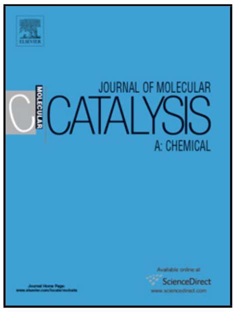

Title: Recyclable CMK-5 supported sulfonic acid as an
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Recyclable CMK-5 supported sulfonic acid as an environmentally benign catalyst for solvent-free one-pot construction of coumarin through Pechmann condensation

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Abstract: Sulfonic acid modified nanostructured CMK-5 is used as an alternative to conventional acid catalysts in the von Pechmann condensation of a neat mixture of substituted phenols with ethyl acetoacetate leading to the formation of coumarin derivatives at 130°C. In comparison, CMK-5-SO_3H showed a greater activity than some other homogeneous and heterogeneous catalysts. Additionally, the catalyst is reused repeatedly for 6 reaction cycles without any evidence of loss of activity, confirming the stability of the covalent bonding of acidic centers. The methodology presented offers reusable strategy for the efficient synthesis of coumarin, simplicity in operation, and green aspects by avoiding toxic conventional catalysts and solvents.

Keywords: Pechmann condensation; Coumarins; Solvent-free; CMK-5; Heterogeneous sulfonic acid.

1. Introduction

Coumarins occupy an important place in the realm of natural products and synthetic organic chemistry. Their applications range from additive in foods, perfumes, cosmetics, pharmaceuticals and in the preparation of insecticides [1], optical brighteners [2] and dispersed fluorescent and tunable laser dyes [3]. In addition, some coumarins have varied bioactivities, such as, inhibitory of platelet aggregation [4], antibacterial [5], anticancer [6], and inhibitory of HIV-1 protease [7]. Coumarins also act as intermediate for the synthesis of furocoumarins, chromones, coumarones

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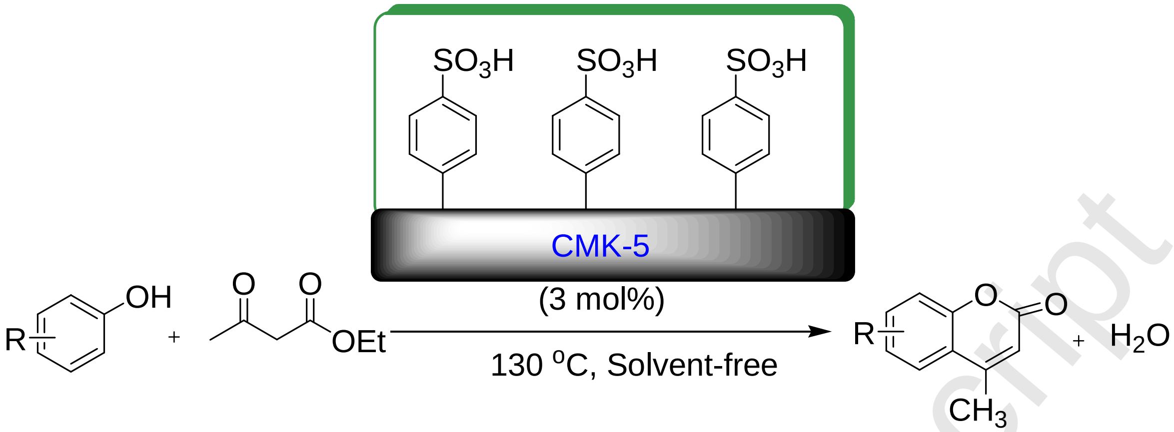
and 2-acylresorcinols [8]. Their properties turn coumarins in very interesting to organic chemists, and several strategies for their synthesis were already reported.

A variety of methods, such as Pechmann [9], Perkin [10], Claisen [11], Knoevenagel [12], Reformatsky [13] and Wittig [14], have been developed to synthesize coumarins. Among these, Pechmann reaction, a two component (phenol and β-ketoester) coupling under acid catalysis, is a very valuable protocol for coumarin ring synthesis. In the conventional production of coumarins by the Pechmann reaction, concentrated sulfuric acid is used as the catalyst [15]. Several other acid catalysts, like P_2O_5 [16], $AlCl_3$ [17], trifluoroacetic acid [18], $InCl_3$ [19], $ZrCl_4$ [20], and $BiCl_3$ [21], are known to affect this condensation. It may also utilize transition metal catalysis [22], ionic liquids [23], and microwave irradiation [24]. However, some of these procedures suffer from sever drawbacks including the use of a large amounts of catalyst, for example sulfuric acid, 10-12 equiv., trifluoroacetic acid, 3-4 equiv., elevated temperature, long reaction times and poor yields. Furthermore, the disposal of acidic waste leads to environmental pollution. For these reasons, there have been several attempts in the literature to find alternative and environmentally benign synthesis routs.

The use of solid acids in organic synthesis and in industrial manufacture of materials is of increasing importance since they provide green alternatives to homogenous catalysts. Nafion-H [25], Amberlyst-15 [26], Montmorillonite clay [27,28], heteropoly acids [29], sulfamic acid [30], sulfated zirconia [31], mesoporous zirconium phosphate [32], and Periodic mesoporous silica chloride [33], have been employed for this purpose in the Pechmann condensation. Although these catalysts are suitable for synthetic conditions, however, some of these procedures are associated with one or more disadvantages like poor thermal stability, lack of reproducibility, complex separation, low surface area, less water tolerance ability and large amount of solid support and tedious workup process which would eventually result in the generation of a large amount of toxic waste. To improve the above mentioned problems, it is important to investigate new methods using less hazardous reagents and solvents or even without harmful organic solvents. Along this line, sulfonic acid groups immobilized on solid supports have generated considerable interest, because they combine in a single solid, both the special chemical reactivity of the organofunctional groups and attractive properties including a mechanically structure, high surface area and large ordered pores [34-47]. In this context, we have recently developed a variety of water-tolerant sulfonic acid based nanoreactors based on ordered nanoporous silica for the von Pechmann reaction to satisfy both recyclability and reactivity. Detailed study revealed that mesoporous solid sulfonic acid nanoreactor SBA-15-Ph-PrSO_3H was a reusable, hydrophobic and easily recyclable catalyst for the von Pechmann synthesis of coumarins [48].

Very recently, we have used ordered nanoporous carbonaceous sulfonic acid (CMK-5-SO_3H) with high surface area, narrow pore size distribution and large pore volume as a recoverable heterogeneous catalyst in some organic transformations [49,50]. Keeping in view the importance of Pechmann condensation and heterogeneous catalysis, and along the line of our studies in the application of new solid acid catalysts in chemical transformations, herein we wish to report a new method for the one-pot synthesis of coumarins using catalytic amounts of nanostrustured CMK-5-SO_3H under solvent-free reaction conditions (Scheme 1) (See supporting information for experimental procedures for the synthesis of CMK-5 and CMK-5-SO_3H, TGA, BJH, N_2 ads-des, TEM, and XRD diagrams for CMK-5 and CMK-5-SO_3H).



Scheme 1: Synthesis of coumarin derivatives using CMK-5-SO_3H under solvent-free reaction conditions.

2. Results and discussion

First, we examined the catalytic activity of various Bronsted acids in a model reaction of resorcinol with ethyl acetoacetate (Table 1). As expected, condensation did not proceed without catalyst (Table 1, entry 1). It can be seen that homogenous unrecoverable catalysts such as H_2SO_4 (Table 1, entry 2), and *p*-toluene sulfonic acid (Table 1, entry 3) are less efficient. Remarkably, it is also clearly seen from these data that no yield of the corresponding 7-hydroxy-4-methyl coumarin was obtained when amorphous silica and SBA-15 were employed as catalysts (Table 1, entries 4,5). Interestingly, the yield was dramatically increased using a hydrophobic nanocatalyst SBA-15-Ph-PrSO_3H and random pore carbon-SO_3H (Table 1, entries 6,7). Additionally, the reaction was very sluggish using non-sulfonated CMK-5 and the corresponding product isolated in only 10% yield after 60 min (Table 1, entry 8). Finally, we observed that the reaction was very efficient in the presence of as low as 3 mol% of CMK-5-SO_3H and the corresponding coumarin product was formed in excellent yield after 20 min (Table 1, entry 9). This study clearly showed that CMK-5-SO_3H exhibits higher activity under the same reaction conditions and the catalyst loading. So CMK-5-SO_3H is a good catalyst for the synthesis of coumarin.

Table 1: Comparison of activity of some homogeneous and heterogeneous solid acid catalysts in Pechmann condensation of resorcinol with ethyl acetoacetate.

Entry	Catalyst	Time (min)	Yield (%)[a,b]
1	None	60	NR
2	H_2SO_4	60	30
3	*p*-TSOH[c]	60	35
4	SBA-15[c]	60	NR
5	Silicagel	60	NR
6	SBA-15-Ph-PrSO_3H[d]	60	90
7	random pore carbon-SO_3H[d]	60	84
8	CMK-5	60	10
9	CMK-5-SO_3H	20	95

a. Isolated yields.

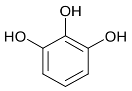
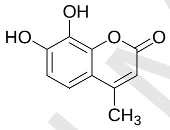
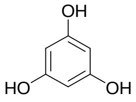
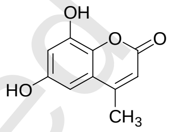
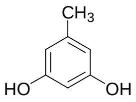
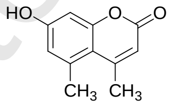
b. Conditions were as follows: resorcinol (1 mmol), ethyl acetoacetate (1 mmol), catalyst (~ 3 mol %) at 130 °C.

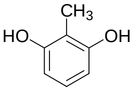
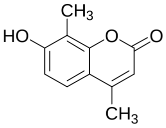
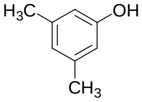
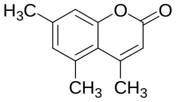
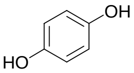
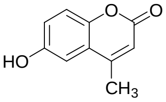
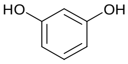
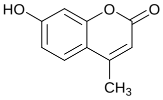
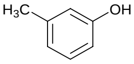
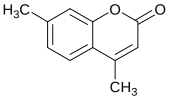
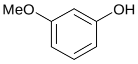
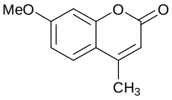
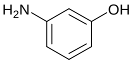
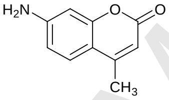
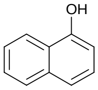
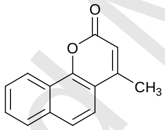
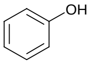
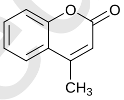
c. 200 mg of SBA-15 or silica was used.

d. ~ 7 mol % of SBA-15-Ph-PrSO_3H was used.

Next, we investigated substrate generality in the CMK-5-SO_3H catalyzed condensation of substituted phenols and ethyl acetoacetate at 130°C under solvent-free reaction condition. The reactions worked well and the results are illustrated in Table 2. Pyrogallol (Table 2, entry 1), phloroglucinol (Table 2, entry 2), orcinol (Table 2, entry 3), 2,6-dihydroxy toluene (Table 2, entry 4), and 3,5-dimethyl phenol (Table 2, entry 5) afforded excellent yields in short reaction times. Hydroquinone (Table 2, entry 6), resorciniol (Table 2, entry 7), and substrates having electron-donating groups in *Para* to the site of electrophilic substitution (Table 2, entries 8-10) also gave good yields in the slightly longer reaction times. 3-Methoxyphenol (Table 2, entry 9) showed no detective demethylation under the given conditions. Interestingly, 3-aminophenol reacted to provide the amino coumarin in good yield with high chemoselectivity (Table 2, entry 10). 1-Naphtol (Table 2, entry 11) requires a longer reaction time, due to the presence of another phenyl rings. Noteworthy, One of the interesting feature of this procedure over most of the previous heterogeneous and homogeneous systems, is the formation of 4-methylcoumarin in acceptable yield from the reaction of unsubstituted phenol (Table 2, entry 12).

Table 2: Synthesis of coumarins using 3 mol% of CMK-5-SO_3H under solvent-free reaction conditions at 130 °C.

Entry	Substrate	Product [a]	Time (min)	Yield (%) [b]
1			20	96
2			15	97
3			20	93

4			30	88
5			25	89
6			25	90
7			20	95
8			30	86
9			30	89
10			35	91
11			45	92
12			120	60

a. All products were characterized by comparison of their ^{1}H, and ^{13}C NMR spectra with those of authentic samples.

b. Isolated yields after recrystallization.

Here it should be mentioned that the use of CMK-5-SO$_3$H as a solid acid catalyst is advantageous not only for its thermal stability, high water tolerance ability, easy sedimentation property, and better catalytic activity, but also it is a reusable catalyst for Pechmann condensation. The stability of the sulfonic acid groups during the reaction was conducted by repeating the condensation of resorcinol over CMK-5-SO$_3$H. In repeated experiments, the catalyst washed with ethanol for three times and then the new substrates added. In six runs, the yields of product were 95%, 92%, 92%, 90%,, 90% and 88% respectively, which verify that the activity of the catalyst remained unchanged throughout these six runs. For better investigation of catalyst recyclability, we established an experiment by conducting successive condensation of resorcinol with ethyl acetoacetate using CMK-5-SO_3H in a shorter time (10 min). The yield of corresponding product reached to 60% after 10 min. Gratifyingly, the catalyst was reused again in six successive runs with no significant decreases in its efficiency, providing almost same yields of the respective product (Figure 1).

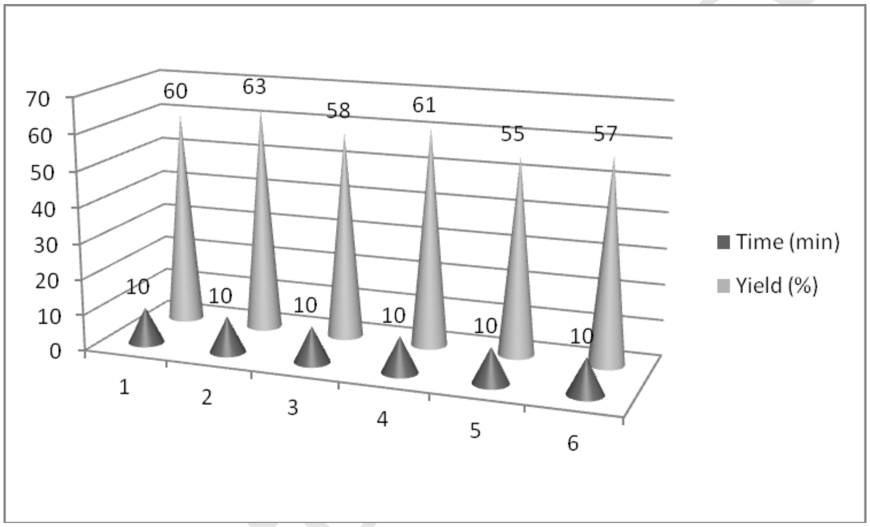


Figure 1: Recyclability of the catalyst for the Pechmann condensation of resorcinol after 10 min.

In order to show whether the reaction is actually proceeding in a heterogeneous pathway or whether it is conducting through a homogeneous manner, we performed a test, in which the reaction of resorcinol with ethyl acetoacetate in the presence of CMK-5-SO_3H were quenched (by dilution with CH_2Cl_2) after 10 min and filtered off (≈60% conversion). Then CH_2Cl_2 was evaporated and the residue was then allowed to further heating under solvent-free condition at 130 °C. We found that no further catalytic activity was observed upon the heating for 3h, thus supporting the heterogeneous nature of the reaction.

3. Conclusions

In summary, CMK-5-SO_3H was shown to be an effective catalyst in solvent-free Pechmann condensation. Furthermore, good to excellent yields of coumarin derivatives were obtained using catalyst CMK-5-SO_3H. The catalyst can be reused in six successive runs with no considerable activity loss. Therefore, green and simple experimental procedure, solvent-free reaction conditions, good yields of products, ease of work-up and recyclability of the catalyst, will make the present method a useful and important addition to the present methodologies for the Pechmann condensation.

4. Experimental

Chemicals were either prepared in our laboratories or were purchased from Alderich or Fluka chemical companies. Reactions monitoring were accompanied by TLC on silica-gel polygram SILG/UV 254 plates. The products are characterized by recording their ^{1}H and ^{13}C NMR spectroscopy by using Bruker 250 or 400 MHz apparatus. Measurements of surface area and pore size distribution were made using the Brunauer–Emmet–Teller (BET) method in a Quanta Sorb machine. X-ray diffraction (XRD) patterns were recorded by an Xpert-Pro, X-ray diffractometer using Cu Kα radiation. Transmission electron microscope, TEM (Philips CM-10) was also used to obtain TEM image.

General procedure for the Pechmann condensation: In a round bottom flask, CMK-5-SO_3H (0.034g, 3mol%) was added to the mixture of phenolic compound (1 mmol) and ethyl acetoacetate (1 mmol) at 130 °C and the reaction mixture stirred for the appropriate time (Table 2). The progress of reaction was monitored by TLC (eluent, n-hexane:ethyl acetate, 4:1). After the completion of the reaction, the reaction mixture was diluted with ethanol and filtrated to obtain the crude product. Compounds with purity below 95% were further purified using column chromatography on silica gel and then recrystallized from hot ethanol to afford pure coumarin derivatives. All compounds were identified by comparison of ^{1}H NMR, and ^{13}C NMR with those reported (see supporting information for copy of ^{1}H and ^{13}C spectra of products). Spectroscopic data for selected examples listed below.

7,8-Dihydroxy-4-methyl-chromen-2-one (Entry 1): ^{1}H NMR (400 MHz; DMSO-d6): δ_H = 2.36 (s, 3H), 6.14 (s, 1H), 6.8 (d, J = 8.8 Hz, 1H), 7.10 (d, J = 8.8 Hz, 1H), 9.7 (brs, 2H); ^{13}C NMR (100 MHz, DMSO-d6): δ_C = 18.7, 110.7, 112.6, 113.2, 115.9, 132.6, 143.8, 149.9, 154.4, 160.7.

5,7-Dihydroxy-4-methyl-chromen-2-one (Entry 2): ^{1}H NMR (400 MHz; DMSO-d6): δ_H = 2.53 (s, 3H), 5.86 (s, 1H), 6.18 (s, 1H), 6.27 (s, 1H), 10.31 (s, 1H), 10.53 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d6): δ_C = 23.9, 94.9, 99.5, 102.5, 109.2, 155.4, 156.9, 158.4, 160.5, 161.5.

7-Hydroxy-4-methyl-chromen-2-one (Entry 7): ^{1}H NMR (400 MHz; DMSO-d6): δ_H = 2.37 (brs, 3H), 6.14 (s, 1H), 6.71 (d, J = 2.4 Hz, 1H), 6.79-6.83 (dd, J = 8.8 Hz, J = 2.4 Hz, 1H), 7.59 (d, J = 8.8 Hz, 1H), 10.55 (brs, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ_C = 18.6, 1026, 110.7, 112.5, 113.3, 127.1, 154.0, 155.3, 160.8, 161.6.

7-Amino-4-methyl-chromen-2-one (Entry 10): ^{1}H NMR (400 MHz; DMSO-d6): δ_H = 2.27 (s, 3H), 5.87 (s, 1H), 6.07 (brs, 2H), 6.38 (d, J = 2.2 Hz, 1H), 6.54 (dd, J = 6Hz, J = 2.2 Hz, 1H), 7.38 (d, J = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d6): δ_C = 18.4, 98.9, 107.9, 109.3, 111.6, 126.7, 153.5, 154.2, 155.9, 161.2.

4-Methyl-benzo[h]chromen-2-one (Entry 11): ^{1}H NMR (400 MHz; DMSO-d6): δ_H = 2.54 (s, 3H), 6.53 (s, 1H), 7.73-7.91 (m, 4H), 8.06-8.08 (m, 1H), 8.38-8.41 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d6): δ_C = 19.2, 114.4, 115.6, 121.8, 122.1, 122.7, 124.5, 127.9, 128.5, 129.2, 134.9, 150.2, 154.7, 160.1.

5. Supplementary data

Experimental procedures for the synthesis of CMK-5 and CMK-5-SO_3H, TGA, BJH, N_2 ads-des, and XRD diagrams for CMK-5 and CMK-5-SO_3H, TEM image for recovered catalyst and copy of ^1H and ^{13}C spectra for products and general procedure for the synthesis of coumarins is available.

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Research highlights

- ✓ efficient synthesis of coumarins with green and simple experimental procedure
- ✓ Solvent-free reaction conditions
- ✓ Exceedingly simple workup and uncomplicated recovery (***six*** reaction cycles)

Outstanding thermal stability of CMK-5-SO_3H

Graphical Abstract