BF$_3$-SiO$_2$ Nanoparticles: An Efficient Catalyst for the Multi-Component Synthesis of 3-(α-aroylamido)-4-hydroxycoumarin Derivatives in Water

Mona Arfavi-Safari$^{1,3}$, Hossein Anaraki-Ardakani$^{2*}$, Rashid Badri$^3$, Elham Tahanpesar$^3$

$^1$Department of Chemistry, Khuzestan Science and Research Branch, Islamic Azad University, Ahvaz, Iran

$^2$Department of Chemistry, Mahshahr Branch, Islamic Azad University, Mahshahr, Iran

$^3$Department of Chemistry, Ahvaz Branch, Islamic Azad University, Ahvaz, Iran

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Abstract

A green and efficient one-pot three component reaction of 4-hydroxycoumarin or 1,3-dimethylbarbutyric acid, aryl glyoxals and amides (thioacetamide) has been developed in the presence of BF$_3$-SiO$_2$ nanoparticles in water. This method has several advantages such as high to excellent product yields in short reaction time, atom economy, environment friendly, reusable catalyst and no need for chromatographic separations.

Keywords: Multi-component reactions, BF$_3$-SiO$_2$ NPs, One-pot, Aryl glyoxal, 4-hydroxycoumarin.

*Corresponding author: Hossein Anaraki-Ardakani, Department of Chemistry, Mahshahr Branch, Islamic Azad University, Mahshahr, Iran. E-mail: hosseinanaraki@yahoo.com; Fax +98(61)52338586.
Introduction

Coumarin and its derivatives are an important class of heterocyclic compounds, which constitute the key core of various natural products [1, 2]. The application of coumarin derivatives as bioactive molecules against different kinds of diseases has gained great interest from medicinal chemists. Coumarin derivatives demonstrate a wide spectrum of biological activities such as anticancer, anticoagulant, anti-HIV, antimalarial, anti-inflammatory, and are usually associated with low toxicity [3-7]. Most significant are 3-substituted-4-hydroxy coumarin derivatives, which have important clinical applications [8-10] (Figure 1).

![Coumarin Derivatives](image)

Figure 1. Representative structures of coumarin derivatives.

Multi-component reactions (MCRs) are important for generating high levels of diversity, as they allow more than two building blocks to be combined in a practical, time-saving, one-pot operation, giving rise to complex structures by simultaneous formation of two or more bonds. MCRs have received considerable attention because of their wide range of applications in pharmaceutical chemistry for the creation of structural diversity and combinatorial libraries for drug discovery [11-12]. Green chemistry has become an important and expanding research area, as it avoids the use of reagents and solvents that have a hazardous impact on the environment, and minimizes the production of waste [13–16]. So designing of multi-component reactions in water is an attractive area in green chemistry, because water is a cheap, non-toxic, non-polluting, non-flammable and an environmentally benign solvent [17]. Recently, the application of nanoparticles (NPs) as catalysts has attracted worldwide attention because of their high catalytic activity and improved selectivity [18]. The high surface area to volume ratio of nanoparticles is mainly responsible for their catalytic properties [19]. The surface of some metal oxides, such as TiO$_2$, ZrO$_2$, Al$_2$O$_3$, ZnO, CuO and MgO, exhibits both Lewis acid and Lewis base character [20, 21]. Recently we reported a three-component process for the synthesis of 3-(α-arylamido)-4-hydroxycoumarin derivatives from reaction of aryl glyoxal, amides, and 4-hydroxycoumarin in the presence of SnCl$_2$-SiO$_2$ as heterogeneous catalyst under solvent-free conditions [22], also...
Khodabakhshi et al. have reported a three-component process for the synthesis of aryloylamido coumarins derivatives from the reaction of aryl glyoxal, benzamide, and 4-hydroxycoumarin in the presence of molybdate sulfuric acid, tungstate sulfuric acid, zirconium oxychloride, and Fe$_3$O$_4$ nanoparticles [23-26]. However, some of these methods displayed drawbacks such as require long reaction times [26], acidic conditions, [23,24] need for column chromatography to purify the products [23-26], expensive catalyst and also catalysts is not recyclable [23, 25]. Therefore, the development of environmentally benign, high-yielding, milder and convenient method to synthesis of 3-(α-aroylamido)-4-hydroxycoumarin derivatives still remains a desired goal in organic synthesis. The best of our knowledge there are no reports on the use of the BF$_3$- SiO$_2$ nanoparticles (NPs) in synthesis of 3-(α-aroylamido)-4-hydroxycoumarin derivatives.

Considering the above reports, and the medicinal importance of the 3-(α-aroylamido)-4-hydroxycoumarin derivatives, in continuation of our studies on one-pot multi-component reactions [27-30], we here reported a one-pot three-component reaction of 4-hydroxycoumarin or dimethylbarbutyric acid 1, aryl glyoxals 2, and aliphatic amides (thioacetamide) 3, in the presence of BF$_3$- SiO$_2$ NPs as none-toxic Lewis acid catalyst to the synthesis of 3-(α-aroylamido)-4-hydroxycoumarin derivatives 4 in aqueous media (Scheme 1).

Scheme 1. Reaction between 4-hydroxycoumarin or dimethylbarbutyric acid, aryl glyoxals and aliphatic amides (thioacetamide), catalyzed by BF$_3$- SiO$_2$ NPs.

Aryglyoxals 2 was prepared by the reaction between their corresponding acetophenone and SeO$_2$ according to the reported procedures [31].

**Experimental**

Melting points were determined with an electrothermal 9100 apparatus. Scanning electron microscopy (SEM) studies of the nanostructures were carried out with a KYKY-EM 3200 instrument operating at an accelerating voltage of 300 kV. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a shimadzu IR-470 spectrometer. $^1$H and $^{13}$C NMR spectra were recorded on Bruker DRX-400
Avance spectrometer at solution in CDCl₃ using TMS as internal standard. The chemicals used in this work purchased from fluka (Buchs, Switzerland) and were used without further purification.

**Preparation of nanoparticles silica-supported boron trifluoride**

Nano silica gel supported boron trifluoride was prepared according to the procedure reported in the literatures with some modification [32,33]. In a typical procedure, 0.35 g BF₃(0.65 ml of BF₃.Et₂O) was added to a suspension of nano particles of silica gel (0.65 g) in chloroform (6 mL). The mixture was stirred at room temperature for 60 min. The resulted suspension was filtered and obtained solid was washed with chloroform and dried at room temperature. The prepared BF₃-nano SiO₂ has been structurally characterized SEM analysis Figure 2 indicates that the original morphology of the particle was approximately spherical with the diameter varying between 25 and 58 nm.

![SEM image of synthesized BF₃-SiO₂ NPs.](image_url)

**General procedure**

A mixture of aryl glyoxal (1 mmol), amides (thioacetamide) (1 mmol), and BF₃- SiO₂ nanoparticle (0.03g) in 10 ml water was stirred and heated at 100 ºC for 20 min. Then the 4-hydroxycoumarin (4-hydroxy-6-methylpyran-1-one) ordimethylbarbutyric acid (1 mmol), was added to the mixture and the reaction allowed to stir for the appropriate amount of time (60–80 min) in reflux condition. The reaction progress was monitored by TLC (EtOAc/hexane, 1:2). After completion of the reaction, the precipitate was filtered, dried, and dissolved in hot EtOH/THF (3:1) to separate the catalyst. The pure 4 was obtained after re-crystallization from EtOH.
Selected spectral data

N-[1-(4-Hydroxy-2-oxo-2H-chromen-3-yl)-2-oxo-2-phenyl-ethyl]-acetamide (4a)

White powder, m.p. 196-198 °C. IR (KBr) (νmax, cm⁻¹): 3376 (N–H), 1695 (C=O). Anal. calcd for C₁₅H₁₅NO₅: C, 67.65; H, 4.48; N, 4.15%. Found: C, 67.52; H, 4.55; N, 4.29 %. MS (m/z, %): 337 (9). ¹H NMR (250MHz, CDCl₃): δ = 2.21 (3 H, s, CH₃), 6.08 (1 H, d, J珅 Valle = 6.5 Hz, CH-NH), 7.09-7.82 (9 H, m, arom), 8.06 (1 H, d, J珅 Valle = 6.5 Hz, NH ). 13C NMR (62.90 MHz, CDCl₃): δ = 23.42 (CH₃), 7.82 (9 H, m, arom), 8.06 (1 H, d, J珅 Valle = 6.5 Hz, NH ). 13C NMR (62.90 MHz, CDCl₃): δ = 23.42 (CH₃), 50.12 (CH), 101.12, 121.54, 125.52, 126.82, 128.41, 128.78, 129.85, 130.81, 133.24, 143.17, 152.11, 161.19 (C arom and olfine ), 163.93, 171.15, 187.46 (3C=O) ppm.

N-[1-(4-Hydroxy-2-oxo-2H-chromen-3-y1)-2-oxo-2-p-tolyl-ethyl]-thioacetamide (4i)

White powder, m.p. 189 °C. IR (KBr) (νmax, cm⁻¹): 3320 (N–H), 1695 (C=O). Anal. calcd for C₂₀H₁₇NO₄S: C, 65.38; H, 4.66; N, 3.81%. Found: C, 65.23; H, 4.51; N, 3.92 %. MS (m/z, %): 367 (11). ¹H NMR (250MHz,CDCl₃): δ = 1.83 (3 H, s, CH₃), 2.41(3H, s, CH₃), 4.88 (1 H, s, CH-NH), 6.94-8.15 (8 H, m, arom and NH), 10.75 (1H, broad, OH) ppm. ¹³C NMR (62.90 MHz, CDCl₃): δ = 21.71(CH₃), 34.28 (CH₃), 54.81 (CH-NH), 102.64,116.53 123.87, 124.21, 128.96, 129.45, 131.61, 132.33, 137.76, 143.30, 153.19, 163.53 (C arom and olfine ), 165.38, 171.61(2C=O), 188.16 (C=S) ppm.

N-[2-(4-Chloro-phenyl)-1-(4-hydroxy-2-oxo-2H-chromen-3-y1)-2-oxo-ethyl]-thioacetamide (4j)

White powder, m.p. 186-188 °C. IR (KBr) (νmax, cm⁻¹): 3312 (N–H), 1689 (C=O). Anal. calcd for C₁₉H₁₄ClNO₄S: C, 58.84; H, 3.64; N, 3.61%. Found: C, 58.75; H, 3.72; N, 3.43%. MS (m/z, %): 387 (7). ¹H NMR (250MHz, CDCl₃): δ = 1.78 (3 H, s, CH₃), 4.83 (1 H, s, CH-NH), 7.28-8.27 (8 H, m, arom and NH), 10.62 (1H, broad, OH) ppm. ¹³C NMR (62.90 MHz,CDCl₃): δ = 36.54 (CH₃), 55.73 (CH-NH), 103.65, 121.04, 121.39, 128.29, 128.49, 135.22, 135.48, 136.46, 139.98, 144.02, 157.38, 161.55 (C arom and olfine ), 167.23, 168.69 (2C=O), 190.22 (C=S) ppm.

N-[1-(4-Hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-2-oxo-2-p-tolyl-ethyl]-thioacetamide (4k)

White powder, m.p. 190-192°C. IR (KBr) (νmax, cm⁻¹): 3287 (N–H), 1690 (C=O), Anal. calcd for C₁₇H₁₇NO₄S: C, 61.61; H, 5.17; N, 4.23 %. Found: C, 61.56; H, 5.32; N, 4.42 %. MS (m/z, %): 331 (6). ¹H NMR (250MHz,CDCl₃): δ = 1.82 (3 H, s, CH₃), 2.20 (3H, s, CH₃), 2.35(3H, s, CH₃), 5.90 (1 H, d, J珅 Valle = 8 Hz, CH-NH), 6.06 (1H, s, CH=C), 7.13-7.73 (5H arom), 8.02 (1 H, d, J珅 Valle = 8 Hz, NH) ppm. ¹³CNMR (62.90 MHz, CDCl₃): δ = 21.01(CH₃), 24.56 (CH₃), 36.53(CH₃), 50.63 (CH-
NH), 105.21, 121.76, 128.85, 129.45, 129.65, 133.49, 134.41, 165.38 (C arom and olfine), 167.68, 171.61 (2C=O), 188.23(C=S) ppm.

N-[1-(1,3-Dimethyl-2,4,6-trioxo-hexahydro-pyrimidin-5-yl)-2-oxo-2-phenyl-ethyl-ethyl]-thioacetamide (4l)

White powder, m.p. 188-190 °C. IR (KBr) (ν<sub>max</sub>, cm<sup>-1</sup>): 3209 (N–H), 1690 (C=O). Anal. calcd for C<sub>16</sub>H<sub>17</sub>N<sub>3</sub>O<sub>4</sub>S: C, 55.32; H, 4.93; N, 12.10%. Found: C, 55.22; H, 4.71; N, 12.32 %. MS (m/z, %): 347 (7).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ = 1.83 (3H, s, CH<sub>3</sub>), 3.05 (6H, s, 2N–CH<sub>3</sub>), 4.23 (1H, broad, CH), 7.19-7.60 (6H, arom and NH), 11.27(1H, broad, OH) ppm. <sup>13</sup>C NMR (62.90 MHz, CDCl<sub>3</sub>): δ = 18.50 (CH<sub>3</sub>), 28.70 (N–C<sub>2</sub>H<sub>3</sub>), 55.39 (CH), 79.94, 127.67, 128.63, 129.36, 131.42, 135.84 (C arom and olfine), 152.96, 161.38, 163.0 (3C=O), 189.15 (C=S) ppm.

N-[1-(6-Hydroxy-1,3-dimethyl-2,4-di oxo-1,2,3,4-tetrahydro-pyrimidin-5- yl)-2-oxo-2-phenyl-ethyl]-acetamide (4m)

White powder, m.p. 179-180 °C. IR (KBr) (ν<sub>max</sub>, cm<sup>-1</sup>): 3289 (N–H), 1687 (C=O). Anal. calcd for C<sub>16</sub>H<sub>17</sub>N<sub>3</sub>O<sub>5</sub>: C, 58.00; H, 5.17; N, 12.68%. Found: C, 58.14; H, 5.26; N, 12.43%. MS (m/z, %): 331 (6).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ = 1.92 (3H, s, CH<sub>3</sub>), 3.33 (6H, s, 2N–CH<sub>3</sub>), 4.23 (1H, broad, CH), 7.22-7.94 (6H, arom and NH), 10.58(1H, broad, OH) ppm. <sup>13</sup>C NMR (62.90 MHz, CDCl<sub>3</sub>): δ = 22.55 (CH<sub>3</sub>), 28.77 (N–CH<sub>3</sub>), 55.49 (CH), 102.12, 124.99, 128.30, 130.82, 133.97, 135.24 (C arom and olfine), 153.56, 167.97, 172.25, 196.92 (4C=O) ppm.

N-[2-(4-Chloro-phenyl)-1-(6-hydroxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl)-2-oxo-ethyl]-acetamide (4n)

White powder, m.p. 175-176 °C. IR (KBr) (ν<sub>max</sub>, cm<sup>-1</sup>): 3378 (N–H), 1698 (C=O). Anal. calcd for C<sub>16</sub>H<sub>16</sub>ClN<sub>3</sub>O<sub>5</sub>: C, 52.54; H, 4.41; N, 11.49%. Found: C, 52.39; H, 4.28; N, 11.56%. MS (m/z, %): 365 (11).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ = 1.92 (3H, s, CH<sub>3</sub>), 3.39 (6H, s, 2N–CH<sub>3</sub>), 4.25 (1H, broad, CH), 7.05-7.75 (5H, arom and NH), 10.56(1H, broad, OH) ppm. <sup>13</sup>C NMR (62.90 MHz, CDCl<sub>3</sub>): δ = 22.87 (CH<sub>3</sub>), 28.90 (N–CH<sub>3</sub>), 55.44 (CH), 85.11, 125.39, 128.29, 129.15, 132.44, 136.92 (C arom and olfine), 163.05, 168.76, 172.15, 198.60 (4C=O) ppm.

**Results and discussion**

Firstly, in order to optimize the reaction conditions the reaction of 4-hydroxycoumarin with phenyl glyoxal and acetamide was selected as a model reaction in the presence of different catalysts.
Because the formation of bis-aroyl coumarins[34] is possible, we firstly treated acetamide with phenyl glyoxal to form corresponding imine and then added 4-hydroxycoumarin to the mixture. We tested several catalysts for this multi component reaction and the results are listed in Table 1. According to these results BF$_3$-SiO$_2$ nanoparticle was the most efficient catalyst for this reaction (Table 1, entry 9). However, only a trace amount of the product was formed in the absence of catalyst (Table 1, entry 1). To find the best amount of catalyst, we screened the model reaction in the presence of several amounts of BF$_3$-SiO$_2$ NPs. In the presence of BF$_3$-SiO$_2$ NPs, it was found that 0.03 gr of BF$_3$-SiO$_2$ NPs is optimal to carry out the reaction in a short duration. However, further increase of the amount of the catalyst from 0.03gr to 0.06gr did not significantly increase the yield of the product (Figure3).

**Table 1.** Optimization of the nanoparticles catalyzed model reaction for synthesis of N-[1-(4-Hydroxy-2-oxo-2H-chromen-3-yl)-2-oxo-2-phenyl-ethyl]-acetamide (4a)$^a$.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Catalyst (g)</th>
<th>Time (min)</th>
<th>Yield (b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>120</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>ZnCl$_2$</td>
<td>0.04</td>
<td>110</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>Al$_2$O$_3$</td>
<td>0.04</td>
<td>110</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>FeCl$_3$</td>
<td>0.04</td>
<td>100</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>SnCl$_2$</td>
<td>0.04</td>
<td>100</td>
<td>35</td>
</tr>
<tr>
<td>6</td>
<td>SiO$_2$ nano</td>
<td>0.04</td>
<td>100</td>
<td>45</td>
</tr>
<tr>
<td>7</td>
<td>BF$_3$(Et$_2$O)</td>
<td>0.04</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>8</td>
<td>BF$_3$-SiO$_2$</td>
<td>0.04</td>
<td>100</td>
<td>65</td>
</tr>
<tr>
<td>9</td>
<td>BF$_3$-SiO$_2$ NPS</td>
<td>0.04</td>
<td>65</td>
<td>85</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: 4-hydroxy coumarin (1.0 mmol), acetamide (1.0 mmol), phenyl glyoxal (1.0 mmol).

$^b$Isolated yield.

**Figure 3.** Influence of the amount of the catalyst on the model reaction.
The choice of solvent is also an important factor in this reaction so we carried out the test reaction in presence of various solvents and the results are presented in Table 2. As can be seen from this table after testing various solvents and solvent-free conditions, it was revealed that water leads to the best result (entry 7, Table 2).

**Table 2.** Solvent effect on the reaction between 4-hydroxycoumarin (1eq), phenyl glyoxal (1 eq) and acetamide (1 eq) catalyzed by BF$_3$- SiO$_2$ NPs (0.03gr).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp(°C)</th>
<th>Time(min)</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Solvent- free condition</td>
<td>90</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>Dichloromethane</td>
<td>Re flux</td>
<td>65</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>1,2 Dichloroethane</td>
<td>Re flux</td>
<td>65</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>Re flux</td>
<td>65</td>
<td>55</td>
</tr>
<tr>
<td>5</td>
<td>Toluene</td>
<td>Re flux</td>
<td>65</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>Ethanol</td>
<td>Re flux</td>
<td>65</td>
<td>75</td>
</tr>
<tr>
<td>7</td>
<td>Water</td>
<td>Re flux</td>
<td>65</td>
<td>85</td>
</tr>
</tbody>
</table>

To study the scope and generality of the reaction, a series of aryl glyoxals, cyclic 1,3-diketone and amid (thioacetamide) were employed. The results are shown in Table 3. In all cases, aromatic ring of the aryl glyoxal substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and gave the corresponding products in good to excellent yields (Table 3). Compounds 4i-n were new and their structures were deduced by elemental and spectral analysis. But compounds 4a-h were known and their structures were deduced by comparison of melting points and spectral data with authentic samples [22].

The $^1$H NMR spectrum of compound 4a exhibited a two singlets signal at $\delta = 2.21$ ppm for the protons of methyl group. The methine and NH protons are coupled and two doublets were observed for them at 6.08 and 8.06 ppm, respectively. When the $^1$H NMR spectrum was recorded after addition of some D$_2$O to the CDCl$_3$ solution of 4a the doublet related to NH proton disappeared and the doublet corresponding to the methine proton was converted to a singlet. The proton of hydroxy group resonated at 12.82 ppm as a broad singlet. The $^{13}$C NMR spectrum of compound 4a showed seventh distinct signals consistent with the proposed structure. A possible mechanism for the formation of the products 4a-n is proposed in Scheme 2.
The reaction of aryl glyoxal $2$ with amides$3$ in the presence of $\text{BF}_3$–$\text{SiO}_2$ as a Lewis acid catalyst is proposed to give corresponding imine $5$. Next attack of 4-hydroxycoumarin (4-hydroxy-6-methylpyran-1-one) or dimethylbarbutyric acid $1$ to imine $5$ followed by 1, 3-H shift leads to form final product $4$ (Scheme 2.)

**Scheme 2.** Suggested pathway for the formation of compounds $4a$-$n$. 

![Scheme 2](image-url)
The reusability of the catalyst was tested in the synthesis of 3-(α-aroylamido)-4-hydroxycoumarin derivatives. The catalyst was recovered after each run, washed with ethylacetate, dried in an oven at 100 °C for 15 min prior to use and tested for its activity in the subsequent run. The catalyst was tested for 5 runs. It was seen that the catalyst displayed very good reusability (Figure 4).
Conclusion

In conclusion, some 3-(α-arylamido)-4-hydroxycoumarin derivatives were successfully synthesized by the reaction between 4-hydroxycoumarin (4-hydroxy-6-methylpyran-1-one) or 1,3-dimethylbarbutyric acid, aryl glyoxals and aliphatic amides (thioacetamide) in the presence of a catalytic amount of BF$_3$-SiO$_2$ NPs in water. The rate of the reactions and yields of the products have increased significantly in water. The presented method offers several advantages such as the use of a safe, inexpensive and recyclable catalyst, shorter reaction times, avoidance of organic solvents, high yields of products. Furthermore, all products were obtained through simple filtration with no need for column chromatography, which reduces the waste as well as environmental pollution.

References