

## Solvent-free single-step synthesis of coumarins using heterogeneous recyclable FeCl<sub>3</sub>/MCM41 catalyst

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### Abstract

A highly efficient, solvent-free and versatile greener protocol was developed for the synthesis of coumarins from resorcinol and ethyl acetoacetate via Pechmann condensation using heterogeneous recyclable FeCl<sub>3</sub>/MCM41 catalyst. This method is simple, cost effective, and benefits from the elimination of waste streams generated with conventional acid catalysts. The influence of catalyst calcination temperature as well as various solvent on conversion and product selectivity has also been studied in this work. The developed FeCl<sub>3</sub>/MCM41 catalysts showed excellent catalytic performance with 60-75% yields for coumarins, depending on the catalyst pretreatment and reaction conditions used. Moreover, FeCl<sub>3</sub>/MCM41 catalyst treated at 400 °C can be reused efficiently for five times without a significant loss of its activity, which was attributed to synergistic effects of metal-support interactions, especially unique acid-redox properties of FeCl<sub>3</sub>.

**Keywords:** Coumarin synthesis, Greener protocol, Solvent-free, FeCl<sub>3</sub>/MCM41 catalyst, Physico-chemical properties.

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### I. Introduction

The synthesis of coumarin and its derivatives have attracted great interest because of their importance in the synthetic organic and medicinal chemistry. They are widely used as additives in perfumes, agrochemicals, food, cosmetics and pharmaceuticals as well as in the production of insecticides, optical brightening agents, dispersed fluorescent and tunable laser dyes [1]. Moreover, coumarin and its derivatives have various bioactivities such as anti-cancer [2], anti-inflammatory [3], anti-pyretic, anti-biotic [4], and also reported for exhibiting photochemical properties [5]. Coumarins can be synthesized by various methods such as Pechmann [6], Perkins [7], Knoevenagel [8], Reformatsky [9] and Wittig reaction [10] by using acid as well as basic catalysts. However, the conventional method for coumarin synthesis often requires harsh reaction conditions and expensive reagents. The recent studies reported that several acid catalysts such as, polyphosphoric acid (PPA) [11], InCl<sub>3</sub> [12], ZrCl<sub>4</sub> [13], Yb(OTf)<sub>3</sub> [14], p-TsOH [15], BiCl<sub>3</sub> [16], AgOTf [17], Sm(NO<sub>3</sub>)<sub>3</sub> [18] as well as chloroaluminate ionic liquids [19-20] show good yields of coumarins. However, most of these acid-catalyzed methods suffer from severe drawbacks including the use of stoichiometric amounts of the catalysts, large amounts of solvents, and often high temperatures to the extent of 150 °C. Another key concern of above catalytic-based protocols is inefficient catalyst recovery and hence, poor catalyst reusability for the next cycle. These results show the need for the development of safe, eco-friendly, and efficient reusable catalysts for the synthesis of coumarins. The use of heterogeneous solid acid catalysts would provide safer operating conditions; ease of product work up, reduction in equipment corrosion and minimization of waste production and above all, the solid catalysts can be recovered and reused efficiently. Therefore, it is of both scientific and practical interest to develop an environmentally benign moisture-insensitive catalyst which shows high catalytic activity under mild reaction conditions. In this communication, we report a simple, effective and greener protocol for coumarin synthesis from resorcinol with ethyl acetoacetate using FeCl<sub>3</sub>/MCM41 as solid acid catalyst (Scheme 1). The catalyst is ligand-free and showed high catalytic activity for coumarin synthesis. It can be easily separated from the reaction mixture by filtration and reused several times without much loss of its activity. To achieve high product yield, we first studied the influence of catalyst parameters (viz. FeCl<sub>3</sub> loading and catalyst pretreatment temperature) and the use of different solvents in coumarin synthesis between ethyl acetoacetate and resorcinol.

## II. Experimental

### 2.1 Synthesis of MCM-41 supported FeCl<sub>3</sub> catalysts

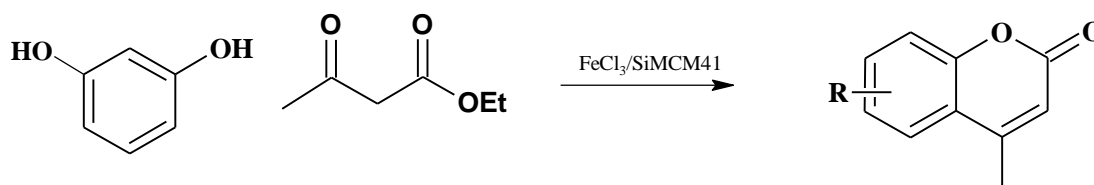
The mesoporous support Si-MCM-41 was synthesized using the surfactant template condensation of silica precursor by employing a modified method that was reported earlier [21-24]. To 160g of water, 3.5g of cetyltrimethyl ammonium bromide (CTAB) was added and the solution was kept under constant stirring to ensure dissolution of CTAB. The pH of the solution was slowly increased and maintained by drop-wise addition of tetramethyl ammonium hydroxide. To this solution, silica precursor, tetraethylorthosilicate (TEOS, 16g) was added and followed by the addition of 30 g of water. This solution was kept at 45 °C and allowed to stir for three hours. Subsequently, this colloidal mixture was transferred into a polypropylene bottle, which was tightly sealed and aged at 110 °C for 48 hours. The resulted material was firstly air dried and calcined at 540 °C in a muffle furnace for six hours, to completely remove the CTAB surfactant template. The obtained Si-MCM-41 was used as support without any other modifications. 48mg (3mmol) of anhydrous FeCl<sub>3</sub> was dissolved in 20 mL of acetonitrile and added drop-wise to 3g of MCM-41 support. This mixture was heated slowly to evaporate acetonitrile and the material dried at 100 °C for overnight, followed by washing the material with hexane few times. This dried FeCl<sub>3</sub>/MCM-41 was divided into five equal parts and each part was dried at 100 °C, 300 °C, 400 °C, 500 °C and 600 °C in a furnace for the period for two hours and used as catalysts without any further modification.

### 2.2 Catalyst characterization

Powder X-ray diffraction of all these materials was carried out using Bruker D8 Advance X-ray diffractometer. Small angle X-ray scattering (SAXS) patterns of these catalysts were studied using a Bruker NanoStar SAXS instrument. Nitrogen adsorption/ desorption isotherms and BET surface area were acquired at liquid nitrogen temperature on a Micromeritics ASAP 2010 instrument. XPS data of these catalyst materials were collected using a Thermo K-Alpha XPS instrument and the core-level spectral were aligned with adventitious C 1s binding energy of 285 eV. Solid state <sup>29</sup>Si NMR studies of these materials were carried out on Agilent/Varian 500 MHz DD2 spectrometers. The catalysts were also characterized for their Fe metal loading by ICP-OES technique using an Agilent 5100 instrument.

### 2.3 Catalyst testing activity

In order to optimize the catalyst parameters and reaction conditions to achieve high product yield, we first studied the influence of catalyst parameters (viz. FeCl<sub>3</sub> loading on MCM41 and catalyst pretreatment temperature) and the use of different solvents on the catalyst performance in the coumarin synthesis reaction between ethyl acetoacetate and resorcinol. All the thermally activated FeCl<sub>3</sub>/MCM-41 catalysts were screened for their activity towards production of coumarin (Scheme 1).



**Scheme 1:** Synthesis of coumarin catalysed by FeCl<sub>3</sub>/MCM41 under solvent-free conditions

A mixture consisting of 2 mmol resorcinol, 2.5 mmol ethyl acetoacetate and catalyst (300 mg) was stirred at 100 °C and the reaction was monitored using thin layer chromatography (TLC). After completion, the reaction mixture was cooled to room temperature and the catalyst was separated from the reaction mixture. The reaction mixture was treated with water followed by the extraction of organic compounds with ethyl acetate to get the crude product, which was subsequently purified by column chromatography on a silica gel column, using petroleum ether/ethyl acetate as an eluent. The reaction product was isolated by the column chromatography. The catalyst was further washed with acetone, dried and reused. All of the products are known and were confirmed from their NMR and by comparison with those reported in the literature.

## III. Results and discussion

The synthesis of 4-methylcoumarin between resorcinol and ethyl acetoacetate was studied over FeCl<sub>3</sub>/MCM-41 catalysts, thermally activated at 100 °C, 200 °C, 300 °C, 400 °C, 500 °C and 600 °C temperatures. The reaction was carried out without any solvent for the period of 1-10 hours and the reaction bath temperature was maintained at 100 °C. The catalytic activities of the afore-mentioned catalysts along with the activity of MCM-41 and without any catalyst are presented in Table 1. The product

4-methyl coumarin yield was found to increase continuously with the increase in activation temperature and the yield was maximum in case of FeCl<sub>3</sub>/MCM-41 activated at 400 °C (75%). However, the product yield was found to decrease when the catalysts was thermally activated at 500 °C (65%) and 600 °C (60%). The results in Table 1 show a strong influence of the calcination temperature of the catalysts on 4-methylcoumarin yield. In contrast, lower yield of 4-methylcoumarin was obtained with pure MCM-41(19%) and under blank conditions (10%). This indicates the importance of FeCl<sub>3</sub>/MCM-41 catalyst for 4-methylcoumarin synthesis.

**Table 1:** Comparison of the MCM-41 supported FeCl<sub>3</sub> catalysts pretreated at different temperature for its performance in coumarin synthesis [Reaction conditions: resorcinol (2 mmol) + ethyl acetoacetate, (2.5 mmol) + catalyst (300mg), bath temperature = 100 °C, reaction time 10h]

No	Catalyst	Calcination temperature (°C)	Yield %
1	MCM-41	550	19
2	FeCl <sub>3</sub> /MCM-41	100	40
3	FeCl <sub>3</sub> /MCM-41	300	64
4	FeCl <sub>3</sub> /MCM-41	400	75
5	FeCl <sub>3</sub> /MCM-41	500	65
6	FeCl <sub>3</sub> /MCM-41	600	60
7	Without catalyst	---	10

The increase in the yield was partially attributed to the fact that presence of FeCl<sub>3</sub> and its Lewis acidity responsible for catalyzing the reaction. ICP-OES analysis of the reaction mixture didn't show any traces of iron, which clearly ruled out the possibility of iron leaching during the reaction. It is interesting that thermal activation of same catalyst at different temperature played a critical role on product yield in the reaction. This was probably due to the interaction between FeCl<sub>3</sub> and MCM-41 support, which must be different when the catalyst was activated at different temperatures because all the other factors were the same other than the activation temperature. In general, metal halides are volatile in nature; therefore thermal activation at higher temperatures may lead to loss of chlorides. Another reason may be the condensation reaction between surface silanol groups and FeCl<sub>3</sub>, which result in the loss of HCl and form the Si-O-Fe-Cl<sub>x</sub> species. The formation of such species was confirmed in our previous work by Perkin-Elmer hyphenated system (Thermo-gravimetric analysis) TGA-FTIR(Fourier Transform Infrared spectroscopy)-GCMS(Gas Chromatography/Mass Spectrometer instrument) technique [21-24]. At high temperatures, the multiple condensations are known to occur as well as loss of the halides resulting in decreased acidity. Therefore, the catalyst screening clearly showed that FeCl<sub>3</sub>/MCM-41 thermally activated at 400 °C was found to be an efficient catalyst.

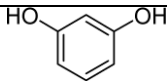
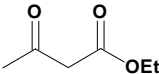
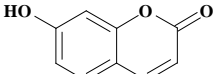
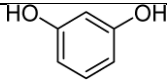
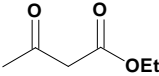
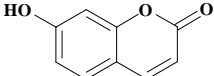
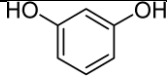
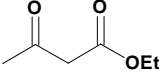
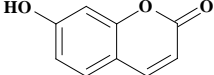
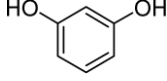
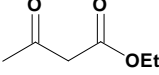
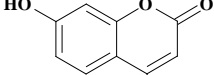
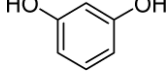
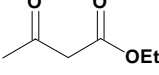
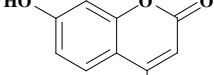
**Table 2:** Performance of FeCl<sub>3</sub>/MCM41 catalyst (calcined at 400 °C) in coumarin synthesis with different solvents, [Reaction conditions: resorcinol (2 mmol) + ethyl acetoacetate, (2.5 mmol) + catalyst (300mg), bath temperature = 100 °C, reaction time 10h]

Entry	Solvent used	Reaction time (h)	Product yield (%)
1	Toluene	10	60
2	Ethanol	10	20
3	Water	10	30
4	without solvent	10	75

The dissolution of the reactants in a solvent may influence the product yield. Therefore, to investigate the effect of different solvents on the product yield, the reaction between resorcinol and ethyl acetoacetate was performed using different solvents such as toluene, methanol, water and the results are presented in Table 2. According to the results, FeCl<sub>3</sub>/MCM41 catalyst treated at 400 °C showed higher activity under solvent-free conditions. Aromatic solvent like toluene competitively adsorb along with phenols, while protic solvents like methanol and water protonate the catalyst surface and thereby blocking part of the active sites of the catalyst, and hence lower product yields were obtained when the reaction performed under solvent conditions (Table 2).

Catalytic Results obtained under different conditions were presented in Table 3. Thermal activation of FeCl<sub>3</sub>/MCM-41 at 400 °C could form an active acid site, which may be one of the reasons for such high product yield (Table 3, entry 1). When FeCl<sub>3</sub>/MCM41 was directly used as a catalyst, the product yield in the same period was much smaller (Table 3, entry 3). This may be due to the formation of solid catalyst with non-uniform distribution of Fe(III) within mesoporous channels of MCM41. It is interesting to note that, even in the absence of catalyst the reaction occurs but a much lower product yield was obtained (Table 3, entry 5). In order to test the catalyst reusability, the catalyst (after the reaction) was removed from the reaction mixture by filtration, washed with acetone, dried and then reused in the reaction at 100 °C. The catalyst showed excellent reusability and about 73% product yield was obtained after 5<sup>th</sup> recycle (Table 3, entry 2). The high catalytic performance of FeCl<sub>3</sub>/MCM-41 calcined at 400 °C can be explained by synergistic metal-support interactions, Lewis acidic FeCl<sub>3</sub> species as well as high BET surface area of MCM-41 support.

**Table 3:** Performance of FeCl<sub>3</sub>/MCM41 catalyst in coumarin synthesis, [Reaction conditions: resorcinol (2 mmol) + ethyl acetoacetate (2.5 mmol) + catalyst (300mg), bath temperature = 100 °C, reaction time 10h].

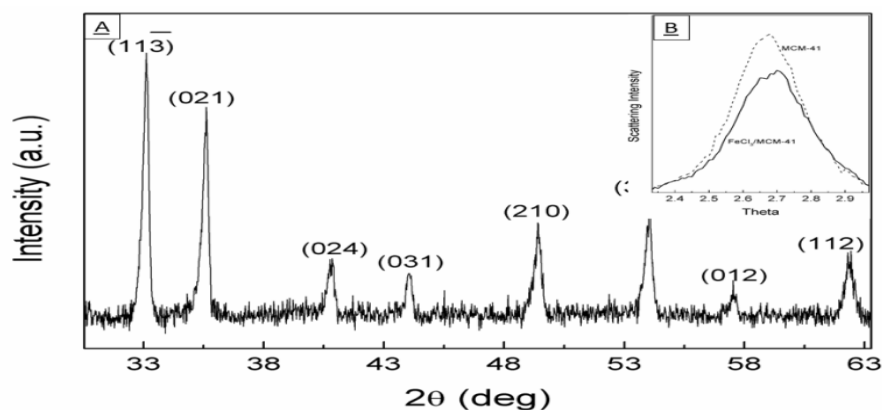
Entry	Phenols	β-Ketoester	Product	Isolated Yield (%)
1				75
2				70 <sup>a</sup>
3				40 <sup>b</sup>
4				60 <sup>c</sup>
5				10 <sup>d</sup>

<sup>a</sup> Fifth reuse of the catalyst, <sup>b</sup> without decomposition was used,

<sup>c</sup> amount used was equivalent to that used in the supported metal chloride catalyst,

<sup>d</sup> without catalyst

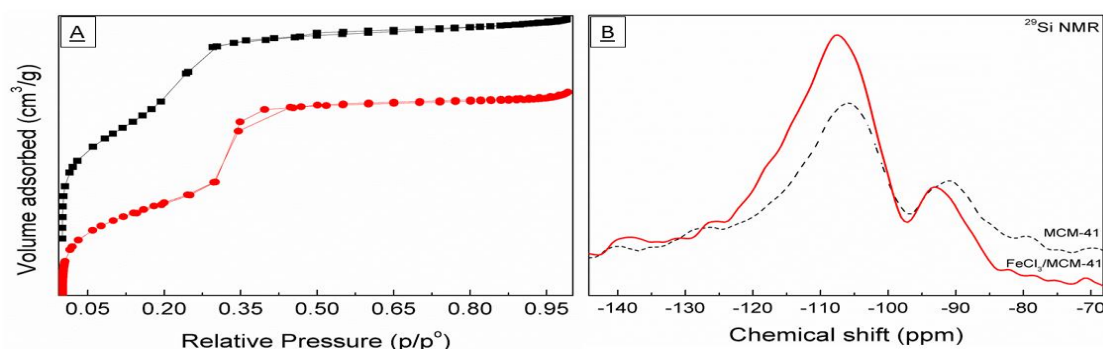
To study the structural changes of FeCl<sub>3</sub> impregnated on MCM-41, followed by thermal activation, XRD patterns of FeCl<sub>3</sub>/MCM-41 thermally activated at 400 °C and SAXS patterns of both MCM-41 and FeCl<sub>3</sub>/MCM-41 thermally activated at 400 °C were collected and shown in Figure 1 A and B, respectively. Figure 1A shows the powder XRD patterns of the FeCl<sub>3</sub>/MCM-41 after thermal activation at 400 °C to identify any crystalline phase formation during calcination. MCM-41 does not exhibit any sharp diffraction patterns due to its amorphous nature. However, FeCl<sub>3</sub>/MCM-41 after thermal activation, exhibits strong X-ray reflections, which were assigned to the poly-crystalline phases of FeCl<sub>3</sub> [PDF # 78-2123] as well as Fe-OCl [PDF # 76-2300, PDF # 01-0081]. As state earlier, these new crystalline phases was probably due to the thermal condensation of FeCl<sub>3</sub> and surface silanol groups leading to the formation of crystalline oxy-chloride species and loss of HCl molecules.



**Figure 1:** (A) Powder XRD patterns of FeCl<sub>3</sub>/MCM-41 thermally activated at 400 °C (B) SAXS profile of MCM-41(dotted), FeCl<sub>3</sub>/MCM-41 thermally activated at 400 °C (solid)

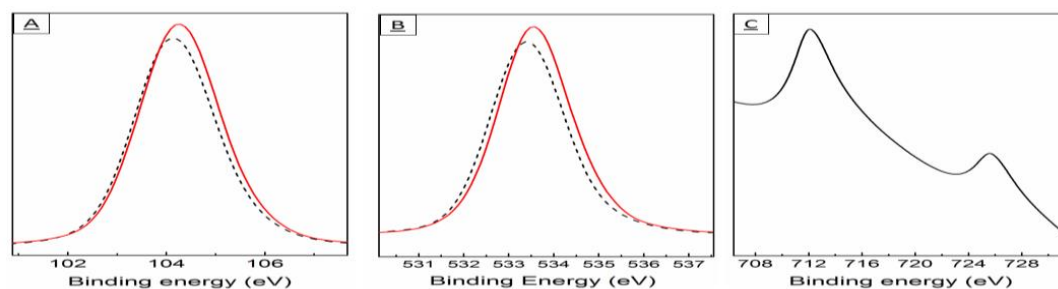
Figure 1B shows the SAXS profiles of pure MCM-41 and FeCl<sub>3</sub>/MCM-41 thermally activated at 400 °C. Both materials show intense scatterings centred at 2.7, which were assigned to the d<sub>100</sub> plane of hexagonal porous MCM-41 materials. The intensity of the scattering correspond to the FeCl<sub>3</sub>/MCM-41 material was found to be lesser and this was due to the partial loss of meso-porosity. Moreover, such local distortion of periodic porous structure can occur, while accommodating a heavier molecular species such as iron chloride. However, the SAXS pattern clearly reveals that highly ordered hexagonal meso-structure of MCM-41 remained intact after thermally activating the FeCl<sub>3</sub>/MCM-41 at 400 °C.

Figure 2A showed the N<sub>2</sub> adsorption-desorption isotherms of both materials after thermal activation. The BET surface area of MCM-41 was estimated to be 1214 m<sup>2</sup>/g, while BET surface area of FeCl<sub>3</sub>/MCM-41 (thermally activated 400 °C) (1022 m<sup>2</sup>/g) was lesser than the parent one, respectively. Pore volume of FeCl<sub>3</sub>/MCM-41 was also slightly lower than the pore volume of MCM-41. The reduction in surface area and pore volume clearly showed that impregnation and thermal activation of FeCl<sub>3</sub> distort the porosity locally. The chemical condensation led to create some more distortion, which might contribute to the lower surface area and pore volume [29-30].



**Figure 2:** (A) BET N<sub>2</sub> adsorption isotherms (B) <sup>29</sup>Si NMR spectral data of pure MCM-41 and FeCl<sub>3</sub>/MCM-41 activated at 400 °C

Additional major confirmation came from the <sup>29</sup>Si NMR spectral data of pure MCM-41 and FeCl<sub>3</sub>/MCM-41 activated at 400 °C, shown in Figure 2B. The NMR spectra provide the direct information of the interaction of FeCl<sub>3</sub> with the silanol groups of the MCM-41. The intense peak having the chemical shift at -106 ppm, was characteristic <sup>29</sup>Si component coming from the framework silica. Another small peak observed at -91 ppm, was assigned to the surface silanol groups. After FeCl<sub>3</sub> impregnation and thermal activation, <sup>29</sup>Si peak corresponds to the framework silica and surface silanol (-108 ppm and -93 ppm) groups shifted as compared to the pure MCM-41. This shift can be explained with the chemical interaction between FeCl<sub>3</sub> and MCM-41 silanol groups. The weak magnetic moment associated with nano-crystalline Fe-OCl<sub>x</sub> species also cause the peak broadening.



**Figure 3:** XPS core-level spectra of Si2p (A), O1s (B) and Fe 2p from MCM-41 (dotted), FeCl<sub>3</sub>/MCM-41 calcined at 400 °C (solid line)

To support the chemical interaction between MCM-41 and FeCl<sub>3</sub> at 400 °C, XPS data of both MCM-41 and MCM-41 supported FeCl<sub>3</sub> after thermal activation and the results are shown in Figure 3. XPS core level spectra of Si2p level in the case of MCM-41 showed slight variation after FeCl<sub>3</sub> impregnation and subsequent calcination. Si2p spectra exhibit two major chemical components and their peak binding energies were observed at 103.3 eV and 104.1 eV, which were assigned to Si in the silanol groups and silica framework respectively. O1s spectra of MCM-41 exhibit two major O1s components observed at 532.3 eV and 533.6 eV, characteristic O1s peak binding energies of hydroxyl oxygen and silica framework oxygen. FeCl<sub>3</sub> impregnation and thermal activation, there was shift in the surface silanol groups BE towards 104.3 eV. After the FeCl<sub>3</sub> impregnation and subsequent thermal activation shift the hydroxide O1s binding energy from 532.1 to 532.7 eV. This usually occurs only when this silanol oxygen interacted with the FeCl<sub>3</sub>. The BE correspond to the Fe2p<sub>3/2</sub> level in the case of FeCl<sub>3</sub>/MCM-41 to 712.3 eV, which was a clear indication of oxy-iron chloride species.

#### IV. Conclusions

In summary, MCM41 supported FeCl<sub>3</sub> thermally activated at 400 °C is a highly active catalyst for the solvent-free condensation of resorcinol and ethyl acetoacetate for coumarin synthesis. This high catalytic performance towards the formation of coumarin can be correlated to the synergistic metal-support interactions, Lewis acidic FeCl<sub>3</sub> species as well as high BET surface area of MCM-41 support. This catalyst showed excellent catalytic performance even after 5<sup>th</sup> reuse of the catalyst, indicating its heterogeneous catalytic performance, which can have numerous applications in various acid-catalysed reactions.

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