

## Silica gel: A very cheap, reusable, and efficient catalyst for green preparation of some bis-4-hydroxycoumarin on water

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### ABSTRACT

Silica gel has been used for synthesis of biscoumarin derivatives starting from 4-hydroxycoumarin and aryl aldehydes. The reaction conditions are completely in agreement with green chemistry principles including using water as media and a recyclable and safe catalyst. This method is also simple and inexpensive and leads to high yield of products in short reaction times.

**Keywords:** Biscoumarin; Catalyst; Silica gel, Water, Aldehyde.

### 1. Introduction

Coumarins have been well known as biologically active heterocycles containing oxygen atom. For example, they reduce the HIV activity and some of them have shown cytostatic activity and therefore can be considered as potential candidates for anti-cancer therapy [1]. Biscoumarins, the bridge substituted dimers of 4-hydroxycoumarin, have enormous potential as anticoagulants [2]. Dicoumarol is also an anticoagulant that functions as a vitamin K antagonist [3]. It is the hemorrhagic agent responsible for the sweet clover disease of cattle [4] and has been also employed for the prevention and treatment of thrombosis [5]. Although, there are some methods for the synthesis of bis-4-hydroxycoumarins using different catalysts or reagents in various conditions [6-12], some of them suffer from drawbacks, such as the use of expensive or synthetic reagents and organic solvents [6,8]. Also, some of them require harsh conditions [10], tedious work-up in certain cases [12] and long reaction times to complete [11]. With an objective to develop environmentally benign reaction conditions and media for organic transformations with excellent efficiency and selectivity, water has been shown to be a useful solvent or media [13]. Recently, organic synthesis on water was reviewed by Fokin and co-workers [14]. In this context, we report the use of silica gel (SiO<sub>2</sub>) as an inexpensive and readily available reagent for the synthesis of substituted biscoumarins on water.

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### 2. Experimental

All chemicals were purchased from Merck and Aldrich. The reactions were monitored by thin layer chromatography (TLC; silica-gel 60 F<sub>254</sub>, n-hexane: ethyl acetate). IR spectra were recorded on a FT-IR JASCO-680 and the <sup>1</sup>H NMR spectra were obtained on a Bruker-Instrument DPX-400 MHz Avance 2 model. The varioEl CHNS Isfahan Industrial University was used for elemental analysis. All products were characterized by comparison of their spectra and physical data with those reported in the literature [6,7].

#### Preparation of bis-4-hydroxycoumarins

A mixture of 4-hydroxycoumarin 1 (2 mmol), aromatic aldehydes 2 (1 mmol) and SiO<sub>2</sub> (0.05 g) in water (10 mL) was refluxed for the appropriate time mentioned in Tables 2. The progress of reaction was monitored by TLC. After completion of reaction, the solid compound obtained was filtered off and dissolved in hot EtOH to separate the catalyst. Catalyst was washed with diethyl ether and dried at 120 °C in order to use in another reaction. The crude products were also obtained by recrystallization from EtOH.

#### Selected spectral data

Compound **3a**: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ ppm: 6.11 (s, 1H), 7.27 (m, 1H), 7.23 (m, 2H), 7.38 (m, 2H), 7.33 (m, 2H), 7.63 (m, 2H), 7.42 (m, 2H), 8.00 (d, *J* = 7.2 Hz, 1H), 8.08 (d, *J* = 6.8 Hz, 1H), 11.41 (b, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ ppm: 36.15, 103.92, 105.60, 116.63, 116.99, 124.38, 124.81, 126.59,

126.88, 128.65, 132.83, 135.19, 152.29, 152.51, 164.62, 165.81, 166.88, 169.30. Anal. Calcd. for  $C_{25}H_{16}O_6$ : C, 72.81; H, 3.91. Found: C, 73.02; H, 3.79.

Compound **3c**:  $^1H$  NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  ppm: 6.28 (s, 1H), 7.12 (d, 2H,  $J = 8.4$  Hz), 7.40-7.29 (m, 6H), 7.58 (t, 2H,  $J = 8.0$  Hz), 7.89 (d, 2H, 8.0 Hz), 9.99 (s, 1H), 10.70 (b, 1H).  $^{13}C$  NMR (DMSO- $d_6$ , 100 MHz)  $\delta$  ppm: 35.72, 90.95, 103.60, 115.84, 116.35, 118.31, 123.16, 123.53, 123.93, 129.08, 130.74, 131.22, 131.72, 132.28, 132.69, 140.22, 152.26, 164.55, 165.89. Anal. Calcd. for  $C_{25}H_{15}ClO_6$ : C, 67.20; H, 3.38. Found: C, 67.35; H, 3.29.

Compound **3e**:  $^1H$  NMR ( $CDCl_3$ , 400 MHz)  $\delta$  ppm: 6.07 (s, 1H), 7.03 (t, 2H,  $J = 8.0$  Hz), 7.21 (dd, 2H,  $J = 8.0$  Hz, 5.2 Hz), 7.44 (d, 4H,  $J = 8.0$  Hz), 7.68-7.64 (m, 2H), 8.03 (d, 1H,  $J = 8.0$  Hz), 8.08 (d, 1H,  $J = 8.0$  Hz), 11.35 (s, 1H), 11.57 (s, 1H).  $^{13}C$  NMR ( $CDCl_3$ , 100 MHz)  $\delta$  ppm: 35.68, 103.95, 105.49, 115.41, 115.63, 116.39, 116.68, 116.87, 124.41, 128.14, 128.22, 124.98, 130.84, 130.87, 133.01, 152.29, 152.54, 160.50, 162.94, 164.63, 165.93, 166.86, 169.23. Anal. Calcd. for  $C_{25}H_{15}NO_8$ : C, 65.65; H, 3.31; N, 3.06. Found: C, 65.89; H, 3.24; N, 3.17.

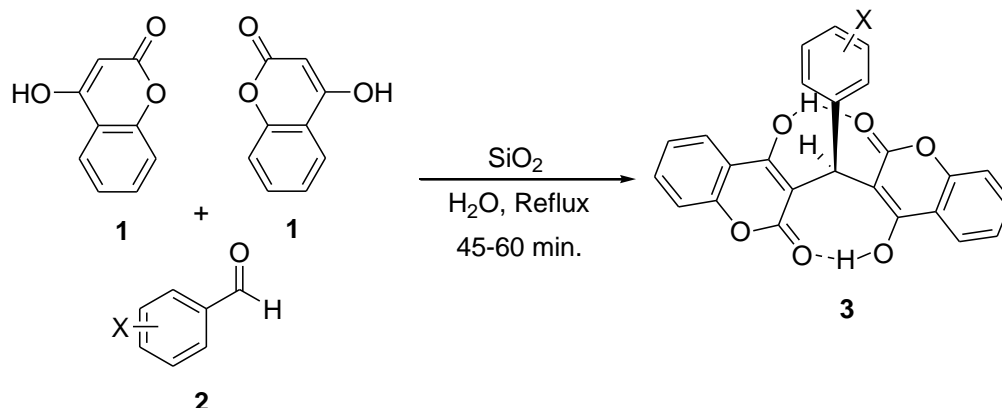
Compound **3g**:  $^1H$  NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  ppm: 5.04 (s, 2H), 6.31 (s, 2H), 6.90 (d, 2H,  $J = 8.8$  Hz), 7.06-7.22 (m, 2H), 7.31-7.44 (m, 9H), 7.58-7.63 (m, 2H), 7.81-7.93 (m, 2H), 11.59 (b, 2H).  $^{13}C$  NMR (DMSO- $d_6$ , 100 MHz)  $\delta$  ppm: 35.21, 69.09, 90.96, 104.32, 114.31, 115.23, 115.95, 116.34, 117.76, 123.16, 123.76, 123.83, 123.90, 127.64, 127.71, 127.75, 127.84, 128.35, 128.48, 131.77, 131.90, 132.68, 137.21, 152.13, 156.44, 164.78, 164.97. Anal. Calcd. for  $C_{32}H_{22}O_7$ : C, 74.12; H, 4.28. Found: C, 74.29; H, 4.15.

### 3. Results and Discussion

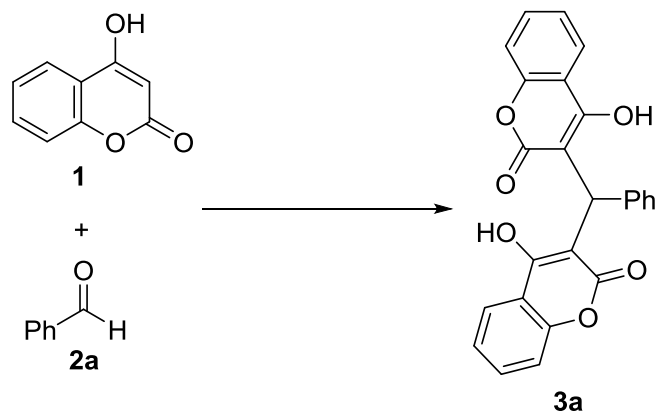
In continuation of our study on the development of novel, efficient, and green procedures for organic reactions [15-18], we turned our attention toward the condensation of 4-hydroxycoumarin (**1**) and aromatic aldehydes **2** in the presence of  $SiO_2$  as catalyst to produce bis-4-hydroxycoumarin derivatives **3** (Scheme 1) [19]. The 4-hydroxycoumarin moieties are intramolecularly hydrogen bonded between hydroxyl and carbonyl oxygen atoms in both structures, thus forming two eight-membered rings. To determine the suitable reaction conditions for the synthesis of **3** using  $SiO_2$ , the reaction of 4-hydroxycoumarin (**1**) and benzaldehyde (**2a**) was selected as a model (Scheme 2).

As can be seen in Table 1, we found that in the absence of the catalyst, the reaction proceeds slowly, even at long reaction times in several solvents (Entry 1-3). In another experiment, in order to show the effect of solvent or media on the reaction progress, we employed several solvents which the results have been shown in Table 1. It can be concluded that protic solvents such as EtOH, MeOH, and  $H_2O$  can accelerate the condensation reaction. It should be also noted that 4-hydroxycoumarin is soluble in alcohol, acetone and ether, but it has low solubility in water.

However, it was found that this reaction will be completed with  $SiO_2$  ( $SiO_2$  g) under refluxing  $H_2O$  about 60 min (Entry 6). Higher loadings of catalyst did not affect a marked influence on the product yield or reaction rate (Entry 8). After optimization of the reaction conditions, to prove the general applicability of this method, the reaction of different aldehydes with 4-hydroxycoumarin was examined (Table 2). The nature of X group on the aldehydes showed no significant effect on the reaction rate or product yield. It should be mentioned that our efforts for the synthesis of bis-4-hydroxycoumarins using aliphatic aldehydes were unsuccessful. The problem with alkyl aldehydes is likely due to their enolization during the reaction.



Scheme 1. Synthesis of bis-4-hydroxycoumarins using  $SiO_2$  under reflux in water.



**Scheme 2.** Reaction of benzaldehyde with 4-hydroxycoumarin in various conditions.

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In order to show the merit of present method in comparison with other methods used for the similar reaction, we have tabulated some of the results in Table 3. Some reports presented the catalyst-free synthesis of bis-4-hydroxycoumarins [Entry 6-8], but, two of them used extra instrument such as ultrasonic

**Table 1.** Optimization of the reaction conditions through various solvents and temperatures. Reaction time: 60 min.

| Entry | Conditions  | Conversion (%) |
|-------|---|----------------|
| 1     | Catalyst-free/EtOH/reflux   | trace          |
| 2     | Catalyst-free/EtOH:H <sub>2</sub> O/reflux                        | 10             |
| 3     | Catalyst-free/H <sub>2</sub> O/reflux                             | 25             |
| 4     | SiO <sub>2</sub> (0.05 g)/EtOH/reflux                             | 75             |
| 5     | SiO <sub>2</sub> (0.05 g)/EtOH:H <sub>2</sub> O/reflux            | 80             |
| 6     | SiO <sub>2</sub> (0.05 g)/H <sub>2</sub> O/reflux                 | 95             |
| 7     | SiO <sub>2</sub> (0.02 g)/H <sub>2</sub> O/reflux                 | 75             |
| 8     | SiO <sub>2</sub> (0.08 g)/H <sub>2</sub> O/reflux                 | 95             |
| 9     | SiO <sub>2</sub> (0.05 g)/MeOH/reflux                             | 80             |
| 10    | SiO <sub>2</sub> (0.05 g)/THF/reflux                              | 50             |
| 11    | SiO <sub>2</sub> (0.05 g)/CH <sub>2</sub> Cl <sub>2</sub> /reflux | 35             |
| 12    | SiO <sub>2</sub> (0.05 g)/solvent-free/100 °C                     | 50             |

and microwave sets, and another one needs to long reaction times to complete. Despite they are clean strategies, sometimes it is not possible to establish everywhere.

**Table 2.** Synthesis of bis-4-hydroxycoumarins in the presence of SiO<sub>2</sub> under reflux in water.

| Entry | X                        | Time (min) | Yield <sup>[a]</sup> (%) | m.p. (°C) [lit.] |
|-------|--------------------------|------------|--------------------------|------------------|
| 3a    | H                        | 60         | 95                       | 229-231 [6]      |
| 3b    | 4-F                      | 45         | 95                       | 267-269 [6]      |
| 3c    | 4-Cl                     | 50         | 98                       | 253-255 [6]      |
| 3d    | 4-Br                     | 60         | 90                       | 265-267 [6]      |
| 3e    | 4-NO <sub>2</sub>        | 35         | 95                       | 232-234 [6]      |
| 3f    | 4-OMe                    | 45         | 90                       | 241-243 [6]      |
| 3g    | 4-PhCH <sub>2</sub> O    | 45         | 85                       | 227-229 [7]      |
| 3h    | 2-Cl                     | 50         | 95                       | 226-228 [6]      |
| 3i    | 4-Me                     | 60         | 90                       | 268-270 [6]      |
| 3j    | 4- <i>i</i> Pr           | 55         | 85                       | 245-247 [20]     |
| 3k    | 4-Cl-3-NO <sub>2</sub>   | 50         | 95                       | 265-267 [7]      |
| 3l    | 3,4,5-(OMe) <sub>3</sub> | 45         | 90                       | 243-245 [7]      |

<sup>[a]</sup> Isolated yields.

**Table 3.** Comparison of our method with other methods for the synthesis of 3a.

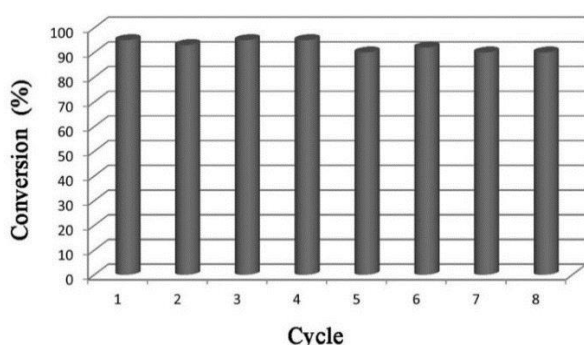
| Entry | Conditions  | Time/Yield (%) [Ref] |
|-------|---|----------------------|
| 1     | NaHSO <sub>4</sub> /SiO <sub>2</sub> /toluene/100 °C                                    | 30 min/89 [6]        |
| 2     | Indion 190 resin/toluene/100 °C   | 30 min/92 [6]        |
| 3     | Silica-supported Preyssler nanoparticles/EtOH/r.t.                                      | 30 min/92 [8]        |
| 4     | SO <sub>3</sub> H-functionalized ILs/70 °C  | 2 h/95 [9]           |
| 5     | H <sub>6</sub> [PMo <sub>9</sub> V <sub>3</sub> O <sub>40</sub> ]/EtOH:H <sub>2</sub> O | 15 h/30 [10]         |
| 6     | Catslyst-free/microwave irradiation/H <sub>2</sub> O/150 W, 150 °C                      | 9 min/ 85 [11]       |
| 7     | Catslyst-free/ultrasound irradiation /H <sub>2</sub> O/ 100 W                           | 5 min/98 [21]        |
| 8     | Catslyst-free/H <sub>2</sub> O/95 °C  | 5 h/93 [22]          |
| 9     | NaCl solution/95 °C   | 30/92 [22]           |
| 10    | SiO <sub>2</sub> /H <sub>2</sub> O/reflux   | 60 min/95 [a]        |

<sup>a</sup>This work

It is obvious that the use of SiO<sub>2</sub> as a catalyst and water as a media can be considerable from the environmental and economic aspects.

It should be noted that the main disadvantage of many of the reported methods for the synthesis of benzopyrazines is that the catalysts are destroyed in the work-up procedure and cannot be recovered or reused. In this process, the recycled catalyst was used for eight cycles during which a little appreciable loss was observed in the catalytic activities (Fig. 1).

Although so many different reagents and catalysts have been reported for this type of condensations, the use of SiO<sub>2</sub> seems to be attractive and provides another valuable option for chemists because it is a safe and easily accessible reagent. Besides, the use of water instead of organic solvents is more reasonable because of its safety and cheapness. All of these factors are in accord with green chemistry principles. The structures and purity of the obtained products were deduced from their IR, elemental analysis, and NMR spectral data.



**Fig. 1.** The recyclability of SiO<sub>2</sub> in the synthesis of 3a under optimizes conditions. Reaction time: 60 min.

#### 4. Conclusion

In summary, we have presented a green and novel route to bis-4-hydroxycoumarin derivatives by the use of SiO<sub>2</sub> under reflux in H<sub>2</sub>O. This procedure may be regarded as a new approach for the preparation of synthetically and pharmaceutically relevant heterocyclic systems. This method includes some advantages such as high yields, short reaction times, simple work-up procedures, and use of water as a clean media and cheap and recyclable catalyst, which make it useful and attractive for synthesis of biscoumarin derivatives.

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