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Modified MCM-41 materials as efficient and reusable catalysts for the synthesis of quinoxaline derivatives

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ABSTRACT

Ce(IV) ion and sulphate ion loaded MCM-41 materials effectively catalyze the condensation of 1,2-aromatic diamine with 1,2-diketones to afford quinoxaline derivatives under milder reaction conditions. Significant role of concentration of Ce(IV) ion has been investigated and comparative studies of catalytic efficiencies of both Ce-MCM-41 and sulfated MCM-41 have also been discussed. Both reagents are found to efficient and reusable with consistent catalytic activity.

1. Introduction

Research on the new protocols for the construction of quinoxaline rings, an important class of nitrogen containing heterocyclic compounds, reached important milestones in recent years due to their uses in the field of drugs and pharmaceuticals. They are also serving as very useful intermediates in organic synthesis [1,2]. Quinoxaline ring is a basic skeleton for the designing of a large number antibiotics such as echinomycin, actinomycin, leromycin, insecticides, fungicides and herbicides [3,4] as well as being important in human health as receptor antagonists. It has been reported that these compounds inhibit the growth of gram-positive bacteria, and are active against various transplantable tumors. They have found applications as dyes, efficient electron luminescent materials, organic semiconductors and DNA cleaving agents [5-10].

The most common method employed for the synthesis of quinoxaline derivatives is the condensation of an aryl-1,2-diamine with a 1,2-dicarbonyl compound in refluxing ethanol or in acetic acid [11-12]. Various other methods have been reported using homogeneous catalysts such as SA/MeOH [13], I_2 [14], $POCl_3$ [15], $CuSO_4.5H_2O$ [16] and CAN [17] etc. As further improvement, heterogeneous catalytic methods involving catalysts such as zeolites, ionic liquids [18], montmorillonite K-10 [19-20], Ni-nanoparticle [21] and MnO_2 have also been reported.

Most of the above methods suffer from the disadvantage of the work-up procedures and the catalysts could not be recovered after the reactions. In search of environmentally benign synthetic protocols using reusable heterogeneous catalysts for the synthesis of quinoxaline derivatives, we herein report the use of Ce(IV)-MCM-41 and sulfated MCM-41 as efficient catalysts for the synthesis of quinoxaline derivatives in high yields by the condensation of 1, 2-diamine with 1, 2- dicarbonyl compounds. To the best of our knowledge from the literature, there are no reports found using Ce(IV)-MCM-41 and sulfated MCM-41 as catalysts for the synthesis of the above said compounds.

2. Experimental Methods

2.1 General Method

All reagents employed in the study such as, CTAB, TEOS, *o*-phenylenediamine, substituted *o*-phenylenediamine, benzil and benzoin are commercially available and were purchased and used without further purification. Solvents were purified by standard procedures. ^{1}H NMR spectra were recorded on 400 MHz NMR Bruker spectrometer using $CDCl_3$ as solvent. Chemical shifts are given in ppm. IR spectra were recorded in Nicolet FT-IR spectrometer in the range 400-4000 cm^{-1}.

2.2. Catalyst preparation

2.2.1. Synthesis of MCM-41

The original method for the preparation of MCM-41 proposed by Beck and co-workers has been adopted. About 1.988 g of cetyl trimethyl ammonium bromide (CTAB, 98%) was dissolved in 120 ml of water at room temperature. After complete dissolution, 8 ml of aqueous ammonia (32% in water) was added to the above solution. Then 10 ml of tetraethyl orthosilicate (TEOS, 99%) was added to the solution with vigorous stirring (300 rpm). The hydrolysis of TEOS takes place during the first 2 min at room temperature (the solution becomes milky and slurry forms) whereas the condensation of the mesostructured hybrid material is achieved after 1 h of reaction. The material was then filtered and allowed to dry under static air at 80 °C for 12 h. The mesoporous material was finally obtained by calcination of the hybrid structure at 550 °C for 5 h.

2.2.2 Preparation of Ce(IV) loaded MCM-41

0.1 g of activated MCM-41 was added into the acetone solution of 0.38 g of ceric ammonium nitrate (CAN). The yellow colour mixture was slowly evaporated to dryness with stirring. The yellow colour solid has been warmed slightly to make it completely dry. Then the solid was calcined for about 1

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h to remove the nitrate ions (liberated as yellow fumes). After calcinations, the yellow colour powder was kept for activation in muffle furnace for 4hs yielding the catalyst with 30 mol percentage of ceric ions. Various concentrations of ceric ion such as 10%, 20%, 40% and 50% were loaded on MCM-41 employing the above method.

2.2.3 Synthesis of sulfated MCM-41

The sulfated MCM-41 sample was prepared by wet impregnation method [22,23]. The sulfate ion was impregnated in the form of H_2SO_4. About 1 g of the calcined sample of MCM-41 was treated with 4 ml of 0.25M H_2SO_4 at room temperature for 2 h and heated at 70 °C until complete dryness. The sample was dried at 110 °C for 10 h, in an oven and subsequently calcined at 550 °C for 5 h in a muffle furnace.

2.2.4 A. Preparation of Quinoxaline Derivatives using Ce-MCM-41

To a mixture of an appropriate *o*-phenylenediamine (1 mmol) and benzil/benzoin (1 mmol), a catalytic amount of Ce-MCM-41 (100 mg of 30 mol% Ce(IV) loaded MCM-41) was added and the mixture was heated at 55 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, the product was extracted with $CHCl_3$. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (eluted with 2:8 EtOAc:hexane). A variety of substituted *o*-phenylenediamines were condensed with either benzil or benzoin

B. Preparation of Quinoxaline using Sulfated MCM-41

To a mixture of an appropriate *o*-phenylenediamine (1 mmol) and benzil/benzoin (1mmol), a catalytic amount of sulfated MCM-41 (100mg) was added and the mixture was stirred at room temperature. The progress of the reaction was monitored by TLC.

After completion of the reaction, the product was extracted with EtOH. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (eluted with 2:8 EtOAc:hexane). A variety of substituted *o*-phenylenediamines were condensed with either benzil or benzoin

3. Results and Discussions

Our aim is to develop the new greener synthetic protocol for making quinoxaline derivatives. Initially, we started the model reaction of *o*-phenylenediamine with benzil at room temperature using MCM-41 as catalyst in both solvent slurry and solventless conditions. The yield of quinoxaline was only 30% in 12 h (Scheme 1).

To improve the yields of the product, same reaction was carried out in the presence of ceric ion loaded MCM-41 as catalyst. For optimization, we have prepared Ce ion loaded MCM-41 with various mol % of ceric ion such as 10%, 20%, 30% and 40%. Among these, 30 mol % of Ce ion loaded MCM-41 was found to be efficient to afford maximum yield of the product in 1 h (Table 1).

Table 1. Effect of Mol % of Ce ions

Entry	Mol % of Ce ion	Time (h)[a]
1	10%	8
2	20%	5
3	30%	1
4	40%	1

[a]Reaction completion time using various mol % of Ce-MCM-41 at 50-55 °C

To reduce the reaction time, we have planned to carry out the same reaction at moderate temperature and obtained excellent results while cyclocondensation of *o*-phenylenediamine with benzil was performed at 50-55 °C. To investigate the performance of this catalyst, we extended this protocol using various ketones and substituted diamines (Scheme 1 & Table 2)

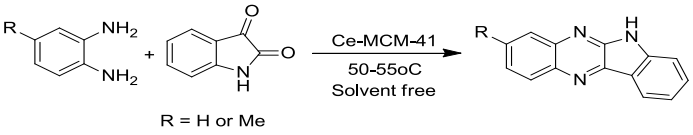
In table 2, cyclocondensation of *o*-phenylenediamine with benzil and benzoin afforded 87% and 85% of the product (entries 1&2), while the methyl substituted *o*-phenylenediamine afforded 82% and 85% of the substituted product (entries 3 & 4).

The reaction was also carried out with benzil and *o*-phenylenediamine in the presence of sulfated MCM-41 in slurry phase at room temperature for 2 h and the yield of the product was found to be 87% (Table 2).

Increase in the activity as well as selectivity was observed with increasing the sulfate amount which might be due to an increase in the number of Brønsted acid sites. The decrease in conversion at high sulfate loading was observed which probably due to formation of poly sulfate that decreased the number of Brønsted acid sites on the surfaces that are expected to play important roles in the condensation reaction. Among the different solvents tried to optimize the reaction conditions, alcoholic (EtOH) solvents seemed to be a better choice in terms of yields of the isolated products.

To investigate the suitability of the catalyst for this cyclocondensation reaction, this catalyst is compared with those reported previously. It is evident from the table 3 that, the performance of the Ceric ion loaded MCM-41 and the sulphated MCM-41 catalysts are better to other catalysts studied. With simple MCM-41 as catalyst, only 30% & 35% yield in both CH_2Cl_2 slurry and solvent free method were observed.

Similar studies were extended to a heterocylic ketone, namely, indoline-2,3-dione which also resulted in good yields of indolo-quinoxaline (Table 4).



R = H or Me

Scheme 2. Synthesis of Indolo-quinoxaline

As can be seen in Table 2, the protocol is efficient and all reactions are proceeded smoothly to provide the desired products with good to excellent yields in relatively shorter reaction times. In this study, the effect of electron-donating substituent on aryl 1, 2-diamines on the reaction was investigated. It was observed that electron-donating groups had no significant effect on the reaction results.

While examining these two catalysts, *viz.*, cerium loaded MCM-41 with Lewis acid sites and sulfated MCM-41 with Brønsted acid sites, it is observed that the synthesis of quinoxaline is not much varied by the two types of acidity.

Spectral data

2,3-Diphenylquinoxaline : mp 126-128 °C : ^{1}H-NMR δ: 7.36 (m,6H), 7.53 (m, 4H), 7.78 (m, 2H), 8.2 (d, 2H, J= 8.0 Hz);

6-Methyl-2,3-diphenylquinoxaline : mp 115-117 °C: ^{1}H-NMR δ:2.61 (s, 3H), 7.35 (m, 6H), 7.54 (m, 4H), 7.63 (d, 1H, J= 8.5 Hz), 8.07 (s, 1H), 8.14 (d, 1H, J= 8.5 Hz);

Scheme 1 Synthesis of Quinoxaline Derivatives

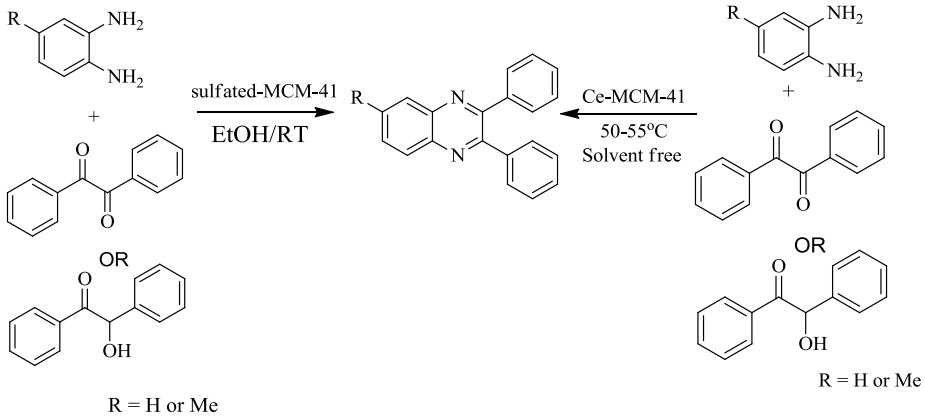
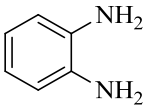
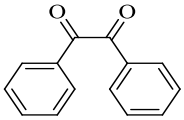
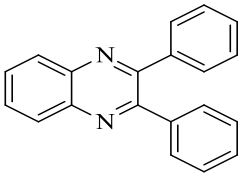
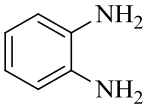
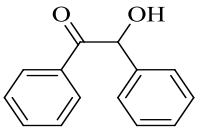
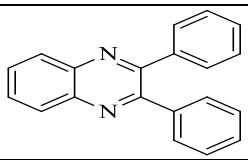
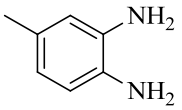
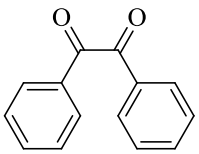
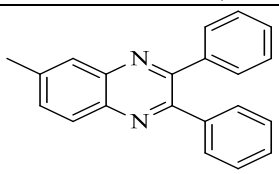
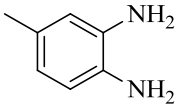
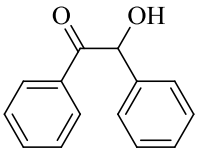
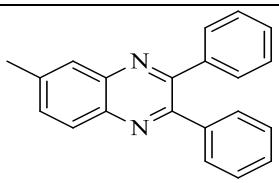


Table 2. Synthesis of Quinoxaline Derivatives

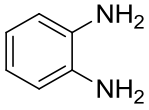
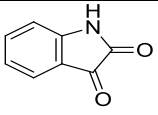
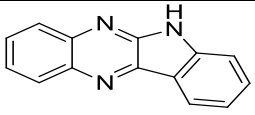
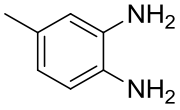
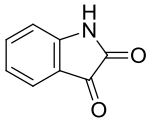
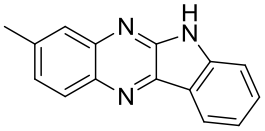
Entry	Diamine	Ketone	Product	Yield (%)[c]		M.p.(°C)
				A[a]	B[b]	
1				87	87	126–128
2				85	85	127–129
3				82	86	115–117
4				85	85	115-117

[a]Product was obtained using 30 mol % of Ce-MCM-41 at 50-55 ºC for 1 h; [c]Isolated yield
[b]Product was obtained using sulphated MCM-41 at RT/EtOH for 2 h; [c]Isolated yield

Table 3. Effects of different Catalysts on Condensation of *o*-Phenylenediamine with Benzil

Entry	Catalyst	Solvent	Time (h)	Yield (%)
1	Without catalyst	CH_3CN	12	20[25]
2	Zn[(L)proline]	CH_3CN	24	40[12]
3	Si-MCM-41	CH_3CN	12	25[25]
4	17% ZrO_2/MCM-41	CH_3CN	2	57[25]
5	[TMPSA]. HSO_4	C_6H_6	0.25	43[18]
6	Cellulose sulfuric acid(0.01 g)	CH_3CN	3	60[24]
7	MCM-41	CH_2Cl_2	12	30
8	MCM-41	Solvent free	10	35
9	Ce-MCM-41	Solvent free	1	80
10	SO^{-2}_4-MCM-41	EtOH	2	87

Table 4. Synthesis of 6*H*-Indolo[2,3-b]quinoxaline

Entry	Diamine	Ketone	Product	Yield %
1				75
2				70

[a]Product was obtained using 30 mol % of Ce-MCM-41 at 50-55 ºC for 1 h; [b]Isolated yield

Reusability of the Catalyst

The feasibility of reusability of the catalyst was also examined for the cyclocondensation of *o*-phenylenediamine with benzil as model reaction with 30% of Ce ion loaded on MCM-41 under solvent-free conditions for seven consecutive cycles. Each time after use, the catalyst was separated by extracting the product with chloroform. The reaction proceeded smoothly indicating that the catalyst can be effectively reused. The reusability of sulphated MCM-41 was observed for about four consecutive cycles with out appreciable loss in activity.

Conclusion

We described a simple, efficient, and ecofriendly synthetic protocol for the cyclocondensation of *o*-phenylenediamine, methyl substituted *o*-phenylenediamine with benzil, benzoin and isatin using Ce-MCM-41and sulfated MCM-41 as catalysts. These catalysts performed well even under milder conditions and after completion, these catalysts were recovered and reused by extracting the product with choloroform.

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