Research Article

A Fast, Highly Efficient, and Green Protocol for Synthesis of Biscoumarins Catalyzed by Silica Sulfuric Acid Nanoparticles as a Reusable Catalyst

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Silica sulfuric acid nanoparticles have been prepared and shown to efficiently catalyse the reaction between an aromatic aldehyde or phenylglyoxal and a 4-hydroxycoumarin at reflux in EtOH to afford the biscoumarin derivatives in high yield.

1. Introduction

A variety of biological activities are associated with coumarins and biscoumarins, for example, anticoagulants and antianthelmintic and antifungal activities [1–3]. Furthermore, these compounds can be complexed with rare earth metals as anti-HIV agents [4]. The synthesis of biscoumarins has been reported in the presence of piperidine [5], molecular iodine [6], tetrabutylammonium bromide [7], [bmim]BF₄ [8], sodium dodecyl sulfate [9], SO₃H-functionalized ionic liquid [10], and [MIM(CH₂)₄SO₃H][HSO₄] [11].

In this paper, we report a simple and efficient method for synthesis of biscoumarin derivatives using different aromatic aldehydes and phenylglyoxals and 4-hydroxycoumarin in the presence of silica sulfuric acid nanoparticles under reflux in ethanol. The catalyst is recyclable with reproducible results without any loss of its activity. The morphology of the silica sulfuric acid nanoparticles was observed using a scanning electron microscope (SEM).

2. Experimental

2.1. General. IR spectra were recorded on a Shimadzu IR-470 spectrometer in KBr discs. The NMR spectra were obtained on a Bruker Avance DRX-500 FT spectrometer (¹H NMR at 500 Hz, ¹³C NMR at 125 Hz) using CDCl₃ as solvent with TMS as internal standard. Melting points were determined

with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Costech ECS 4010 CHNS-O analyzer at Analytical Laboratory of Science and Researches Unit of Islamic Azad University. The morphology of the catalyst was observed using an SEM model VEGA//TESCAN with an accelerating voltage of 15 kV. The chemicals used in this work were purchased from Sigma Aldrich and Fluka (Buchs, Switzerland) and were used without further purification.

2.2. Synthesis of Silica Sulfuric Acid Nanoparticles. The reagent was prepared by combination of chlorosulfonic acid (23.3 g) drop by drop over 10 min via a syringe to nanosilica gel powder (60 g) in a 100 mL flask at 0°C. The reaction mixture was then stirred, and then after 30 min, the white powder was separated. The dimensions of nanoparticles were observed with SEM (Figure 1). The size of particles is between 28 and 32 nm.

2.3. General Procedure for the Synthesis of Biscoumarin. A mixture of 4-hydroxycoumarin (2 mmol), aromatic aldehyde or arylglyoxal (1 mmol), SiO₂-OSO₃H NPs (0.003 g), and EtOH (5 mL) was placed in a round bottom flask. The materials were mixed and refluxed for 20 min. The progress of the reaction was followed by TLC (*n*-hexane:ethylacetate). After completion of the reaction, the mixture was filtered to remove the catalyst. By evaporation of the solvent, the crude

FIGURE 1: The SEM images of $\text{SiO}_2\text{-OSO}_3\text{H}$ NPs.

product was recrystallized from hot ethanol to obtain the pure compound.

2.4. Selected Spectral Data

3,3'-Bis (4-hydroxy coumarin-3yl) (3-nitro-4-chlorophenyl) methane (4m). IR (KBr) ν_{max} : 3450, 3015, 1664, 1603, 1561, 1348, 761 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 6.3 (s, 1H, CH), 7.27 (d, 2H, $J = 7.5$ Hz, aromatic), 7.34 (d, 2H, $J = 8.2$ Hz, aromatic), 7.48 (d, 1H, $J = 8.2$ Hz, aromatic), 7.55–7.59 (m, 3H, aromatic), 7.79 (s, 1H, aromatic), 7.88 (d, 2H, $J = 7.7$ Hz, aromatic), 12.3 (broad s, 2H, OH) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ 36.9, 104.1, 116.8, 118.9, 122.6, 124.6, 131.7, 132.7, 133.3, 143.4, 148.5, 153.2, 165.2, 166.6 ppm. Anal. Calcd. For $\text{C}_{25}\text{H}_{14}\text{ClNO}_8$: C, 61.03; H, 2.83; N, 2.83 Found: C, 61.02; H, 2.87; N, 2.85.

3,3'-Bis (4-hydroxy coumarin-3yl) (2,4-dichlorophenyl) methane (4n). IR (KBr) ν_{max} : 3485, 3085, 1664, 1603, 766 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 6.1 (s, 1H, CH), 7.26 (td, 2H, $J = 8.5$ Hz, $J = 2$ Hz, aromatic), 7.39 (td, 2H, $J = 6.1$ Hz, $J = 2$ Hz, aromatic), 7.41 (d, 2H, $J = 8$ Hz, aromatic), 7.43 (s, 1H, aromatic), 7.66 (td, 2H, $J = 8.5$ Hz, $J = 1.3$ Hz, aromatic), 8.05 (d, 2H, $J = 6.4$ Hz, aromatic), 11.68 (broad s, 2H, OH) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ 31.9, 102.1, 114.2, 119.1, 121.4, 123.7, 130.3, 132.9, 133.3, 135.8, 143.5, 152.1, 165.9, 167.1 ppm. Anal. Calcd. For $\text{C}_{25}\text{H}_{14}\text{Cl}_2\text{O}_6$: C, 62.38; H, 2.93 Found: C, 62.32; H, 2.79.

3,3'-Bis (4-hydroxy coumarin-3yl) (4-nitrophenyl) ethanon (5a). IR (KBr) ν_{max} : 3355, 3015, 1696, 1664, 1547, 1357, 754 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 6.4 (s, 1H, CH), 7.34 (td, 2H, $J = 7.4$ Hz, $J = 2$ Hz, aromatic), 7.36 (m, 2H, aromatic), 7.58 (dd, 2H, $J = 7.4$ Hz, $J = 2$ Hz, aromatic), 7.78 (m, 2H, aromatic), 7.91 (d, 2H, $J = 8$ Hz, aromatic), 8.29 (d, 2H, $J = 8$ Hz, aromatic), 11.3 (broad s, 2H, OH) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ 80.2, 104.1, 115.7, 119.2, 121.7, 124.2,

128.4, 130.2, 132.9, 142.1, 153.7, 158.2, 162.9, 167.2, 198.0 ppm. Anal. Calcd. For $\text{C}_{26}\text{H}_{15}\text{NO}_9$: C, 64.33; H, 3.11; N, 2.88 Found: C, 64.21; H, 3.04; N, 2.85.

3,3'-Bis (4-hydroxy coumarin-3yl) (4-bromophenyl) ethanon (5b). IR (KBr) ν_{max} : 3335, 3085, 1696, 1648, 759 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 6.31 (s, 1H, CH), 7.24 (d, 2H, $J = 7.5$ Hz, aromatic), 7.27 (d, 2H, $J = 8.3$ Hz, aromatic), 7.5 (t, 2H, $J = 7$ Hz, aromatic), 7.58 (d, 2H, $J = 8.5$ Hz, aromatic), 7.71 (d, 2H, $J = 8.5$ Hz, aromatic), 7.84 (d, 2H, $J = 7.5$ Hz, aromatic), 10.41 (broad s, 2H, OH) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ 80.0, 102.5, 116.7, 119.0, 121.6, 124.2, 124.7, 130.2, 132.0, 132.4, 153.1, 164.3, 167.2, 165.2, 196.5 ppm. Anal. Calcd. For $\text{C}_{26}\text{H}_{15}\text{BrO}_7$: C, 60.13; H, 2.91 Found: C, 60.08; H, 2.89.

3,3'-Bis (4-hydroxy coumarin-3yl) (phenyl) ethanon (5c). IR (KBr) ν_{max} : 3405, 3015, 1692, 1637, 764 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 6.35 (s, 1H, CH), 7.29 (td, 2H, $J = 7.4$ Hz, $J = 2$ Hz, aromatic), 7.35 (m, 3H, aromatic), 7.47 (d, 2H, $J = 7.8$ Hz, aromatic), 7.57 (m, 2H, aromatic), 7.71 (m, 2H, aromatic), 7.82 (d, 2H, $J = 8$ Hz, aromatic), 10.41 (broad s, 2H, OH) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ 80.3, 101.9, 115.5, 118.7, 121.0, 124.3, 129.7, 130.1, 131.8, 133.2, 136.2, 151.3, 161.8, 167.4, 194.2 ppm. Anal. Calcd. For $\text{C}_{26}\text{H}_{16}\text{O}_7$: C, 70.9; H, 3.66 Found: C, 70.7; H, 3.59.

3. Results and Discussion

In continuation of our investigations of the application of solid acids in organic synthesis [12–16], we have investigated the synthesis of biscoumarin derivatives by condensation of a 4-hydroxycoumarin **1** and an aromatic aldehyde **2** or phenylglyoxals **3** in the presence of 0.003 g $\text{SiO}_2\text{-OSO}_3\text{H}$ NPs catalyst.

The stable silica gel nanoparticles are easily prepared [17] and used for preparation of catalyst ($\text{SiO}_2\text{-OSO}_3\text{H}$ NPs).

To optimize the reaction conditions, the reaction of benzaldehyde and 4-hydroxycoumarin was used as a model reaction. Initially, the catalytic activity of $\text{SiO}_2\text{-OSO}_3\text{H}$ NPs has been compared with other catalysts, according to the obtained data, and this catalyst afforded good yields; however, it has limitations of long reaction time, harsh reaction conditions, and often expensive catalysts (Table 1, entry 1–6). In order to determine the optimum quantity of $\text{SiO}_2\text{-OSO}_3\text{H}$ NPs, model reaction was carried out at reflux in ethanol condition (Table 1, entry 7–9). $\text{SiO}_2\text{-OSO}_3\text{H}$ NPs (0.003 g) gave an excellent yield in 20 min (Table 1, entry 8). The previous reaction was also examined in various solvents. The best results were obtained when EtOH was used as a solvent at reflux (Table 1, entry 8). An interesting feature of this method is that the reagent can be regenerated at the end of the reaction and can be used several times without losing its activity. To recover the catalyst, after completion of the reaction, the mixture was filtered, and catalyst was washed with CHCl_3 , and then the solid residue dries. This process was repeated for two cycles, and the yield of product **4a** did not change significantly (Table 1, entry 12, 13).

TABLE 1: Synthesis of **4a** under various conditions.

Entry	Catalyst (amount)	Cond./Sol.	Time (min)	Yield ^a (%)	Reference
1	I ₂ (10 mol%)	100°C/H ₂ O	25	97	[6]
2	TBAB ^b (4 mol%)	120°C/—	20	85	[7]
3	[bmim]BF ₄ (4 mmol)	60–70°C/—	120	84	[8]
4	SDS ^c (0.2 mol, 57.6 mg)	60°C/H ₂ O	140	90	[9]
5	[PSebim][OTf] (0.5 mol%)	70°C/—	120	95	[10]
6	[MIM(CH ₂) ₄ SO ₃ H][HSO ₄](3 mol%)	80°C/—	30	92	[11]
7	SiO ₂ -OSO ₃ H NPs (0.001 g)	80°C/EtOH	20	89	—
8	SiO ₂ -OSO ₃ H NPs (0.003 g)	80°C/EtOH	20	93	—
9	SiO ₂ -OSO ₃ H NPs (0.005 g)	80°C/EtOH	20	93	—
10	SiO ₂ -OSO ₃ H NPs (0.003 g)	100°C/H ₂ O	20	87	—
11	SiO ₂ -OSO ₃ H NPs (0.003 g)	40°C/CH ₂ Cl ₂	20	82	—
12	SiO ₂ -OSO ₃ H NPs (0.003 g), 2nd run	80°C/EtOH	20	89	—
13	SiO ₂ -OSO ₃ H NPs (0.003 g), 3rd run	80°C/EtOH	20	87	—

^aIsolated yield, ^btetrabutylammonium bromide, and ^csodium dodecyl sulfate.

TABLE 2: SiO₂-OSO₃H NPs catalyzed the synthesis of biscoumarin derivatives.

Entry	Ar	Product	Yield ^a %	m.p./°C	
				Found	Reported [Ref]
1	C ₆ H ₅	4a	93	228–230	229–231 [11]
2	4-BrC ₆ H ₄	4b	86	266–268	265–267 [9]
3	4-FC ₆ H ₄	4c	90	211–213	213–215 [9]
4	4-MeC ₆ H ₄	4d	96	268–270	266–269 [11]
5	2-OHC ₆ H ₄	4e	94	253–255	254–256 [11]
6	4-OHC ₆ H ₄	4f	93	194–196	193 [5]
7	4-(CH ₃) ₂ NC ₆ H ₄	4g	92	221–223	222–224 [9]
8	3-NO ₂ C ₆ H ₄	4h	95	215–217	214–215 [11]
9	4-NO ₂ C ₆ H ₄	4i	96	233–235	233–235 [11]
10	3-ClC ₆ H ₄	4j	91	222–224	221–223 [11]
11	4-ClC ₆ H ₄	4k	95	262–264	261–263 [11]
12	3-Pyridyl	4l	88	279–281	278 [5]
13	3-NO ₂ -4-ClC ₆ H ₃	4m	92	249–252	—
14	2,4-ClC ₆ H ₃	4n	89	198–200	—
15	4-NO ₂ C ₆ H ₄ CO	5a	96	249–251	—
16	4-BrC ₆ H ₄ CO	5b	90	204–207	—
17	C ₆ H ₅ CO	5c	93	209–211	—

^aIsolated yield.

To study the scope of the reaction, a series of aromatic aldehydes or phenylglyoxals and 4-hydroxycoumarin catalysed by SiO₂-OSO₃H NPs were examined (Scheme 1). The results are shown in Table 2. In all cases, aromatic aldehyde or phenylglyoxals substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and gave products in excellent yields.

The compounds **4a–l** were characterised by their ¹H-NMR and IR spectroscopies and elemental analyses. Spectral data were compared with the literature data [5, 9, 11].

Compounds **4m**, **n** and **5a–c** were new, and their structures were deduced by elemental and spectral analysis. The ¹H-NMR spectrum of compound **5a** exhibited proton of methine at 6.4 ppm, and OH proton is observed at 11.3 ppm

which disappears after addition of some D₂O to the CDCl₃ solution of **5a**. There are observed multiplets between 7.34 and 8.29 ppm which are related to aromatic protons. The ¹³C-NMR spectrum of compound **5a** showed 15 signals in agreement with the proposed structure. The IR spectrum of compound **5a** also supported the suggested structure.

4. Conclusion

In summary, we have reported an easy and efficient protocol for the synthesis of biscoumarins in the easily accessible SiO₂-OSO₃H nanoparticles. The method offers marked improvement with its operational simplicity and short reaction time and affords excellent yield. The solid phase acidic catalyst was

SCHEME 1: Synthesis of biscoumarins by condensation of 4-hydroxycoumarin with an aromatic aldehyde or phenylglyoxals using $\text{SiO}_2\text{-OSO}_3\text{H}$ NPs as catalyst.

reusable for a number of times without appreciable loss of activity. The present method does not involve any hazardous organic solvent. Therefore, this procedure could be classified as green chemistry.

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