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One-pot and chemoselective synthesis of bis(4-hydroxycoumarin) derivatives catalyzed by nano silica chloride

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Abstract

Nano silica chloride (nano SiO_2Cl) has been found to be an efficient, chemoselective and recyclable catalyst for facile and simple condensation of 4-hydroxycoumarin with aromatic and heteroaromatic aldehydes into bis(4-hydroxycoumarin)methanes in dry CH_2Cl_2. The products were obtained in high to excellent yields.

Keywords: 4-hydroxycoumarin; Knoevenagel condensation; Michael addition; bis(4-hydroxycoumarin)methane; Chemoselective; Recyclable; Nano silica chloride

Background

4-Hydroxycoumarin derivatives are of interest because of their widespread biological activities [1,2]. These compounds are used as anticoagulant and sustaining agents [3-5]. They have also been reported as antibiotics [6] and antitumor drugs [7]. Recently, for the preparation of biscoumarins by the reaction of 4- hydroxycoumarin and various aldehydes (one-pot Knoevenagel condensation and Michael addition), a variety of Lewis acid catalysts [8-12], phase transfer catalysts [13-18], microwave reactions [19-22], and molecular iodine were utilized. Although these methods may be effective, some of them have relatively long reaction times and unsatisfactory yields. This finding prompted us towards further investigation in search for a cheap catalyst, which will carry out the synthesis of biscoumarins under simpler experimental set-up and easy workup. Thus, in continuation of our ongoing research for the development of simple and efficient methods for the synthesis of various compounds [23,24], herein we wish to report a simple, economic, and efficient one-pot method for the synthesis of bis(4-hydroxycoumarin)methanes in CH_2Cl_2 using nano silica chloride as the catalyst. One such modified nano silica gel is nano silica chloride (nano SiO_2Cl). Our studies have shown that it was easily prepared by the addition of thionyl chloride to the nano silica gel. Nano silica chloride was reported to be an efficient catalyst for the synthesis of many organic compounds such as amorphous silica chloride [25-27]. It must be noted that the preparation of nano silica chloride is simple, clean, and without workup procedure. Nano silica chloride can be a useful, cheap, and chemoselective catalyst for the synthesis of bis(4-hydroxycoumarin)methanes, which was prepared by the readily available material and can also be easily removed from the reaction mixture.

Results and discussion

First, the effective catalytic route for the synthesis of bis (4-hydroxycoumarin)methanes is described. Amorphous silicon dioxide (75 mg), amorphous silica chloride (75 mg), nano silicon dioxide (75 mg), and nano silica chloride (75 mg) catalyzed the synthesis of bis(4-hydroxycoumarin) methanes. In order to show the applicability and efficiency of this method, our results have been compared with those of some of the same catalysts on the synthesis of bis (4-hydroxycoumarin)methanes [23,24]. As you can see in Table 1, nano silica chloride is superior to the other catalysts.

In the continuation of our study, the reaction of 4-hydroxycoumarin with 4-chlorobenzaldehyde (2j) was chosen as a model reaction in the presence of nano SiO_2Cl (55 mg) in dry dichloromethane at 40°C. The corresponding product (3j) was obtained after 8 h (71%) (Scheme 1; Table 2, entry 1). In a search for an even higher yield, we varied the amount of nano silica chloride;

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Table 1 Comparison of results for the synthesis of 3,3′-((4-chlorophenyl)methylene)bis(4-hydroxycoumarin) catalyzed by some silicon catalysts at same conditions

Entry	Catalyst	Time (h)	Yield (%)
1	SiO_2	12	88
2	Nano SiO_2	5.5	92
3	SiO_2Cl	9	87
4	Nano SiO_2Cl	3	92

Table 2 Optimization studies using 4-hydroxycoumarin (1) and 4-chlorobenzaldehyde (2j)

Entry	SiO_2Cl (mg)	Temperature (°C)	Time (h)	Yield[a] (%)
1	55	40	8	71
2	65	40	5.5	85
3	75	40	3	92
4	75	room temperature	12	69
5	75	30	9.5	73
6	75	35	5.5	83

[a]Reaction performed with aldehyde 2j (0.5 mmol), 4-hydroxycoumarin (1 mmol), and product 3j as determined by GC based on the amount of 4-hydroxycoumarin.

gratifyingly, a 92% yield of 3j was obtained when 75 mg was used (Table 2, entry 3). Finally, the reaction was performed at different temperatures. When the reaction was carried out at 25°C, 30°C, and 35°C, the product was also obtained in low yields comparable to the reaction performed at 40°C (Table 2, entries 4 to 6 vs. entry 3). Furthermore, we kept the catalyst concentration constant, and a number of different solvents such as toluene, THF, Et_2O, n-hexane, CH_3CN, and CH_2Cl_2 were also investigated. We found that dichloromethane was better suited as solvent for this purpose.

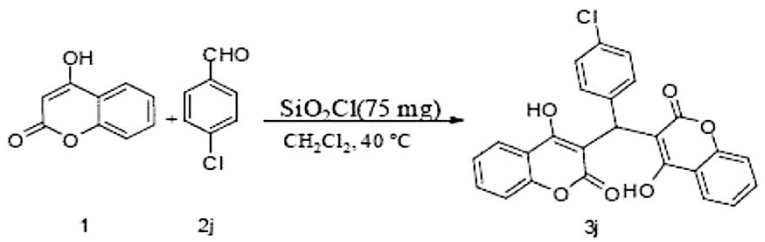
Thus, the best condition for the reaction was the use of nano silica chloride (75 mg), 4-hydroxycoumarin (1.0 mmol), and aldehyde (0.5 mmol) in dry CH_2Cl_2 (5 ml) at 40°C under air atmosphere (Scheme 2). This result prompted us to investigate the scope and the generality of this new protocol for various aromatic and heteroaromatic aldehydes under optimized conditions (Table 3).

After the optimized reaction condition, several aldehydes were examined. The results of their reaction with 4-hydroxycoumarin are summarized in Table 3. Aromatic aldehydes both with electron-withdrawing and electron-donating groups underwent smooth transformation to the corresponding biscoumarins, without the formation of any side products, in high to excellent yields. However, synthesis could not be achieved in the absence of the catalyst.

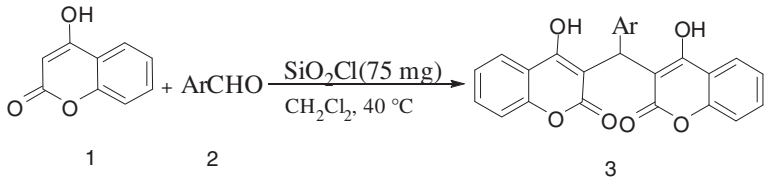
Using the same method, the catalytic system is capable of selective condensation of bisaldehydes, as a terephthaldehyde, to the corresponding 4-(bis(4-hydroxy-2-oxo-2H-chromen-3-yl)methyl)benzaldehyde by controlling the molar ratio of 4-hydroxycoumarin (Scheme 3). The results showed that 83% (3v) would be achieved in the presence of two equivalents of 4-hydroxycoumarin, whereas a treatment using four equivalents of 4-hydroxycoumarin with terephthaldialdehyde led to the occurrence of the corresponding 3,3′,3″,3‴-(1,4-phenylenebis(methanetriyl)) tetrakis(4-hydroxy-2H-chromen-2-one) (three times).

This method is also a very good way for the chemoselective conversion of aryl aldehydes in the presence of aliphatic ketones and aliphatic aldehydes. For example, when a 1:1 mixture of 4-chlorobenzaldehyde and cyclohexanone was allowed to react with 4-hydroxycoumarin in the presence of nano SiO_2Cl, it was found that only 4-chlorophenyl-3,3′-bis(4-hydroxycoumarin)methane was obtained; there is no corresponding product of cyclohexanone. Also, in an equimolar mixture of aryl aldehyde and aliphatic aldehyde, it was found that the aryl aldehydes were chemoselectively converted to the corresponding bis(4-hydroxycoumarin) methane, but the aliphatic ones were converted slightly (Scheme 4). The product was obtained in high yield without the formation of any side reactions.

The formation of compound **3** can be explained by the mechanism that is presented in Scheme 5. The reaction



Scheme 1 The reaction of 4-hydroxycoumarin with 4-chlorobenzaldehyde (2j) and the corresponding product (3j).



Scheme 2 Nano silica chloride-catalyzed synthesis of bis(4-hydroxycoumarin)methanes.

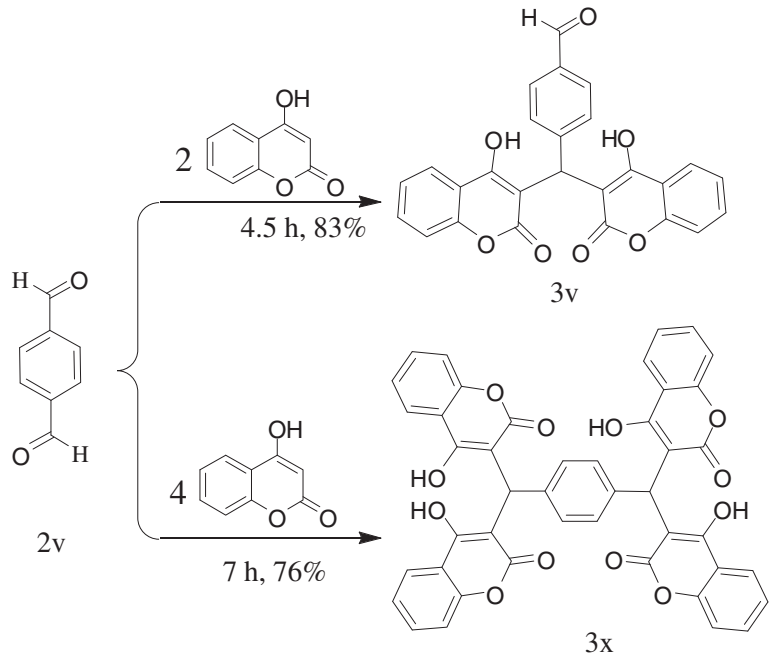
sequence is one-pot Knoevenagel condensation, Michael addition, and tautomerization. 4-Hydroxycoumarin adds easily to electron-poor alkenes in the Michael addition fashion. Thus, cascade reactions of addition, elimination, and addition could be achieved, but the intermediate alkenes **12** were not available even in 1:1 experiments according to the present reaction conditions [22]. The electron-poor alkenes **12** are useful intermediates for Michael additions.

Inspection of the SEM and TEM images of a sample catalyst from this reaction indicates the involvement of silica chloride nanoparticles with a size distribution of 15 to 35 nm (average ≈25 nm; Figures 1 and 2). After the reaction, nano silica chloride can be easily separated (by centrifuge and filtration) and reused without a decrease in its activity. For example, the reaction of 4-hydroxycoumarin with 4-chlorobenzaldehyde afforded the corresponding bis(4-hydroxycoumarin)methanes in 95%, 95%, and 91% isolated yield over three cycles. When we carried out the reaction in CH_2Cl_2, the reaction proceeded very slowly to give moderate yields.

Table 3 Nano silica chloride catalyzed synthesis of bis(4-hydroxycoumarin)methanes

Entry	ArCHO	Product	Time (h)	Yield[a,b](%)	Melting point (°C)
1	PhCHO	3a	2.5	85	231-234
2	2-OH PhCHO	3b	2	88	254-256
3	2-OMe PhCHO	3c	2.5	82	236-238
4	2-Cl PhCHO	3d	3	93	224-226
5	2-Br PhCHO	3e	3	95	256-258
6	2-NO_2 PhCHO	3v	3.5	91	104-106
7	3-NO_2 PhCHO	3f	3.5	90	234-236
8	4-NO_2 PhCHO	3g	3.5	85	232-234
9	4-CF_3 PhCHO	3h	3.5	71	258-260
10	4-F PhCHO	3i	6	71	212-214
11	4-Cl PhCHO	3j	3	92	254-256
12	4-Br PhCHO	3k	3.5	91	266-268
13	4-Me PhCHO	3l	2.5	90	266-268
14	4-OMe PhCHO	3m	2	78	246-248
15	4-NMe_2 PhCHO	3n	1	95	222-224
16	4-OH PhCHO	3o	2.5	90	222-224
17	3,4-$(OMe)_2$ PhCHO	3p	2	88	263-265
18	2,6-Cl_2 PhCHO	3q	3.5	78	178-180
19	Furfural	3r	2.5	70	200-202
20	2-Thenaldehyde	3s	3	75	210-212
21	2-Formylpyrrole	3t	2	75	161-163
22	3-Formylindole	3u	5.5	68	238-240

[a]Yields refer to crude product (isolated product).
[b]All products were identified by comparing their physical and spectral data with those of authentic samples.



Scheme 3 Selective condensation of dialdehyde with 4-hydroxycoumarin.

Conclusion

A facile and highly efficient method for the condensation of 4-hydroxycoumarin with aromatic and heteroaromatic aldehydes has been described using nano silica chloride as a recyclable and chemoselective catalyst. The products were obtained in high to excellent yields after stirring for a few hours with operational simplicity.

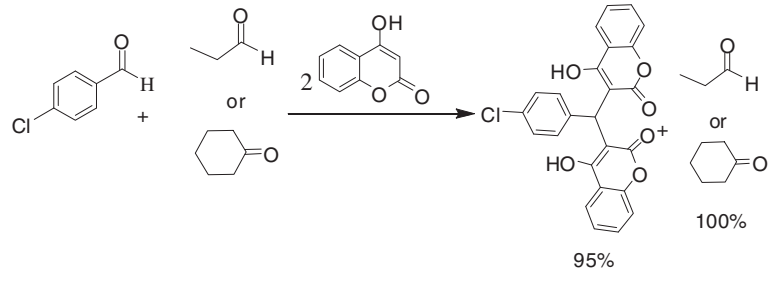
Methods

Preparation of nano silica chloride

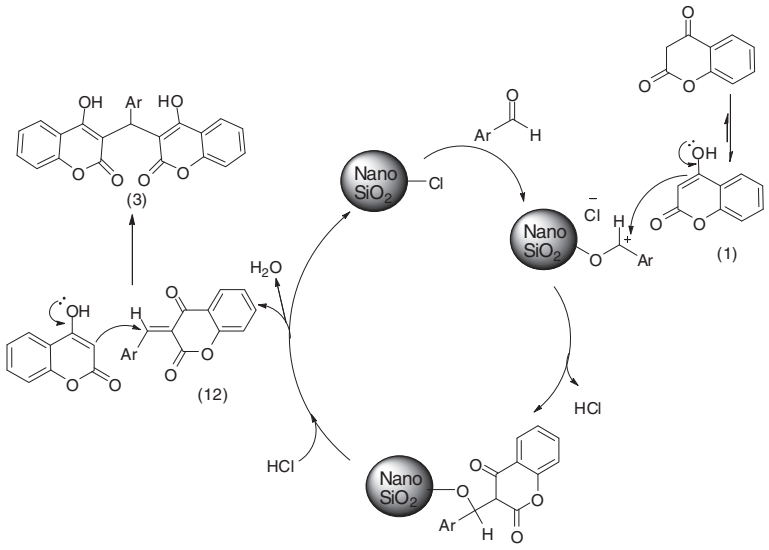
Nano SiO_2Cl powder was prepared according to the procedure reported [23,24]. To an oven-dried (120°C) nano silica gel (5 g) in a round-bottomed flask (250 mL) equipped with a condenser and a drying tube, thionyl chloride (toxic and should be used with caution) (100 mL) was added, and the mixture was refluxed for 1 week. The excess thionyl chloride was distilled off. The resulting white-grayish powder was flame-dried and stored in a tightly capped bottle.

Typical experimental procedure

To a mixture of 4-hydroxycoumarin (1 mmol) and aldehydes (0.5 mmol) in CH_2Cl_2 (5 mL), nano silica chloride (75 mg) was added at 40°C. The mixture was stirred for a specified period (Table 3). The progress of the reaction was monitored by thin layer chromatography (TLC).



Scheme 4 Chemoselectivity of aryl aldehyde reacting with 4-hydroxycoumarin in the presence of ketone and aliphatic aldehyde.



Scheme 5 Mechanism of synthesis of bis(4-hydroxycoumarin)methane.

After the complete conversion of the starting material, as indicated by TLC, the reaction mixture was filtered and concentrated under reduced pressure. The obtained product was filtered and recrystallized from ethanol to get the pure product. The products were characterized according to their ^{1}H nuclear magnetic resonance (NMR), IR, and melting point data. The representative spectral (^{1}H NMR and IR) data of bis(4-hydroxycoumarin)methane derivatives 3a to 3u are given below.

Compound 3a. White solid; ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.18 (s, 1H), 6.82 to 7.56 (m, 13H), 10.72 (brs, 2OH); IR (KBr disk): 3034, 1652, 1608, and 754.

Compound 3g. Yellow solid; ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.56 (s, 1H), 7.13 to 8.38 (m, 12H), 11.22 (brs, 2OH); IR (KBr disk): 3033, 1652, 1615, 1529, 1347, and 761.

Compound 3m. White solid; ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.78 (s, 3H), 6.38 (s, 1H), 7.1 to 8.31 (m, 12H), 11.49 (brs, 2OH); IR (KBr disk): 3388, 3026, 1666, 1605, 1255, 1050, and 768.

Compound 3r. Black solid; ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.09 (s, 1H), 6.35 to 6.55 (m, 3H), 7.23 to 8.38 (m, 8H), 12.02 (brs, 2OH); IR (KBr disk): 3038, 1668, 1615, and 767.

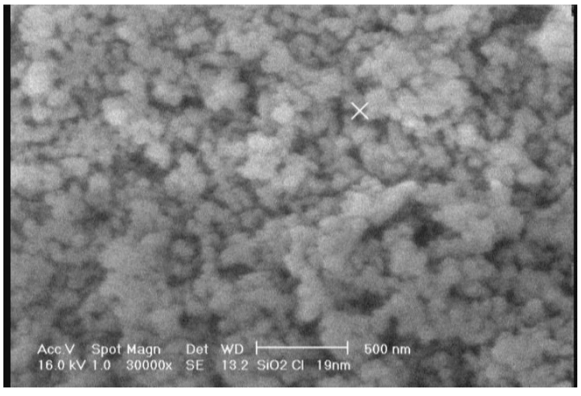


Figure 1 SEM image of silica chloride nanoparticle.

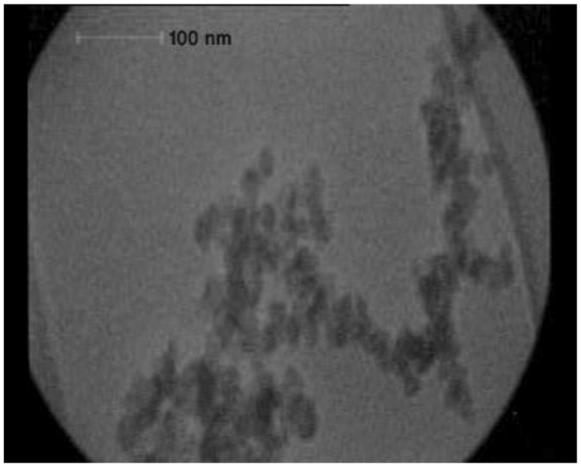


Figure 2 TEM image of silica chloride nanoparticle.

Competing interest
The authors declare that they have no competing interests.

Authors' contributions
RK and AAS have contributed to all experiments and has been supervised by FP who supervised the project. SJD has participated in the statistical analysis and in the preparation of the manuscript. All authors read and approved the final manuscript.

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RK is an assistant professor of Organic Chemistry in Applied Biotechnology Research Center at Baqiyatallah University of Medical Sciences. FP is an assistant professor of Organic Chemistry at University of Zanjan. AAS is an assistant professor of Organic Chemistry at Islamic Azad University of Zanjan. SJD is an assistant professor of Biology in Applied Biotechnology Research Center at Baqiyatallah University of Medical Sciences.

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