Microwave-assisted solvent free synthesis of hydroxy derivatives of 4-methyl coumarin using nano-crystalline sulfated-zirconia catalyst

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Abstract

Nano-crystalline sulfated-zirconia solid acid catalyst has been studied for microwave-assisted solvent free synthesis of hydroxy derivatives of 4-methyl coumarin by Pechmann reaction. The catalyst showed good activity for activated *m*-hydroxy phenol substrates, viz., phloroglucinol and pyrrogallol with ethyl acetoacetate for the synthesis of 5,7-dihydroxy 4-methyl coumarin and 7,8-dihydroxy 4-methyl coumarin, respectively, showing significant yields ranging from 78 to 85% within 5–20 min at 130 °C. However, the less activated phenol and *m*-methyl phenol was observed to be inactive for the synthesis of 4-methyl coumarin and 4,7-dimethyl coumarin, respectively, under the studied experimental conditions.
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1. Introduction

The coumarins are heterocyclic organic compounds, also known as benzo-2-pyrone derivatives and constitute an important group of natural products having varied activities. Hydroxy derivatives of 4-methyl coumarin are important group of coumarin derivatives showing medicinal as well as other applications. For example, 5,7-dihydroxy 4-methyl coumarin and 7,8-dihydroxy 4-methyl coumarins are useful precursors to synthesize respective diacetoxy and hydroxy-amino derivatives of 4-methyl coumarin, which are known to be good antioxidants having excellent radical scavenging properties [1]. Amides of 5,7-dihydroxy 4-methyl coumarin containing substituents at third position also show improved antioxidant properties [2].

Pechmann reaction is a well-known simple method and has been widely used to synthesize coumarins from activated phenols, mostly *m*-substituted phenols and acetoacetic esters or an unsaturated carboxylic acid in presence of an acid catalyst [3]. Besides the use of various conventional homogeneous acids such as H_2SO_4, H_3PO_4, CF_3COOH, *p*-toluene sulfonic acid, P_2O_5, $POCl_3$ and metal halides, different solid acid catalysts [4–9] have also been studied for the synthesis of the hydroxy derivatives of 4-methyl coumarin . However, to obtain high yield with solid acid catalysts longer reaction times are required.

The use of microwave irradiation has been employed for a number of organic syntheses to reduce the reaction time, rate enhancement and to increase the selectivity and yields. Microwave irradiation has also been used for coumarin synthesis via Pechmann reaction catalyzed by homogeneous liquid acids such as sulfuric acid, *p*-toluene sulfonic acid and ionic liquid [10–12]. However, sulfuric acid and *p*-toluene sulfonic acid are corrosive, hazardous and require careful handling in open chamber of domestic microwave system. The separation of ionic liquid catalyst to recover from reaction mixture by solvent extraction adds an extra step in synthesis.

The use of solid acids for microwave-accelerated synthesis of coumarins is scanty [10,13,14]. Singh et al. [10] studied the synthesis of coumarins on solid support K-10 montmorillonite clay using domestic microwave oven and observed higher selectivity, however, with poor yields of coumarins. Singh et al. [13] obtained good yield (55–85%) of other coumarin derivatives using montmorillonite K-10 clay, however, reaction was

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promoted with the addition of one drop of concentrated sulfuric acid and high power of microwave irradiation (640 W) was required. Frère et al. [14] obtained good yields (66%) of coumarin derivatives in 30 min on solid support graphite/K-10 using a focused microwave reactor (300 W, monomode system), however, they observed that the use of appropriate solvent is required for controlled microwave reactions.

Recently, we [15] have reported excellent catalytic activity of nano-crystalline sulfated-zirconia solid acid catalyst for the synthesis of 7-substituted 4-methyl coumarins by thermal heating as well as by microwave irradiation using a commercial microwave reactor (Ethos 1600 Microwave Lab Station, Italy), which resulted into higher yield (99%, 150 °C, 15 min) of 7-hydroxy 4-methyl coumarin as compared to thermal synthesis (77%, 170 °C, 3–6 h). In the present study, we extended the microwave synthesis of other hydroxy derivatives using activated phenols (phloroglucinol and pyrrogallol) as well as less-activated (phenol and *m*-methyl phenol) substrates with ethyl acetoacetate using the sulfated-zirconia catalyst under solvent free conditions.

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 procured from s.d. Fine chemicals, India. Phloroglucinol, pyrogallol, phenol and *m*-methyl phenol were from Central Drug House, India and ethyl acetoacetate was procured from Loba Chemie, India. All chemicals were used as such.

2.2. Catalyst synthesis

Sulfated zirconia catalyst was prepared using one-step sol–gel technique [15]. Concentrated sulfuric acid (1.02 ml) was added to zirconium *n*-propoxide (30 wt.%) and water (4.2 ml) was then added drop wise under continuous stirring, just sufficient to form a gel. The water and Zr-P molar ratio was kept at 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.

2.3. Catalyst characterization

The sulfated zirconia sample was characterized by powder X-ray diffractometer (Philips X'pert), FT-IR spectrophotometer (Perkin Elmer GX, USA), N_2 adsorption–desorption isotherms at 77.4 K (ASAP 2010, Micromeritics, USA) and CHNS/O elemental analyzer (Perkin Elmer 2400, Sr II USA) for bulk sulfur analysis (wt.%) retained in the samples after calcination at 600 °C as described in our previous report [15]. Crystallite size of tetragonal phase was determined from the characteristic peak ($2\theta = 30.18$ for the (1 1 1) reflection) by using Scherrer formula with a shape factor (K) of 0.9 [16] as below:

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

Where, $W = Wb - Ws$; Wb is the broadened profile width of experimental sample and Ws is the standard profile width of reference silicon sample.

2.4. Acidity measurement

2.4.1. Cyclohexanol dehydration

Brönsted acidity present in the sulfated-zirconia catalyst was assessed using a Brönsted acid catalyzed model test reaction of cyclohexanol dehydration to cyclohexene in vapor phase. The catalyst (0.5 g) was packed in a fixed bed glass reactor and was *in situ* activated at 450 °C for 2 h under flow of N_2. Cyclohexanol (5 ml) was delivered by syringe pump injector (Cole Parmer, 74900 series) with a flow rate of 0.042 cm³ min⁻¹ under N_2 flow (15 cm³ min⁻¹) after bringing down the reaction temperature to 175 °C. The vapors of reaction mixture were condensed, collected after 1 h and were analyzed by gas chromatography (HP 6890, USA) having a FID detector, a HP50 (30 m long) capillary column with a programmed oven temperature from 50 to 200 °C and a 0.5 cm³ min⁻¹ flow rate of N_2 as a carrier gas. The conversion of cyclohexanol and selectivity for cyclohexene was calculated on weight percent basis.

2.4.2. FT-IR spectroscopy

The presence of Brönsted and Lewis acid sites in the sulfated-zirconia sample was assessed by FT-IR spectroscopy of adsorbed pyridine using an FT-IR spectrophotometer equipped with The Selector DRIFT accessory (Graseby Specac, P/N 19900 series) incorporating an environmental chamber assembly (Graseby Specac, P/N 19930 series). The heating was done by an automatic temperature controller (Graseby Specac, P/N 19930 series) connected with the environmental chamber. The activated (450 °C for 2 h) sample (0.2 g) was cooled in desiccator under vacuum and was exposed to pyridine (25 ml) for 1 h. The spectra were recorded at room temperature in the range of 400–4000 cm⁻¹ and after *in situ* heating at 150 °C under dry N_2 flow (30 cm³ min⁻¹).

2.5. Catalytic activity: microwave-assisted solvent free synthesis of hydroxy derivatives of 4-methyl coumarins

Phloroglucinol, pyrogallol, phenol and *m*-methyl phenol substrates were reacted with ethyl acetoacetate under microwave irradiation (250 W) in presence of nano-crystalline sulfated-zirconia catalyst under solvent free conditions. In a typical reaction, phenol substrate and ethyl acetoacetate (1:2 molar ratio) were taken along with the activated (450 °C, 2 h) catalyst (phenol to catalyst weight ratio = 10) in a 100 ml Teflon vessel of the microwave reactor (Ethos 1600 Microwave Lab Station, Italy). The reaction mixture was kept in microwave reactor at different temperatures ranging from 110 to 150 °C for 5–20 min. 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, dried and slowly re-crystallized in ethanol–water system. The
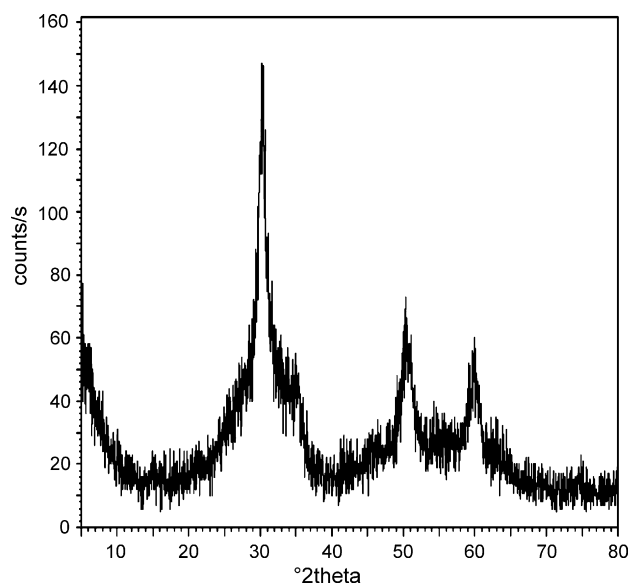
Fig. 1. XRD pattern of sulfated-zirconia after calcination at 600 °C.

Fig. 2. N$_2$ adsorption–desorption isotherm of sulfated-zirconia calcined at 600 °C.

products were characterized by melting point, FT-IR (Perkin Elmer GX, USA) and ^{1}H NMR spectroscopy (Bruker, Avance DPX 200 MHz). The yields of coumarin products were obtained as follows:

$$\text{yield (wt.\%)} = \left(\frac{\text{obtained weight of product}}{\text{theoretical weight of product}} \right) \times 100$$

3. Results and discussion

3.1. Catalyst characterization

The sulfated-zirconia catalyst, after calcination at 600 °C for 2 h, showed characteristic peaks of tetragonal crystalline phase (Fig. 1) and crystallite size of 9 nm (Table 1). However, the observed crystallinity of the sample is poor. The higher sulfur content (3.9 wt.%) retained after calcination could be attributed to poor crystallinity of the sample as higher thermal energy is required for dehydroxylation during crystallization in presence of sulfate groups that enhances the crystallization temperature.

N$_2$ adsorption–desorption isotherms of the sulfated-zirconia sample, calcined at 600 °C, shows the isotherm of type II as per IUPAC, with a hysteresis of type H3 at relative pressure, p/p_0, of 0.6 indicating the slit-shaped pores in the sample (Fig. 2). The surface area, pore volume and pore size of the sample, after

calcination were measured to be 150 m^2/g, 0.33 cm^3/g and 89 Å, respectively (Table 1).

Brönsted acid catalyzed dehydration reaction of cyclohexanol to cyclohexene, which results into 85% conversion of cyclohexanol with 100% selectivity of cyclohexene indicates the presence of significant Brönsted acidity in sulfated-zirconia catalyst.

FT-IR spectrum shows the presence of inorganic chelating bidentate sulfate group in the region of 1200–900 cm^{-1} [15]. FT-IR spectrum of pyridine adsorbed sulfated-zirconia sample at 150 °C (Fig. 3) shows bands in the region of 1400–1700 cm^{-1}. Pyridine adsorption has been known to distinguish between Brönsted and Lewis acidic sites [17–18]. The characteristic peaks for pyridinium ion (Brönsted sites) and co-valently bonded pyridine (Lewis sites) at 1541 and 1445 cm^{-1}, respectively, show the presence of both Brönsted and Lewis acidic sites in sulfated-zirconia catalyst. The other peaks at 1636 and 1612 cm^{-1} show Brönsted sites. The peak at 1489 cm^{-1} represents the total acidic sites in the sample.

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

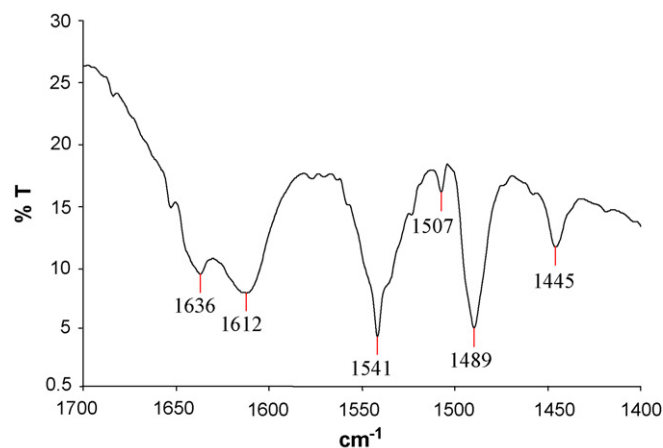| Crystallite phase	Tetragonal
Crystallite size (nm)	9
S (wt.%)	3.9
Pore volume (cm^3/g)	0.33
Pore size (Å)	89
BET Surface area (m^2/g)	150

Fig. 3. FT-IR spectrum of pyridine adsorbed sulfated-zirconia after desorption at 150 °C.
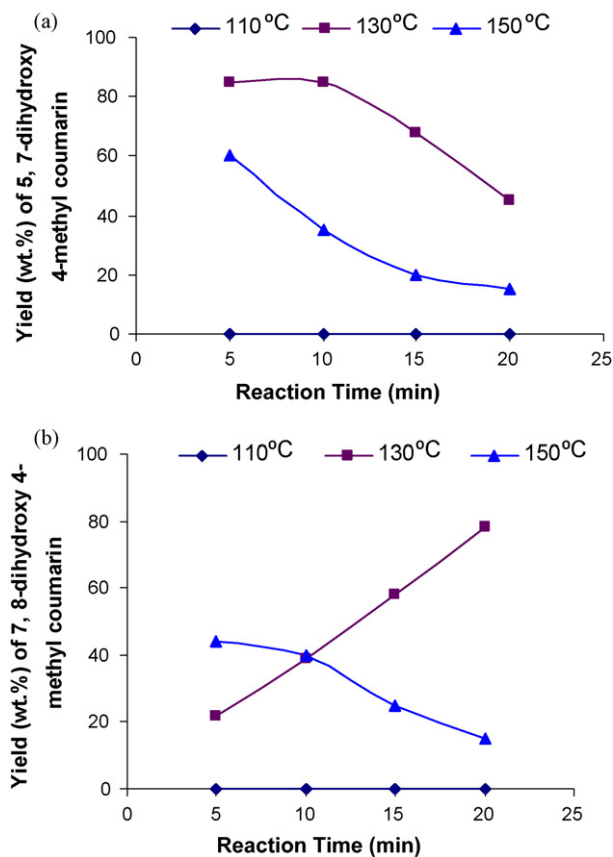
Fig. 4. Yield (wt.%) of (a) 5,7-dihydroxy 4-methyl coumarin and (b) 7,8-dihydroxy 4-methyl coumarin under solvent free microwave irradiation (250 W) at different temperatures (°C) and time (min).

3.2. Catalytic activity for microwave accelerated solvent free synthesis of hydroxy derivatives of 4-methyl coumarins

Table 2 shows the reactivity of activated as well as less-activated phenolic substrates with ethyl acetoacetate using the sulfated-zirconia catalyst for solvent free microwave accelerated synthesis of various hydroxy derivates of 4-methyl coumarins. For the synthesis of 5,7-dihydroxy 4-methyl coumarin, no product was observed with phloroglucinol and ethyl acetoacetate at 110 °C till 20 min of microwave irradiation using sulfated zirconia catalyst. However, by increasing the temperature to 130 °C, 85% yield of the coumarin was obtained within 5 min. By increasing the irradiation time from 5 to 20 min, the yield of the coumarin was observed to decrease (Fig. 4a). By further increasing the temperature to 150 °C, the yield was decreased and was observed to successively decrease with increasing the irradiation time (Fig. 4a).

For the synthesis of 7,8-dihydroxy 4-methyl coumarin, gradual increase in yield was observed with pyrrogallol and ethyl acetoacetate at 130 °C with time and maximum yield (78%) was obtained after 20 min (Fig. 4b). At lower temperature (110 °C), no product formation was observed till 20 min and at higher temperature (150 °C), the yield of coumarin was gradually decreased with increasing the irradi-

ation time as was observed in case of 5,7-dihydroxy 4-methyl coumarin.

The lower yield at higher temperature and higher microwave irradiation time in both the cases is explained due to the formation of side products such as chromones, the products from self condensation of ethyl acetoacetate, isomerization and cleavage of hydroxy coumarin derivatives, as was observed in our previous findings in case of 7-hydroxy 4-methyl coumarin [15].
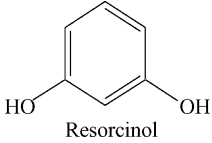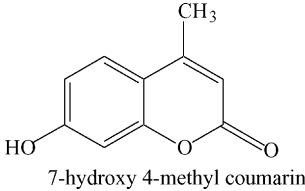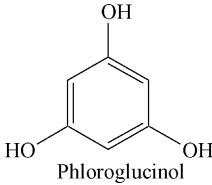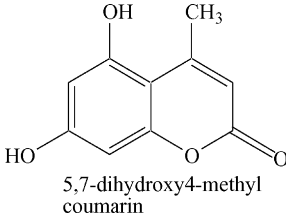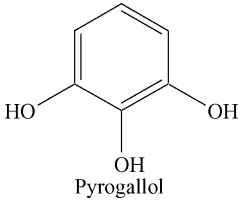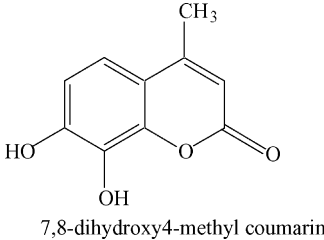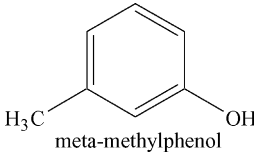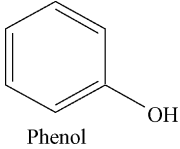
For the synthesis of 4-methyl coumarin and 4,7-dimethyl coumarin from phenol and *m*-methyl phenol, respectively, with ethyl acetoacetate, no product formation was observed at temperatures from 110 to 170 °C till 20 min as checked by thin layer chromatography (TLC) as well as by crystallization of the reaction mixture.

The earlier reports [19,20,8] on the synthesis of the hydroxy derivatives of 4-methyl coumarin, viz., 5,7-dihydroxy 4-methyl coumarin and 7,8-dihydroxy 4-methyl coumarin using different solid acid catalysts such as Nafion-H [8], W/ZrO2 solid acid [19] and K-10 [20] under thermal condition and in presence of solvent showed the yields of the coumarin products in the range of 51–85%, however, the reaction takes longer time ranging from 3 to 10 h to achieve the maximum yield. The microwave-assisted synthesis of these hydroxy derivatives of 4-methyl coumarins using sulfated-zirconia solid acid catalyst was found to reduce the reaction time from several hours to few minutes, with increased yield of the coumarin derivatives under solvent free conditions. The phenolic substrate and ethyl acetoacetate are polar molecules, therefore, microwave active and absorb the microwave radiations rapidly and accelerate the rate of reaction. Formation of polar ethanol as a by-product of the reaction also helps in absorption of microwave radiation and thereby accelerating the reaction.

The reactivity of phloroglucinol with ethyl acetoacetate was observed to be higher than pyrrogallol due to two hydroxy groups at *meta*-positions in phloroglucinol compared to one hydroxy group in pyrrogallol. Presence of *meta*-hydroxy group strongly activates the substrates due to resonance effect. However, phenol and *m*-methyl phenol, which are less reactive due to absence of any activating group in phenol; and presence of weakly activating methyl group in *m*-methyl phenol, were found inactive to synthesize 4-methyl coumarin and 4,7-dimethyl coumarin respectively under the experimental conditions of microwave irradiation studied using sulfated-zirconia catalyst. Though, reaction under thermal conditions (150–160 °C) over other solid acid catalysts such as K-10 [20] and Nafion-H solid acid [8] were found to result 4-methyl coumarin (65 % in 10 h) and 4,7-dimethyl coumarin (25% in 3.5 h). These results show that besides the catalyst acidity and the reactivity of phenolic substrates, the structural and textural features of catalyst could also play significant role in influencing the course of this reaction. For example, the physical adsorption of phenolic hydroxyl group of phenol and *m*-methyl phenol substrates on the surface of the sulfated zirconia catalyst might be responsible for making the substrate inactive to react with ethyl acetoacetate for esterification step of Pechmann reaction, whereas, in the case of di- and tri-hydroxy phenol, adsorption

Table 2
Yields (wt.%) of hydroxy derivatives of 4-methyl coumarin under solvent free microwave irradiation (250 W) using nano-crystalline sulfated-zirconia catalyst and ethyl acetoacetate

Phenols	Reaction temperature (°C)	Reaction time (min)	Products	Yield (wt.%)	Melting point (°C)
Resorcinol	150	15	7-hydroxy 4-methyl coumarin	99	185–190 *Ref.*[15]
Phloroglucinol	130	5	5,7-dihydroxy4-methyl coumarin	85	282–285
Pyrogallol	130	20	7,8-dihydroxy4-methyl coumarin	78	241–245
meta-methylphenol	110–170	5–20	Not obtained	–	–
Phenol	110–170	5–20	Not obtained	–	–

Phenolic substrate:ethyl acetoacetate = 1:2 molar ratio and substrate to catalyst weight ratio = 10.

of one phenolic hydroxyl group to the surface of the catalyst could facilitate the esterification by making free hydroxyl group electronic rich. However, to substantiate this, the reaction mechanism on the surface of solid acid catalyst needs to be studied.

3.3. Characterization of the products

The isolated products were characterized by melting point, FT-IR and ^{1}H NMR spectroscopy.

3.3.1. 5,7-Dihydroxy 4-methyl coumarin
Melting point: 282–285 °C; FT-IR (KBr): 3159 cm^{-1} (ν_{OH}), 1670 cm^{-1} ($\nu_{C=O}$); ^{1}H NMR (DMSO-d_6): δ10.5 (s, 1H,–OH), 10.3 (s, 1H, –OH), 6.3 (s, 1H, ArH), 6.2 (s, 1H, ArH), 5.9 (s, 1H, C=CH), 2.5 (s, 3H, –CH$_3$).

3.3.2. 7,8-Dihydroxy 4-methyl coumarin
Melting point: 241–245 °C; FT-IR (KBr): 3231 cm^{-1} (ν_{OH}), 1648 cm^{-1} ($\nu_{C=O}$); ^{1}H NMR (DMSO-d_6): δ10.0 (s, 1H, –OH), 9.4 (s, 1H, –OH), 7.1 (d, 1H, ArH), 6.8 (d, 1H, ArH), 6.1 (s, 1H, C=CH), 2.3 (s, 3H, –CH$_3$).

4. Conclusions

Nano-crystalline sulfated-zirconia showed significantly good yield (78–85%) of 5,7-dihydroxy 4-methyl coumarin and 7,8-dihydroxy 4-methyl coumarin under solvent free microwave irradiation at 130 °C within 5–20 min. The catalyst showed good activity for activated *m*-hydroxy phenol substrate viz., phloroglucinol and pyrrogallol with ethyl acetoacetate. However, the less activated phenol and *m*-methyl phenol substrates were observed to be inactive for the synthesis of 4-methyl coumarin and 4,7-dimethyl coumarin, respectively, under the

studied experimental conditions. This may be attributed to the physical adsorption of the substrate through the hydroxyl group over the surface of the catalyst making the substrate inactive for the reaction with ethyl acetoacetate as there is no free hydroxy group available for esterification step of the reaction.

Acknowledgments

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