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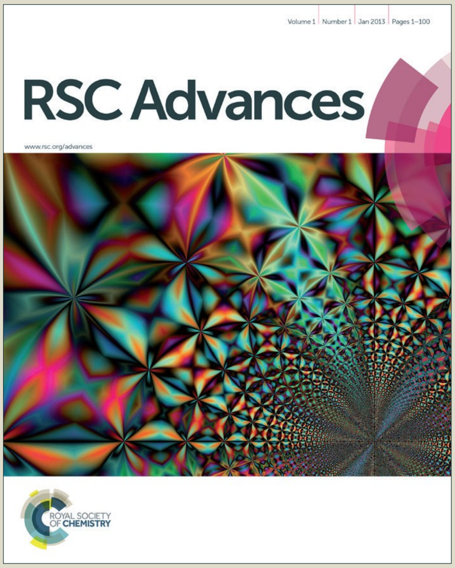

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ARTICLE

Novel ionic liquid [2-Eim] HSO_4 as a dual catalytic-solvent system for preparation of hexahydroquinolines under green condition

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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A novel Brønsted acidic ionic liquid 2-ethyl imidazolium hydrogen sulfate, [2-Eim] HSO_4, was synthesized. Its structure was investigated using FT-IR, ^1H NMR, ^{13}C NMR, UV, TGA and DTA spectra. This ionic liquid is utilized as a highly efficient and homogeneous catalyst for the promotion of hexahydroquinolines via one-pot multi-component condensation of aromatic aldehydes, dimedone, ethyl acetoacetate, and ammonium acetate at room temperature and neat conditions. Also, optimization of the reaction conditions was investigated using the response surface method {Central Composite Design (CCD)}. This new method consistently has the advantages of excellent yields and short reaction times. Further, the catalyst could be reused and recovered at least four times without appreciable loss of activity.

1. Introduction

Ionic liquids, ILs, (based imidazolium or other organic cations) have received considerable interest as eco-friendly solvents, catalysts and reagents in green synthesis because of their unique properties, such as low volatility, nonflammability, high thermal stability, negligible vapor pressure and ability to dissolve a wide range of materials [1-4]. Recently ionic liquids have been successfully employed as dual reagents (solvents + catalysts) for a variety of the reactions, but their use as catalyst under solvent-free conditions needs to be given more attention[5]. Among them, Brønsted acidic ionic liquids have designed to replace solid acids and traditional mineral liquid acids like sulfuric acid and hydrochloric acid in chemical procedures[6]. On the other hand, in recent years, an increasing interest has been focused on the synthesis of 1,4 dihydropyridine compounds owing to their significant biological activities[7]. In particular, dihydropyridine drugs such as nifedipine, nicardipine and amlodipine (Fig. 1) are effective cardiovascular agents for the treatment of hypertension[8]. In view of the importance of polyhydroquinoline derivatives, many classical methods for the synthesis of polyhydroquinoline derivatives were reported [9-13]. Also response surface method (RSM) is collection of mathematical and statistical techniques useful for designing experiments, building models, evaluating relative significance of several independent variables and their interactions, and determining optimum conditions for desirable responses[14]. The above mentioned subjects encouraged us to synthesize a new ionic liquid with Brönsted acidic property, named as 2-ethyl imidazolium hydrogen sulfate, [2-Eim] HSO_4, for the first time (Scheme 1), and its characterization by using FT-IR, ^1H NMR, ^{13}C NMR, UV, thermal gravimetric analysis (TGA) and differential thermal analysis (DTA). Our investigations showed that this reagent can be used as an efficient catalyst in the Hantzsch reaction. The method is easy and the products are obtained in high yields and short reaction times (Scheme 2).

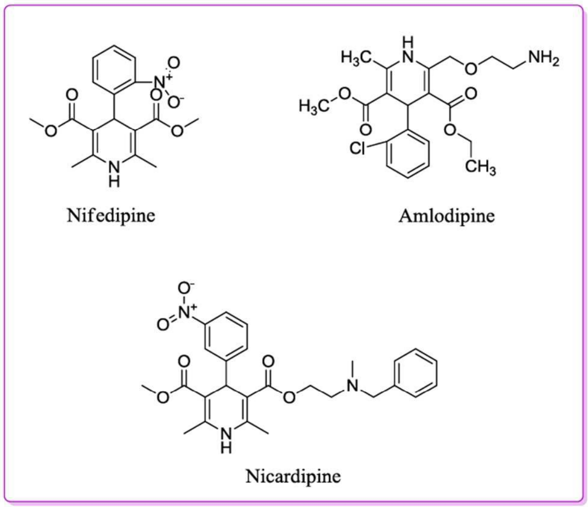

Fig. 1. Typical dihydropyridine drugs.

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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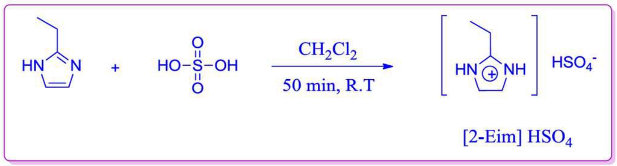
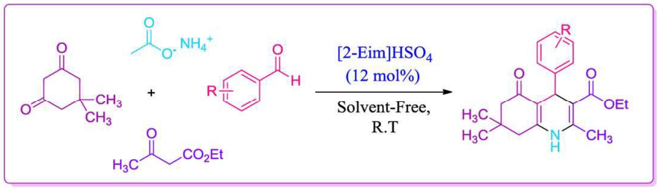


Scheme. 1. The synthesis of 2-ethyl imidazolium hydrogen sulfate, [2-Eim] HSO_4

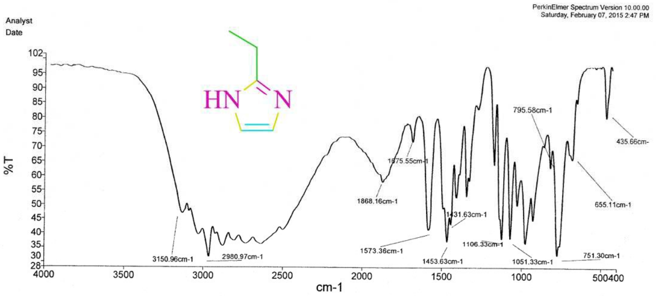


Scheme. 2. The one-pot multi-component preparation of ethyl 4-(aryl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate derivatives catalysed by [2-Eim] HSO_4

2. Results and discussion

2.1. Characterization of the catalyst

2.1.1. FT-IR studies. FT-IR (KBr, cm^{-1}) $υ_{max}$: 582, 761, 867, 1048, 1191, 1462, 1509, 1623, 2500-3500 cm^{-1}. The corresponding FT-IR spectral data of [2-Eim] HSO_4 are presented in Fig. 1. Spectrum of the ionic liquid indicated an abroad peak at 3112 cm^{-1} which can be related to N–H stretching group on imidazolium ring. The strong absorptions at 582, and 867 in [2-Eim] HSO_4 ionic liquid were assigned to the stretching and bending for S–O vibrations of hydrogen sulfate, also the absorption at 1191 and 1048 cm^{-1} is related to O=S=O asymmetric and symmetric stretching peaks that were absent in 2-ethyl imidazole. In addition, C=N, N-H, and C=C vibrations are observed at 1623, 1509, and 1462 cm^{-1}, respectively. The broad and strong bands at 2400–3600 cm^{-1} can be arising from the stretching of the hydroxyl group in the ionic liquid catalyst. These special IR peaks indicated that hydrogen sulfate was successfully assembled by 2-ethyl imidazole molecule as an anion for corresponding ionic liquid.



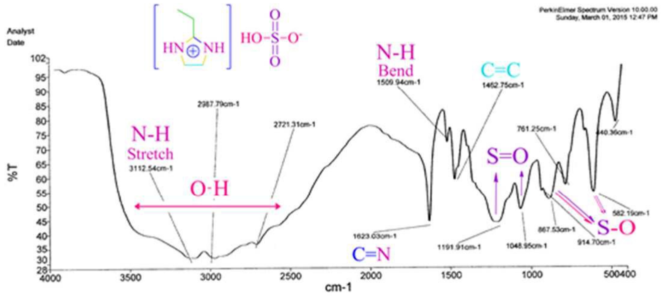
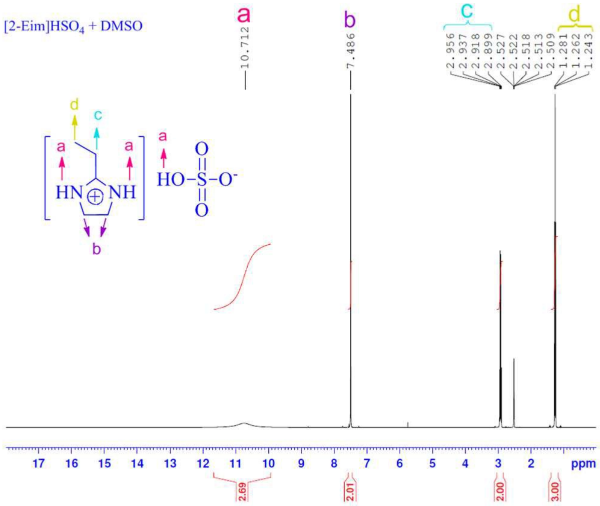


Fig. 2. FT-IR spectra of 2-ethyl imidazole (top), and [2-Eim] HSO_4 (down)

2.1.2. ^{1}H NMR and ^{13}C NMR studies. ^{1}H and ^{13}C NMR spectra of [2-Eim] HSO_4 ionic liquid are presented in Fig. 3. As Figure 3, indicates that, the important peak of ^{1}H NMR spectra of ionic liquid catalyst is linked to the acidic hydrogens (NH groups on imidazolium ring and hydrogen sulfate) which is observed in δ = 10.71 ppm. To confirm that this peak (10.71 ppm) is really related to the (NH groups on imidazolium ring and hydrogen sulfate) in the compound, not hydrogen of H_2SO_4 (its unreacted starting material) H_2SO_4: ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ=12.54 (s, 1H) [15] was investigated. The difference between the peaks of the acidic hydrogens in [2-Eim] HSO_4 and H_2SO_4 [15] confirmed that the peak observed in 10.71 ppm of the ^{1}H NMR spectra of [2-Eim] HSO_4 is correctly related to the acidic hydrogens of this compound. The structure of [2-Eim] HSO_4 confident to accept that this reagent can act as an efficient catalyst in reactions that needs acidic reagents to speed up. Our investigations clarified that this prediction is correct and can act as a promotion of the synthesis of hexahydroquinolines (Scheme 2).



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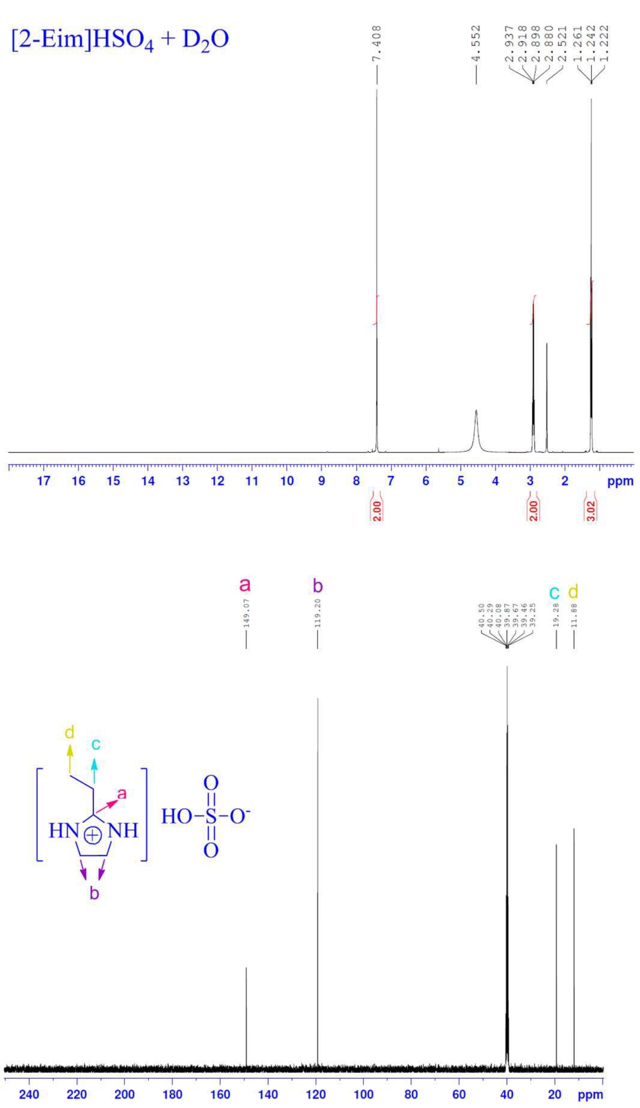

Fig. 3. ^{1}H NMR and ^{13}C NMR of 2-ethyl imidazolium hydrogen sulfate, [2-Eim] HSO_4.

Spectral data of [2-Eim] HSO_4 viscous pale yellow oil; ^{1}HNMR (400.22 MHz, DMSO-d_6): δ (ppm) 1.262 (t, J = 7.6, 3H, CH_3), 2.899-2.956 (m, J = 7.6, 2H, CH_2), 7.486 (s, 2H), 10.712 (s, 3H); ^{13}C NMR (100.64 MHz, DMSO-d6): (ppm) 11.88, 19.28, 119.20, 149.07.

2.1.3. Study on thermal gravimetric analysis (TGA) of [2-Eim] HSO_4. The corresponding diagrams are shown in Fig. 4. As it can be seen in Fig. 4, TGA and differential thermal analysis (DTA) of the catalysts showed weight losses in one step; [2-Eim] HSO_4 was decomposed above 319.8 °C in one step. This subject confirmed that the catalyst is one-system, not binary systems. In binary systems, the thermogravimetry (TG) diagrams must be showed weight losses in two or more steps. Moreover, the TGA and DTA diagrams of [2-Eim] HSO_4 are different. Therefore, the molecular decomposition of the ionic liquid occurred above 319.8 °C.

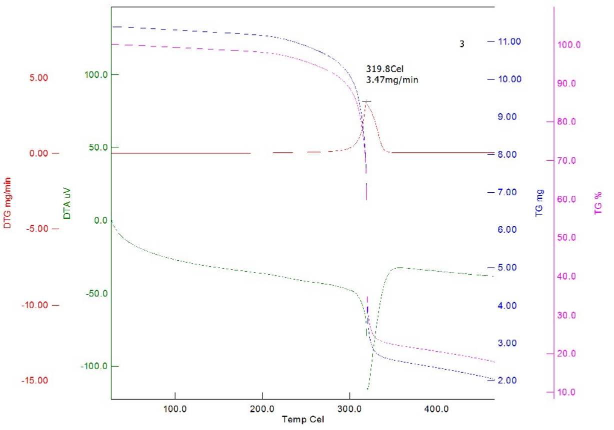

Fig. 4. The TG/DTG diagrams of [2-Eim] HSO_4

Molecular self-assembly including intramolecular and intermolecular, is the process by which molecules adopt a defined arrangement without guidance or management from an outside source. Most often the term molecular self-assembly refers to intermolecular self-assembly, and assembly of molecules is directed through non-covalent interactions (such as hydrogen bonding, metal coordination, hydrophobic forces, van der Waals forces, π–π interactions and electrostatic) as well as electromagnetic interactions[16]. The specific structure of [2-Eim] HSO_4 as a functional Brønsted acidic ionic liquid with hydrogen-bond donor, can give it the ability to produce a molecular self-assembly through hydrogen bonds (Fig. S1†).

On the basis of the structure of [2-Eim] HSO_4, it can act as an efficient catalyst in reactions which need the use of acidic catalysts to accelerate the rate of reaction. These functional groups provide the ability to produce a molecular self-assembly through intermolecular hydrogen bonds (Fig. S2†) and as a result go up its thermal stability.

2.1.4. UV spectra. UV–vis (DMSO): λ_{max} 295 nm; UV spectra was another evidence to confirm that [2-Eim] HSO_4 was really synthesized. For this purpose, UV–vis spectra of 2-ethyl imidazole and [2-Eim] HSO_4 were recorded. At first, some solutions of the mentioned compounds in DMSO with the same concentration were prepared. The concentration of these compounds in DMSO for UV study was 0.005molL^{-1}. The maximum absorptions of 2-ethyl imidazole (at 268, 293 nm) and [2-Eim] HSO_4 (at 295 nm) appeared, at 0.1082, 0.2978 and 0.1940 respectively. The difference between maximum absorptions of 2-ethyl imidazole and [2-Eim] HSO_4 confirmed the preparation of the catalyst Fig. 5.

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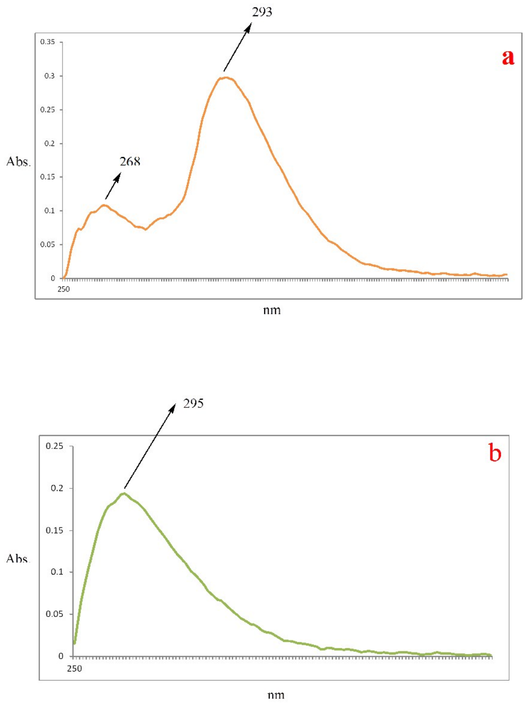


Fig. 5. UV spectra of a) 2-ethyl imidazole and b) [2-Eim] HSO_4 at room temperature in DMSO (the concentration of these compounds in DMSO was 0.005molL^{-1}).

2.1.5. Measuring pH in aqueous media. The pH profile was investigated and its corresponding diagram was shown in Fig. 6. At first, a solution of the mentioned compound in water was also prepared. The concentration of this compound in water for pH study was 0.05molL^{-1}. The pH was found 2.218 (at 25 °C). For approaching overall to this main scope we have titrated the solution by NaOH 0.05 N. The result is summarized in Fig. 6.

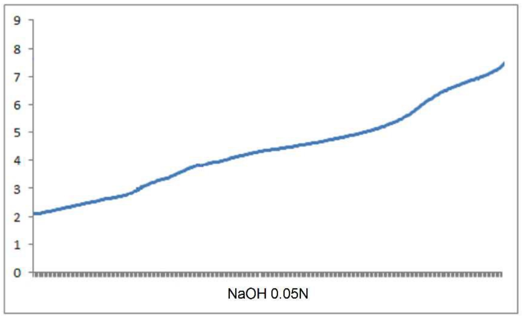


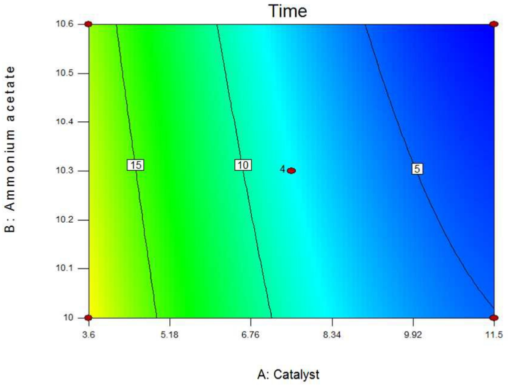
Fig. 6. pH Control, titrated aqueous media by NaOH 0.05N

2.1.6. Catalyst activity. RSM is one of the relevant multivariate techniques which can deal with multi variant experimental design strategy, statistical modeling and process optimization. [18-19] RSM usually contains three steps: (1) design and experiments; (2) response surface modeling through regression; and (3) optimization. The CCD is an effective design that provides reasonable amount of information for testing the goodness of fit. This method does not require large number of design points so reducing the overall cost associated with the experiment. [20] After the characterization of [2-Eim] HSO_4, we tested the catalytic activity of it to promote the preparation of hexahydroquinolines. For this purpose, a mixture of dimedone, 4-methoxybenzaldehyde, ethyl acetoacetate and ammonium acetate in the present of [2-Eim] HSO_4 under solvent-free condition was chosen as model reaction, optimization of the reaction condition was investigated using the response surface method {Central Composite Design (CCD)} with four replicate at central point for developing a second order model with 12 runs (Table S1†). Two variables that can effect on yield and time of the reaction are catalyst (A with levels of the variables 3.6 to 11.5 mol%) and amount of ammonium acetate (B with levels of the variables 10 to 10.6mmol). Yield and time of the reaction were used as the dependent variables and were fitted to a quadratic polynomialmodel. After programming optimization (Table S2† and S3†), two polynomial response surface models based on significant levels and actual values for time and yield were obtained.

$$\text{Time} = +8.22 - 6.84A - 1.08B + 2.60A^2 \quad (1)$$

$$\text{Yield} = +93.00 + 9.82A + 1.19B - 6.31A^2 - 1.81B^2 \quad (2)$$

Figs. 7-8 show the three-dimensional response surfaces, as well as contour plots of the relationship between different parameters at the optimized values. According to the models, interactions between variables have significant effects on the responses; therefore, results were presented and discussed in terms of interactions.



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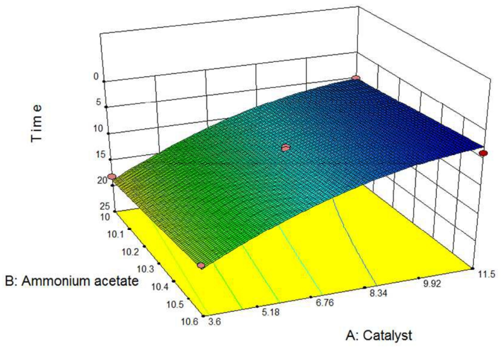

Fig. 7. Contour plot and response surface for the effect of factors on the reaction time.

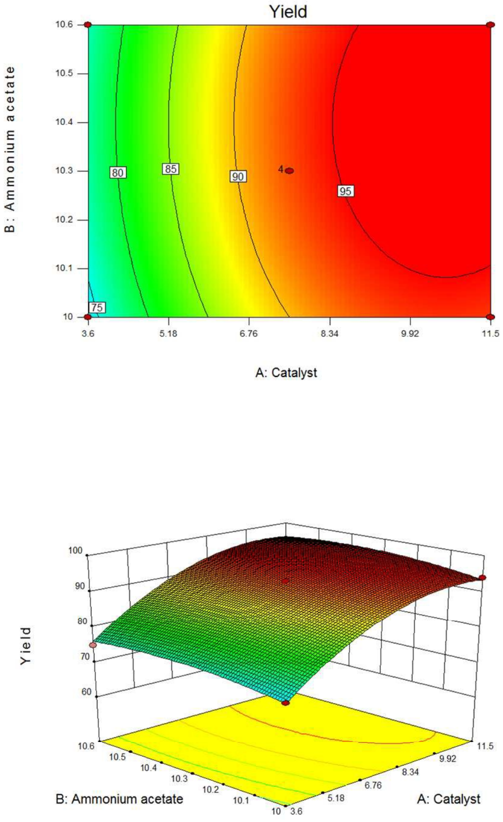

Fig. 8. Contour plot and response surface for the effect of factors on the reaction Yield.

2.1.7 Determination of model adequacy. It should be noted that polynomial models are reasonable approximations of the true functional relationship over relatively small regions of the entire space of independent variables[17]. Fig. 9. represents predicted vs. actual values of Yield. The clustering of the points around the diagonal line indicates a satisfactory correlation between the experimental data and the predicted values, confirming the robustness of the model.

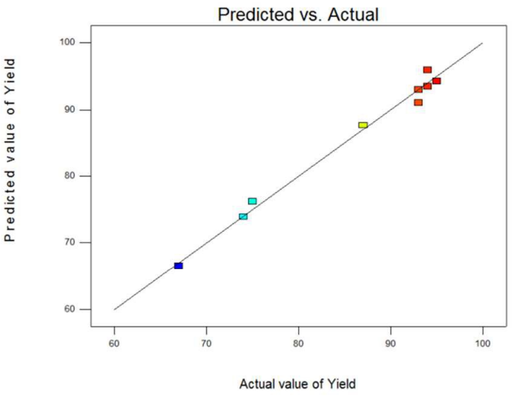

Fig. 9. Predicted vs. actual values of Yield

For finding of accurate optimum area, with using of obtained equations and calculation of desirability functions, the results showed that accurate optimal operational conditions was (A = 7.55 mol%, B = 10.3 mmol). It should be mentioned that corresponding maximum prediction conversion was 98.44% in introduced optimal point. In the next step, the accuracy of the theoretical results, were examined by empirical research. For this purpose, as model reaction, a mixture of dimedone (10 mmol), 4-methoxybenzaldehyde (10 mmol), ethyl acetoacetate (10 mmol) and ammonium acetate (10.3mmol), was stirred in the presence 7.5 mol% of [2-Eim] HSO_4 under solvent-free condition. The respective result is displayed in Table 1. As it can be seen in Table 1, indicates that (7.5 mol%) of [2-Eim] HSO_4 was suitable to catalyze the reaction at room temperature. In this reaction condition, the desired hexahydroquinoline was efficiently prepared in 93% yield within 8 min (Table 1) which is in a good accordance with the response surface method.

Table 1

Optimization conditions for the one-pot synthesis of ethyl 4-(4-methoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8 hexahydroquinoline-3-carboxylate in the presence of [2-Eim] HSO_4 under solvent-free conditions .

Catalyst (mol%)	Temp (^oC)	Time (min)	Yield[a] (%)
7.5	25	8	93

[a] Yields refer to the pure isolated products based on the reaction of 4-methoxybenzaldehyde (10 mmol), dimedone (10 mmol), ethyl acetoacetate (10 mmol) and ammonium acetate (10.3 mmol).

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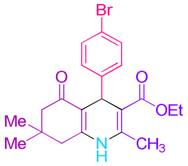
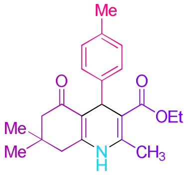
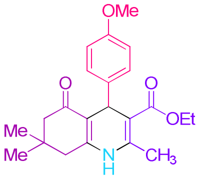
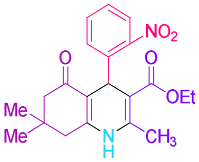
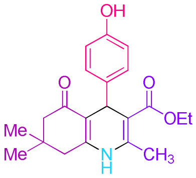
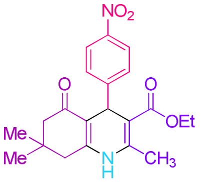
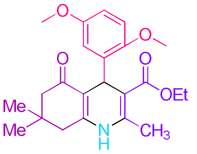
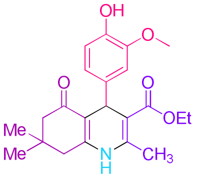
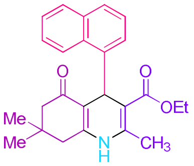
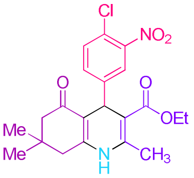
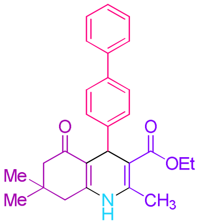
Further investigation shows that 7.5 mol% of catalyst at room temperature is optimum condition and the yield of products was excellent. To investigate the generality of present protocol, we also run the various aldehydes that were converted to hexahydroquinolines under the optimum condition (Table 2).

Table 2

Synthesis of ethyl 4-(aryl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate derivatives catalyzed by [2-Eim]HSO_4.

Entry	Product	Time (min)	Yield[a] (%)	M.P/M.P [ref](℃)
1		9	92	255–257/255–256[15]
2		9.5	91	263–265/262–264[22]
3		8	93	256–258/257–259[21]
4		8	94	204-206/205–207[22]
5		10	90	229–231/228–230[21]
6		9	93	242–244/242–244[21]
7		7	94	190-192/191-193[23]
8		7.5	95	206-208/205-206[22]
9		11	92	232-234/232–233[22]
10		10.5	91	218-220/(220)[24]
11		11	92	195-197/196-198[23]

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[a] Yields refer to the isolated pure products. The desired known pure products were characterized by comparison of their physical data (melting points, IR, ^1H NMR) with those of known compounds.

Considering the reaction mechanism (Scheme 3), it can be proposed that in the first step of reaction dimedone is converted to its enol form by using [2-Eim] HSO_4 and readily undergoes Knoevenagel condensation with benzaldehyde to generate a 2-

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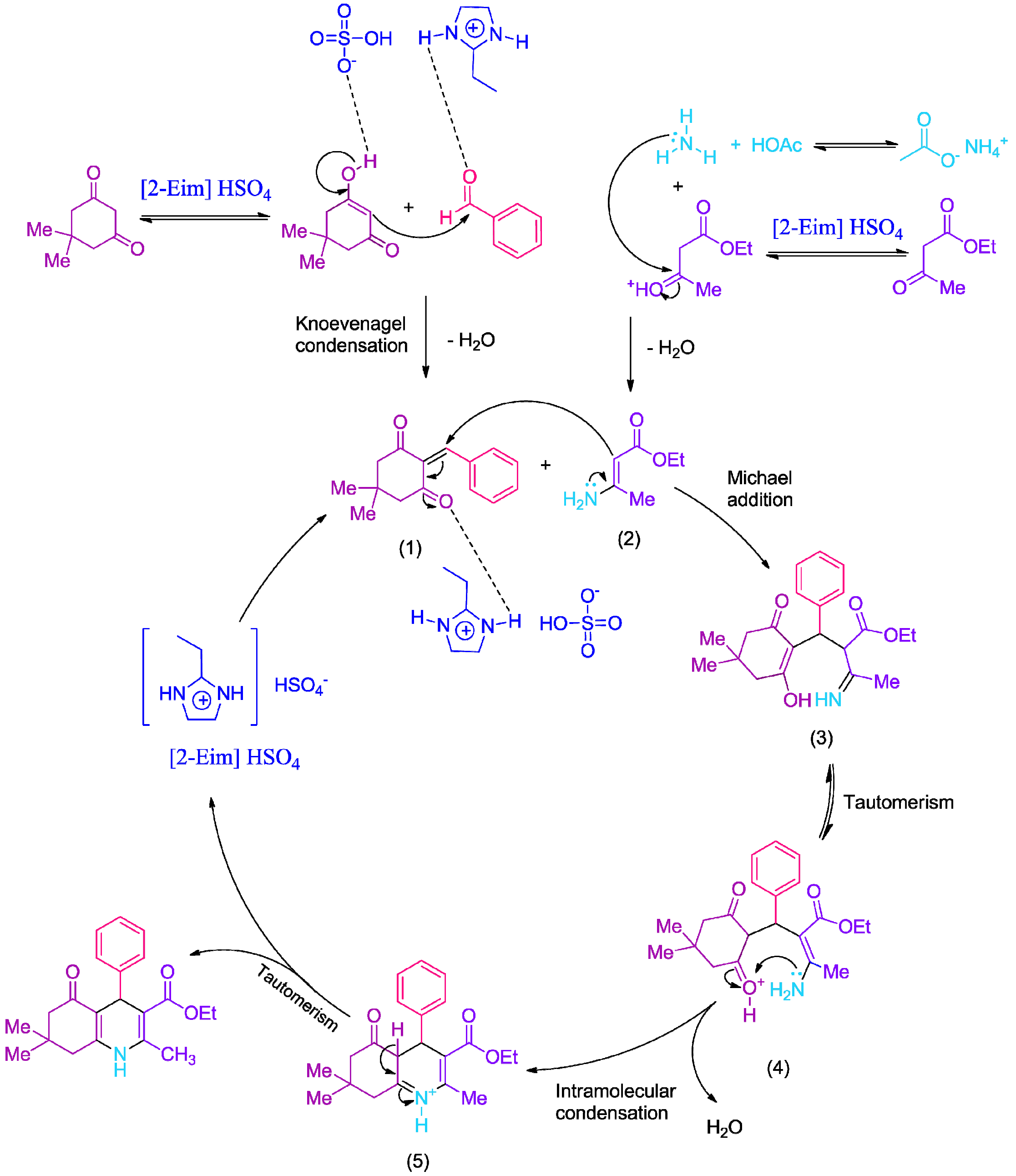
benzylidenedimedone (1). On the other hand, the activated β-ketoester (by the catalyst) with liberation of ammonia from NH_4OAc gives enamine (2). Afterward, the 2-benzylidenedimedone (1) and enamine (2) react together by michael addition to afford intermediate (3). The intermediate (3) is converted to intermediate (4) by tautomerization, and the intermediate (4) affords intermediate (5) by intramolecular nucleophilic attack of the NH_2 group to the activated carbonyl group. The obtained results relating of intermediates are agreement with those reported in the literatures. Thus our suggested mechanism was confirmed with experimental data and also by the literatures [15, 25-26].



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Scheme. 3. Plausible mechanism for the catalytic synthesis of ethyl 4-(phenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate derivatives catalyzed by [2-Eim] HSO_4.

2.1.8. Catalyst recycling. An important aspect of catalysts in large scale production is the recyclability and reusability of applied catalysts. In order to examine the recyclability of the [2-Eim] HSO_4, the reaction between 4-methoxybenzaldehyde, dimedone, ethyl acetoacetate, and ammonium acetate was chosen Fig. 10. For recycling experiment, the reaction was carried out in the same condition. At the end of the reaction, it was cooled to room temperature. Then, 3 mL of water was added to the mixture. The ionic liquid was dissolved in water, and filtered for separation of the crude product. The separated product was washed twice with water (2×3 mL). For recycling the catalysts, after washing the solid products with water completely, the water containing the ionic liquid (IL is soluble in water) was evaporated under reduced pressure and the ionic liquid was recovered and reused. The solid product was purified by recrystallization procedure in ethanol. All of the desired product(s) were characterized by comparison of their physical and spectral data (melting points, IR, ^1H NMR) with those of known compounds. [15, 27-28]

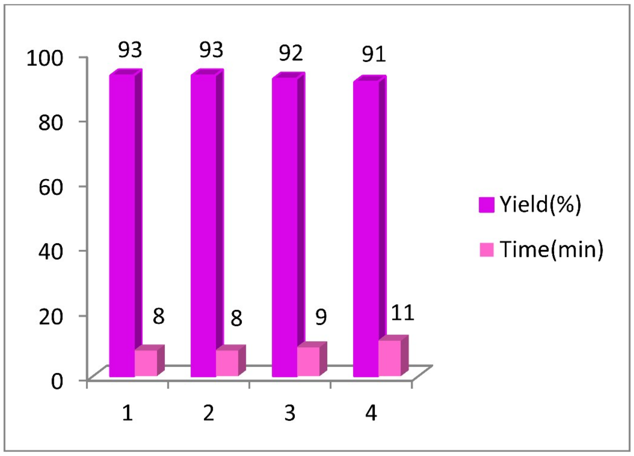

Fig. 10. The investigation of the reusability of the ionic liquid under solvent-free conditions using a model reaction of 4-methoxybenzaldehyde, dimedone, ethyl acetoacetate, and ammonium acetate in the presence of reused [2-Eim] HSO_4 as catalyst.

2.1.9. Effect of impurity of water on the catalytic activity of 2-ethyl imidazolium hydrogen sulfate

The ionic liquid is sensitive to moisture and water. To study effect of impurity of water on the catalyst activity, the condensation of 4-methoxybenzaldehyde (10 mmol), dimedone (10 mmol), ethyl acetoacetate (10 mmol) and ammonium acetate (10.3 mmol), using [2-Eim] HSO_4 (7.5 mol%) was examined in the presence of various amounts of H_2O at room temperature. (Table 3). As Table 3 indicates, 11 mmol of H_2O did not affect significantly on the catalytic activity of [2-Eim] HSO_4; however, more increasing the amount of H_2O decreased their activity. This can be attributed to partial protonation of water as H_3O^+ instead of substrates.

Table 3
Effect of impurities of water on the condensation of 4-methoxybenzaldehyde, dimedone, ethyl acetoacetate and ammonium acetate.

Entry	Water amount (mmol)	Time (min)	Yielda (%)
1	1	9	93
2	3	12	92
3	5	17	90
4	7	28	90
5	9	33	88
6	11	40	81

[a] Isolated Yield

2.1.10. Comparison catalyst synthesized with reported results in another literatures. In order to show the accessibility of the present work in comparison with reported results in the literatures, some of the results for the preparation of hexahydroquinolines were summarized in Table 4. The results show that [2-Eim] HSO_4 as catalyst is the most efficient catalysts with respect to the reaction time, low temperature, and exhibits broad applicability in terms of the obtained yields.

Table 4
comparison the results of 2-ethyl imidazolium hydrogen sulfate, [2-Eim] HSO_4 with other catalysts reported in the literature in the synthesis of ethyl 4-(4-methoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate

Entry	Catalyst	Amount of the catalyst	Conditions	Time (min)	Yield(%)[ref]
1	[2-Eim] HSO_4	7.5 mol%	Solvent-free , r.t	8	93(the present work)
2	[DSim]HSO_4	3 mol%	Solvent-free, 50 °C	32	91[27]
3	[Pyridine-SO_3H]Cl	3 mol%	solvent free, 50°C	10	95[29]
4	silica sulfuric acid (SSA)	0.20 mmol	solvent free, 60 °C or MW	30	94[30]
5	$HClO_4$-SiO_2	50 mg	Solvent-free, 50 °C	10	96[31]
6	$[(CH_2)_4SO_3HMIM][HSO_4]$	0.25 mmol	reflux, EtOH	55	93[32]
7	[Bsim]Cl	10 mol%	Solvent-free, 60 °C	8	92[33]

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8	nano-γ -Fe_2O_3-SO_3H	0.031gr	Solvent-free, 60 °C	90	93[34]
9	(MSAIm) HSO_4	3.8 mol%	Solvent-free, 50 °C,	22	89[35]
10	[MPIm][HSO_4]@SBA-15	2 mol%	H_2O, 45 °C	180	88[36]

3. Experimental

3.1. Materials

All chemicals were purchased from Merck or Fluka chemical companies. All yields refer to the isolated products. Products were characterized by their physical constants and comparison with authentic samples. The purity determination of the substrates and the reaction monitoring were accompanied by TLC using silica gel SIL G/UV 254 plates.

3.2. Instrumentation

Melting points were measured using a Galen Kamp melting point apparatus and are uncorrected. ^1H NMR spectra were recorded by Bruker Avance 400.22 using DMSO-d6 as the solvent and TMS as the internal standard. FT-IR spectra were recorded with PerkinElmer Spectrum Version 10.00.00. TG and DTA data were obtained by a PerkinElmer pyris diamond TG-DTA. UV–vis spectra were recorded by a Shimadzu UV-mini-1240V spectrophotometer.

3.3. Procedure for the preparation of ionic liquid [2-Eim] HSO_4

To a round-bottomed flask (100 mL) containing 2-ethyl imidazole (0.9613 g, 10mmol) in dry CH_2Cl_2 (50 mL), was added sulfuric acid (0.9808 g, 10mmol) dropwise over a period of 10 min at room temperature. After the addition was completed, the reaction mixture was stirred for 50 min, stand for 5min, and the CH_2Cl_2 was decanted. The residue was washed with dry CH_2Cl_2 (3×50 mL) and dried under vacuum to give [2-Eim] HSO_4 as pale yellow oil in 96% yield (1.866gr).

3.4. General procedure for the synthesis of hexahydroquinolines under solvent-free conditions

The mixture of the aldehydes (10 mmol), dimedone (10 mmol), ethyl acetoacetate (10 mmol), ammonium acetate (10.3 mmol) and [2-Eim] HSO_4 containing (7.5 mol%) as acidic ionic liquid catalyst was stirred at room temperature for the specific time. After completion of the reaction (monitored by TLC), 3 mL of water was added to the mixture. The ionic liquid was dissolved in water, and filtered for separation of the crude product. The separated product was washed twice with water (2×3 mL). For recycling the catalysts, after washing the solid products with water completely, the water containing the ionic liquid (IL is soluble in water) was evaporated under reduced pressure and the ionic liquid was recovered and reused. The solid product was purified by recrystallization procedure in ethanol.

Conclusions

In this research, Brønsted acidic ionic liquid [2-Eim] HSO_4 as a novel, highly efficient, general and homogeneous catalyst for the one-pot multi-component reaction between various aldehydes, dimedone, ethyl acetoacetate, and ammonium acetate leading to hexahydroquinolines. The synthesized catalyst showed excellent activity in the synthesis of various hexahydroquinolinein a green way. Also, optimization of the reaction condition was investigated using the response surface method {Central Composite Design (CCD)} which was in a good accordance with empirical research. In addition, catalyst was recycled four times without the significant loss of activity. In the view of green chemistry the present protocol could find industrial application.

Acknowledgements

The authors gratefully acknowledge partial support of this work by the University of Payame Noor (Grant No. 62370) and Bu-Ali Sina University.

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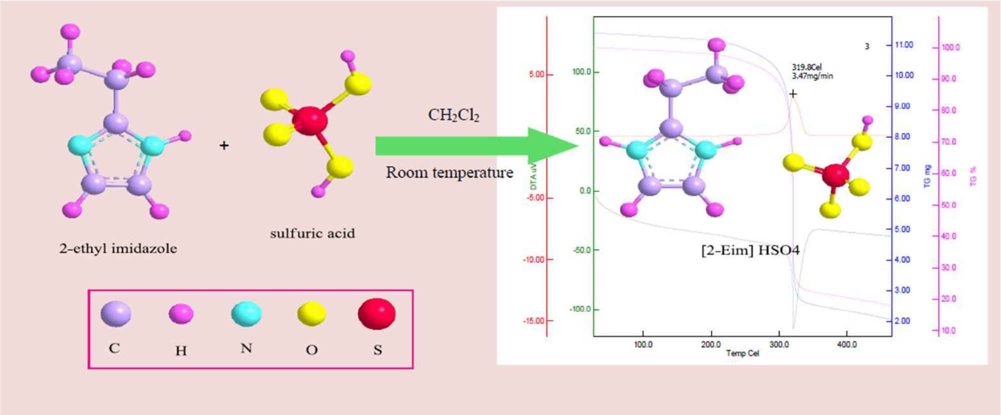

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