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Synthesis of 7-substituted 4-methyl coumarins by Pechmann reaction using nano-crystalline sulfated-zirconia

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Abstract

The nano-crystalline sulfated-zirconia catalysts, prepared by one-step as well as two-step sol–gel technique, showed excellent catalytic activity with a high substrate to catalyst weight ratio for the synthesis of 7-substituted 4-methyl coumarins via solvent free Pechmann reaction. The *m*-amino phenol was found to be more reactive than *m*-hydroxy phenol. The catalyst results 100% conversion of *m*-amino phenol with ∼100% selectivity of 7-amino 4-methyl coumarin at 110 °C within 2 min. For 7-hydroxy 4-methyl coumarin, 94% yield was obtained after 3 h at 170 °C with phenol to catalyst weight ratio of 80. Slow kinetics was observed in polar nitrobenzene as well as in non-polar toluene for both coumarin derivatives, due to the slow bulk diffusion of reactant molecules in presence of solvent. The solvent free microwave assisted synthesis seems advantageous way to synthesize the hydroxy derivative resulting excellent yield (99%) in much lesser time (15 min) at lower temperature (150 °C) as compared to thermal heating. The use of very small catalytic amount of sulfated-zirconia catalyst for the synthesis of coumarins and the reusability of the catalyst after simple activation for several times with similar catalytic activity are novel properties of the catalyst.

Keywords: Nano-crystalline sulfated-zirconia; 7-Amino 4-methyl coumarin; 7-Hydroxy 4-methyl coumarin; Microwave assisted coumarin synthesis

1. Introduction

Coumarins are the benzo-2-pyrone derivatives mainly found in plants of the family of Rutaceae and Umbelliferae. Among the various coumarin derivatives, 7-substituted coumarins are important group of coumarin derivatives showing various bioactivities and also other applications [1]. For example, 7-hydroxy 4-methyl coumarin (β-methylumbelliferone) is used as fluorescent brightener, efficient laser dye, standard for fluorometric determination of enzymatic activity, as a starting material for the preparation of insecticide and furano coumarins [2–4]. Similarly, 7-amino 4-methyl coumarin is mainly used as laser dye and intermediate for the synthesis of bioactive compounds [5]. Studies [6] suggested that amino group is an effective substitute for the hydroxyl group for antioxidant property.

Coumarins can be obtained from the plants by different extraction methods such as Maceration under sonication, infusion and supercritical fluid extraction [7]. However, the extraction from plants is time consuming tedious job and needs sophisticated instrument based separation process to get the pure product. Therefore, the chemical synthesis of coumarin derivatives is done to fulfill their requirements in vast applications. The natural biosynthesis of 7-hydroxy coumarin derivatives involves the transformation of the *trans*-cinnamic acid derivative to *cis*-form with the help of glucose followed by the cyclization in presence of beta-glucosidase enzyme.

Chemically, coumarins can be synthesized by various methods such as the Pechmann reaction [8a–f], Knoevenagel condensation [9a–d], Claisen rearrangement [10], Perkin [11a–c], Wittig [12a–d], Reformatsky [13] and catalytic cyclization reactions [14]. However, acid catalyzed Pechmann reaction is the simple and commonly used method for synthesizing coumarins from activated phenols, mostly *m*-substituted phenols containing electron donating substituent at *m*-position and β-keto-esters or an unsaturated carboxylic acid [8a & b, 15]. Conventionally, the Pechmann reaction is carried out in

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presence of concentrated sulfuric acid catalyst [8c, 16], phosphorous pentaoxide [17], trifluoroacetic acid [18] and aluminum chloride [19]. These acids are corrosive and required in excess amount. For example, nearly one litre concentrated H_2SO_4 is required to synthesize 1 mol of 7-hydroxy 4-methyl coumarin [20], require 12–24 h of reaction time [8c] and may also results in the formation of undesired side products [21]. Homogeneous metal chlorides such as $ZnCl_4$, $TiCl_4$, $InCl_3$, GaI_3 [22–25], triflates [26], sulfonic acid [27] and ionic liquids [28–30] are reported to produce 7-hydroxy coumarin derivatives in high yield at ambient temperature. Due to non-reusability of these homogeneous catalysts different solid acid catalysts such as Amberlyst ion-exchange resins [31] zeolites [32,33] montmorillonite K-10 [34], polyaniline sulfate salt [35,36], heteropoly acids [37] and nafion resin/silica nanocomposites [38] have been studied for the synthesis of 7-hydroxy 4-methyl coumarin. However, some of these catalysts suffer from either a tedious synthetic methodology [35,36], or requirement of large amount of catalyst for high yield. For example, zeolites [32,33] and Amberlyst [31] are required in almost stochiometric amount (phenol to catalyst weight ratio = 1); nafion resin/silica nanocomposites [38] and Amberlyst ion-exchange resins [31] are required in phenol to catalyst weight ratio of 2, for giving 80–96% yield of 7-hydroxy-derivative. Furthermore, in most of the cases toluene has been employed as a solvent as it is reported that non-polar solvents favors the Pechmann reaction and polar solvents cause the cleavage [31]. For the synthesis of 7-amino 4-methyl coumarin only few studies are reported [21] using solid catalysts, wherein, graphite supported on montmorillonite K-10 yields 66% product in 30 min. Microwave irradiation has been found more useful for synthesis of these coumarin derivatives in order to minimize the reaction time [21,39]. Recently, ultrasound assisted Pechmann synthesis has also been reported producing good yields of 7-hydroxy 4-methyl coumarin, however, with homogenous $BiCl_3$ catalyst [40].

In view of our previous experience over nano-crystalline sulfated-zirconia [41,42], which showed excellent results for isomerization of longifolene [43,44], we studied the catalytic activity of nano-crystalline sulfated-zirconia, prepared by one-step and two-step sol–gel technique for the synthesis of 7-amino 4-methyl coumarin along with 7-hydroxy 4-methyl coumarin from activated phenols, namely *m*-amino phenol and *m*-hydroxy phenol, respectively, with ethyl acetoacetate in solvent free conditions. The effect of solvent both polar (nitrobenzene) and non-polar (toluene) was also studied on the synthesis of both amino and hydroxy coumarin derivatives. In addition, microwave assisted synthesis of 7-hydroxy 4-methyl coumarin has also been studied.

2. Experimental

2.1. Materials

Zirconium *n*-propoxide (70 wt% solution in *n*-propanol) was procured from Sigma–Aldrich, USA; *n*-propanol, aqueous ammonia (25%) and concentrated sulfuric acid were from s.d. Fine Chemicals, India; *m*-amino phenol and ethyl acetoacetate were from Loba Chemie, India and *m*-hydroxy phenol was procured from Central Drug House, India.

2.2. Catalyst synthesis

Sulfated zirconia (SZ) samples were synthesized using one-step as well as two-step sol–gel technique. The zirconium *n*-propoxide was used as a precursor after dilution (30 wt%) with *n*-propanol. In the one-step method, addition of sulfuric acid was done by two ways: (i) an aqueous solution of concentrated sulfuric acid (1.02 ml acid in 6.4 ml water with water to alkoxide molar ratio = 4) was added drop wise into the zirconium precursor under continuous stirring. (ii) sulfuric acid (1.02 ml) was added to zirconium precursor and water was then added drop wise under continuous stirring, just sufficient to form a gel (4.2 ml, water to propoxide molar ratio = 2.7). The resulting gel was dried at 110 °C for 12 h followed by calcination at 600 °C for 2 h in static air atmosphere. The samples thus prepared are named as SZ-1 and SZ-2, respectively.

In the two-step procedure, two samples were prepared, wherein, hydrolysis of zirconium precursor (30 wt% solution) was done with (i) aqueous ammonia at pH 9–10 and (ii) with water (water to alkoxide molar ratio = 4). After aging for 3 h at room temperature, the gel was filtered and dried at 110 °C for 12 h in the first step. The dried gel was meshed (170 mesh) and sulfated with concentrated sulfuric acid solution (0.5 M, 15 ml/g $Zr(OH)_4$ gel) under stirring for 30 min in the second step. After filtration, the sulfated samples were dried at 110 °C for 12 h followed by calcination at 600 °C for 2 h in static air atmosphere. The samples are named as SZ-3 and SZ-4, respectively.

2.3. Catalyst characterization

2.3.1. X-ray powder diffraction (XRD) studies

The crystalline phase formed and the crystallinity of sulfated zirconia after calcination at 600 °C was measured by X-ray powder diffractometer (Philips X'pert) using Cu Kα radiation (λ = 1.54056 Å). The samples were scanned in 2θ range of 0–80° at a scanning rate of 0.04° s^{-1}. Crystallite size of tetragonal phase was determined from the characteristic peak (2θ = 30.18 for the (1 1 1) reflection) by using Scherrer formula with a shape factor (*K*) of 0.9 [45] as below:

$$\text{Crystallite size} = \frac{K\lambda}{W\cos\theta}$$

where $W = W_b - W_s$; W_b is the broadened profile width of experimental sample and W_s is the standard profile width of reference silicon sample.

2.3.2. FT-IR spectroscopic studies

The nature of bonding of sulfate ions with zirconia surface after calcination at 600 °C was studied by FT-IR spectrophotometer (Perkin-Elmer GX). The spectra were recorded in the range 400–4000 cm^{-1} with a resolution of 4 cm^{-1} as KBr pellets.

2.3.3. Sulfur analysis

The bulk sulfur (wt%) retained in sulfated zirconia samples before and after calcination at 600 °C was analyzed by C H N S/O elemental analyzer (Perkin-Elmer 2400, Sr II).

2.3.4. Surface area and pore size distribution

Specific surface area, pore volume and pore size distribution of sulfated zirconia samples calcined at 600 °C were determined from N_2 adsorption–desorption isotherms at 77 K (ASAP 2010 Micromeritics). Surface area was calculated by using BET equation; pore volume and pore size distribution were calculated by BJH method [46]. The samples were degassed under vacuum at 120 °C for 4 h, prior to adsorption measurement to evacuate the physisorbed moisture.

2.4. Synthesis of 7-amino 4-methyl coumarin

The sulfated zirconia catalysts were studied for the synthesis of 7-amino 4-methyl coumarin using *m*-amino phenol and ethyl acetoacetate under solvent free conditions and also in presence of nitrobenzene as a solvent. In a typical experiment, *m*-amino phenol and ethyl acetoacetate were taken (1:1 molar ratio) with nitrobenzene (3 g) and tridecane (0.1 g, internal standard) in a 50 ml reaction tube of reaction station (12 Place Heated Carousel Reaction Station, RR99030, Radleys Discovery Technologies, UK) along with the pre-activated (at 450 °C, 2 h) catalyst (phenol to catalyst weight ratio = 10). The phenol and ethyl acetoacetate were taken in 1:2 molar ratio, when reaction was carried out under solvent free condition for the proper solubility of phenol and ease of proper stirring of the reaction mixture. The reaction was carried out at different temperatures in the range of 90–150 °C under stirring for 2 min–3 h. The reaction tubes were taken out at different time intervals, dimethyl sulfoxide (2 g) was added to dissolve the crystallized product on cooling, and was analyzed by gas chromatography (HP6890) having a HP50 (30-m long) capillary column with a programmed oven temperature from 50 to 200 °C, at 0.5 cm^3/min flow rate of N_2 as carrier gas and FID detector. The conversion of *m*-amino phenol and selectivity of 7-amino 4-methyl coumarin was calculated on the basis of its weight percent as follows:

$$\text{Conversion (wt\%)} = \frac{100 \times \text{[Initial wt\%} - \text{Final wt\%]}}{\text{Initial wt\%}}$$

Selectivity (wt%) = 100 × [GC peak area% of 7-amino 4-methyl coumarin]/$\sum$Total GC peak area% for all the products.

The effect of reaction temperature and time, molar ratio of reactants and phenol to catalyst ratio were studied with one of the catalysts (SZ-2), to achieve maximum conversion and selectivity in solvent free conditions and also in presence of solvent. The product was isolated after cooling the solvent free reaction mixture and slowly re-crystallized in ethanol–water system and was characterized by melting point, FT-IR (Perkin-Elmer GX) and NMR spectroscopy (Bruker, Avance DPX 200 MHz).

2.5. Synthesis of 7-hydroxy 4-methyl coumarin

In a typical experiment, *m*-hydroxy phenol and ethyl acetoacetate were taken (1:1 molar ratio) with nitrobenzene (3 g) in a 50 ml reaction tube of reaction station along with the pre-activated (at 450 °C, 2 h) catalyst (phenol to catalyst weight ratio = 10). The phenol and ethyl acetoacetate were taken in 1:2 molar ratio, when reaction was carried out in solvent free condition for the proper solubility of phenol and ease of proper stirring of the reaction mixture. The reaction was carried out at 150 and 170 °C under stirring for 0.5–24 h. The effect of reaction temperature and time, molar ratio of reactants and phenol to catalyst weight ratio were studied with one of the catalysts (SZ-2), to achieve maximum yield of 7-hydroxy 4-methyl coumarin under solvent free conditions as well as in presence of nitrobenzene. After the reaction, the hot reaction mixture was filtered to separate the catalyst and the product was crystallized after cooling the reaction mixture. The crystals of the product were filtered and washed with petroleum ether to remove unreacted reactants and solvent, dried and slowly re-crystallized in ethanol–water system. The product was characterized by melting point, FT-IR and NMR spectroscopy. The yield of 7-hydroxy 4-methyl coumarin was obtained as follows:

$$\text{Yield (wt\%)} = \left(\frac{\text{Obtained weight of product}}{\text{Theoretical weight of product}}\right) \times 100$$

2.6. Microwave assisted solvent free synthesis of 7-hydroxy 4-methyl coumarin

Solvent free synthesis of 7-hydroxy 4-methyl coumarin was also carried out by using microwave irradiation (250 W). In a 100 ml microwave reaction vessel (Ethos 1600 Microwave Lab Station, Italy), *m*-hydroxy phenol and ethyl acetoacetate (1:2 molar ratio) were taken along with the activated (at 450 °C, 2 h) catalyst (with phenol to catalyst weight ratio = 10). The reaction mixture was kept in microwave reaction vessel at different temperatures ranging from 90 to 170 °C for 5–20 min. The product was isolated, re-crystallized and characterized as described above in Section 2.5.

2.7. Catalyst regeneration

The regeneration study was done with the catalyst, SZ-2, which was used in the solvent free synthesis of both amino and hydroxy coumarin derivatives. The used catalyst was filtered from the reaction mixture, washed with hot ethanol and acetone to remove the adsorbed reactants and products and activated at 450 °C for 4 h in air. Thus, regenerated catalyst was studied under similar reaction conditions till 6th reaction cycles. After every reaction cycle, the catalyst was recovered from reaction mixture and regenerated as described above.

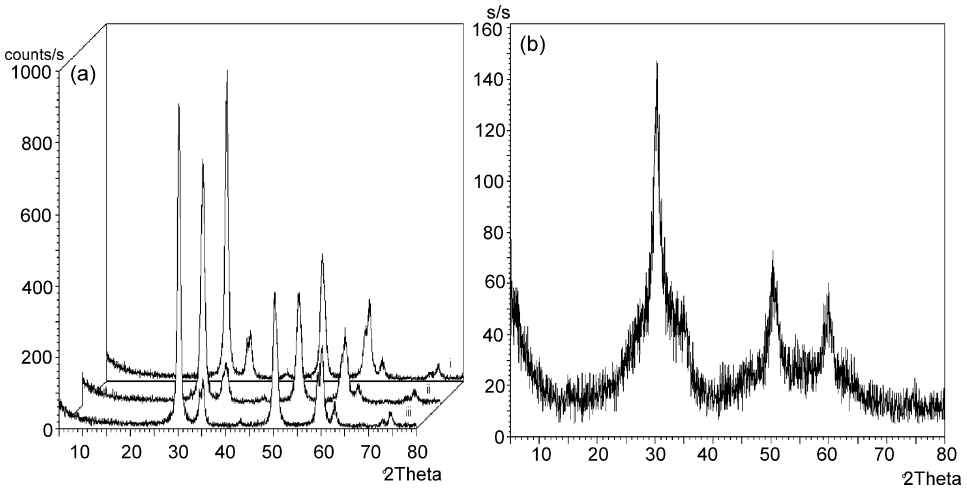


Fig. 1. XRD pattern of sulfated-zirconia samples: (a) SZ-1(i), SZ-3(ii) and SZ-4(iii) and (b) SZ-2 after calcination at 600 °C.

Table 1
Characterization of nano-crystalline sulfated zirconia catalysts after calcination at 600 °C

Sample	Cryst. size (nm)	Surface area (m^2/g)	Pore volume (cm^3/g)	Pore size (Å)	*S* (wt%)
SZ-1	14	101	0.152	58	1.27
SZ-2	9	150	0.330	89	3.93
SZ-3	11	101	0.087	35	1.38
SZ-4	16	81	0.081	42	1.31

3. Results and discussion

3.1. Characterization of sulfated-zirconia catalysts

All the sulfated zirconia catalysts, after calcination at 600 °C, showed purely tetragonal crystalline phase (Fig. 1a and b), having nano-crystallite size in the range of 9–16 nm (Table 1). Sulfate group binding with zirconia surface in a chelating bidentate fashion (Structure A) shows the IR bands of the SO_4^{2-} group in the region of 1200–900 cm^{-1} (Fig. 2), with peaks at 1242, 1142, 1073, 1045, and 998 cm^{-1}, which are the characteristic of inorganic chelating bidentate sulfate, and are assigned to asymmetric and symmetric stretching frequencies of partially ionized S=O double bonds and S–O bonds [47] as shown in Structure A. This ionic structure of SO_4^{2-} group in presence of adsorbed water molecules is responsible for the Brönsted acidity [41] in sulfated-zirconia catalysts.

Among the four catalysts, SZ-2 was observed to possess highest sulfur loading, surface area, pore volume, pore diameter and smallest crystallite size (Table 1). It was also observed to have lower crystallinity compared to other three catalysts (Fig. 1b). This is due to higher sulfur content (3.9 wt%) compared to other three catalysts, which have sulfur in the range of 1.27–1.38 wt%. It has been earlier observed by us [41] that crystallization temperature of zirconia increases on sulfation due to the presence of SO_4^{2-} ions, which require higher thermal energy for the removal of hydroxyl groups for dehydroxylation during crystallization. The difference in structural and textural properties of the catalysts is attributed to the difference in method of sulfation and water to alkoxide molar ratio.

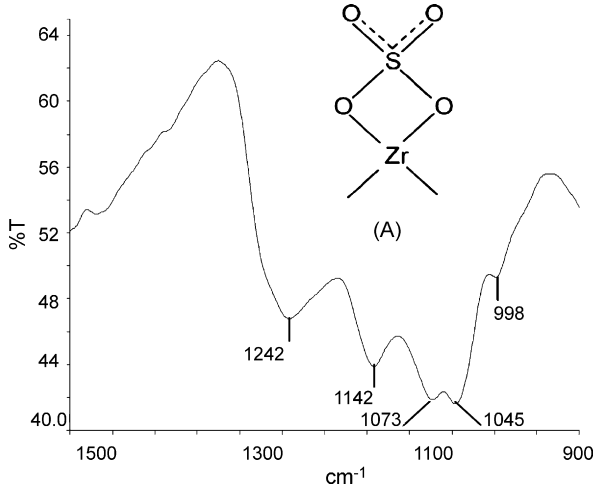
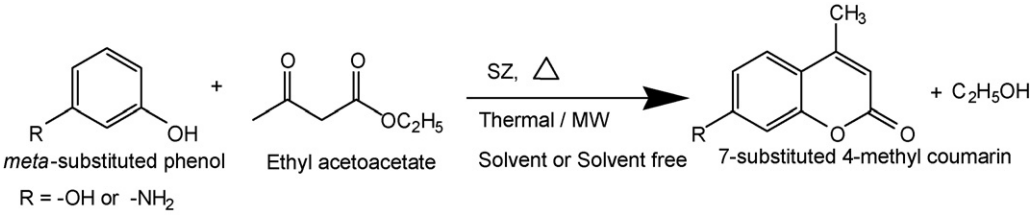


Fig. 2. FT-IR spectrum of sulfated zirconia sample after calcination at 600 °C.



Scheme 1. Schematic synthesis of 7-substituted 4-methyl coumarins.

Table 2
Conversion (%) of *m*-amino phenol (AP) and selectivity (%) of 7-amino 4-methyl coumarin (AMC) with sulfated-zirconia catalysts

Catalyst	Solvent free[a]		With nitrobenzene[b]	
	Conversion of *m*-AP[a] (%)	Selectivity of AMC[a] (%)	Conversion of *m*-AP[b] (%)	Selectivity of AMC[b] (%)
SZ-1	100	100	100	99.7
SZ-2	100	100	100	98.8
SZ-3	100	100	100	99.7
SZ-4	100	100	100	98.6

Reaction temperature = 150 °C, reaction time = 1 h, phenol:catalyst wt. ratio = 10.
[a] *m*-Amino phenol:ethyl acetoacetate molar ratio = 1:2 (0.1 g tridecane, internal standard).
[b] *m*-Amino phenol:ethyl acetoacetate molar ratio = 1:1, nitrobenzene = 3 g (0.1 g tridecane, internal standard).

3.2. Synthesis of 7-amino 4-methyl coumarin

Synthesis of 7-amino 4-methyl coumarin was carried out with all four nano-crystalline sulfated-zirconia catalysts using *m*-amino phenol and ethyl acetoacetate (Scheme 1) under solvent free conditions and also in presence of nitrobenzene solvent. All catalysts showed high and similar catalytic activity giving 100% conversion of *m*-amino phenol with 99–100% selectivity for 7-amino 4-methyl coumarin in both solvent free condition and nitrobenzene within 1 h at 150 °C (Table 2). As all the catalysts showed similar catalytic activity for the synthesis of 7-amino 4-methyl coumarin, one of the catalysts, SZ-2, was chosen for further study to optimize the reaction parameters for obtaining maximum yield, as this catalyst has been observed to have slight difference in structural and textural properties than other three catalysts (Table 1).

To study the effect of temperature, synthesis of 7-amino 4-methyl coumarin was carried out in the temperature range of 90–150 °C in both solvent free condition and in presence of nitrobenzene.

Solvent free synthesis shows (Table 3) that 100% conversion of *m*-amino phenol with 100% selectivity for 7-amino 4-methyl coumarin could be achieved at 110 °C temperature after 1 h. The kinetics studied at 110 °C was observed to be very fast showing 100% conversion and selectivity within 2 min of the reaction, which further remains steady with increasing time without showing any deactivation of the catalyst and formation of any side-products. To optimize the other reaction parameters, 110 °C reaction temperature and 15 min reaction time were chosen as optimized temperature and time for solvent free synthesis.

The results in the presence of polar nitrobenzene show (Table 4) that the conversion of *m*-amino phenol was observed to be similar at 110 and 130 °C, however, at 150 °C, significantly increases from 65 to 100% with 99% selectivity of 7-amino 4-methyl coumarin after 1 h. The kinetics of the reaction studied at 150 °C showed 100% conversion within 45 min of the reaction with ~98–99% selectivity, which increased to 100% after 2 h. The maximum conversion and selectivity remained steady till 3 h of the reaction. The reaction carried out in non-polar solvent, toluene showed comparatively lower conversion (45%) after 2 h, however with 100% selectivity. For further studies in nitrobenzene solvent, 150 °C temperature and 2 h time was chosen as optimized temperature and time.

The study clearly shows the slow kinetics in presence of nitrobenzene, which also requires higher temperature to obtain 100% conversion. This may be explained due to the (i) slow diffusion of the reactant molecules through the bulk solvent and (ii) the interaction of solvent molecules with the acid sites of the catalyst. Lower conversion in presence of toluene (45%) as compared to nitrobenzene (100%) indicates that the polarity of nitrobenzene is not responsible for the slow kinetics of the reac-

Table 3
Effect of temperature and kinetic study on solvent free synthesis of 7-amino 4-methyl coumarin (AMC) with sulfated zirconia

Temperature (°C)	Time (min)	Conversion of *m*-AP (%)	Selectivity of AMC (%)
90	60	95	100
110		100	100
130		100	100
150		100	100
110	2	100	100
	4	100	100
	6	100	100
	8	100	100
	10	100	100
	12	100	100
	15	100	100

m-Amino phenol:ethyl acetoacetate molar ratio = 1:2, phenol:catalyst wt. ratio = 10, 0.1 g tridecane.

Table 4
Effect of temperature and kinetic study on synthesis of 7-amino 4-methyl coumarin (AMC) with sulfated zirconia in presence of nitrobenzene solvent

Temperature (°C)	Time (min)	Conversion of *m*-AP (%)	Selectivity of AMC (%)
110	60	65	99.7
130		64	98.5
150		100	98.8
150	15	77	98.6
	30	91	97.7
	45	100	98.5
	60	100	96.0
	90	100	96.8
	120	100 (45[a])	100 (100[a])
	150	100	100
	180	100	100

m-Amino phenol:ethyl acetoacetate molar ratio = 1:1, nitrobenzene = 3 g, phenol:catalyst wt. ratio = 10, 0.1 g tridecane.
[a] Reaction in toluene.

Table 5
Effect of phenol to ester molar ratio on selectivity of 7-amino 4-methyl coumarin (AMC) with sulfated zirconia in solvent free conditions and in presence of nitrobenzene

m-AP:EAA	Solvent free[a]		With nitrobenzene[b]	
	Conversion of *m*-AP (%)	Selectivity of AMC (%)	Conversion of *m*-AP (%)	Selectivity of AMC (%)
1:1	100	100	100	100
1:1.5	100	100	100	97
1:2	100	100	100	97

Phenol:catalyst wt. ratio = 10.
[a] Reaction temperature = 110 °C and time = 15 min (0.1 g tridecane).
[b] Reaction temperature = 150 °C and time = 3 h (0.1 g tridecane).

Table 6
Effect of phenol to catalyst weight ratio on conversion of phenol and selectivity of 7-amino 4-methyl coumarin (AMC) with sulfated zirconia in presence of nitrobenzene and solvent free synthesis

Substrate/catalyst wt. ratio	Solvent free[a]		With nitrobenzene[b]	
	Conversion of *m*-AP (%)	Selectivity of AMC (%)	Conversion of *m*-AP (%)	Selectivity of AMC (%)
10	100	100	100	100
20	100	100	100	96
40	100	100	100	96
80	100	100	100	94

[a] *m*-Amino phenol:ethyl acetoacetate molar ratio = 1:2, reaction temperature = 110 °C and time = 15 min (0.1 g catalyst, 0.1 g tridecane).
[b] *m*-Amino phenol:ethyl acetoacetate molar ratio = 1:1, nitrobenzene = 3 g/phenol, reaction temperature = 150 °C and time = 3 h (0.1 g catalyst, 0.1 g tridecane).

tion. It is mainly due to the decreased diffusion of the reactant molecules in the presence of the solvent.

3.2.1. Effect of molar ratio of m-amino phenol and ethyl acetoacetate

The effect of molar ratio of *m*-amino phenol to ethyl acetoacetate ranging from 1:1 to 1:2 was observed to have no effect on the maximum conversion in both solvent free condition and nitrobenzene. However, the selectivity was observed to slightly decrease from 100% to 97% by increasing the molar ratio in nitrobenzene (Table 5), which indicates that nitrobenzene plays a role in decreasing the selectivity and not the ester, as in solvent free condition the selectivity of the same was not affected with the increase in the molar ratio of the ester.

3.2.2. Effect of substrate to catalyst weight ratio

The effect of *m*-amino phenol to catalyst weight ratio was studied by carrying out the reaction at different phenol to catalyst weight ratio in the range of 10–80. Table 6 shows that when the reaction was carried out in solvent free conditions, conversion and selectivity was not affected by increasing the substrate to catalyst weight ratio from 10 to 80. In presence of nitrobenzene solvent, there is no effect on the conversion of *m*-amino phenol, however, the selectivity for 7-amino 4-methyl coumarin was observed to decrease from 100 to 94 by increasing substrate to catalyst weight ratio, which indicates the effect of nitrobenzene solvent on selectivity of the product.

3.3. Synthesis of 7-hydroxy 4-methyl coumarin

Initially, synthesis of 7-hydroxy 4-methyl coumarin with all four nano-crystalline sulfated-zirconia catalysts using *m*-hydroxy phenol and ethyl acetoacetate (Scheme 1) in solvent free conditions and also in presence of nitrobenzene solvent was carried out at 150 °C temperature for 1 h. The yield of 7-hydroxy 4-methyl coumarin was found to be significantly higher (42–43%) in solvent free synthesis as compared to that with nitrobenzene (21–24%) (Table 7). Catalyst SZ-2 was chosen for further study to optimize the reaction parameters for obtaining maximum yield, similarly as for amino derivative.

To study the effect of temperature, synthesis of 7-hydroxy 4-methyl coumarin was carried out at 150 and 170 °C from 0.5 to 24 h. The results (Table 8) show that yields are higher at 170 °C temperature in both solvent and solvent free conditions. Kinetic study at both the temperatures showed that highest yield of 7-hydroxy 4-methyl coumarin can be obtained in 3–6 h at 170 °C and after 12 h at 150 °C. Therefore, 170 °C reaction temperature and 3 h reaction time was chosen as optimized temperature and time for further studies in both the conditions. Furthermore, solvent free synthesis results in significantly higher yields (78%)

Table 7
Yield (wt%) of 7-hydroxy 4-methyl coumarin (HMC) with sulfated-zirconia catalysts

Catalyst	Yield of HMC (wt%)	
	Solvent free[a]	With nitrobenzene[b]
SZ-1	42	23
SZ-2	43	24
SZ-3	43	21
SZ-4	42	22

Reaction temperature = 150 °C, reaction time = 1 h, phenol:catalyst wt. ratio = 10.
[a] *m*-Hydroxy phenol:ethyl acetoacetate molar ratio = 1:2.
[b] *m*-Hydroxy phenol:ethyl acetoacetate molar ratio = 1:1, nitrobenzene = 3 g.

Table 8
Yield (wt%) of 7-hydroxy 4-methyl coumarin with sulfated-zirconia catalyst under solvent free and in presence of nitrobenzene at 150 and 170 °C

Time (h)	Yield of HMC (wt%)			
	Solvent free[a]		With nitrobenzene[b]	
	150 °C	170 °C	150 °C	170 °C
0.5	–	43	–	–
1	43	72	24	30
3	56	78	24	32 (15[c])
6	74	77	27	34
12	75	78	34	37
18	74	–	34	–
24	74	–	35	43

Phenol:catalyst wt. ratio = 10.
[a] *m*-Hydroxy phenol:ethyl acetoacetate molar ratio = 1:2.
[b] *m*-Hydroxy phenol:ethyl acetoacetate molar ratio = 1:1, nitrobenzene = 3 g.
[c] Reaction in toluene (3 g).

as compared to nitrobenzene (32%) and toluene (15%) after 3 h at 170 °C. Similar observations of higher yields in solvent free conditions (56%) as compared to nitrobenzene (24%) are made at 150 °C after 3 h (Table 8). The data show the effect of the solvent (polar as well as non-polar) on the synthesis of 7-hydroxy 4-methyl coumarin. The lower yields in the presence of solvent may be due to (i) bulk diffusion effect or (ii) interaction of solvent with the acid sites of the catalyst (iii) polarity of the solvent resulting into interaction of substrate molecule with solvent as discussed above in Section 3.2. The slow kinetic data in presence of nitrobenzene (Table 8) reveals the possibility of (i) slow diffusion of the reactant molecule through the bulk solvent. Furthermore, toluene is the most commonly used solvent during coumarin synthesis by Pechmann reaction [31–33] as it is reported that non-polar solvents favor the Pechmann reaction and polar solvents cause the cleavage [31]. However, in the present study, we observed lower yield with toluene (15%) as compared to nitrobenzene (32%) indicating that polarity of nitrobenzene does not seems to be responsible for lower yields and slow kinetics in the present experimental conditions.

Several studies have been carried out to study the effect of solvent on coumarin synthesis, however, with different observations. For example, Wang et al. [26] found the yield of 7-hydroxy 4-methyl coumarin using $Yb(OTf)_3$ in various solvents in the increasing order as follows: Solvent free (95) >THF (85) > CH_3CN (83) > Toluene (78) > CH_2Cl_2 (53) > H_2O (35) and reported THF is good solvent. Sabou et al. [31] have reported the yield of same derivative using Amberlyst ion-exchange resin in various solvents in the increasing order as follows: Toluene (89) > CH_2Cl_2 (62) > THF (48). Hoefnagel et al. [33] reported similar yield of same derivative using zeolite and amberlyst catalysts in both toluene and solvent free condition (77–80%). Romanelli et al. [37] also found similar yield of the same derivative using heteropoly acid catalyst, however, more time is required in toluene (4.5 h) as compared to solvent free conditions (30 min) to obtain maximum yield (82–87%). From these studies, nature of the catalyst seems to be responsible for the variation in the yield of the same derivative in the presence of solvent.

Table 9
Effect of phenol to ester molar ratio on yield (wt%) of 7-hydroxy 4-methyl coumarin (HMC), with sulfated-zirconia catalyst under solvent free and in presence of nitrobenzene

m-HP:EAA	Yield of HMC (wt%)	
	Solvent free[a]	With nitrobenzene[b]
1:1	76	32
1:1.5	78	31
1:2	77	32
1:3	77	31

Phenol:catalyst wt. ratio = 10, reaction temperature = 170 °C, reaction time = 3 h.
[a] *m*-Hydroxy phenol:ethyl acetoacetate molar ratio = 1:2.
[b] *m*-Hydroxy phenol:ethyl acetoacetate molar ratio = 1:1, nitrobenzene = 3 g.

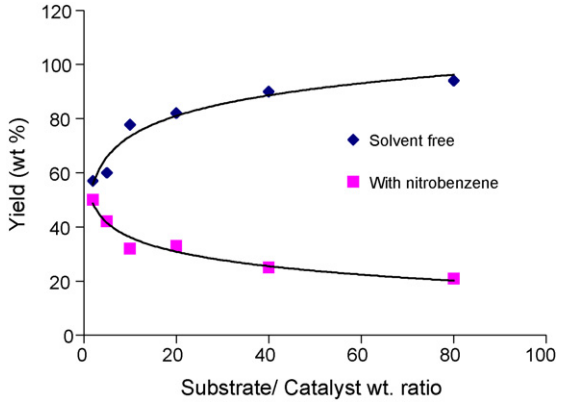


Fig. 3. Effect of substrate to catalyst weight ratio on yield (wt%) of 7-hydroxy 4-methyl coumarin under solvent free conditions and with nitrobenzene over sulfated zirconia.

3.3.1. Effect of molar ratio of m-hydroxy phenol and ethyl acetoacetate

In the present study the effect of molar ratio of *m*-hydroxy phenol to ethyl acetoacetate ranging from 1:1 to 1:3 was observed to have no significant effect on the yield of 7-hydroxy 4-methyl coumarin in both solvent free condition (76–78%) and nitrobenzene (31–32%) at 170 °C for 3 h (Table 9). However, Palaniappan and Shekhar [35] found significant increase in the yield of same derivative at 150 °C after 6 h in sol-

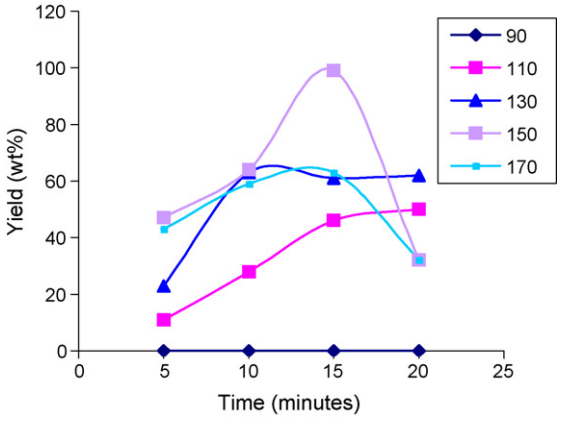


Fig. 4. Yield (wt%) of 7-hydroxy 4-methyl coumarin with time under solvent free microwave irradiation (250 W) at different temperatures.

vent free condition, using polyaniline supported catalyst, with increase in the molar ratio from 1:1 to 1:2 as follows: 1:1(41) > 1:1.1(54) > 1:1.5(62) > 1:2(72) = 1:3, which could be due to the different nature of the catalyst.

3.3.2. *Effect of substrate to catalyst weight ratio*

The effect of phenol to catalyst weight ratio has been studied with a wide range of (2–80 wt%) phenol to catalyst weight ratio in both solvent free condition and nitrobenzene at 170 °C for 3 h and was found to have significant effect on the yield of 7-hydroxy 4-methyl coumarin. Interesting results were observed that under solvent free synthesis a significant increase from 57 to 94% in the yield of 7-hydroxy 4-methyl coumarin was observed on increasing phenol to catalyst ratio from 2 to 80 (Fig. 3). At highest phenol to catalyst ratio of 80, yield of 7-hydroxy 4-methyl coumarin was found to be maximum (94%) showing the excellent catalytic activity of sulfated-zirconia catalyst that is required in very small catalytic amount for the synthesis of 7-hydroxy 4-methyl coumarin. However, in nitrobenzene, yield was successively decreased from 49 to 21% with the increase in phenol to catalyst weight ratio.

The increase of yield of hydroxy derivative in solvent free condition with increasing phenol to catalyst weight ratio is explained in terms of the increased dispersion of the catalyst with increasing substrate that increases the availability of the catalytically active acid sites to reactant molecules. It is to be noted here that at increasing phenol to catalyst weight ratio, a fixed amount of the catalyst was taken (0.1) g for accuracy in

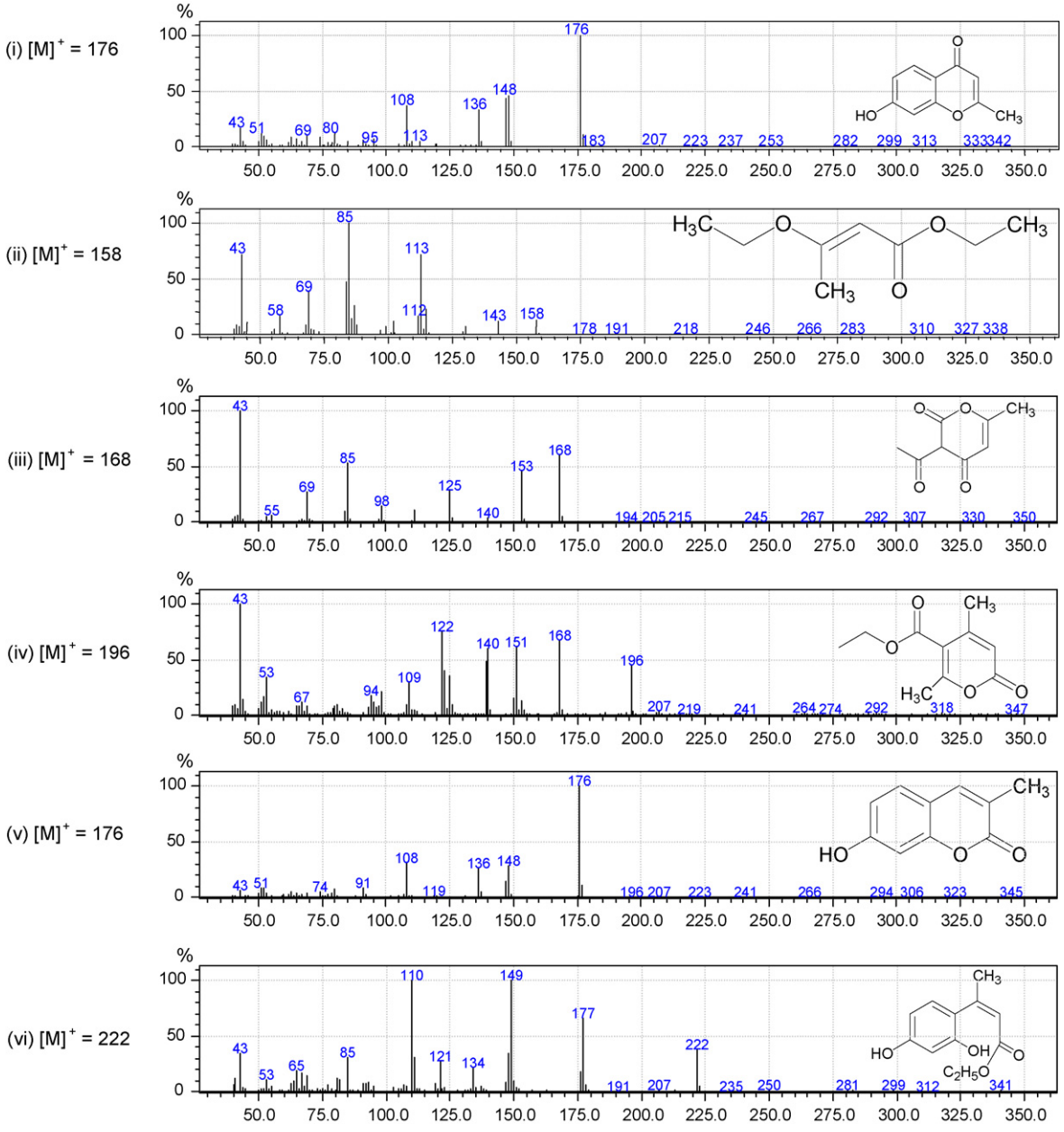


Fig. 5. GC-mass spectra of side products formed in microwave assisted synthesis of 7-hydroxy 4-methyl coumarin at higher time and temperature [(i) chromone; (ii), (iii) and (iv) products formed by self-condensation of ethyl acetoacetate; (v) isomerized and (vi) cleaved products from 7-hydroxy 4-methyl coumarin].

the experiment and amount of reactants have been increased subsequently for required substrate to catalyst weight ratio. The increased amount of reactants also act as solvent and may be helpful in the diffusion of the reactants and the products and also enhancing the acidity due to acidic nature of phenol. Whereas, in presence of nitrobenzene, the increasing amount of nitrobenzene (3 g/phenol) with respect to increasing amount of reactants results more resistance in bulk diffusion of reactants. Furthermore, small amount of catalyst (0.1 g) provides less availability of acidic sites. Therefore, successive decrease was observed in the yield with increasing phenol to catalyst weight ratio due to increasing amount of nitrobenzene.

3.4. Microwave assisted synthesis of 7-hydroxy 4-methyl coumarin

Fig. 4 shows the yield (%) of 7-hydroxy 4-methyl coumarin synthesized by microwave irradiation at different temperatures and time. The results showed that the yield gradually increases with increasing the temperature from 110 to 150 °C and also with time from 5 to 20 min, while there is no formation of 7-hydroxy 4-methyl coumarin at lower temperature (90 °C). Maximum yield (99%) of 7-hydroxy 4-methyl coumarin was found in 15 min at 150 °C without any other side product, which was confirmed by GC–MS analysis (Shimadzu GC MS-QP 2010 having Petrocol capillary column of 50-m length and 0.2-mm diameter with a programmed oven temperature from 40 to 250 °C, at 1.2 cm^3/min flow rate of He as carrier gas and ion source at 473 K) of the mother liquor. By increasing the time from 15 to 20 min the yield of the coumarin was found to decrease. At higher temperature of 170 °C, yield was also low.

The lower yield of 7-hydroxy 4-methyl coumarin at higher temperature and higher reaction time was found to decrease due to formation of side products such as chromones, the products from self-condensation of ethyl acetoacetate, isomerization and cleavage of 7-hydroxy 4-methyl coumarin (Fig. 5). The formation of these side products was confirmed by GC–MS analysis of the solid residue obtained after separation of the crystals of 7-hydroxy 4-methyl coumarin. The residue was dissolved in dimethyl sulfoxide for GC–MS analysis.

4. Regeneration of catalyst

The spent catalyst was thermally regenerated at 450 °C for 4 h in flow of air after filtration from the hot reaction mixture and washing with hot ethanol and acetone. The regenerated catalyst showed similar yield/conversion and selectivity as the fresh catalyst, i.e. 100% conversion and selectivity for amino derivative and 75–76% yield of hydroxy derivative, till the 6th reaction cycles to synthesize 7-substituted 4-methyl coumarin derivatives. FT-IR spectra of used and regenerated catalyst for both 7-substituted 4-methyl coumarin derivatives showed the absence of IR peaks of adsorbed reactants and products on the surface of regenerated sulfated-zirconia catalyst (Fig. 6a and b) indicating the easy regenerability of the catalyst.

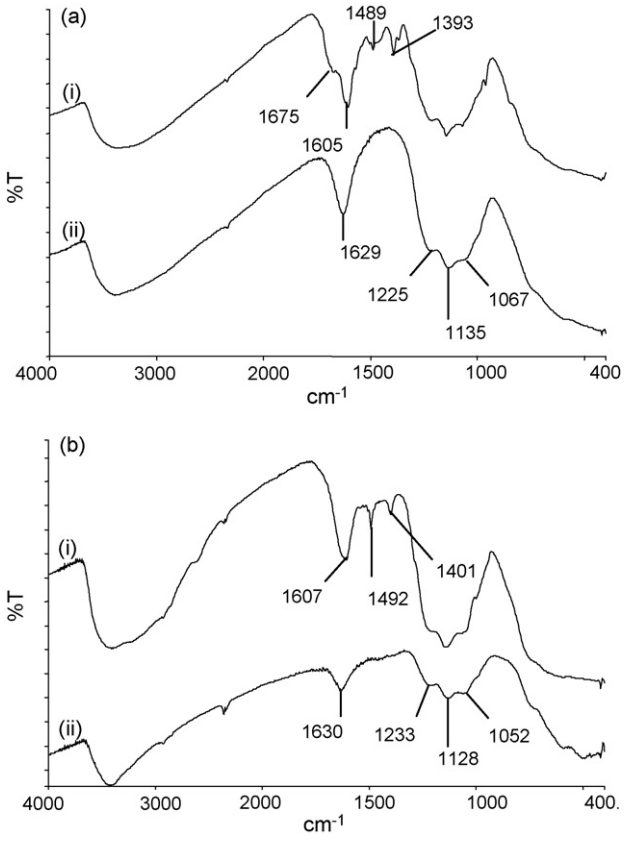


Fig. 6. FT-IR spectra of (i) used and (ii) regenerated sulfated-zirconia catalyst for the synthesis of (a) 7-amino 4-methyl coumarin and (b) 7-hydroxy 4-methyl coumarin.

5. Conclusions

The nano-crystalline sulfated-zirconia catalysts, prepared by one-step as well as two-step sol–gel technique are observed to show excellent catalytic activity with a high substrate to catalyst weight ratio for the synthesis of 7-substituted 4-methyl coumarins via solvent free Pechmann reaction. The *m*-amino phenol was found to be more reactive than *m*-hydroxy phenol. The catalyst results 100% conversion of *m*-amino phenol with ~100% selectivity of 7-amino 4-methyl coumarin in solvent free synthesis and also in presence of nitrobenzene solvent. However, reaction is very fast in solvent free condition and the complete conversion could be attained at comparatively lower temperature within few minutes than nitrobenzene. Slow kinetics was observed in presence of solvents, in polar nitrobenzene as well as in non-polar toluene for both coumarin derivatives, which is due to the slow bulk diffusion of reactant molecules in presence of solvent. The polarity of the solvent did not seem to be responsible for slow kinetics. The effect of nitrobenzene was observed more for 7-hydroxy 4-methyl coumarin. With increasing phenol to substrate weight ratio, proper dispersion of catalytic active sites results into higher yields.

The solvent free microwave assisted synthesis seems most suitable way to synthesize the hydroxy derivative giving excellent yield at lower temperature and in much lesser time as compared to thermal heating. The use of very small amount

of sulfated-zirconia catalyst for the synthesis of coumarins and the reusability of the catalyst after simple activation for several times with similar activity are advantageous properties of the catalyst.

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