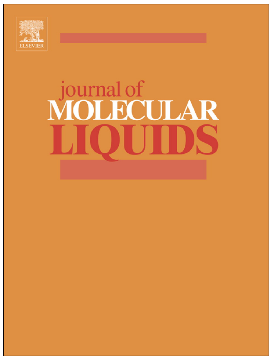

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PII: S0167-7322(18)30771-2
DOI: doi:10.1016/j.molliq.2018.04.121
Reference: MOLLIQ 9024

To appear in: *Journal of Molecular Liquids*

Received date: 11 February 2018
Revised date: 18 April 2018
Accepted date: 24 April 2018

Please cite this article as: Nan Yao, Ming Lu, Xiao Bing Liu, Jin Tan, Yu Lin Hu , Copper-doped mesoporous silica supported dual acidic ionic liquid as an efficient and cooperative reusability catalyst for Biginelli reaction. The address for the corresponding author was captured as affiliation for all authors. Please check if appropriate. Molliq(2017), doi:10.1016/j.molliq.2018.04.121

Copper-doped mesoporous silica supported dual acidic ionic liquid as an efficient and cooperative reusability catalyst for Biginelli reaction

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ABSTRACT

A series of MCM-41 supported functionalized ionic liquids doped with copper species were prepared, characterized and evaluated as catalysts in the Biginelli reaction. Most of these supported ionic liquids perform well in the reaction, especially the multifunctional copper coordinated MCM-41 supported heterogeneous catalysts (0.5)IL-$TiCl_5$@MCM-41@Cu(15) and (0.5)IL-HSO_4@MCM-41@Cu(15). The catalytic tests revealed that (0.5)IL-HSO_4@MCM-41@Cu(15) was the best and powerful catalyst in the Biginelli reaction for the preparation of 3,4-dihydropyrimidinones with high to excellent yields. The catalyst can be easily separated from the reaction mixture by filtration and reused in six consecutive cycles without significant loss in catalytic activity.

Keywords: Ionic liquid; Mesoporous silica; Biginelli reaction; Heterogeneous catalysis; Cooperative catalysis

1. Introduction

Biginelli reaction is one of the most important multi-component reactions (MCRs) due to a wide range of applications of the target products dihydropyrimidinones (DHPMs) in medicinal and pharmaceutical chemistry [1-4]. In general, the one pot condensation reaction of aldehyde, 1,3-dicarbonyls and urea can proceed under protonic or Lewis acidic conditions [5-7]. However, these traditional acid catalysts are not entirely satisfactory owning to the limitations of corrosive wastes, tedious work-up, and harsh reaction conditions. To overcome these restrictions, some representative catalysts used for Biginelli reaction have been developed, including Fe_3O_4@SBA-15 [8], nano-γ-Fe_2O_3-SO_3H [9], PAFMS-1 [10], nanoZnO [11], MOFs [12,13], TiO_2-SiO_2 [14], Zn^{2+}/MCM-41 [15], BFO-RGO [16], BPAT·TfOH [17], and others [18-23]. Most of these catalytic methodologies however still suffer from several shortcomings such as the use of expensive reagents, unsatisfactory activity, difficulties in work up, and environmental hazards. Consequently, there is an enormous demand for the development of efficient and eco-friendly catalytic systems for Biginelli reaction.

Ionic liquids (ILs), completely composed of ions, could be designed to possess a definite set of properties, and thus have wide applications in a variety of organic synthesis and catalytic reactions. Further, due to their low vapor pressure and non-flammable, ILs were assigned as a class of environmental materials [24]. Nowadays, examples of their applications as catalysts in Biginelli reaction were reported and demonstrated good catalytic activities [25,26]. Because of the difficulties associated with catalyst separation and recyclability, novel and efficient heterogeneous catalysts are still highly desirable. To overwhelm these shortcomings, many studies have reported the concept of immobilization of homogenous ILs on diverse solid support materials [27-32]. The immobilization process could transfer the desired property of ionic liquids to the carriers and convert the homogeneous catalysis into the heterogeneous catalysis, which would greatly reduce waste and pollution. In addition, these immobilized heterogeneous catalysts decrease the required amount of expensive ILs in the process, facilitate the separation of catalyst from the reaction media, and to realize the application of them in the continuous and commercial reactors [32]. Among the various solid support materials, mesoporous materials (e.g. MCM-41, SBA-15, etc.) have attracted increasing interests due to their large specific surface areas and pore sizes, high thermal and mechanical stabilities, and well-defined surface properties [31,32]. However, their weak surface acidity and hydrothermal stability limited their wide application in acid catalyst. Recently, some publications have reported that their acidic nature could be greatly improved by the incorporation of different metal oxides on the inactive mesoporous silica [33]. The concept of modified metal doping mesoporous molecular sieve by ionic liquid would combine the advantages of two materials, which would exhibit more outstanding catalytic performances. In this study, a serial of copper-doped mesoporous silica supported ionic liquids with different Brønsted and Lewis acid sites IL-anion@MCM-41@Cu are designed and prepared. The catalytic activities of the IL-anion@MCM-41@Cu are investigated in the Biginelli reaction. Moreover, the effect of reaction time, reaction temperature, dose of catalyst and other reactant parameters were systematically studied (Scheme 1). The aim of the present study is to explore a novel, simple operation, green and highly efficient catalytic system for the Biginelli reaction.

Scheme 1

2. Experimental

2.1. Preparation of catalysts IL-anion@MCM-41@Cu (Scheme 2)

Preparation of MCM-41: MCM-41 mesoporous compound was prepared according to the reported methods [33-35]. Typically, cetyltrimethylammonium bromide (CTAB, 5.5 g) was dissolved in 120 mL distilled water and the mixture was stirred to form a transparent solution. Then, to the resulting suspension were added ammonium hydroxide (25%, 60 mL) and tetraethylorthosilicate (TEOS, 25 mL), and the mixture was stirred for another 36 h at 40 ^oC and then transferred into a Teflon-lined autoclave and crystallized for 48 h at 100 ^oC. After cooling to room temperature, the product was filtered and washed with a large amount of distilled water, and dried at 60 ^oC for 24 h. The as-synthesized MCM-41 sample was obtained after calcined at 550 ^oC for 6 h.

Preparation of IL-anion@MCM-41: MCM-41 supported ILs were prepared according to published process [29-31]. Sodium ethoxide (0.5 mol) was dispersed in dry ethanol (500 mL) and imidazole (0.5 mol) was added to flask. Then, the mixture was stirred at 70 ^oC under N_2 atmosphere for 6 h to afford **1**. Subsequently, (3-chloropropyl) triethoxysilane (0.5 mol) was added and the resulting mixture was refluxed under N_2 atmosphere for 24 h. The reaction progress was monitored by HPLC. After completion of the reaction, the obtained mixture was filtrated and the filtrate was concentrated with rotary evaporation in vacuo. The residue was then purified by recrystallization from *n*-hexane and EtOAc (1:1) and dried at 50 °C under vacuum for 5 h to afford **2**. In a round bottom flask, **2** (0.4 mol) was dispersed in dry ethanol (200 mL), and 1,4-butane sultone (0.4 mol) was slowly added and the mixture was stirred at 80 °C for 12 h under N_2 atmosphere. The solvent was evaporated and the product was washed with dichloromethane (2 × 20 mL) and dried under vacuum at 40 °C to give **3**. Afterward, **3** (0.15 mol) was dispersed in dry ethanol (80 mL), and H_2SO_4 or HBF_4 or CF_3SO_3H or TsOH (0.15 mol) was added, and the mixture was stirred at 80 °C for 8 h to produce **4-1**. Meanwhile, **3** (0.15 mol), hydrochloric acid (0.15 mol), and ethanol (80 mL) were stirred at 80 °C for 8 h, then the solvent was evaporated, and $FeCl_3$ or $SnCl_4$ or $TiCl_4$ (0.15 mol) in dichloromethane (60 mL) were added and the mixture was refluxed for 24 h to produce **4-2**. (x)IL-anion@MCM-41 was synthesized according to the mass ratio of 1 g MCM-41: x g ILanion (**4-1** and

4-2). In a typical preparation process: x g of ILanion was added to dry ethanol (50 mL) at room temperature. Then 1 g of MCM-41 was added to the solution. Thereafter, the mixture was continuously refluxed for 24 h. Finally, the mixture was filtrated, and the resulting solid was washed with dichloromethane (3 × 10 mL) and dried at 50 °C under vacuum for 8 h to afford the supported ILs **5** (x)IL-anion@MCM-41.

Preparation of IL-anion@MCM-41@Cu: IL-anion@MCM-41@Cu nanocatalyst with different Cu contents were synthesized via an isovolumetric impregnation method [33,34]. Typically, 1 g of IL-anion@MCM-41 was dispersed in 20 mL distilled water and 10 mL copper dinitrate solution was added to the reaction vessel. The mixture was stirred for 24 h at room temperature and then at 80 °C for 10 h. After cooling to room temperature, the mixture was filtered and washed with distilled water, and dried under vacuum at 60 °C for 12 h. The resulting powder was denoted as **6** IL-anion@MCM-41@Cu(y), changing the concentration of copper dinitrate solution, a series of copper loading of the samples relative to MCM-41 (5, 10, 15, 20, wt.%) were explored. The catalysts were systematically characterized by FT-IR (Fig. S1), XRD (Fig. S2), UV-Vis (Fig. S3), SEM (Fig. S4), EDX (Fig. S5) and N_2 adsorption-desorption techniques (Fig. S6) as depicted in supporting information.

Scheme 2

2.2. Catalyst performance test

In a typical process, 0.05 mol aromatic aldehyde, 0.05 mol ethyl acetoacetate, 0.05 mol urea, 10 mL EtOH, and 0.5 g (0.5)IL-HSO_4@MCM-41@Cu(15) were mixed and stirred at 80 °C for the desired time. After the completion of the reaction, monitored by LC-MS, the solution was cooled down to room temperature and centrifugalized to obtain the catalyst. The catalyst was washed with ethanol for reuse. The filtrate was concentrated under reduced pressure to give the corresponding pure product. Fresh substrates were then recharged to the recovered catalyst and then recycled under identical reaction conditions. The products were identified by ^{1}H NMR, LC-MS and Elemental analysis, and the characterization data and spectras are provided in the supporting information.

3. Results and discussion

Catalytic activities of multifunctional supported ILs were assessed using Biginelli reactions. Initial experiments was using the reaction of benzaldehyde with ethyl acetoacetate and urea to screen of catalysts. The catalytic activities of MCM-41 supported ILs with various anions as well as the different content of ionic liquid were tested on the reaction (Table 1, entries 1-12). The results demonstrated that the anions of ILs had great effects on the catalytic activity. Among the anions, the catalytic activity showed the following order: $HSO_4^- > TiCl_5^- > TsO^- > BF_4^- > SnCl_5^- > CF_3SO_3^- > Cl^- > FeCl_4^-$ (Table 1, entries 1-8). Results showed that the supported IL with HSO_4^- as anion exhibited the highest reactivity (Table 1, entry 2). The high catalytic efficiency of IL-HSO_4@MCM-41 catalyst may be attributed to superior abilities of providing hydrogen proton, stabilizing and activating the substrates, which increases the portion of the active sites for the substrate molecules to react. Additionally, the effects of different content of ionic liquid were discussed (Table 1, entries 9-12). As presented, the reaction progress was strongly affected with the content of ionic liquid, the increase of ionic liquid could enhance the catalytic activity from the 41% benzaldehyde conversion over (0.2)IL-HSO_4@MCM-41 to 77% over (0.5)IL-HSO_4@MCM-41. Further increase in the content of ionic liquid had a slight effect on the reaction (Table 1, entries 9 and 10), probably owning to the limitation of thermodynamic equilibrium of reaction. For more investigation, it was noted that neither MCM-41 nor MCM-41 supported ILs demonstrated good catalytic activities, whilst the copper loaded MCM-41 supported ILs catalysts exhibited excellent catalytic activities (Table 1, entries 13-17). Compared with purely siliceous MCM-41, the presence of copper significantly promoted the catalytic activity of the reaction, which was resulted from the presence of active sites with loading of Cu on MCM-41. The increase of copper sites could enhance the catalytic activity from the 80% benzaldehyde conversion over (0.5)IL-HSO_4@MCM-41@Cu(5) to 92% over (0.5)IL-HSO_4@MCM-41@Cu(15). However, when Cu loading amount further increased to 20%, it did not improve the catalytic activity, which may be attributed to steric hindrance of overloaded copper species [32,33]. Besides these, a decrease in the catalytic activities were observed when common ILs and supports such as IL-$TiCl_5$, IL-HSO_4, MCM-41, (15)Cu@MCM-41 as the catalysts were used (Table 1, entries 18-21). These results indicate that a higher catalytic activity for the supported heterogeneous ILs (0.5)IL-$TiCl_5$@MCM-41@Cu(15) and (0.5)IL-HSO_4@MCM-41@Cu(15) were observed, and the activity of (0.5)IL-HSO_4@MCM-41@Cu(15) is slightly higher than that of (0.5)IL-$TiCl_5$@MCM-41@Cu(15). (0.5)IL-HSO_4@MCM-41@Cu(15) supported IL was the most suitable catalyst for the Biginelli reaction in terms of conversion and yield. The basic sites of this catalyst was sufficient for the reaction, which may be attributed to the synergistic effects of copper site of mesoporous silica carrier and the acidic sites of ILs.

Table 1

Some reaction parameters such as catalyst loading and solvent have an effect on the reaction. As seen in Fig. S7, when the reaction was performed in the absence of catalyst, no significant amount of product was produced. With increase of the catalyst loading from 0.2 to 0.5 g, there is a sharp increase of product yield from 46 to 90% in 2 h. When catalyst loading amount further increased to 0.6 g, it did not significantly improve reaction yield and conversion. Effect of solvents in reaction was also studied (Fig. S8). Reaction activities of (0.5)IL-HSO_4@MCM-41@Cu(15) in solvents of ethanol and water were found to be more than other solvents such as DMSO, DMF, CH_3CN and toluene. Attractively, in the absence of solvent, the reaction can also be performed, and an excellent yield 88% of desired product was obtained at 3 h.

The recyclability and stability of heterogeneous catalyst are very important characteristic properties for its industrial application. The reusability of the designed catalyst was investigated in the Biginelli reaction of benzaldehyde with ethyl acetoacetate and urea over (0.5)IL-HSO_4@MCM-41@Cu(15). In all cycles, after the completion of reaction, the catalyst was easily separated and recovered by simple filtration and washed with ethanol to remove unreacted substrates. Then the catalyst was dried under vacuum and subjected for the recyclability experiments under the optimized reaction conditions (Fig. 1). The study illustrated that the heterogeneous catalyst could be recovered and reused at least six times with no obvious decrease in catalytic activity, indicating its excellent stability and recyclability. TGA analysis was conducted to investigate the thermal stability of (0.5)IL-HSO_4@MCM-41@Cu(15) (Fig. S9), the small weight loss before 100 °C resulted from the loss of the adsorbed water onto sample surface. The significant weight loss of about 46 % at a temperature between 260 and 400 °C was due to the decomposition of the organic moieties. TGA profile clearly showed that the supported catalyst is thermally stable up to 260 °C, which is beneficial for the reusability experiments. The SEM image of catalyst after recycling confirmed that its microspheres displayed obviously unchangeable during the reaction (Fig. S4). Moreover, the FT-IR analysis of the reused catalyst after six times showed that the position of peaks did not show obvious change, which indicated that the catalyst is featured by a good structural durability in the reaction (Fig. S10). Besides, the XRD patterns of the reused catalyst after six times are similar with the fresh one (Fig. S11), which indicated that the crystalline structure has no changed of the composite before and after used during the reaction. In addition, the elemental analysis of the reused catalyst did not show obvious change in copper species, which indicated that the catalyst is highly stable and durable during the reaction, confirming leaching is negligible under this condition (Tables S1).

Fig. 1

Having the optimized reaction conditions in hand, the generality of the present protocol toward various aldehydes was examined, and the results are presented in Table 2. All terminal aldehydes including electron-deficient and electron-rich groups were smoothly and successfully converted and gave their corresponding products in good to excellent yields (Table 2, entries 1-13). It is worth noting that this novel heterogeneous catalytic system could tolerate a broad range of groups. However, aromatic aldehydes with electron-donating groups decreased the reaction rate, and slightly longer reaction times were needed to obtain excellent yields (Table 2, entries 2-7). In addition, other aldehydes such as 1-naphthaldehyde, 3-hydroxy-1-naphthaldehyde and nicotinaldehyde were also studied in the reaction, furnishing the expected products in good to excellent yields (Table 2, entries 14-16).

Table 2

On the basis of the above results and previously reported works [9,10,20,22], a possible catalytic mechanism for the Biginelli reaction is proposed in Scheme 3. Aldehyde is firstly activated by (0.5)IL-HSO_4@MCM-41@Cu(15) by coordination of Cu@MCM-41 with O atom, followed by nucleophilic addition of urea to form the condensation intermediate **I**. Meanwhile, the enoltautomerism of ethyl acetoacetate gives intermediate **II** and then reacted with **I** by intramolecular cyclodehydration to afford the intermediate **III** undergoes the nucleophilic addition and copper-oxygen coordination. The intermediate **III**, which finally regenerates the cooperative catalyst followed by dehydration to give the corresponding product.

Scheme 3

4. Conclusion

In summary, a type of novel bifunctional acidic ionic liquids were synthesized and successfully supported onto MCM-41 mesoporous materials. After copper (II) immobilization, the multifunctional copper doped MCM-41 supported ILs catalysts are really active in heterogeneous one-pot Biginelli reaction. The catalytic tests revealed that the two supported catalysts (0.5)IL-$TiCl_5$@MCM-41@Cu(15) and (0.5)IL-HSO_4@MCM-41@Cu(15) are significantly more active than other supported or unsupported catalysts, and (0.5)IL-HSO_4@MCM-41@Cu(15) displayed the best catalytic property in the condensation of various aldehydes bearing electron-donating or electron-withdrawing groups with ethyl acetoacetate and urea among various catalysts. The developed multifunctional cooperative catalyst could realize the synthesis of 3,4-dihydropyrimidinones under ambient conditions due to the synergetic effects involving acidic sites of ILs and the copper site of mesoporous silica carrier. And it was permissible for the Biginelli conversion with the perfect equimolar molar ratio of substrates. Also, this heterogeneous catalytic system can be easily separated from the reaction mixture and reused in six consecutive catalytic cycles without significant loss of its catalytic activity. Particularly, compared with the previous catalytic systems, the present catalytic system have several attractive features such as simple operation, high to excellent yields with good purity, short reaction times at moderate temperature, high catalytic activity, low loading of catalyst, environmentally benign and safe. The studies demonstrate that the well designed supported heterogeneous catalysts via cooperative catalysis of the supported carrier, anion sites of ILs is a promising platform for construction of novel and highly efficient catalytic transformation systems.

Acknowledgements

The authors are grateful to the National Natural Science Foundation of China (no. 21506115) for financial support of this research.

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Table 1

The catalytic reaction of benzaldehyde with ethyl acetoacetate and urea over different catalysts.[a]

Entry	Catalyst	Time (h)	Conversion (%)[b]	Yield (%)[c]
1	(0.5)IL-BF_4@MCM-41	8	70	65
2	(0.5)IL-HSO_4@MCM-41	6	77	73
3	(0.5)IL-TsO@MCM-41	6	72	67
4	(0.5)IL-CF_3SO_3@MCM-41	8	66	55
5	(0.5)IL-Cl@MCM-41	12	48	41
6	(0.5)IL-$FeCl_4$@MCM-41	10	50	33
7	(0.5)IL-$TiCl_5$@MCM-41	6	73	69
8	(0.5)IL-$SnCl_5$@MCM-41	10	65	58
9	(0.6)IL-$TiCl_5$@MCM-41	6	75	70
10	(0.6)IL-HSO_4@MCM-41	6	79	73
11	(0.4)IL-HSO_4@MCM-41	8	67	62
12	(0.2)IL-HSO_4@MCM-41	10	41	30
13	(0.5)IL-$TiCl_5$@MCM-41@Cu(15)	2	90	88
14	(0.5)IL-HSO_4@MCM-41@Cu(5)	3	80	77
15	(0.5)IL-HSO_4@MCM-41@Cu(10)	2	87	84
16	(0.5)IL-HSO_4@MCM-41@Cu(15)	2	92	90
17	(0.5)IL-HSO_4@MCM-41@Cu(20)	2	91	89
18	MCM-41	24	<10	<10
19	(15)Cu@MCM-41	6	56	48
20	IL-$TiCl_5$	3	74	65
21	IL-HSO_4	3	83	74

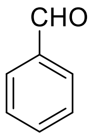
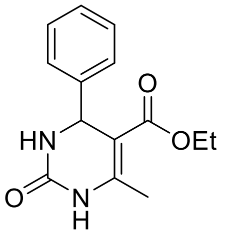
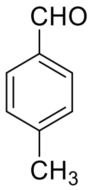
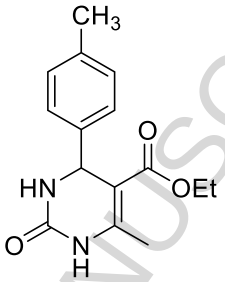
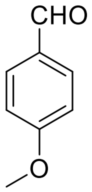
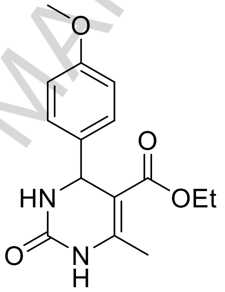
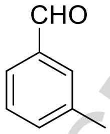
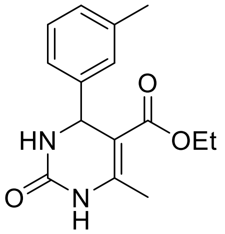
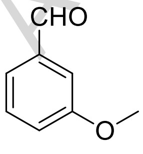
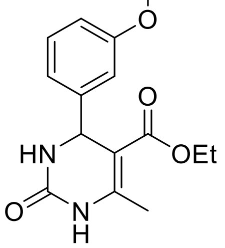
[a] The reactions were carried out with benzaldehyde (0.05 mol), ethyl acetoacetate (0.05 mol), urea (0.05 mol), catalyst (0.5 g), and EtOH (10 mL) at 80 °C.

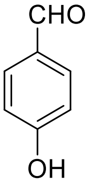
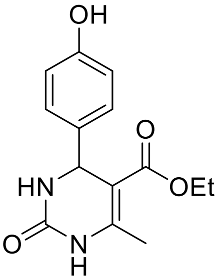
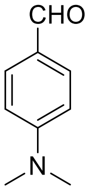
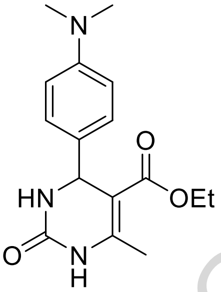
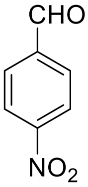
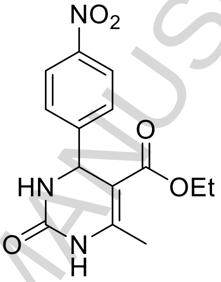
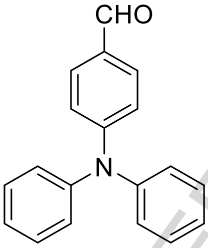
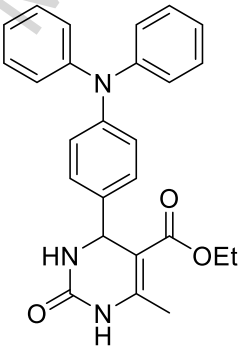
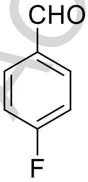
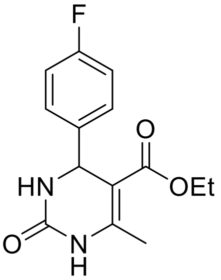
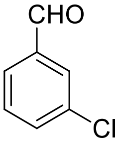
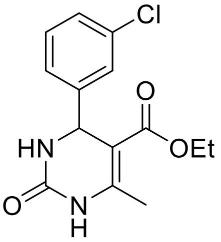
[b] Isolated conversion.

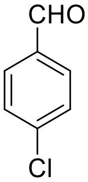
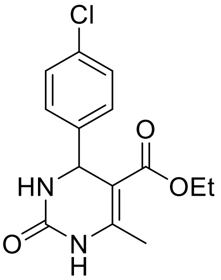
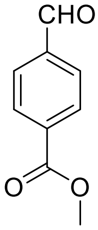
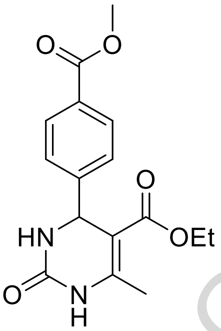
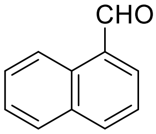
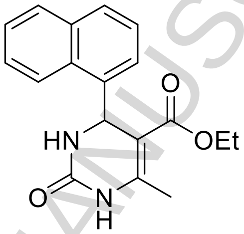
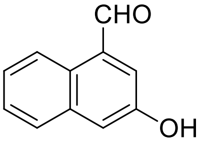
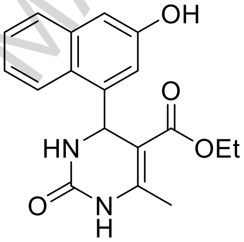
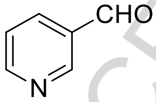
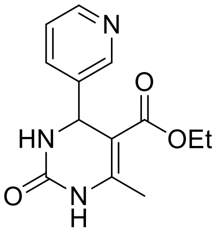
[c] Isolated yield.

Table 2

Catalytic performance of (0.5)IL-HSO_4@MCM-41@Cu(15) in the Beginelli reaction. [a]

Entry	Substrate	Product	Time (h)	Yield (%)[b]
1			2	90
2			2	94
3			2	96
4			2	93
5			2	95

6			2	91
7			2	92
8			1	97
9			1	94
10			1	98
11			1	97

12			1	98
13			1	99
14			1	97
15			1	96
16			2	92

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[a] Reaction conditions: aromatic aldehyde (0.05 mol), ethyl acetoacetate (0.05 mol), urea (0.05 mol), (0.5)IL-HSO_4@MCM-41@Cu(15) (0.5 g) were stirred in EtOH (10 mL) at 80 °C.

[b] Isolated yield.

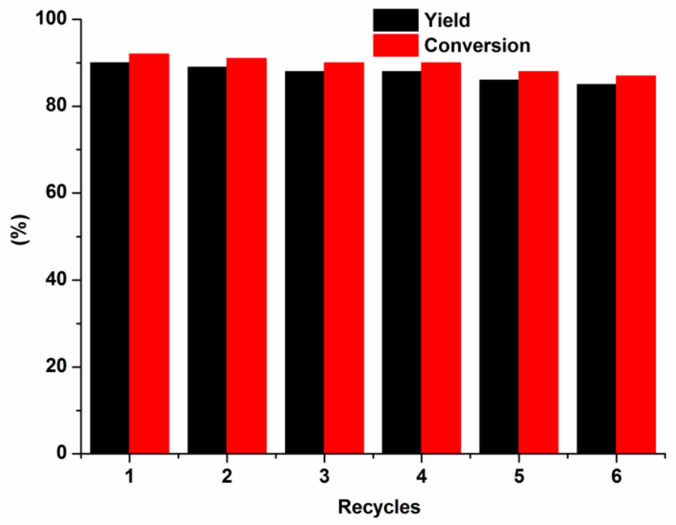
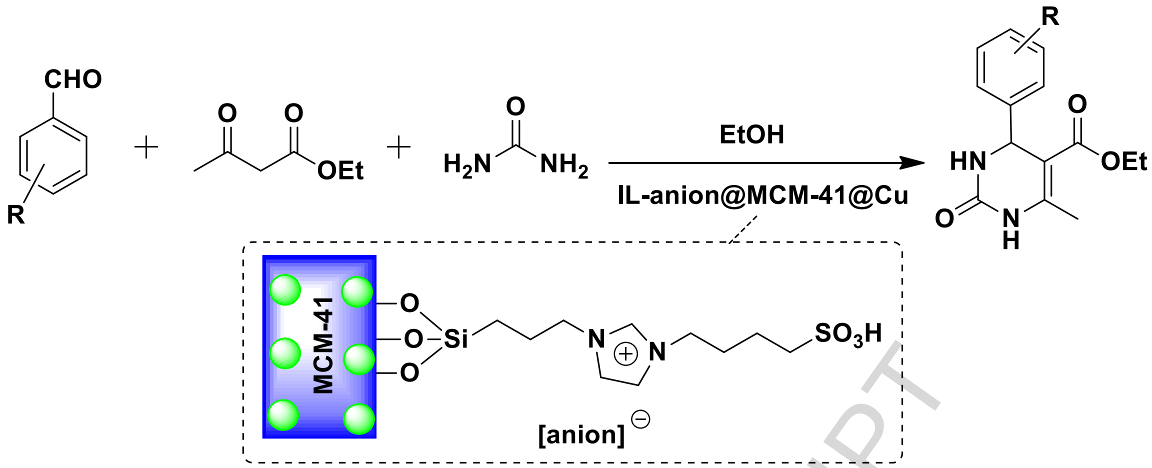
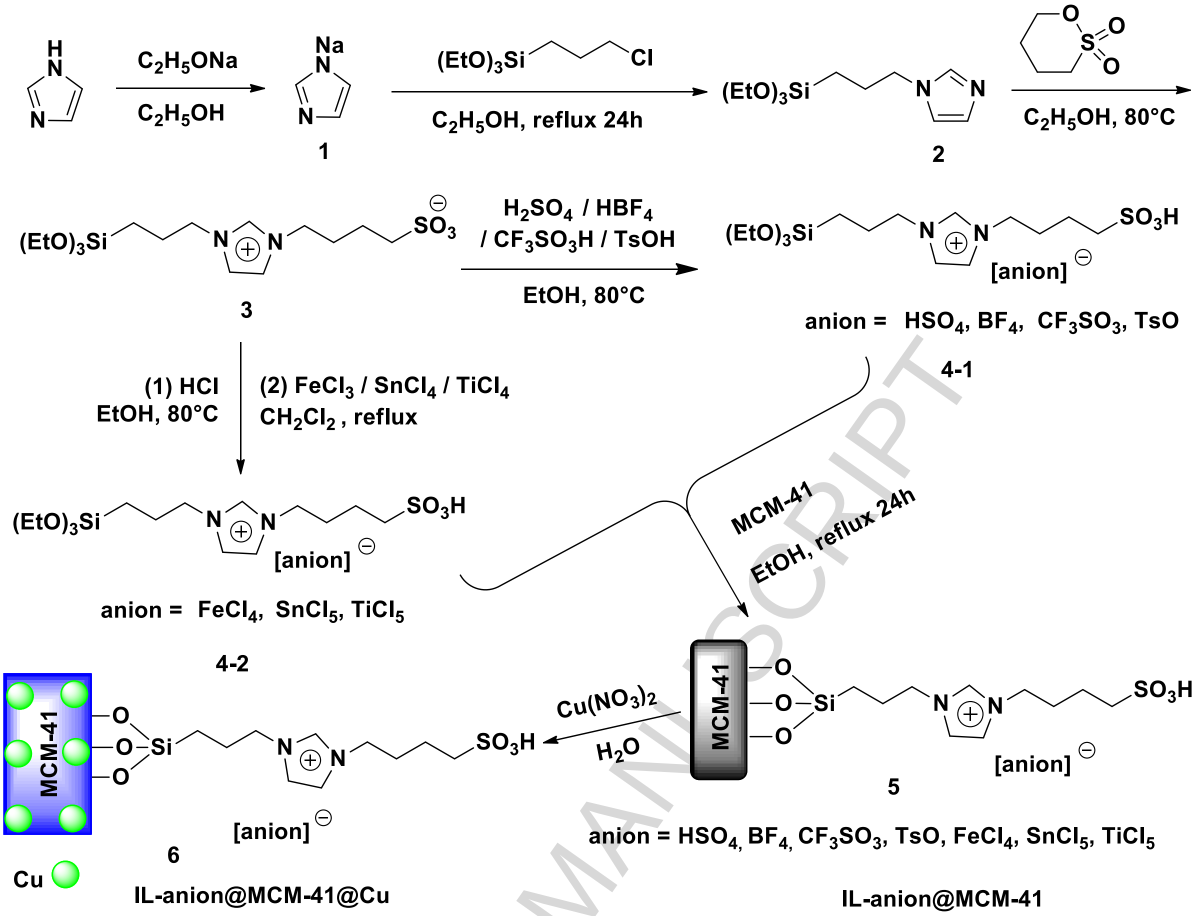


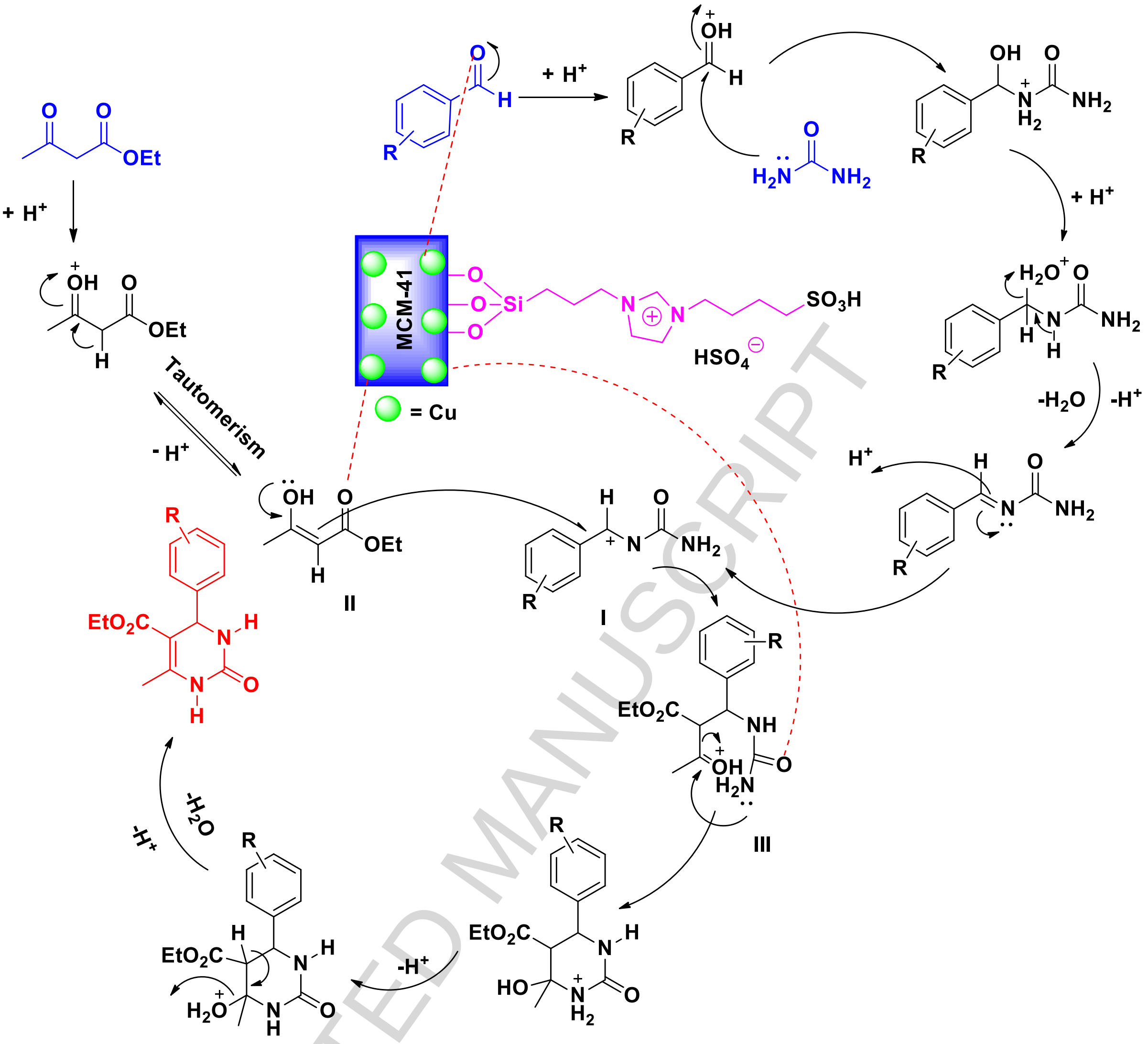
Fig. 1. Recyclability of the heterogeneous catalyst.



Scheme 1. Catalytic Biginelli reaction with IL-anion@MCM-41@Cu.



Scheme 2. Preparation of catalysts IL-anion@MCM-41@Cu.



Scheme 3. Possible mechanism for the Biginelli reaction.

Graphical Abstract

Copper--doped mesoporous silica supported dual acidic ionic liquid as an efficient and cooperative reusability catalyst for Biginelli reaction

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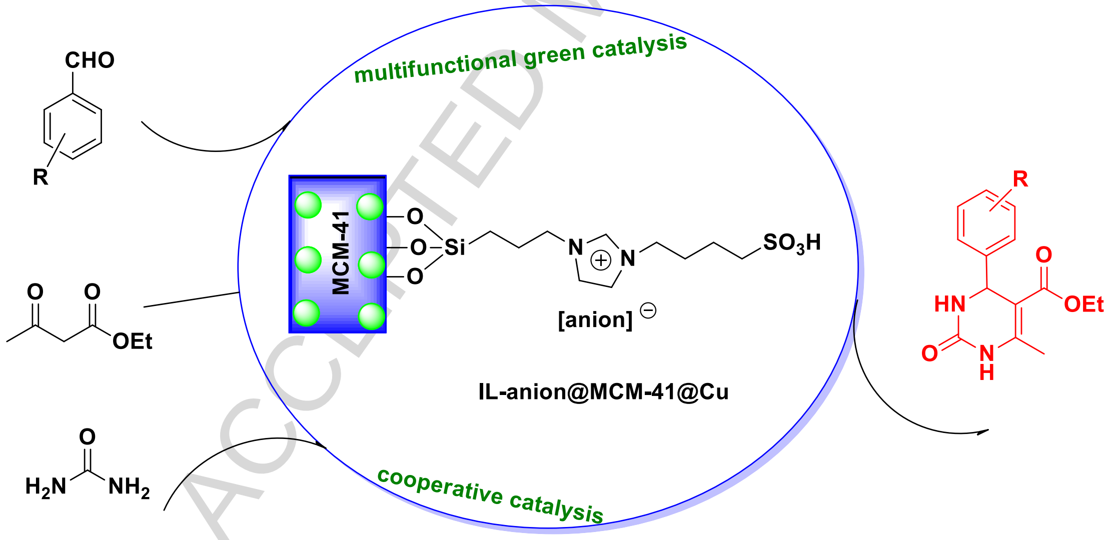
[b] College of Chemical Engineering, Nanjing University of Science and Technology, Nanjing 210094, P. R. China

[c] College of Chemistry and Chemical Engineering, Jinggangshan University, Ji'an 343009, P. R. China



Highlights

Copper--doped mesoporous silica supported dual acidic ionic liquids were prepared.

Catalytic activities of supported ionic liquids were tested in the Biginelli reaction.

The (0.5)IL-HSO_4@MCM-41@Cu(15) catalyst exhibited good catalytic performance.

The target products were produced in high to excellent yields.

The catalytic system take on favorable reusability.