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Full Paper

One-Pot Synthesis of Substituted Piperidinones and 3,4-Dihydropyrimidinones Using a Highly Active and Recyclable Supported Ionic Liquid Phase Organocatalyst

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1-Ethyl-3-methylimidazolium ethyl sulfate was synthesized and its supported ionic liquid phase form was prepared and used as an organocatalyst for the synthesis of substituted piperidinones and 3,4-dihydropyrimidinones. The ionic liquid was characterized by ^{1}H NMR, ^{13}C NMR, and mass spectrometry. The catalyst is novel, stable, completely heterogeneous, and recyclable for several times and can be easily recovered by filtration. It was characterized with scanning electron microscopy, transmission electron microscopy, thermogravimetric analysis, and energy-dispersive X-ray spectroscopy techniques. The workup procedures are very simple, and products were obtained in good-to-excellent yields with reasonable purities without the need for further chromatographic purification.

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Introduction

Ionic liquids are considered as alternative 'green' solvents because they offer great potential for the development of clean catalytic technologies due to their unique properties such as undetectable vapour pressure and the ability to dissolve many organic and inorganic substances.[1] They can also be designed to offer high activity by immobilizing them on the surface of solid catalysts; heterogenization of catalysts can offer important advantages in handling and in separation and reuse. The idea of supported ionic liquid catalysis was developed by Mehnert et al.[2] in 2002. Supported ionic liquid catalysis has been the subject of enormous interest in the field of catalysis because of its potential and wide-range applications in synthetic chemistry. Homogeneous or liquid-phase catalysts offer several important advantages e.g. all catalytically active sites are accessible and uniform. Usually, solvents are indispensable as reaction media and have even important role in efficient homogeneous catalysis. Over the past years, ionic liquids have been applied as catalysts in different forms, e.g. as supported ionic liquid phase (SILP) catalyst, solid catalyst with ionic liquid layer (SCILL), or ionogels. SILP catalysis concept is based on a classical homogeneous catalyst that is dissolved in a thin film of ionic liquid, with the latter being dispersed over the high internal surface area of a porous support.[3] The SCILL concept is based on coating of the heterogeneous catalyst material with a thin layer of ionic liquid to induce specific modifications in the catalytic performance. Due to extremely low vapour pressure, the IL film resides on the catalyst surface. In both concepts, the IL is immobilized on a porous solid.[4] Modification of supported catalysts with IL is reported to change both the reactivity and stability of the catalyst. Immobilized ILs offer combined benefits of ILs and heterogeneous catalysts such as high designability, ease of handling, separation, and recycling. Furthermore, based on an economic criterion, it is desirable to minimize the amount of ionic liquid used in a potential process. Currently, ionic liquid-based hybrid materials called 'ionogels' are also in the ambit of great potential and attractive systems for synthetic chemistry.[5] Immobilized ionic liquids have been widely applied as novel solid catalysts e.g. in esterification, nitration,[6] Baeyer–Villiger reactions,[7] acetal formation,[8] hydrolysis of cellulose,[9] citral hydrogenation,[10] in the synthesis of many organic compounds,[11] and in the separation of rare metals.[12]

Diarylpiperidinones and dihydropyrimidinones (DHPMs) are also important compounds due to their wide range of bioactivities and their applications in the field of drug research. Compounds having a piperidinone nucleus have a wide variety of biological properties such as anti-tumour,[13] anti-cancer,[14] anti-viral,[15] anti-inflammatory,[16] nutagenic,[17] local anaesthetic,[18] anti-microbial,[19] and analgesic anti-pyretic properties.[20] The piperidinone nucleus is also present as an intermediate in the synthesis of many physiologically active compounds as reviewed by Prostakov and Gaivoronkaya.[21] Of the five major bases found in DNA and RNA, three are pyrimidinone derivatives, which comprise cytosine, uracil, and thymine. Thus, they have become very important in the world of synthetic organic chemistry. 3,4-Dihydropyrimidinones have also been reported to posses diverse pharmacological properties such as anti-viral, anti-bacterial, and anti-hypertensive properties, as well as efficacy as calcium channel modulators and 1a-antagonist.[22] Numerous methods are available in the literature on the synthesis of DHPMs,[23–25] which includes certain drawbacks, such as the use of harsh reaction conditions and expensive and toxic catalysts, and long reaction times, low yields, and tedious workup procedures.

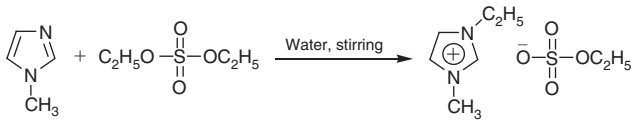
Our method involves a metal-free and cost-effective catalyst that can afford higher yields in shorter reaction times. The literature survey again reveals that there are a number of methods for the synthesis of piperidinones,[26–29] but there is lot of scope to develop more advanced methods. The use of L-proline, as a homogeneous catalyst, for the synthesis of piperidinones is well explored in literature.[30,31] Our method involves the use of L-proline and ionic liquid in heterogeneous form, resulting in enhanced catalytic activity and recyclability, thus making the process eco-friendly. Keeping in view the importance of piperidinones and pyrimidinones and the scope of SILPC, we wish to report an efficient method for the synthesis of 1-ethyl-3-methylimidazolium ethyl sulfate [EMIM][$EtSO_4$] and its supported ionic liquid phase organocatalyst form, silica-L-proline [EMIM][$EtSO_4$] (SILPOC). The heterogeneous organocatalyst was used in catalytic amounts in the one-pot synthesis of piperidinones and 3,4-dihydropyrimidinones.

Based on the literature, the combination of L-proline with ionic liquids is also known to catalyze organic reactions.[32] Thus, herein, we tried this combination with silica to explore the supported ionic liquid catalysis for the synthesis of piperidinones and pyrimidinones. In an earlier study, we reported the use of solid catalyst with ionic liquid layer for the synthesis of 1,4-dihydropyridines (DHPs).[33]

Results and Discussion

Synthesis of [EMIM][$EtSO_4$]

[EMIM][$EtSO_4$] was prepared by first transferring 10 mmol of 1-methylimidazole (0.82 g) and 20 mL of water to a 100-mL round-bottom flask placed in an ice bath. The resulting mixture was allowed to stir (Scheme 1). Then, 3.6 mmol of diethylsulfate (0.54 g) was added dropwise to control the vigorous nature of the reaction. After 10 h, 3.2 mmol of diethylsulfate (0.5 g) was slowly added under continuous stirring in an ice bath. After 20 h of reaction, 3.2 mmol of diethylsulfate (0.5 g) was added slowly, and the reaction was stirred continuously for 10 h, after which the ice bath was removed and the reaction was stirred further for 30 h at room temperature. After completion of the reaction (monitored via thin layer chromatography (TLC)), water was removed using rotary evaporation, and the ionic liquid obtained was kept in an oven for 1 h at 110°C to remove the residual water.



Scheme 1. Preparation of 1-ethyl-3-methylimidazolium ethyl sulfate.

Preparation of SILPOC

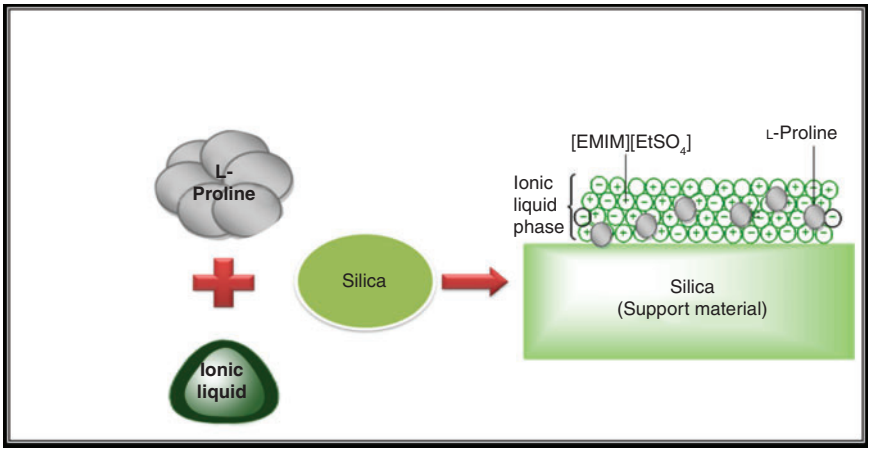
SILPOC was prepared by dissolving 5 mmol of L-proline (0.575 g) and 4 mmol (0.944 g) of ionic liquid [EMIM][$EtSO_4$] in 5 mL of methanol in a 250-mL round-bottom flask. The solution was stirred for 10 min at room temperature under vacuum conditions. To this reaction mixture, silica (5 g; calcined at 400°C) was added and stirred at room temperature for 20 h. The solvent was evaporated under reduced pressure until free-flowing powder of the catalyst was obtained. The powder was then dried at 120°C for 4 h (Scheme 2).

Characterization of the Catalyst

The surface morphology of the catalyst was studied using scanning electron microscopy (SEM). The SEM images of the surface of the catalyst are presented in Fig. 1. The SEM image showed that the catalyst have porous irregular shaped particles.

The transmission electron microscopy (TEM) (Fig. 2) images of the catalyst provide direct observation of the morphology and distribution of L-proline and ionic liquid on the surface of silica and indicate the fine structure of the catalyst with no bulk aggregation of ionic liquid or L-proline. It is further inferred that some molecules are arranged in a way to form blobs.

The stability of the catalyst was determined by thermogravimetric analysis (TGA). The TG curve shows an initial weight loss at 31.9°C,which may be attributed to the loss of physically adsorbed gases and residual solvent on the surface of the catalyst. The small weight loss near 100°C can be attributed to the loss of water trapped into the surface of the catalyst. The subsequent weight loss above 250°C can be attributed to the loss of L-proline and the weight loss above 500°C may be due to the thermal degradation of the ionic liquid. Hence, from the TG curve (Fig. 3), we may conclude that the catalyst is stable and it



Scheme 2. Illustration of the synthesis of supported ionic liquid phase organocatalyst.

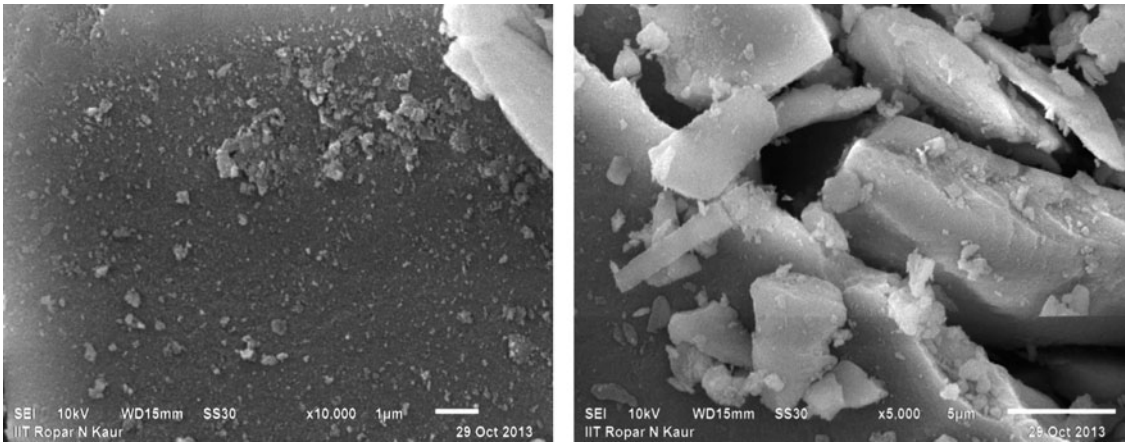


Fig. 1. SEM images of the supported ionic liquid phase organocatalyst.

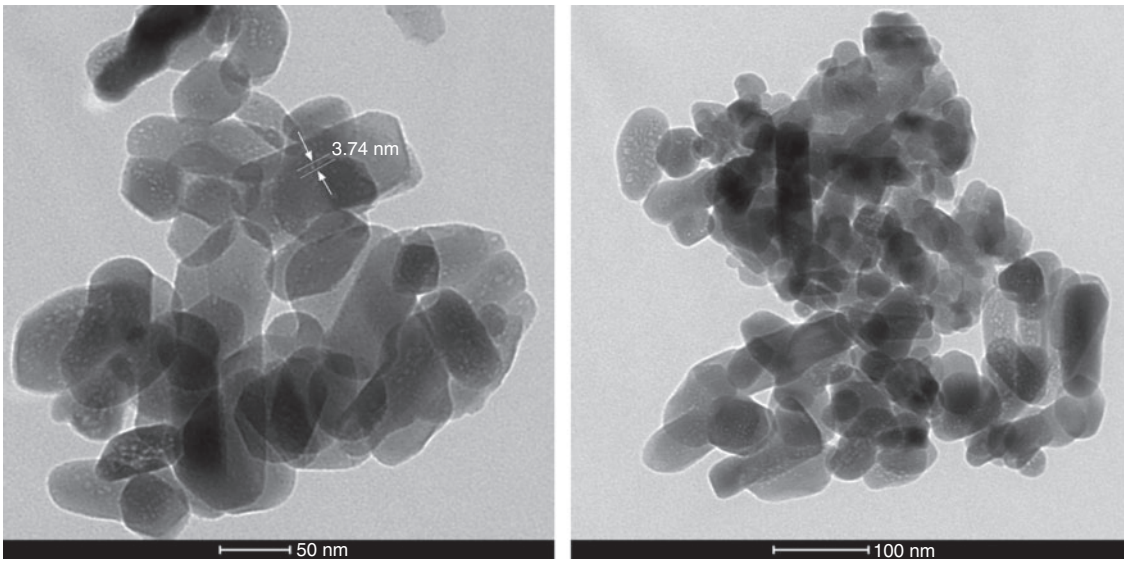


Fig. 2. TEM images of the supported ionic liquid phase organocatalyst.

is safe to conduct the synthesis of pyrimidinones and piperidinones at 60°C. The energy-dispersive X-ray spectroscopy (EDX) pattern of the catalyst showed the presence of all the important elements i.e. C, N, O, Si, and S of the supported ionic liquid phase catalyst (Fig. 4).

Optimization of Reaction Conditions for the Synthesis of Piperidinones

For the optimization of temperature for the synthesis of 2,6-diarylpiperidinoes, we tried the reaction among ethylmethylketone, 4-methoxybenzaldehyde, and ammonia at different temperatures (room temperature (r.t.), 40°C, 60°C, 80°C) under solvent-free conditions. It was found that at room temperature and at 40°C, traces of products were formed (monitored by TLC). At 60°C, the reaction yielded excellent amounts of the products (Table 1), whereas at 80°C, the products obtained were not very pure, likely due to multiple product formation (monitored by TLC). Hence, a temperature of 60°C was found to be the optimum reaction temperature for the synthesis of 2,6-diarylpiperidinones. Furthermore, some other solvents, such as acetonitrile, toluene, and water, were also tried. Unfortunately, the results obtained were not satisfactory as presented in Table 1.

Optimization of Reaction Conditions for the Synthesis of 3,4-Dihydropyrimidinones

For the optimization of temperature for the synthesis of 3,4-dihydropyrimidinones, we tried the reaction among ethylacetoacetate, 4-methoxybenzaldehyde and urea at different temperatures (r.t., 40°C, 60°C, 80°C) under solvent-free conditions, and results are presented in Table 1. It was observed that at room temperature and at 40°C, products were formed in lower yields. At 60°C, the reaction yielded excellent amounts of products, whereas at 80°C, there was no significant increase in the yield of the product. Hence, a temperature of 60°C was found to be the optimum reaction temperature for the synthesis of 3,4-dihydropyrimidinones. Furthermore, we explored the effect of solvent on the synthesis of 3,4-dihydropyrimidinones, and results are presented in Table 1. As observed, the solvent-free conditions gave the best results.

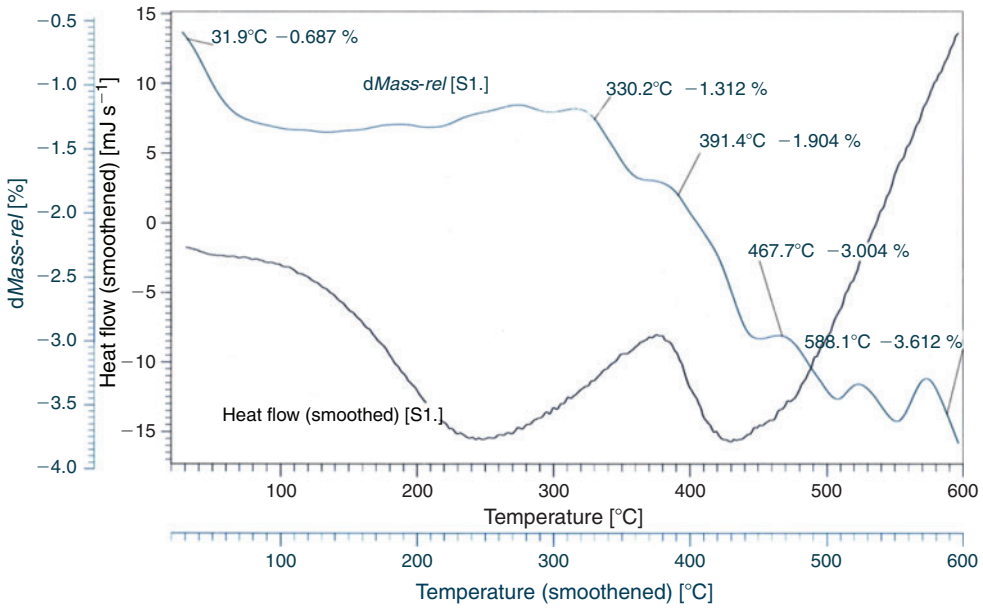


Fig. 3. TG graph (blue curve) and differential thermal analysis curve (black curve) of the supported ionic liquid phase organocatalyst.

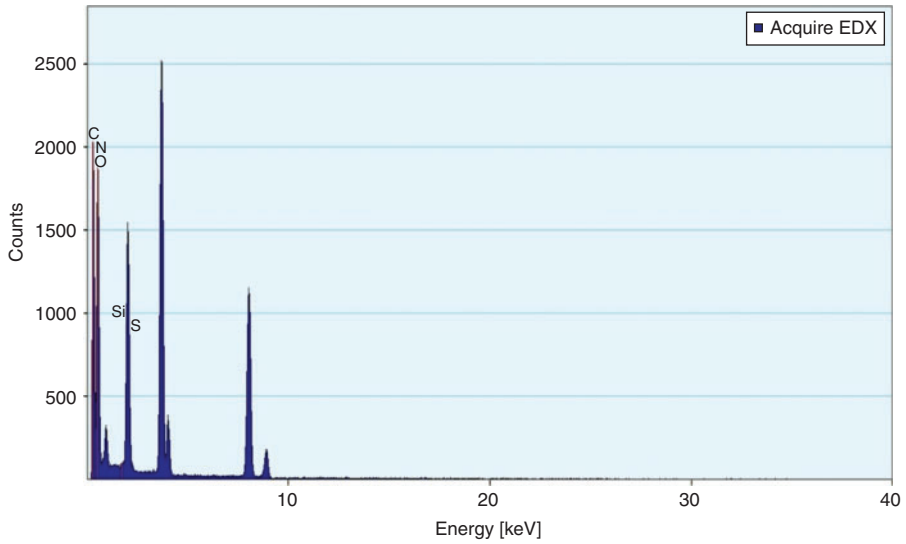


Fig. 4. EDX spectrum of the supported ionic liquid phase organocatalyst.

In order to determine the role of supported ionic liquid phase organocatalyst, as the heterogeneous catalyst, the reactions with test substrates for the synthesis of 2,6-diarylpiperidinones and 3,4-dihydropyrimidinones were carried out in the presence of activated silica, silica-L-proline, homogeneous L-proline-IL, and absence of catalyst. The results are summarized in Table 2.

Under homogeneous conditions, using ionic liquid and L-proline only, the reactions did not yield satisfactory results for further investigation. Moreover, to make the process cost effective and heterogeneous, the loading of ionic liquid with L-proline on the surface of silica makes the system attractive, selective, and effective, thereby giving higher yields and affording simple workup procedures. Moreover, the catalyst can be easily recovered and recycled for several runs, thus making the process more efficient and cost effective. Thus, the heterogeneous catalyst was selected for the synthesis of 2,6-diarylpiperidinones and 3,4-dihydropyrimidinones.

To make the developed protocol general, the synthesis of these heterocyclic compounds was extended using different aromatic aldehydes, possessing both electron-withdrawing and electron-donating groups, α,β-unsaturated aldehydes, and heterocyclic aldehydes. It was found that aromatic aldehydes that possess electron-withdrawing groups are more efficient for the synthesis of their corresponding products. In contrast, aliphatic aldehydes did not afford a satisfactory product yield.

Recyclability

The recyclability and deactivation of a catalyst is more important when dealing with heterogeneous catalysts. To test these

Table 1. Comparison of solvents and temperature in the synthesis of heterocycles

Entry	Solvent	Conditions	Piperidinone[A]		3,4-Dihydropyrimidinone[B]	
			Time [min]	Yield[C] [%]	Time [min]	Yield[C] [%]
1	No solvent	r.t.	60	Trace	20	40
2	No solvent	40°C	60	40	20	60
3	No solvent	60°C	60	95	20	97
4	No solvent	80°C	60	95	20	97
5	Acetonitrile	60°C	60	50	20	60
6	Ethanol	60°C	60	60	20	70
7	Toluene	60°C	60	50	20	40
8	Water	60°C	60	45	20	50
9	DMF	60°C	60	55	20	60

[A]Reaction conditions: ethyl methyl ketone (1 mmol), 4-methoxybenzaldehyde (2 mmol), ammonia (1 mmol), and catalyst (0.1 g).
[B]Reaction conditions: 4-methoxybenzaldehyde (2 mmol), ethyl acetoacetate (2 mmol), urea (2 mmol), and catalyst (0.1 g).
[C]Isolated yields.

Table 2. Comparison of catalyst activity for the synthesis of piperidinones[A] and 3,4-dihydropyrimidinones[B] at 60°C under solvent-free conditions

Catalyst (0.1 g for entries 2 and 5, 0.01 g L-proline and 0.1 g activated silica for entry 3, 0.01 g L-proline and 0.2 g [EMIM][$EtSO_4$] for entry 4)

Entry	Catalyst	Piperidinone[A]		3,4-Dihydropyrimidinone[B]	
		Time [min]	Yield[C] [%]	Time [min]	Yield[C] [%]
1	No catalyst	60	No reaction	20	No reaction
2	Activated silica	60	No reaction	20	Trace
3	Silica-L-proline	60	30	20	40
4	L-Proline-[EMIM][$EtSO_4$]	60	40	20	55
5	SILPOC	60	95	20	97

[A]Reaction conditions: ethyl methyl ketone (1 mmol), 4-methoxybenzaldehyde (2 mmol), and ammonia (1 mmol).
[B]Reaction conditions: 4-methoxybenzaldehyde (2 mmol), ethyl acetoacetate (2 mmol), and urea (2 mmol).
[C]Isolated yields.

properties, a series of seven consecutive runs for the synthesis of 2,6-diarylpiperinones and 3,4-dihydropyrimidinones was carried out using 4-methoxybenzaldehyde as the test substrate in the synthesis of both heterocycles and each time the amount of substrate used was proportional to the amount of catalyst recovered. The results of the recyclability studies are shown in Fig. 5. As observed, the catalyst is highly active and recyclable up to seventh run with small loss of activity. The small loss in activity after every use may be due to the deactivation of the some active sites.

Proposed Mechanism for the Synthesis of Piperidinones

In the proposed mechanism (Scheme 3), besides providing larger surface area and active sites for catalysis, SILPOC played an important role in the synthesis of 2,6-diarylpiperidinoes as this catalytic system involves more efficient use of ionic liquid, L-proline, and catalyst. In the first step, aldehyde was activated by catalyst for nucleophilic attack, leading to the formation of α, β-unsaturated ketones **A**. The second step involves nuclephilic attack of ammonia on the electrophilic centre of the second aldehyde activated by the catalyst, thereby resulting in the formation compound **B**. Then, the catalyst activated compounds **A** and **B** for cyclization to give the final product as shown in Scheme 3.

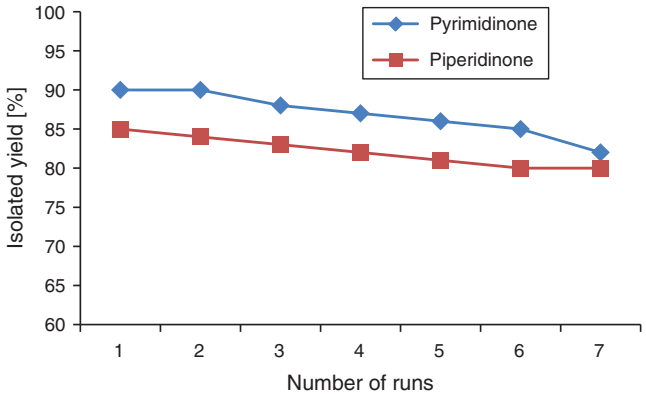
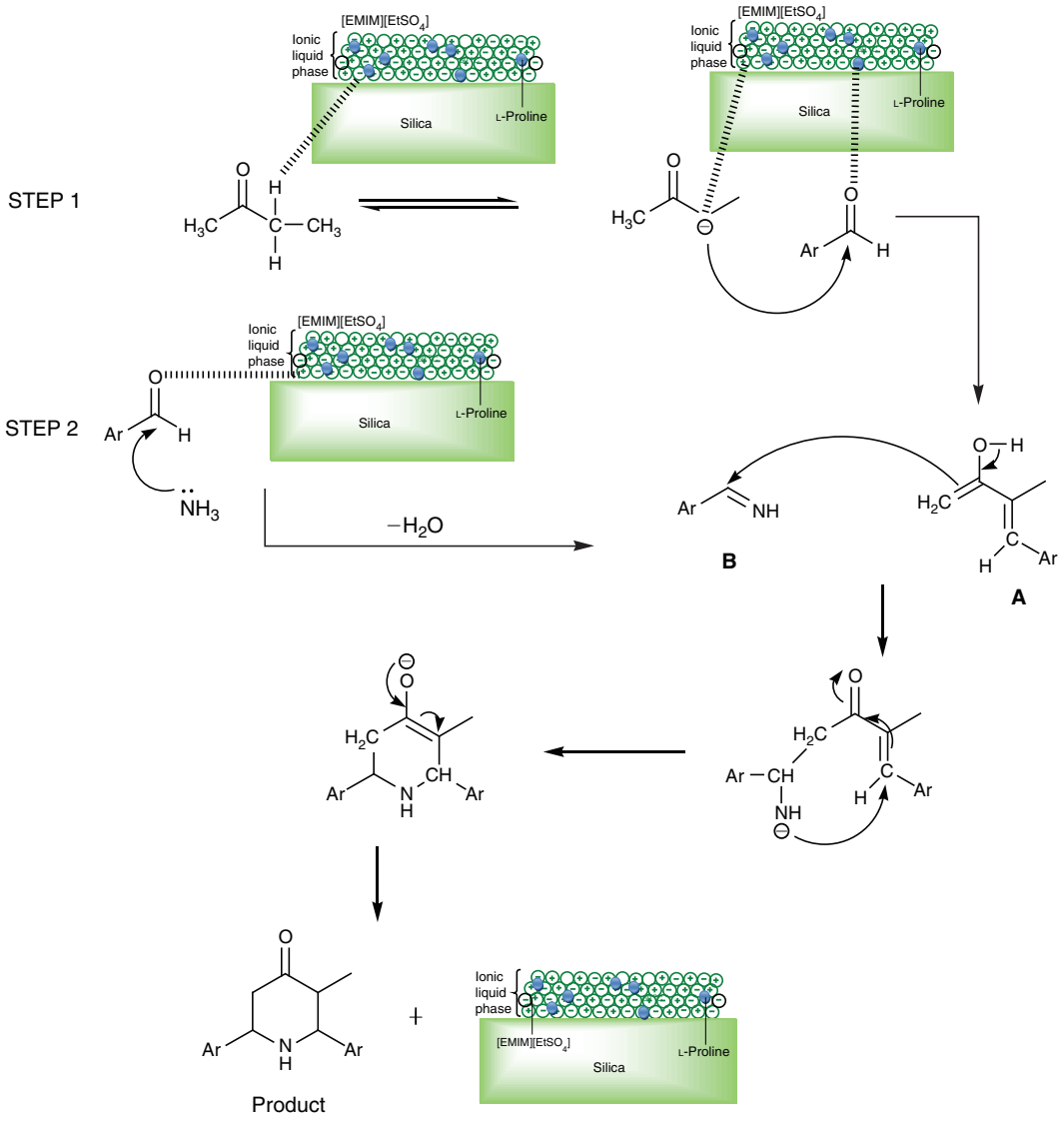


Fig. 5. Recyclability graph of the supported ionic liquid phase organocatalyst.

Proposed Mechanism for the Synthesis of 3,4-Dihydropyrimidinones

The supported ionic liquid phase organocatalyst, as a heterogeneous catalyst, provided active sites and larger surface area for the reaction to proceed. Moreover, the ionic liquid phase provided polarity for the reaction to proceed. In the proposed



Scheme 3. Proposed mechanism for the synthesis of piperidinones.

mechanism (Scheme 4), the initial step involves the formation of imine **1**. The catalyst coordinated with the nitrogen atom of imine to give an intermediate **2**, which activates the C=N bond towards nucleophilic attack. Furthermore, complexation of β-ketoester with the catalyst increases the nucleophilicity of α-carbon of enolate, thus facilitating the attack on imine carbon and attack of free amidic group to β-carbonyl carbon, thereby resulting in the formation of six-membered heterocyclic intermediate **3**, which upon dehydration gives the desired DHPMs **D** as shown in Scheme 4.

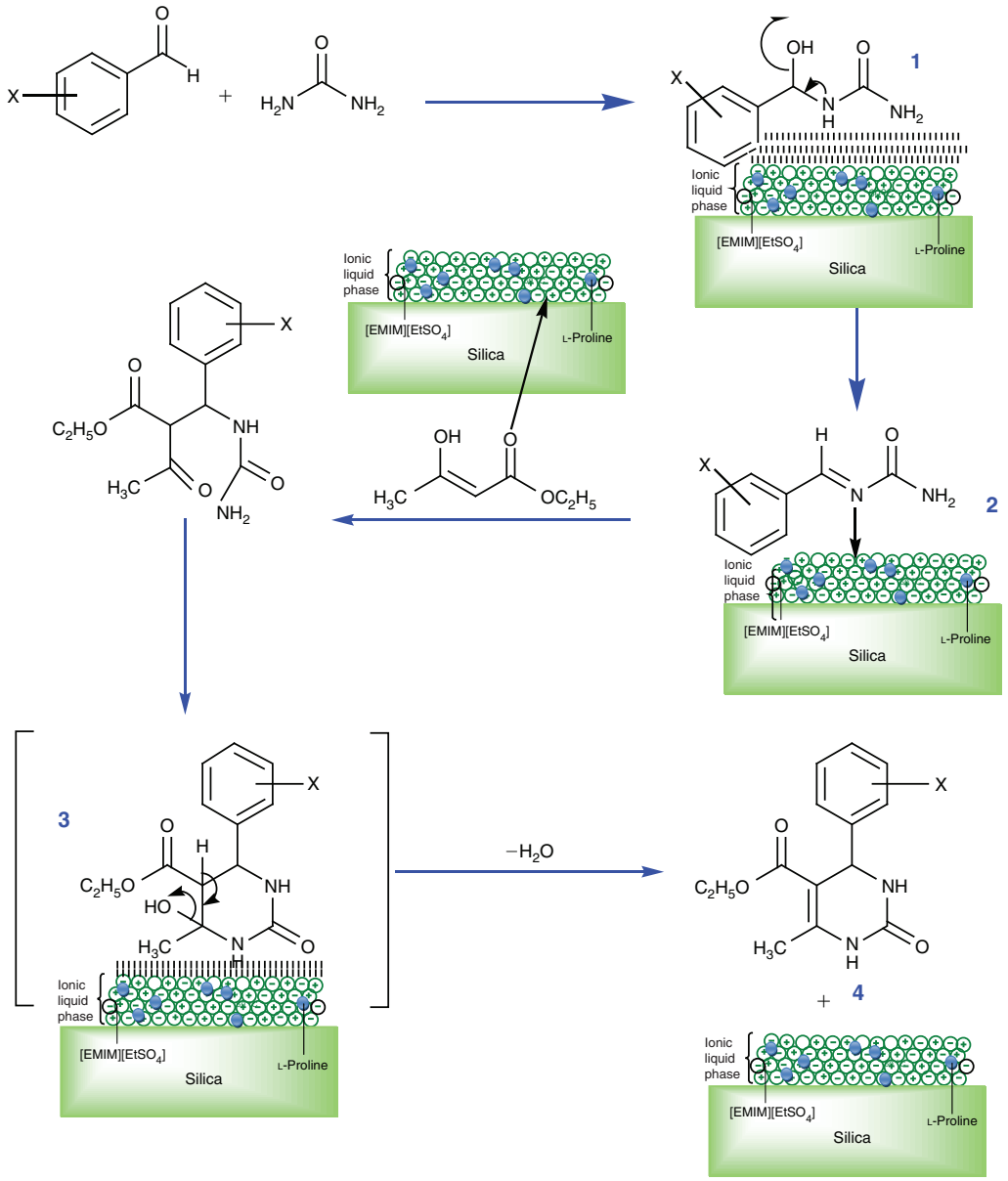
Conclusion

In conclusion, we prepared 1-ethyl-3-methylimidazolium ethyl sulfate and used this IL for the synthesis of supported ionic liquid phase organocatalyst. By using this catalyst, we have developed a clean methodology for the synthesis of substituted piperidinones and 3,4-dihydropyrimidinones using silica immobilized with L-proline in [EMIM][$EtSO_4$] as a re-useable, non-toxic, and cost-effective organocatalyst. Moreover, the low temperature, mild reaction conditions, ease of workup, compatibility with various functional groups, high yield of products, and ecologically clean procedure will make the present method a useful and attractive strategy for the synthesis of these biologically important heterocycles.

Experimental

Materials and Instrumentation

Silica gel was purchased from ACROS Organics, and diethylsulfate and 1-methylimidazole were purchased from Sigma-Aldrich; these chemicals were used without further purification. The infrared (IR) spectra of the catalyst and synthesized compounds were recorded in the range of 4000–300 cm^{-1} on a Shimadzu Prestige-21 spectrophotometer. TGA of the catalyst was conducted on a Linesis thermal analyzer, using a heating rate of 10°C min^{-1}. The SEM images were recorded on a JEOL scanning electron microscope and the TEM images were recorded on a TECHNAI G^2 20 S-TWIN microscope (FEI, The Netherlands). ^1H NMR and ^{13}C NMR analyses of the compounds were performed on a Bruker Avance III (400 MHz) spectrometer. Mass spectra of the products were obtained on a Bruker Daltonics Esquire 3000 spectrometer.



Scheme 4. Proposed mechanism for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones.

Scheme 5. General procedure for the synthesis of piperidinones.

General Procedure for the Synthesis of Piperidinones

To a mixture of 2 mmol of aldehyde, 1 mmol of ketone, and 1 mmol of ammonia in a round-bottom flask, the catalyst (0.1 g) was added. The reaction mixture was stirred at 60°C using a magnetic stirrer (Scheme 5) for an appropriate time (Table 3).

After completion of the reaction (monitored by TLC), the product was extracted with ethylacetate and filtered using a vacuum pump. The filtrate was treated with water, and the organic layer was separated, concentrated, and kept at room temperature till a solid product was formed, which was finally crystallized from ethanol to obtain the pure product.

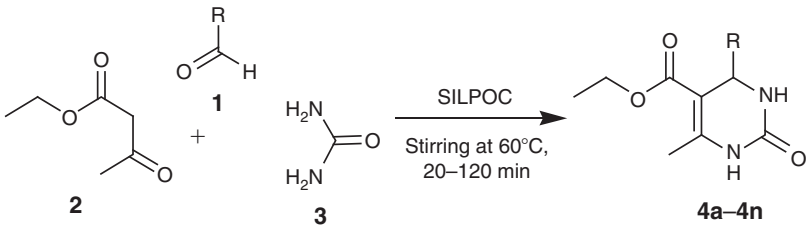
General Procedure for the Synthesis of 3,4-Dihydropyrimidinones

First, 2 mmol of aldehyde, 2 mmol of ethyl acetoacetate, and 2 mmol of urea were stirred for 5 min at 60°C, and then the catalyst (0.1 g) was added, and stirring was continued at 60°C using a magnetic stirrer (Scheme 6) for an appropriate time (Table 4). After completion of the reaction (monitored by TLC), the product was extracted with ethylacetate and filtered off using a vacuum pump. The product was obtained after removal of the solvent under reduced pressure and finally crystallized from ethanol.

Table 3. One-pot synthesis of piperidinones at 60°C under solvent-free conditions[A] using SILPOC

Entry	Product	R	R_1	Time [min]	Yield[B] [%]	mp/lit. mp [°C]
1	**1a**	CH_3	C_6H_5	90	90	86–89/87[34]
2	**1b**	CH_3	4-$OCH_3C_6H_4$	60	95	136–138/138[35]
3	**1c**	CH_3	2-$OCH_3C_6H_4$	80	85	93–94/93[35]
4	**1d**	CH_3	4-$CH_3C_6H_4$	80	88	124–126/126[31]
5	**1e**	CH_3	2-ClC_6H_4	90	80	128–130/132[31]
6	**1f**	CH_3	4-ClC_6H_4	70	90	126–128/128[31]
7	**1g**	$COOC_2H_5$	C_6H_5	70	85	110–113/113[35]
8	**1h**	$COOC_2H_5$	4-$OCH_3C_6H_4$	60	92	87–88/88[35]
9	**1i**	$COOC_2H_5$	4-ClC_6H_4	90	92	129–130/128[31]
10	**1j**	CH_3	3-$NO_2C_6H_4$	60	89	75–77/78[36]
11	**1l**	CH_3	2-Furyl	70	87	42–45/40[37]
12	**1n**	CH_3	H	90	Trace	–
13	**1o**	CH_3	CH_3	90	–	–
14	**1p**	$COOC_2H_5$	H	90	–	–

[A]Reaction conditions: aldehyde (2 mmol), ketone (1 mmol), ammonia (1 mmol), and catalyst (0.1 g) stirred at 60°C under solvent-free conditions.
[B]Isolated yields.



Scheme 6. General procedure for the synthesis of 3,4-dihydropyrimidinones.

Table 4. One-pot synthesis of 3,4-dihydropyrimidinones at 60°C under solvent-free conditions[A] using SILPOC

Entry	Product	R	Time [min]	Yield[B] [%]	mp/lit. mp [°C]
1	**4a**	C_6H_5	30	90	205–206/206–208[38]
2	**4b**	4-$MeOC_6H_4$	20	97	200–202/201–202[38]
3	**4c**	4-OH-3-$MeOC_6H_3$	25	85	232–234/232–234[39]
4	**4d**	2-$NO_2C_6H_4$	30	90	209–210/ 208–210[38]
5	**4e**	3-$NO_2C_6H_4$	20	90	226–227/227–229[38]
6	**4f**	4-$NO_2C_6H_4$	30	95	210–211/211–213[38]
7	**4g**	4-$CH_3C_6H_4$	40	85	214–215/215–216[40]
8	**4h**	2-Thienyl	25	96	206–207/206–208[41]
9	**4i**	2-Furyl	20	92	198–200/200–201[41]
10	**4j**	CH=CH–C_6H_5	60	80	230–232/230–232[38]
11	**4k**	4-ClC_6H_4	40	97	213–215/216–217[42]
12	**4l**	H	90	88	239/242–244[40]
13	**4m**	CH_3	120	Trace	–
14	**4n**	n-Bu	120	Trace	–

[A]Reaction conditions: aldehyde (2 mmol), ethyl acetoacetate (2 mmol), urea (2 mmol), and catalyst (0.1 g) stirred at 60°C under solvent-free conditions.
[B]Isolated yields.

Supplementary Material

NMR and mass spectra of the ionic liquid and products are available on the Journal's website.

Acknowledgements

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