and ketoconazole (Fig. 1)[9]. The major therapeutic activities of imidazole-based drugs have motivated the organic and medicinal researchers to fabricate and assess a huge number of new molecules. Some of these medicinal drugs possess anti-cancer, antidiabetic, anti-inflammatory, antibacterial characteristics[10–12]. Since the 19th century, the development of novel synthetic methodologies for imidazole-based derivatives has been a focal point of research. In 1882, Japp and colleagues introduced a classical approach for the synthesis of 2,4,5-triaryl-imidazoles by condensing different aldehydes with 1,2-dicarbonyl reagents and ammonia[13]. In recent years, various methods have been reported in the literature for the preparation of tri and tetra-substituted imidazoles, highlighting their significant applications as solvents, fungicides, therapeutic agents, and herbicides[14–21]. While each synthetic approach has its advantages, some of them suffer from drawbacks, including the use of hazardous reagents, toxic organic solvents, low yields, long reaction times, and highly acidic

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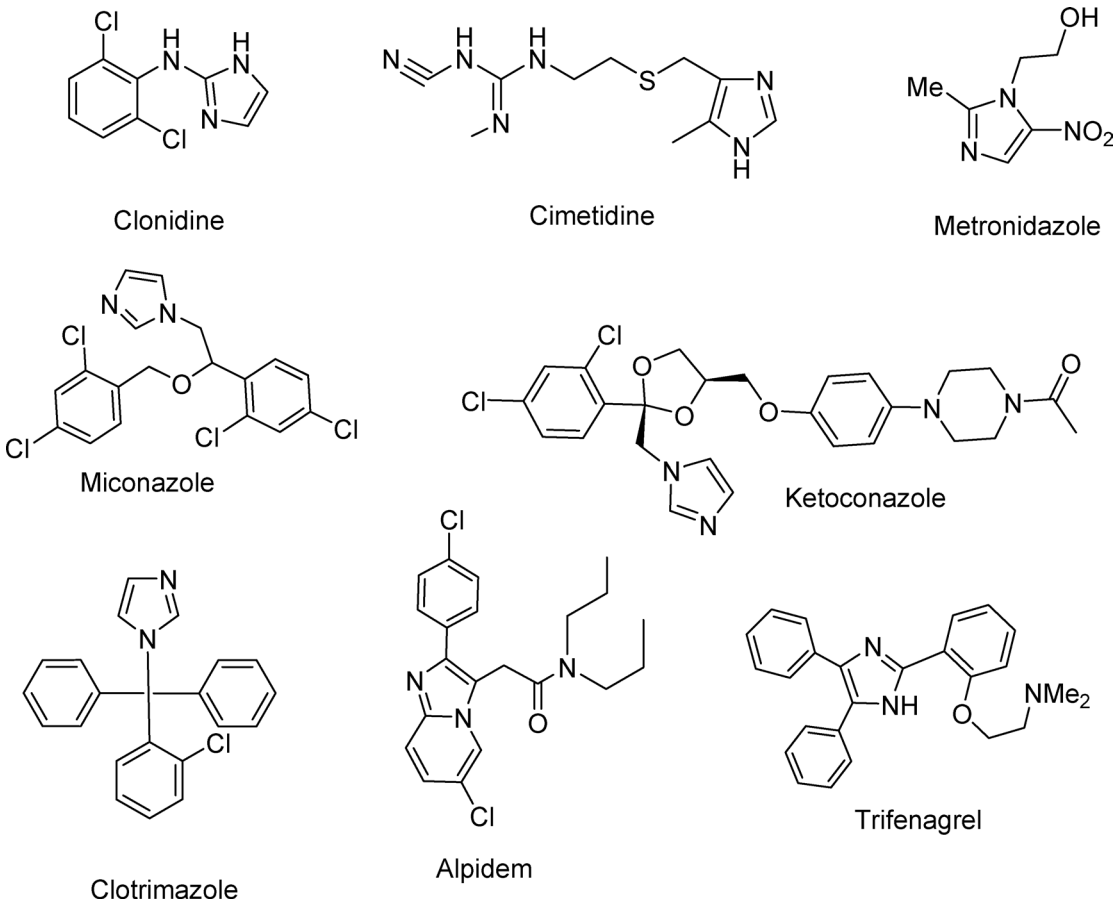


Fig. 1. Representative examples of some imidazole-based drugs.

media[21,22]. Consequently, overcoming these limitations and developing greener and milder procedures for the construction of substituted imidazoles are vital. Efforts are underway to design synthetic methodologies that address these challenges.

In the context of green chemistry, organic chemists have been actively engaged in the development and utilization of novel eco-friendly solvents, including ionic liquids, supercritical fluids, water, and carbon dioxide[23,24]. Ionic liquids (ILs), in particular, have garnered significant interest as green solvents due to their favorable properties such as non-flammability, high electrochemical stability, low vapor pressure, excellent tunability, and good solubility[25–27]. However, certain challenges associated with ILs, such as high cost, toxicity, and difficulties in purification and synthesis, have prompted the search for cheaper and safer alternatives[25,28,29]. The concept of deep eutectic solvent (DESs) was first introduced by Abbott in 2003 who developed an eutectic solvent composed of urea and choline chloride[30,31]. These solvents enjoy environmentally friendly properties, have good thermal stability and low vapor pressure[32–35]. Additionally, DESs are easy to prepare, cost-effective, and exhibit low toxicity[35]. They have obtained attentions as transformation media for various chemical processes and, in some cases, can even serve as both solvents and acidic catalysts due to the presence of metallic salts[36–38]. The catalytic applications of DESs have been explored extensively in several organic reactions, including Petasis reactions, Aldol-type couplings, synthesis of spirooxindoles and indolyl derivatives[39–42]. DESs have also shown promising catalytic performance in multicomponent reactions (MCRs) such as Mannich-type reactions, Biginelli reactions, Ugi reactions, Passerini reactions, and the synthesis of quinazolines, pyrroles, and imidazole derivatives[43–46].

Following our ongoing research, we have made significant discoveries in enhancing the understanding of deep eutectic solvents chemistry and their dual functionality as both catalysts and solvents in various organic synthetic processes[28,44]. In this study, we wish to report a novel ternary DES system composed of dimethylurea (DMU), tin(II) chloride ($SnCl_2$), and hydrochloric acid (HCl), which demonstrates enhanced reaction efficiency and accelerated reaction rates.

Experimental

Materials

All solvents and starting materials were obtained from a commercial chemical supplier and used without further purification unless otherwise specified. Melting point determinations were carried out using a Büchi 535 melting point apparatus. Fourier transform infrared (FT-IR) spectra were recorded using a Bruker Vector-22 FT-IR

spectrometer. For the analysis of the DMU: $SnCl_2$:HCl-based DES, energy-dispersive X-ray spectroscopy (EDS) was performed using a Zeiss Sigma VP model instrument (Germany).

Preparation of the ternary DES

The preparation of the DES based on DMU: $SnCl_2$:HCl is straightforward and efficient. Dimethylurea (DMU, 10 mmol, 0.9 g), tin(II) chloride dihydrate ($SnCl_2{\cdot}2H_2O$, 10 mmol, 2.3 g), and hydrochloric acid (37%, 10 mmol, 0.82 mL) were combined in a reaction vessel and stirred at room temperature until a homogeneous, colorless liquid was obtained, indicating the successful formation of the DES.

General protocol for the preparation of 2,4,5-trisubstituted imidazoles

The benzil (0.5 mmol, 105.0 mg), benzaldehyde (0.5 mmol, 51.0 µL), and ammonium acetate (1.0 mmol, 77.0 mg) were added in a test tube contains the DES based on DMU: $SnCl_2$:HCl (0.5 mL), and the mixture was stirred at 60 °C for 45 min. The progress of the reaction was monitored using thin layer chromatography (TLC). After completion of the reaction, water (10 mL) was added to the reaction mixture. The resulting mixture was then cooled, and the precipitate formed was filtered out. The filtered precipitate was subsequently subjected to recrystallization from ethanol. All the compounds obtained in this work were already known, and their identification and purity were confirmed through melting point analysis.

General protocol for the preparation of 1,2,4,5-tetrasubstituted imidazoles using DMU: $SnCl_2$:HCl

In the experimental procedure, a mixture consisting benzaldehyde (0.5 mmol,51.0 µL), aniline (0.5 mmol, 45.0 µL), benzil (0.5 mmol,105.0 mg) and ammonium acetate (0.5 mmol, 39 mg) was added to DES based on DMU: $SnCl_2$:HCl (0.5 mL) as both the catalyst and solvent system. The reaction mixture was then heated at 90 °C for 110 min, and the progress of the reaction was monitored using TLC. Upon completion of the reaction, the ethyl acetate (10 mL) and water (10 mL) were added to the reaction mixture. The resulting mixture was then separated into a water and an organic phase. The ethyl acetate was then removed by rotary evaporation to isolate crude 1,2,4,5-tetrasubstituted imidazole derivatives. The crude products were further recrystallized in ethanol or ethyl acetate.

Results and discussion

Characterization of the DMU: $SnCl_2$:HCl based DES

A novel ternary DES composed of dimethyl urea (DMU), $SnCl_2$, and HCl was successfully prepared and subjected to characterization using FT-IR analysis. Figure 2 displays the FT-IR spectrum of the DMU: $SnCl_2$:HCl based DES, revealing distinctive absorption bands. Notably, strong broad absorption bands were observed at 3388 and 3589 cm^{-1}, corresponding to the O–H and N–H stretching vibrations, respectively. Additionally, bands at 2956 and 2550 cm^{-1} were observed, arising from the stretching vibrations of the C–H bonds in the $-CH_3$ and $-CH_2$ groups, respectively. Characteristic bands at 1455 and 1185 cm^{-1} can be attributed to the C–N bending and stretching vibrations, respectively. Moreover, an absorption peak at 1616 cm^{-1} can be ascribed to the N-H in-plane bending vibrations. A characteristic band at 1682 cm^{-1} which is associated with the C = O stretching vibration, was observed with a slight shift. This shift is indicative of the formation of coordination bonds between the oxygen atom in the C = O group and Sn^{2+} ions present in the DES. The characteristic peaks in the FT-IR region below 900 cm^{-1} were observed, which can be attributed to the Sn-Cl stretching modes.

To verify the chemical composition of the DMU: $SnCl_2$:HCl ternary DES, EDS (Energy-Dispersive X-ray Spectroscopy) analysis was conducted. The EDS pattern, represented in Fig. 3a, demonstrates the presence of elements associated with Sn, Cl, C, O, and N. The appearance of these components in the EDS pattern provides strong evidence for the successful incorporation of Sn and N in the prepared DES. The presence of Sn indicates the successful addition of $SnCl_2$, while the presence of C and N confirms the integration of dimethylurea. EDS spectra were recorded on sample surfaces that had been coated with a thin layer of gold (Au) to enhance conductivity. A strong signal was observed in the range of 1.6–1.8 keV, along with a weaker peak at approximately 2.1 keV, both corresponding to the characteristic emission lines of gold. Furthermore, EDS mapping analysis, as shown in Fig. 3b, also confirms the presence of only O, C, N, Sn, and Cl peaks, showing the absence of impurities in the DES. Moreover, these species are distributed uniformly, as observed from the homogeneous distribution of peaks which indicate the appropriate uniformity of the DMU: $SnCl_2$:HCl based ternary DES.

To assess the thermal stability of the deep eutectic solvent system, thermogravimetric analysis (TGA) was conducted, and the results are presented in Fig. 4. Due to the presence of water in the DES system, the initial mass loss observed from room temperature corresponds to the dehydration process, accounting for approximately 18% of the total weight. The second significant mass loss is attributed to the thermal decomposition of dimethyl urea and the conversion of $SnCl_2$ to SnO.

Study of the catalytic performance of DMU: $SnCl_2$:HCl based DES for the preparation of Tri and four-substituted imidazole derivatives

After successfully fabricating and characterizing the DMU: $SnCl_2$:HCl ternary DES, its catalytic activity was evaluated for the one-pot synthesis of substituted imidazoles. This research aims to establish a green and recyclable protocol for preparing the corresponding substituted imidazoles using readily available reactants. The catalytic procedure employed in this study offered a benign and selective approach, utilizing inexpensive and non-toxic materials. Furthermore, the effect of various nitrogen sources, including NH_3, NH_4F, NH_4Cl, NH_3NO_3, and NH_4OAc, on the yield of the model reaction was investigated (Fig. 5). Among the nitrogen sources tested, ammonium acetate (NH_4OAc) was found to be the most suitable choice for the desired reaction, providing high yields (142 mg, 96%) of the 2,4,5-triphenylimidazole derivative. NH_4OAc was determined to be the most suitable

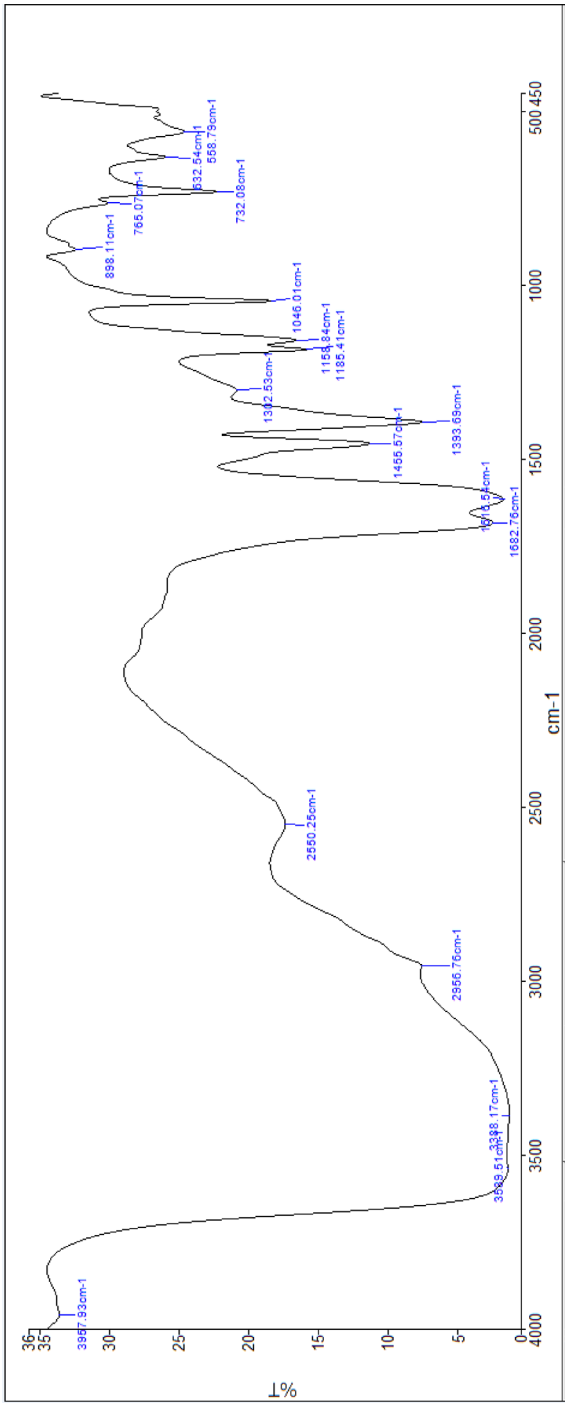


Fig. 2. FI-IR spectra of DMU: $SnCl_2$:HCl

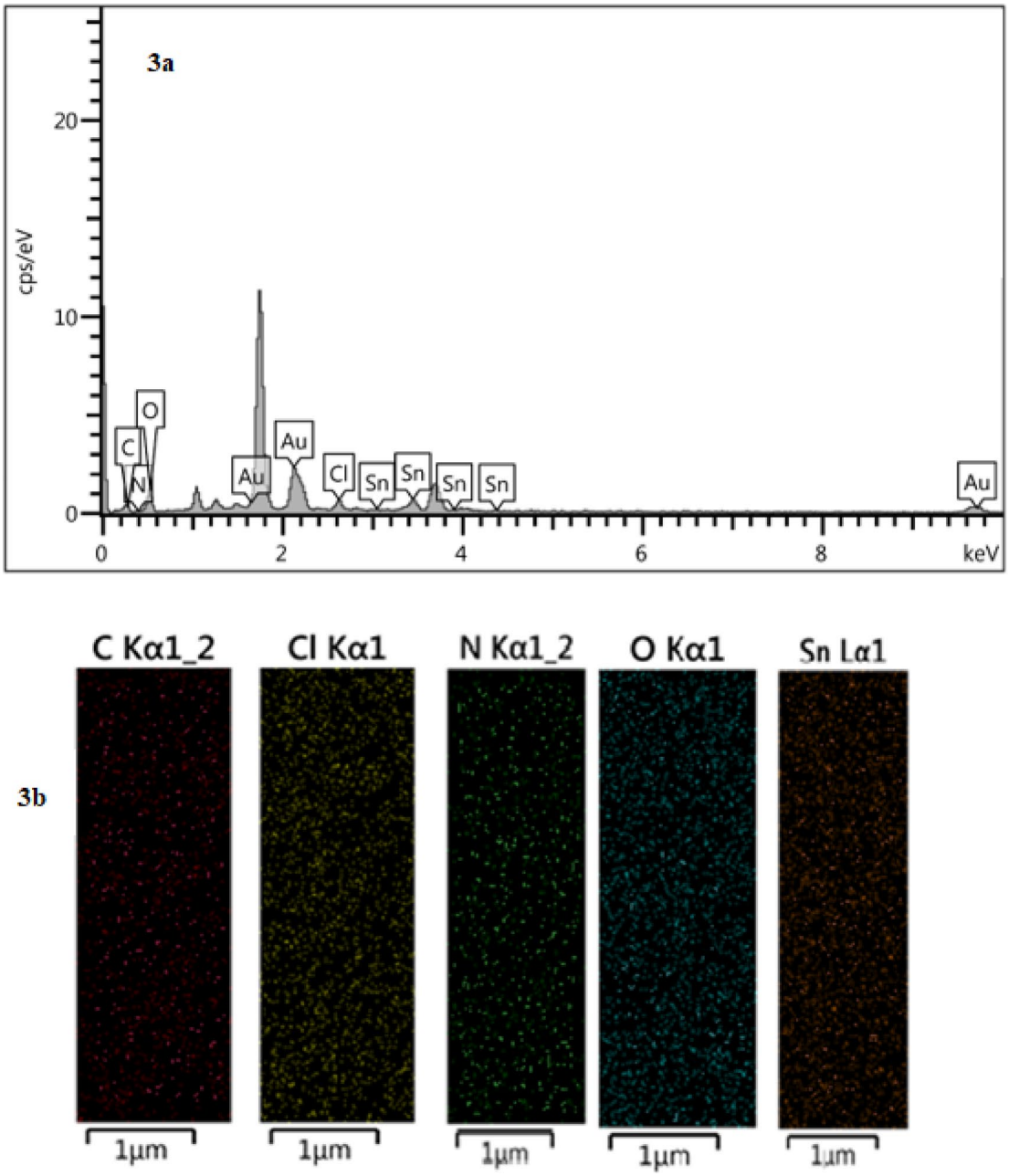


Fig. 3. EDX pattern (**a**) and mapping images (**b**) of the prepared DMU: $SnCl_2$:HCl.

nitrogen source for the desired reaction, as it results in high yields of the 2,4,5-triphenylimidazole derivative. This finding suggests that NH_4OAc effectively provides the necessary nitrogen atoms for the formation of the desired product. Table 1 illustrates the optimization results of the model reaction using various catalysts. It is evident that the representative model reaction performed in the absence of the DMU: $SnCl_2$:HCl ternary DES as a catalyst resulted in a low yield. Furthermore, it is important to note that lower yields of the desired product were observed when pure $SnCl_2$, dimethyl urea, and HCl were used as dual catalyst/solvents. The best outcome was obtained when using DMU: $SnCl_2$:HCl in a 1:1:1 ratio which indicates the synergistic combination of the components in the DMU: $SnCl_2$:HCl ternary DES is a key factor for achieving higher yields in the reaction.

During the optimization of the solvent, it was observed that the highest yield (142 mg, 96%) was achieved in a DES condition within 45 min. Various solvents such as ethanol, methanol, ethyl acetate, water, toluene, DMF, and tetrahydrofuran were found to be unsuitable for this conversion (Table 2). Table 2 also illustrates that among the solvents tested, including ethanol, methanol, ethyl acetate, water, toluene, DMF (dimethylformamide), and tetrahydrofuran (THF), none of them were found to be suitable for the conversion of the starting materials to the desired 2,4,5-triphenylimidazole derivative. The model reaction was conducted at ambient temperature for 45 min, resulting in (118.0 mg) 40% isolated yield of the desired product. Our findings prompted further investigation into enhancing the product yield by varying the reaction temperature. Through temperature

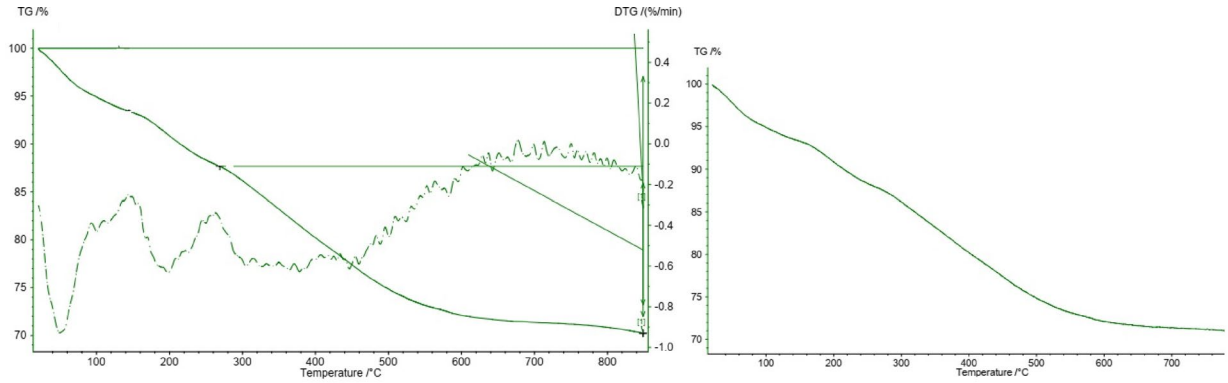


Fig. 4. TG and DTG analysis of DMU: $SnCl_2$:HCl.

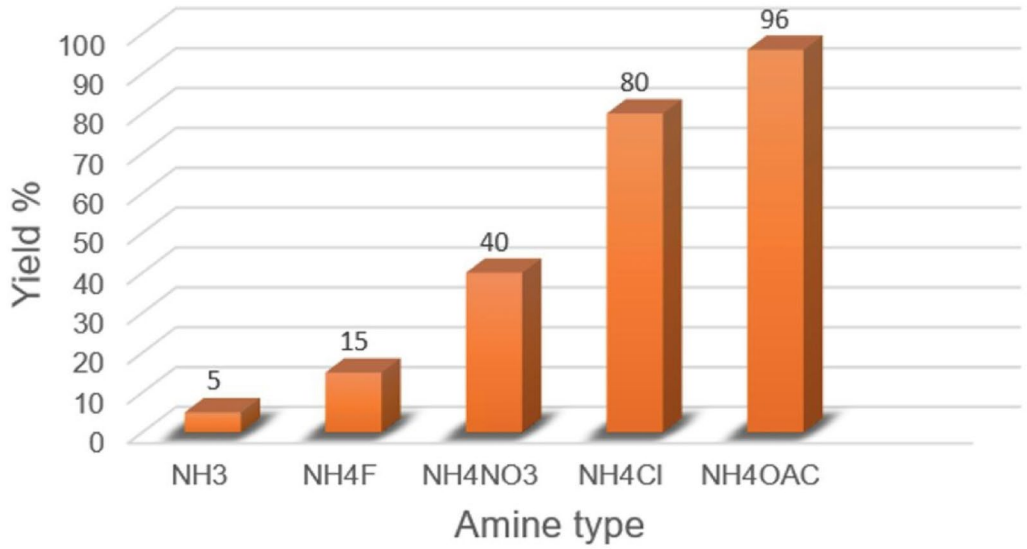


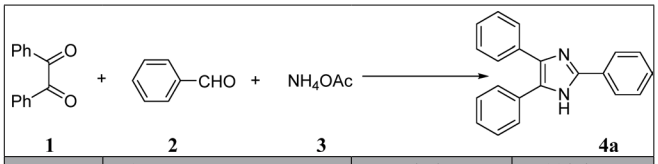
Fig. 5. Effect of different nitrogen sources.

Entry	Cat.	Yield (%)
1	HCl	30
2	$SnCl_2$	25
3	DMU	10
4	DES	96

Table 1. Optimization of catalyst type on the yield of the model reaction for preparing 2,4,5-triphenyl-1*H*-imidazole.

optimization, the highest yield of 2,4,5-triphenyl-1 H-imidazole was obtained at 60 °C using DMU: $SnCl_2$:HCl as a dual solvent/catalyst (Table 2). The optimal conditions for the synthesis of 2,4,5-triphenyl-1 H-imidazole involve using benzil (0.5 mmol) and aldehyde (0.5 mmol) as reactants, with ammonium acetate (1 mmol) as the nitrogen source. The reaction was carried out in a mixture of 0.5 mL of DMU: $SnCl_2$:HCl-based deep eutectic solvent as a dual catalyst and solvent while the reaction temperature was maintained at 60 °C.

With these optimal reaction conditions in hand, we attempted to test the substrate scope of this three-component reaction by employing several aldehydes, such as aliphatic, aromatic, and heteroaromatic (Table 3). Generally, utilizing various benzaldehydes containing different substituents like electron-donating and electron-withdrawing moieties lead to obtain good to excellent yields of 2,4,5-trisubstituted imidazole derivatives[12]. However, employing aldehydes bearing electron-donating substituents resulted in achieving lower yields of the corresponding products when compared to the benzaldehyde having an electron-withdrawing group. These remarks emphasize the important impact of the nature of functional groups in the benzaldehydes on the reaction



1 2 3 4a

Entry	Solvents	Temp. (°C)	Yield (%)
1	DES	r.t	40
2	DES	40	46
3	DES	60	96
4	DES	80	96
5	DES + ethanol	60	82
6	DES + methanol	60	78
7	DES + water	60	68
8	DES + ethyl acetate	60	74
9	DES + DMF	60	66
10	DES + THF	60	44
11	DES + toluene	60	42
12	DES + CH_3CN	60	52

Table 2. Solvent and temperature optimization for tri-substituted imidazole synthesis.

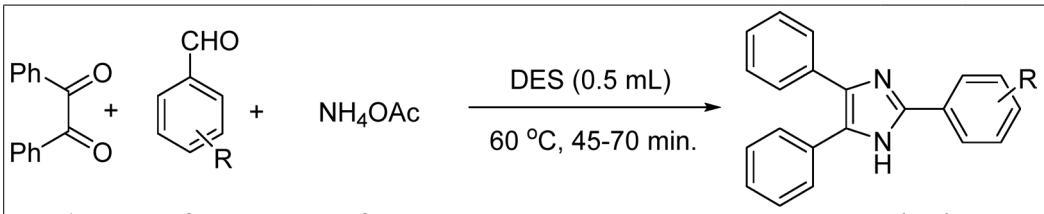
yields. Moreover, heterocyclic aldehydes such as 2-furaldehyde and thiophene-2-carboxaldehyde indicate high reactivity in obtaining resultant poly-substituted imidazoles with excellent yields (entries 4 and 5).

Optimization parameters for the preparation of 1,2,4,5-tetrasubstituted imidazoles

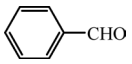
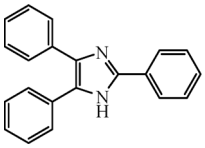
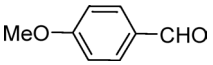
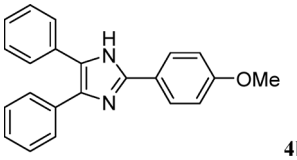
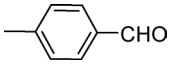
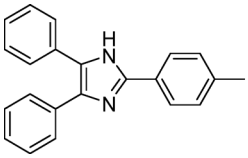
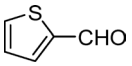
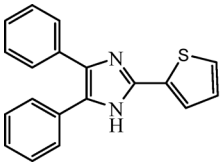
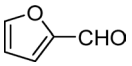
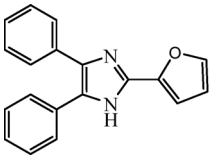
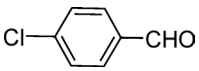
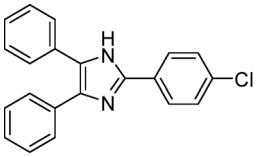
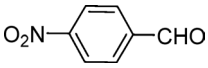
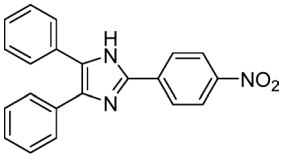
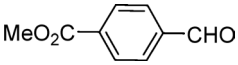
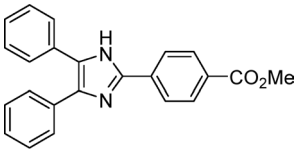
The model reaction between benzil, aniline, benzaldehyde, and NH_4OAc was selected to investigate the optimization parameters such as solvents, temperatures, and catalyst, and the results were demonstrated in Table 4. When the reaction was carried out in the absence of a solvent and a catalyst, the lowest yields of desired products were achieved (Table 4, entry 1). Next, the catalytic activity of DMU: $SnCl_2$:HCl in comparison to that of other catalysts, such as DMU, $SnCl_2$, DMU: $SnCl_2$, and HCl was explored. According to Table 4, the synthesized ternary DES based on DMU: $SnCl_2$:HCl showed high catalytic performance and gave quantitative yields at short reaction times. The experimental results presented in Table 4 demonstrate the effect of different temperatures on the model reaction for the synthesis of 1,2,4,5-tetraphenyl imidazole. Initially, at 25 °C (Table 4, entry 2), a yield of only (68 mg, 37% was achieved after 110 min. However, increasing the reaction temperature to 40 °C (Table 4, entry 3) resulted in an improved yield of (85 mg, 46%. The highest yield of the desired product was obtained at temperatures of 90 °C (Table 4, entry 5), indicating that higher temperatures promote the reaction and enhance product formation. Furthermore, various organic solvents were tested for the preparation of 1,2,4,5-tetraphenyl imidazole (Table 4, entries 6–11). Interestingly, the highest isolated yield (177 mg, 95%, entry 5) was obtained when the reaction was carried out in a DES condition, which suggests that the use of a green deep eutectic solvent played a dual role as both a catalyst and a solvent in facilitating the reaction. The relationship between reaction time and the yield of 1,2,4,5-tetraphenyl imidazole in the described reaction was investigated within a time range of 20 to 110 min, as shown in Fig. 6. The graph indicates that as the reaction time increases, the yield of the product also increases. However, after 110 min, the graph demonstrates a plateau where the yield percentage remains relatively constant. This indicates that beyond this point, the reaction reaches a maximum yield, and further prolonging the reaction time does not significantly improve the yield of the product. The optimal parameters for the preparation of 1,2,4,5-tetraphenyl imidazole can be summarized as follows: a reaction temperature of 90 °C, a reaction time of 110 min, and the utilization of DMU: $SnCl_2$:HCl as a double solvent/catalyst system.

After determining the optimal condition for preparing 1,2,4,5-tetra-substituted imidazoles, several benzaldehydes were applied to obtain the corresponding products. The obtained results are listed in Table 5. Under the above conditions, most studied benzaldehyde derivatives were highly active in providing 1,2,4,5-tetra substituted imidazoles in moderate-to-high yield under mild reaction condition and short reaction duration. A variety of benzaldehydes containing electron-donating and electron-withdrawing groups gave good-to-high yields of the corresponding imidazoles. The presence of electron-withdrawing groups on the benzaldehyde resulted in higher yields of the desired imidazoles compared to the benzaldehydes with electron-donating functional groups.

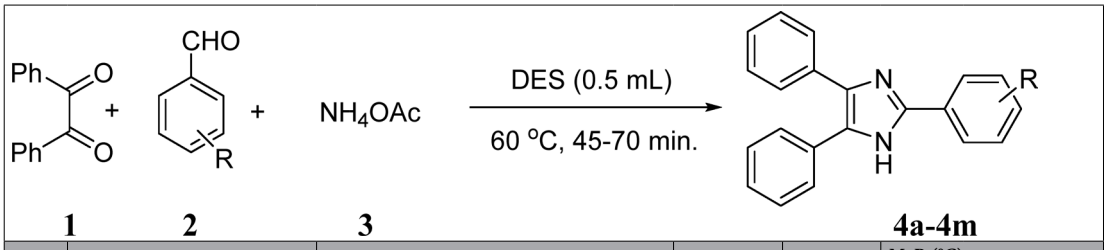
The reusability of the DMU: SnCl2: HCl-based DES was carried out to evaluate its potential as a sustainable catalyst and highlight the importance of benign chemistry. The focus was on assessing the possibility of reusing the DES system in the model reaction under optimal conditions. After the completion of the reaction, ethyl acetate (10 mL) was added to the reaction tube to facilitate the separation of the product and the DES system. The resulting DMU: $SnCl_2$:HCl was insoluble in ethyl acetate and was separated and then washed with ethyl acetate and reused in subsequent reaction cycles. The experimental results, depicted in Fig. 7, demonstrate that the catalyst can be successfully recovered and reused for up to five cycles without a significant decline in its catalytic activity. FTIR and EDX analyses of the reused catalyst were included in the Supporting Information.



1 **2** **3** **4a-4m**

Entry	Aldehydes	Products	Time (min)	Yields (%)	M. P. (°C)	
					Found	Reported [Ref.]
1		 **4a**	45	96	275–276	276–277[47]
2		 **4b**	45	82	225–227	227–228[47]
3		 **4c**	45	87	229–231	231–232[47]
4		 **4d**	55	93	261–263	262–264[53]
5		 **4e**	55	90	201–202	202–203[53]
6		 **4f**	50	95	261–263	262–264[47]
7		 **4g**	60	97	239–241	241–242[50]
8		 **4h**	55	90	256–258	257–258[47]

Continued



1 2 3 4a-4m

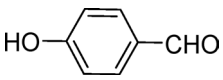
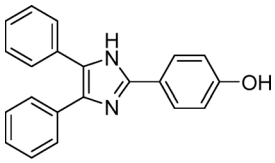
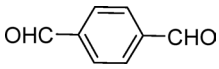
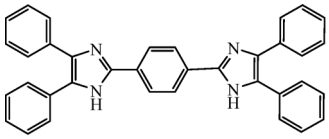
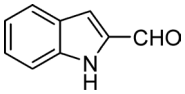
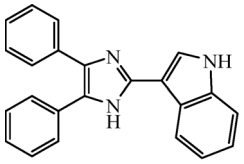
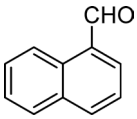
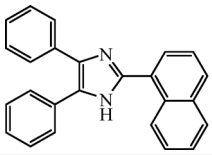
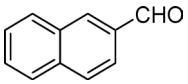
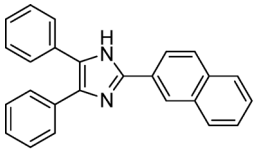
Entry	Aldehydes	Products	Time (min)	Yields (%)	M. P. (°C)	
					Found	Reported [Ref.]
9		 4i	65	82	230–231	232–233[51]
11		 4j	60	77	> 300	> 300[52]
12		 4k	65	76	306–308	307–309[53]
13		 4l	70	80	296–298	297–299[49]
14		 4m	70	84	275–277	277–279[49]

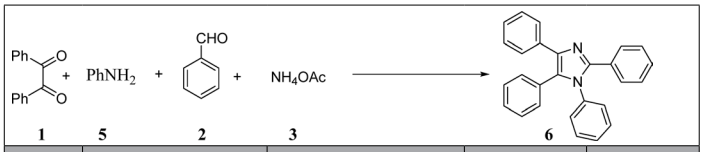
Table 3. Preparation of 2,4,5-tri-phenyl imidazole substituted using DMU: $SnCl_2$:HCl.

A comparison with the fresh DES system revealed no significant structural changes after five catalytic cycles, indicating the stability and reusability of the DES system.

Finally, the catalytic activity of the DMU: $SnCl_2$:HCl based ternary deep eutectic solvent was compared to the results reported in the literature for the synthesis of 2,4,5-triphenyl imidazole and 1,2,4,5-tetraphenyl imidazole. The collected data from these comparisons are summarized in Tables 6 and 7. Based on the data presented, it was observed that the produced DMU: SnCl2:HCl-based DES exhibited several advantages as a reaction medium compared to other reported methodologies. Moreover, the DES system demonstrated a high product yield in the absence of any additives or catalysts, which implies that the DES itself acted as an efficient medium for facilitating the synthesis of 2,4,5-triphenyl imidazole and 1,2,4,5-tetraphenyl imidazole. Secondly, the reaction time required for the DES-based system was found to be favorable. The DES allowed for a relatively shorter reaction time compared to other reported methods[58–62], which shows its efficiency in promoting the desired reactions.

Conclusion

In summary, we have established a simplified and cost-effective method to prepare novel ternary deep eutectic solvents using readily available starting materials. Interestingly, the DES acts as dual catalysts and solvents, providing a green and sustainable approach for synthesizing tri and tetra-substituted imidazole compounds. The procedure offers many advantages, such as mild reaction conditions, high purity of products, short reaction times, a clean reaction profile, a straightforward procedure, and the ability to recycle the catalyst. Overall, this



Entry	Catalysts	Solvent	Temp (°C)	Yield (%)
1	None	None	90	20
2	DMU:$SnCl_2$: HCl	DES	25	37
3	DMU:$SnCl_2$: HCl	DES	40	46
4	DMU:$SnCl_2$: HCl	DES	60	76
5	DMU:$SnCl_2$: HCl	DES	90	95
6	DMU:$SnCl_2$: HCl	DES + ethanol	90	87
7	DMU:$SnCl_2$: HCl	DES + methanol	90	79
8	DMU:$SnCl_2$: HCl	DES + water	90	67
9	DMU:$SnCl_2$: HCl	DES + ethyl acetate	90	72
10	DMU:$SnCl_2$: HCl	DES + DMF	90	65
11	DMU:$SnCl_2$: HCl	DES + THF	90	38
12	$SnCl_2$	None	90	58
13	DMU	None	90	38
14	DMU:$SnCl_2$	None	90	79
15	HCl	None	90	28

Table 4. Optimization of reaction conditions for four component synthesis of imidazole.

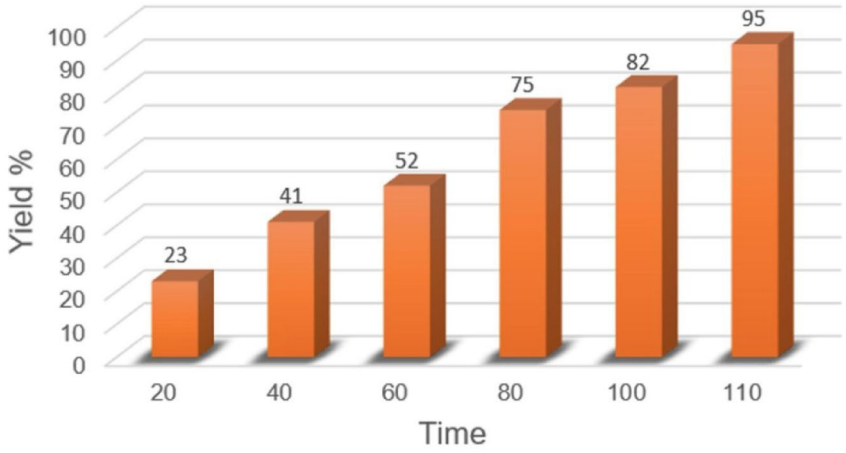
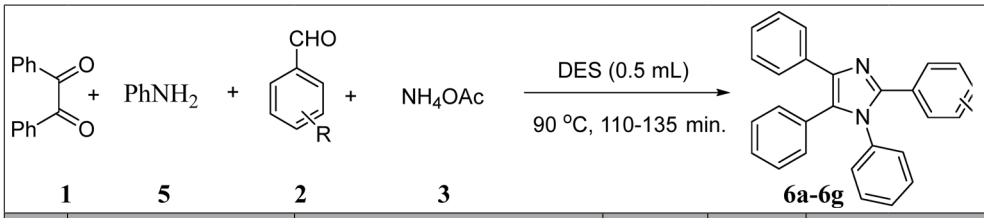
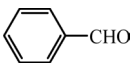
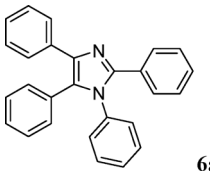
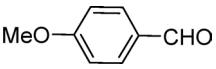
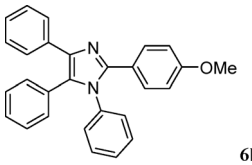
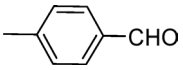
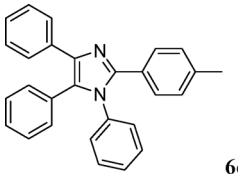
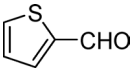
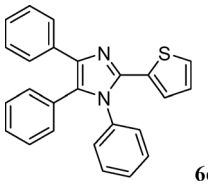
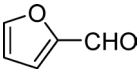
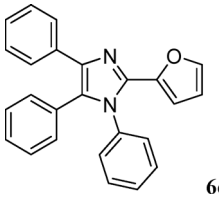
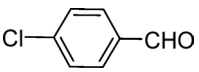
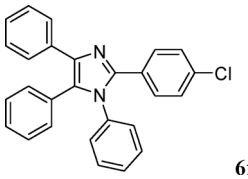
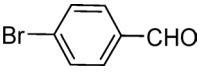
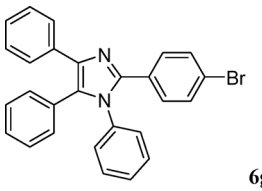
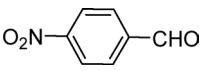
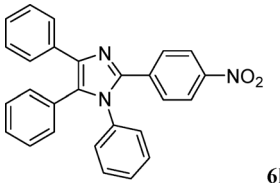


Fig. 6. A graph of yield and reaction time on the tetra-substituted model reaction.

approach contributes to the advancement of environmentally friendly synthesis methods and highlights the potential for sustainable chemistry in imidazole synthesis.



1 5 2 3 6a-6g

Entry	Aldehydes	Products	Time(min)	Yields (%)	M. P. (°C)	
					Found	Reported [Ref.]
1		 6a	1 10	95	217–218	218–219 [54]
2		 6b	120	86	180–183	181–183 [57]
3		 6c	110	91	162–165	163–165 [57]
4		 6d	130	71	248–250	247–250 [55]
5		 6e	130	74	204–205	205–207 [54]
6		 6f	120	95	155–157	156–158 [57]
7		 6g	120	93	194–196	195–197 [55]
8		 6h	130	92	211–213	212–214 [55]

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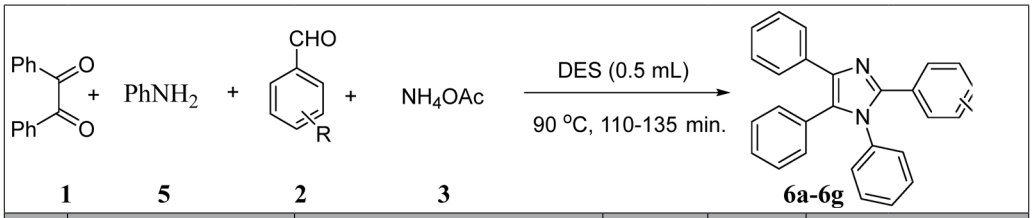


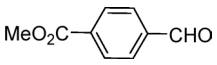
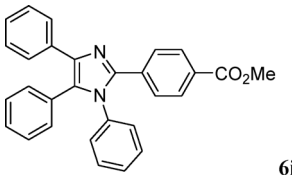
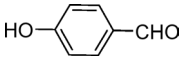
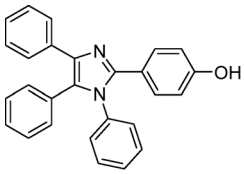
Entry	Aldehydes	Products	Time(min)	Yields (%)	M. P. (°C)	
					Found	Reported [Ref.]
9		 6i	135	81	208–210	207–209 [56]
10		 6j	120	82	276–277	276–278 [54]

Table 5. Synthesis of 1,2,4,5-tetra phenyl imidazole derivatives using DMU: $SnCl_2$:HCl.

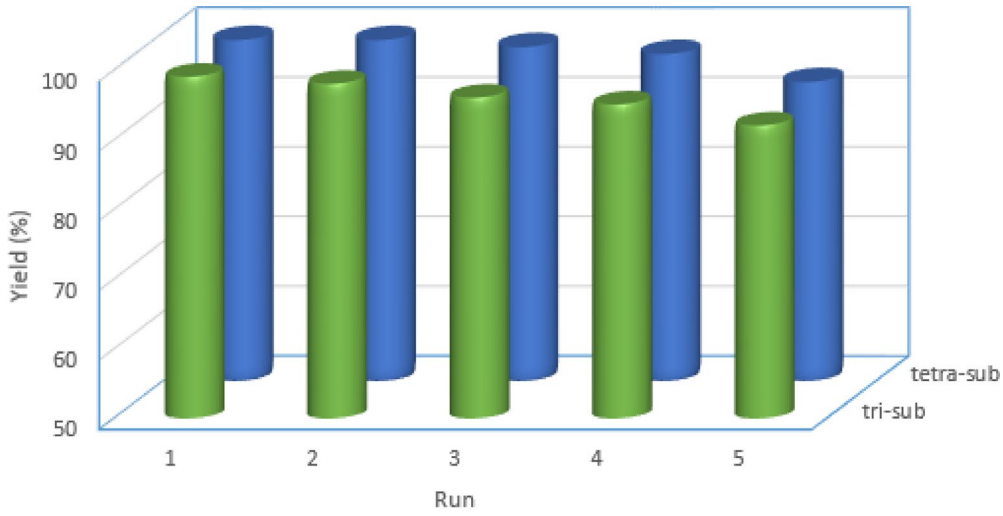


Fig. 7. Reusability of the DMU: $SnCl_2$:HCl catalyst for model reactions of tri and tetra-substituted imidazole.

Entry	Catalyst	Condition	Time (min)	Yield (%)	Ref
1	[Hbim]BF_4	100 °C	60	94	[58]
2	Montmorilonite K10	Reflux/EtOH	90	70	[59]
3	$NiCl_2{\cdot}6H_2O/Al_2O_3$	Reflux/EtOH	90	89	[60]
4	$KMnO_4/CuSO_4$	Reflux/EtOH	70	89	[14]
5	$InCl_3{\cdot}3H_2O$	RT/MeOH	498	82	[61]
6	L-Proline	60 °C/MeOH	540	90	[51]
7	Mo(IV) salen complex nanoparticles on silica	50 °C/EtOH	50	93	[62]
8	HTS-400-SO_3H	110 °C	90	93	[63]
9	DMU: $SnCl_2$: HCl	60 °C	45	96	Present work

Table 6. Comparison of the catalytic efficiency of DMU: $SnCl_2$:HCl with other catalysts in the preparation of 2,4,5-tri-substituted imidazoles.

Entry	Catalyst	Condition	Time (min)	Yield (%)	Ref
1	$InCl_3{\cdot}3H_2O$	RT/MeOH	531	83	[61]
2	[Bmim]Br	140 °C	150	91	[64]
3	DABCO	t-BuOH/60 °C	800	92	[65]
4	PEG-400	Solvent-free/110 °C	360	86	[66]
5	$BF_3{\cdot}SiO_2$	Solvent free/140 °C	120	92	[67]
6	L-Proline	MeOH/60 °C	540	78	[51]
7	DMU: $SnCl_2$:HCl	90 °C	110	95	Present work

Table 7. Comparison of the catalytic activity of the DMU: $SnCl_2$:HCl with other catalysts in the 1,2,4,5-tetra-substituted imidazoles synthesis.

Data availability

All data generated during this study are included in this published article.

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References

1. Dömling, A. Recent developments in isocyanide based multicomponent reactions in applied chemistry. *Chem. Rev.* **106**, 17–89 (2006).
2. Gu, Y. Multicomponent reactions in unconventional solvents: state of the Art. *Green Chem.* **14**, 2091–2128 (2012).
3. Touré, B. B. & Hall, D. G. Natural product synthesis using multicomponent reaction strategies. *Chem. Rev.* **109**, 4439–4486 (2009).
4. Zhi, S., Ma, X. & Zhang, W. Consecutive multicomponent reactions for the synthesis of complex molecules. *Org. Biomol. Chem.* **17**, 7632–7650 (2019).
5. Ruijter, E. & Orru, R. V. Multicomponent reactions–opportunities for the pharmaceutical industry. *Drug Discovery Today: Technol.* **10**, e15–e20 (2013).
6. Liu, C. et al. Discovery of new imidazole derivatives containing the 2, 4-dienone motif with broad-spectrum antifungal and antibacterial activity. *Molecules* **19**, 15653–15672 (2014).
7. Rani, N., Sharma, A., Kumar Gupta, G. & Singh, R. Imidazoles as potential antifungal agents: A review. *Mini Rev. Med. Chem.* **13**, 1626–1655 (2013).
8. Andrei, G. Ş., Andrei, B. F. & Roxana, P. R. Imidazole derivatives and their antibacterial activity-a mini-review. *Mini Rev. Med. Chem.* **21**, 1380–1392 (2021).
9. El-Remaily, M. et al. Tailoring of novel Ru (III) and cr (III) Salen complexes as catalysts for a sustainable and green synthesis of dihydro-tetrazolo [1, 5-a] Thiazolo [4, 5-d] pyrimidin-6-yl morpholine: experimental and theoretical approaches. *Appl. Organomet. Chem.* **39**, e7879 (2025).
10. Abd El-Lateef, H. M. et al. Synthesis and structure design of novel unsaturated copolyesters based on Indazole moiety in the main chain with good thermal stability for catalytic activity and anti-corrosion applications. *J. Mol. Struct.* **1273**, 134345 (2023).
11. Luca, L. D. Naturally occurring and synthetic imidazoles: their chemistry and their biological activities. *Curr. Med. Chem.* **13**, 1–23 (2006).
12. Kumar, D., Kommi, D. N., Bollineni, N., Patel, A. R. & Chakraborti, A. K. Catalytic procedures for multicomponent synthesis of imidazoles: selectivity control during the competitive formation of tri- and tetrasubstituted imidazoles. *Green Chem.* **14**, 2038–2049 (2012).
13. Kommi, D. N., Kumar, D., Bansal, R., Chebolu, R. & Chakraborti, A. K. All-water chemistry of tandem N-alkylation-reduction-condensation for synthesis of N-arylmethyl-2-substituted benzimidazoles. *Green Chem.* **14**, 3329–3335 (2012).
14. Nagargoje, D., Mandhane, P., Shingote, S., Badadhe, P. & Gill, C. Ultrasound assisted one pot synthesis of imidazole derivatives using diethyl bromophosphate as an oxidant. *Ultrason. Sonochem.* **19**, 94–96 (2012).
15. Ahmed, N. S. & Hanoon, H. D. A green and simple method for the synthesis of 2, 4, 5-trisubstituted-1 H-imidazole derivatives using acidic ionic liquid as an effective and recyclable catalyst under ultrasound. *Res. Chem. Intermed.* **47**, 4083–4100 (2021).
16. Ahooie, T. S., Azizi, N., Yavari, I. & Hashemi, M. M. Magnetically separable and recyclable g-C_3N_4 nanocomposite catalyzed one-pot synthesis of substituted imidazoles. *J. Iran. Chem. Soc.* **15**, 855–862 (2018).

17. Sharma, P., LaRosa, C., Antwi, J., Govindarajan, R. & Werbovetz, K. A. Imidazoles as potential anticancer agents: an update on recent studies. *Molecules* **11**, 4213 (2021).
18. Kadu, V. D., Mali, G. A., Khadul, S. P. & Kothe, G. J. Simple practical method for synthesis of trisubstituted imidazoles: an efficient copper catalyzed multicomponent reaction. *RSC Adv.* **11**, 21955–21963 (2021).
19. Ali, M. A. E. A. A. & Abu-Dief, A. M. CuFe2O4 nanoparticles: an efficient heterogeneous magnetically separable catalyst for synthesis of some novel propynyl-1H-imidazoles derivatives. *Tetrahedron* **71**, 2579–2584 (2015).
20. Tolomeu, H. V. & Manssour Fraga, A. Imidazole: synthesis, functionalization and physicochemical properties of a privileged structure in medicinal chemistry. *Molecules* **28**, 838 (2023).
21. Wolkenberg, S. E. et al. Efficient synthesis of imidazoles from aldehydes and 1,2-diketones using microwave irradiation. *Org. Lett.* **6**, 1453–1456 (2004).
22. Rossi, R., Angelici, G., Casotti, G., Manzini, C. & Lessi, M. Synthesis of 1,2,4,5-tetrasubstituted 1H-imidazole derivatives: state of the Art. *Adv. Synth. Catal.* **361**, 2737–2803 (2019).
23. Cvjetko Bubalo, M., Vidović, S., Radojčić Redovniković, I. & Jokić, S. Green solvents for green technologies. *J. Chem. Technol. Biotechnol.* **90**, 1631–1639 (2015).
24. Häckl, K. & Kunz, W. Some aspects of green solvents. *C. R. Chim.* **21**, 572–580 (2018).
25. Clarke, C. J., Tu, W. C., Levers, O., Bröhl, A. & Hallett, J. P. Green and sustainable solvents in chemical processes. *Chem. Rev.* **118**, 747–800 (2018).
26. Hessel, V. et al. Sustainability of green solvents—review and perspective. *Green Chem.* **24**, 410–437 (2022).
27. Liu, P., Hao, J. W., Mo, L. P. & Zhang, Z. H. Recent advances in the application of deep eutectic solvents as sustainable media as well as catalysts in organic reactions. *RSC Adv.* **5**, 48675–48704 (2015).
28. Azizi, N., Khajeh, M. & Alipour, M. Rapid and selective oxidation of alcohols in deep eutectic solvent. *Ind. Eng. Chem. Res.* **53**, 15561–15565 (2014).
29. Zhang, M., Liu, Y. H., Liu, Shang, Z. R. & Hu, H. C. Supported molybdenum on graphene oxide/Fe3O4: an efficient, magnetically separable catalyst for one-pot construction of spiro-oxindole dihydropyridines in deep eutectic solvent under microwave irradiation. *Catal Commun.* **88**, 39–44 (2107).
30. Shahbaz, K. et al. M. A novel calcium chloride hexahydrate-based deep eutectic solvent as a phase change materials. *Sol. Energy Mater. Sol. Cells*. **155**, 147–154 (2016).
31. Abbott, A. P., Capper, G., Davies, D. L. & Rasheed, R. K. Tambyrajah, V. Novel solvent properties of choline chloride/urea mixtures. *Chem. Commun.* **1**, 70–71 (2003).
32. Ünlü, A. E., Arıkaya, A. & Takaç, S. Use of deep eutectic solvents as catalyst: A mini-review. *Green. Process. Synthesis*. **8**, 355–372 (2019).
33. Smith, E. L., Abbott, A. P. & Ryder, K. S. Deep eutectic solvents (DESs) and their applications. *Chem. Rev.* **114**, 11060–11082 (2014).
34. Zhang, Q., De Oliveira Vigier, K., Royer, S. & Jérôme, F. Deep eutectic solvents: syntheses, properties and applications. *Chem. Soc. Rev.* **41**, 7108–7146 (2012).
35. Vigier, K. D. O., Chatel, G. & Jérôme, F. Contribution of deep eutectic solvents for biomass processing: opportunities, challenges, and limitations. *ChemCatChem* **7**, 1250–1260 (2015).
36. Handy, S. & Westbrook, N. M. A mild synthesis of Bis (indolyl) methanes using a deep eutectic solvent. *Tetrahedron Lett.* **55**, 4969–4971 (2014).
37. Procopio, D., Marset, X., Guillena, G., Di Gioia, M. L. & Ramón, D. J. Visible-light-mediated amide synthesis in deep eutectic solvents. *Adv. Synth. Catal.* **366**, 870–876 (2023).
38. Krishnan, A. et al. Ionic liquids, deep eutectic solvents and liquid polymers as green solvents in carbon capture technologies: a review. *Environ. Chem. Lett.* **18**, 2031–2054 (2020).
39. Li, X. & Row, K. H. Development of deep eutectic solvents applied in extraction and separation. *J. Sep. Sci.* **39**, 3505–3520 (2016).
40. Nguyen, H. T., Truong, V. A. & Tran, P. H. Preparation of polysubstituted imidazoles using AC-SO 3 H/[Urea] 7 [ZnCl 2] 2 as an efficient catalyst system: a novel method, and α-glucosidase inhibitor activity. *RSC Adv.* **13**, 12455–12463 (2023).
41. Capua, M. et al. Capriati, V. An expeditious and greener synthesis of 2-aminoimidazoles in deep eutectic solvents. *Molecules* **21**, 924 (2016).
42. Liu, C., Cao, Y., Sun, W., Rao, Z. & Gu, Y. Highly efficient lithium-ion battery cathode material recycling using deep eutectic solvent based nanofluids. *RSC Sustain.* **1**, 270–281 (2023).
43. Thakur, A., Verma, M., Bharti, R. & Sharma, R. Recent advances in utilization of deep eutectic solvents: an environmentally friendly pathway for multi-component synthesis. *Curr. Org. Chem.* **26**, 299–323 (2022).
44. Azizi, N. & Edrisi, M. Multicomponent reaction in deep eutectic solvent for synthesis of substituted 1-aminoalkyl-2-naphthols. *Res. Chem. Intermed.* **43**, 379–385 (2017).
45. Paiva, A. et al. Natural deep eutectic solvents–solvents for the 21st century. *ACS Sustain. Chem. Eng.* **2**, 1063–1071 (2014).
46. Saavedra, B. & Ramón, D. J. Deep eutectic solvent as a sustainable medium for C-C bond formation via multicomponent radical conjugate additions. *ACS Sustain. Chem. Eng.* **9**, 7941–7947 (2021).
47. Balalaie, S., Arabanian, A. & Hashtroudi, M. S. Zeolite HY and silica gel as new and efficient heterogenous catalysts for the synthesis of triarylimidazoles under microwave irradiation. *Chem. Monthly*. **131**, 945–948 (2000).
48. Chary, M. V., Keerthysri, N. C., Vupallapati, S. V., Lingaiah, N. & Kantevari, S. Tetrabutylammonium bromide (TBAB) in isopropanol: an efficient, novel, neutral and recyclable catalytic system for the synthesis of 2, 4, 5-trisubstituted imidazoles. *Catal Commun.* **9**, 2013–2017 (2008).
49. Zhou, J. F., Song, Y. Z., Yang, Y. L., Zhu, Y. L. & Tu, S. J. One-step synthesis of 2-aryl-4, 5-diphenylimidazoles under microwave irradiation. *Synth. Commun.* **35**, 1369–1373 (2005).
50. Xia, M. & Lu, Y. D. A novel neutral ionic liquid-catalyzed solvent-free synthesis of 2, 4, 5-trisubstituted imidazoles under microwave irradiation. *J. Mol. Catal. A: Chem.* **265**, 205–208 (2007).
51. Samai, S., Nandi, G. C., Singh, P. & Singh, M. S. L-Proline: an efficient catalyst for the one-pot synthesis of 2, 4, 5-trisubstituted and 1, 2, 4, 5-tetrasubstituted imidazoles. *Tetrahedron* **65**, 10155–10161 (2009).
52. Aziizi, N., Manochehri, Z., Nahayi, A. & Torkashvand, S. A facile one-pot synthesis of tetrasubstituted imidazoles catalyzed by eutectic mixture stabilized ferrofluid. *J. Mol. Liq.* **196**, 153–158 (2014).
53. Azizi, N., Dado, N. & Amiri, A. K. Highly efficient one-pot synthesis of trisubstituted imidazoles under catalyst-free conditions. *Can. J. Chem.* **90**, 195–198 (2012).
54. Azizi, N., Saadat, M. & Edrisi, M. Facile synthesis of FeCeOx nanoparticles encapsulated carbon nitride catalyst for highly efficient and recyclable synthesis of substituted imidazoles. *Sci. Rep.* **13**, 17474 (2023).
55. Mobinikhaledi, A. & Amiri, A. K. One-pot synthesis of tri-and tetrasubstituted imidazoles using eutectic salts as ionic liquid catalyst. *Res. Chem. Intermed.* **41**, 2063–2070 (2015).
56. Gabla, J. J., Mistry, S. R. & Maheria, K. C. An efficient green protocol for the synthesis of tetra-substituted imidazoles catalyzed by zeolite BEA: effect of surface acidity and Polarity of zeolite. *Catal. Sci. Technol.* **7**, 5154–5167 (2017).
57. Mohammadi Ziarani, G., Zeinab, D., Shakiba Nahad, M. & Badiei, B. One-pot synthesis of 1,2,4,5-tetra substituted imidazoles using sulfonic acid functionalized silica (SiO_2-Pr-SO_3H). *Arab. J. Chem.* **8**, 692–697 (2014).
58. Siddiqui, S. A. et al. Room temperature ionic liquid promoted improved and rapid synthesis of 2, 4, 5-triaryl imidazoles from Aryl aldehydes and 1, 2-diketones or α-hydroxyketone. *Tetrahedron* **61**, 3539–3546 (2005).

59. Teimouri, A. & Chermahini, A. N. An efficient and one-pot synthesis of 2, 4, 5-trisubstituted and 1, 2, 4, 5-tetrasubstituted imidazoles catalyzed via solid acid nano-catalyst. *J. Mol. Catal. A: Chem.* **346**, 39–45 (2011).
60. Heravi, M. M., Bakhtiari, K., Oskooie, H. A. & Taheri, S. Synthesis of 2, 4, 5-triaryl-imidazoles catalyzed by $NiCl_2$· 6H2O under heterogeneous system. *J. Mol. Catal. Chem.* **263**, 279–281 (2007).
61. Sharma, S. D., Hazarika, P. & Konwar, D. An efficient and one-pot synthesis of 2, 4, 5-trisubstituted and 1, 2, 4, 5-tetrasubstituted imidazoles catalyzed by $InCl_3$·$3H_2O$. *Tetrahedron Lett.* **49**, 2216–2220 (2008).
62. Sharghi, H., Aberi, M. & Doroodmand, M. M. A mild, three-component one-pot synthesis of 2, 4, 5-trisubstituted imidazoles using mo (IV) Salen complex in homogeneous catalytic system and mo (IV)salen complex nanoparticles onto silica as a highly active, efficient, and reusable heterogeneous nanocatalyst. *Mol. Diversity*. **19**, 77–85 (2015).
63. Song, H., Xing, C., Li, B. & Shen, W. Spherical carbon with SO3H groups as an efficient solid acid catalyst for 2, 4, 5-triphenyl–imidazole synthesis. *ChemistrySelect* **1**, 301–308 (2016).
64. Hasaninejad, A., Zare, A., Shekouhy, M. & Rad, A. Catalyst-free one-pot four component synthesis of polysubstituted imidazoles in neutral ionic liquid 1-butyl-3-methylimidazolium bromide. *J. Comb. Chem.* **12**, 844–849 (2010).
65. Murthy, S. N., Madhav, B. & Nageswar, Y. V. D. DABCO as a mild and efficient catalytic system for the synthesis of highly substituted imidazoles via multi-component condensation strategy. *Tetrahedron Lett.* **51**, 5252–5257 (2010).
66. Wang, X. C., Gong, H. P., Quan, Z. J., Li, L. & Ye, H. L. PEG-400 as an efficient reaction medium for the synthesis of 2, 4, 5-triaryl-1H-imidazoles and 1, 2, 4, 5-tetraaryl-1H-imidazoles. *Chin. Chem. Lett.* **20**, 44–47 (2009).
67. Sadeghi, B., Mirjalili, B. B. F. & Hashemi, M. M. BF3· SiO_2: an efficient reagent system for the one-pot synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles. *Tetrahedron Lett.* **49**, 2575–2577 (2008).

Author contributions

Fatemeh Mohammad performed material preparation, data collection, and Writing—original draft. Najmedin Azizi Conceptualization, Methodology and Writing—Review & Editing. Zohreh Mirjafari: Resources, Supervision and Writing—Original Draft. Javad Mokhtari: Formal analysis, Investigation, Software, Writing—review & editing.All authors reviewed the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

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