

## Melamine trisulfonic acid: An efficient and recyclable solid acid catalyst for the green synthesis of Biscoumarin derivatives

Nasir Iravani<sup>a,\*</sup>, Mosadegh Keshavarz<sup>b</sup>, Maryam Mousavi<sup>a</sup>, Mojtaba Baghernejad<sup>c</sup>

<sup>a</sup>Department of Chemistry, Faculty of Science, Gachsaran Branch, Islamic Azad University, Gachsaran, Iran.

<sup>b</sup>Department of Gas and Petroleum, Yasouj University, Yasouj, Zip Code 75918-74831, Iran.

<sup>c</sup>Young and Reasearcers Elite, Gachsaran Branch, Islamic Azad University, Gachsaran, Iran.

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### ABSTRACT

A novel catalytic synthesis of 3,3'-(arylmethylene)-bis-(4-hydroxy-2H-chromene-2-one) derivatives from a tandem condensation reaction of 4-hydroxycoumarin and aromatic aldehydes has been developed. The reaction occurs in water in the presence of Melamine trisulfonic acid as catalyst to give the corresponding products in good to high yields. This green approach has several advantages such as short reaction times, clean reaction profiles, and simple experimental and workup procedures. Moreover, the catalyst can be easily recovered by filtration and used at least seven times with only slight reduction in its catalytic activity. The results of the presented protocol in comparison with the different available catalysts in condensation reaction of benzaldehyde with 4-Hydroxycoumarin show that MTSA presented better results due to the structure of MTSA.

**Keywords:** Aromatic aldehydes; Biscoumarins; 4-Hydroxycoumarin; Melamine trisulfonic acid.

### 1. Introduction

Coumarin derivatives form an important class of compounds. These compounds possess several types of pharmacological properties. For example, 4-Hydroxycoumarin and its derivatives are known for their various biological activities such as anticoagulant, anticancer, spasmolytic, antibacterial, insecticidal, antihelminthic, hypnotic, antifungal, phytoalexin, and HIV protease inhibition [1-4]. Biscoumarins, 3,3'-(arylmethylene)-bis-(4-hydroxy-2H-chromene-2-ones), are the bridge substituted dimers of 4-hydroxycoumarin and have enormous potential as anticoagulants and hemorrhagic agents in the spoiled clover disease of cattles [5-7]. A number of biscoumarins have also been found to be urease inhibitors [8]. Recently, a number of methods have been reported for the synthesis of biscoumarins by reaction of 4-hydroxycoumarin and various aldehydes in organic solvents, use of expensive catalysts, tedious work-up, and unsatisfactory yields. Thus, the search for better conditions (especially catalyst and solvent) is still of practical importance.

[9-21]. However, in spite of their potential utility and effectiveness, some of these methods suffer from some drawbacks or at least one limitation, such as relatively long reaction times, requirement of refluxing for hours. With the increasing public concern over environmental degradation, the use of environmentally benign solvents like water represent very powerful green chemical technology procedures from both the economical and synthetic points of view. They have many advantages, such as reduced pollution, lower cost, and simplicity in processing which are beneficial to the industry as well as to the environment [22]. Moreover, these finding prompted us towards further investigation in search for better and more efficient catalyst, which will carry out the organic transformations (such as synthesis of biscoumarins) under simpler experimental set up and eco-friendly conditions. During the last decade many industrial processes shifted towards using solid acid catalysts [23,24]. In contrast to liquid acids that possess well-defined acid properties, solid acids may contain a variety of acid sites [25]. Generally they are categorised by their Brønsted or Lewis acidity, the strength and number of sites, and the textural properties of the support (porosity and surface area)

\*Corresponding author email: iravaninasir56@gmail.com  
Tel.: +987432334751; Fax: +987432332003

[26]. One of the efficient solid acid catalysts in organic transformations is melamine trisulfonic acid (MTSA), (Scheme 1) and in this article, we described a mild, efficient and environmentally friendly method for the preparation of biscoumarin derivatives in the presence of catalytic amounts of melamine trisulfonic acid as catalyst and in water as a green solvent [27-36].

## 2. Experimental

### 2.1. General

Aromatic aldehydes and 4-Hydroxycoumarin were obtained from Fluka and Merck and were used without further purification. The IR spectra: Shimadzu IR-460 and Perkin Elmer RXI FT-IR spectrometers with solid cell;  $^1\text{H}$  and  $^{13}\text{C}$ NMR spectra: Bruker DRX-400 AVANC instrument; in  $\text{CDCl}_3$  or  $\text{DMSO}-d_6$  at 400 MHz and 100 MHz, respectively,  $\delta$  in ppm,  $J$  in Hz; Elemental analyses (C, H, and N) were performed with a Heraeus CHN-O-Rapid analyzer. Melting points were determined using a Melting Point UK-Barnstead Electrothermal 9100 BZ apparatus in open capillary tubes and are uncorrected. All the products were characterized by comparing their spectral (IR,  $^1\text{H}$  and  $^{13}\text{C}$  NMR), TLC, and physical data with those reported in the literatures and obtained results showed that the analyses data were in agreement with the proposed structures [6,14-17,19,20].

### 2.2. Catalyst preparation

A 250-mL suction flask charged with chlorosulfonic acid (5mL, 75.2 mmol) was equipped with a gas inlet tube for conducting HCl gas over an adsorbing solution (i.e., water). Melamine (3.16 g, 25.07 mmol) was added in small portions over a period of 30 min at room temperature. HCl gas evolved from the reaction vessel immediately. After completion of the addition

of melamine, the mixture was shaken for 30 min; meanwhile, the residual HCl was removed by suction. Melamine trisulfonic acid (7.9 g, 87%) was obtained as a white solid, which was stored in a capped bottle.

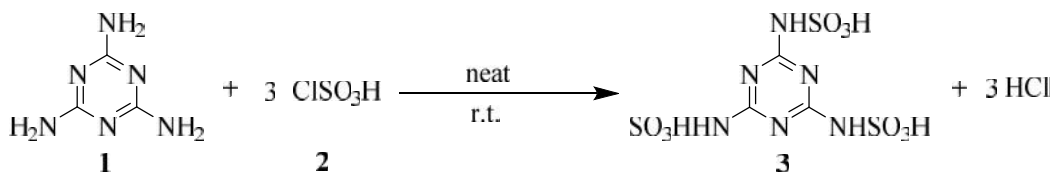
### 2.3. General procedure for the synthesis of 3,3'-(arylmethylene)-bis-(4-hydroxy-2H-chromene-2-ones)

A mixture of aromatic aldehyde (1 mmol), 4-Hydroxycoumarin (2 mmol), and MTSA (0.05 gr), in  $\text{H}_2\text{O}$  (15 ml) were added to a flask and then stirred and heated on the oil bath at  $80^\circ\text{C}$  for the appropriate times (Table 3). After completion of reaction, as indicated by thin layer chromatography (TLC, silica gel SILG/UV 254 plates,  $n\text{-Hexane}/\text{AcOEt} = 3:1$ ), catalyst was separated by filtration. The crude product was collected from the filtration after cooling to room temperature and for more purification was purified by recrystallization from ethanol (95%) to give compounds **6a-x** in good to high yields. The recovered catalyst was washed with diethyl ether, dried, and reused in subsequent runs.

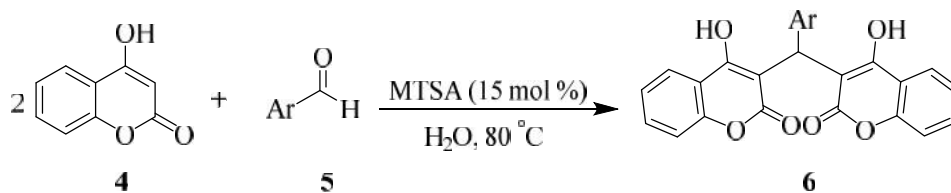
## 3. Results and Discussion

In continuation of our studies to introduce and development of catalytic properties and new applications of melamine trisulfonic acid, we report herein an efficient, green, and environmentally benign method for the synthesis of biscoumarin derivatives from the reaction of aromatic aldehydes with 2 equivalents of 4-Hydroxycoumarin in the presence of catalytic amounts of melamine trisulfonic acid as catalyst and water as solvent (Scheme 2) [36].

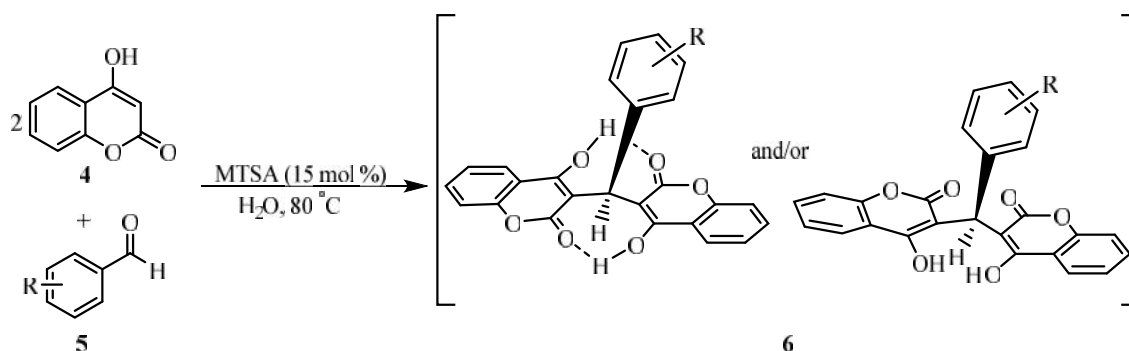
As shown in Scheme 3, the 4-hydroxycoumarin moieties are intramolecularly hydrogen bonded between hydroxyl and carbonyl oxygen atoms in both structures, thus two eight-membered rings can be formed and more than two signals can be observed for carbonyl groups in more of products.



Scheme 1. Preparation of Melamine trisulfonic acid.



Scheme 2. Synthesis of biscoumarin derivatives catalyzed by MTSA.



**Scheme 3.** Intramolecular hydrogen bonded between hydroxyl and carbonyl oxygen atoms.

In an initial attempt, in order to find optimum reaction conditions (catalyst amount, solvent, and temperature), at first we studied the synthesis of 3,3'-(phenylmethylene)-bis-(4-hydroxy-2*H*-chromene-2-one) **6a** from the condensation reaction of 4-Hydroxycoumarin with benzaldehyde as the model reaction and then different conditions were examined in the model reaction (Table 1). The obtained results clearly show that in the absence of MTSA the condensation reaction proceeds slowly and gives very low yield after 24h (Entry 1), and the best amount of yield to prepare the products was achieved when 15 mol% of melamine trisulfonic acid was used in the presence of H<sub>2</sub>O as solvent and at 80 °C temperature (Entry 4). Although under presented conditions in

entries 3 and 8 this condensation was accomplished however, 15 mol % (0.05 gr) of MTSA per 1mmol of benzaldehyde and 2 mmol of 4-Hydroxycoumarin was optimum in terms of reaction time and isolated yield. It is important to explain that because of the molecular weight of MTSA is 365.94 gr.mol<sup>-1</sup> and so on the based on stoichiometric calculations 15 mol % of the title catalyst was calculated to be 0.05 gr. Therefore, after optimization of the reaction conditions, to prove the general applicability of this method, we employed the optimized conditions (0.15 mmol of MTSA in water at 80 °C) for the condensation reaction of various aromatic aldehydes with 4-Hydroxycoumarin into the corresponding 3,3'-(phenylmethylene)-bis-(4-hydroxy-2*H*-chromene-2-one) (Scheme 2).

**Table 1.** Condensation reaction of benzaldehyde with 4-Hydroxycoumarin in the presence of different conditions <sup>a</sup>.

Entry	Catalyst (mol %)	Solvent	Temperature (°C)	Time (min)	Yield (%) <sup>b</sup>
1	None	H <sub>2</sub> O	80	24h	15
2	5	H <sub>2</sub> O	80	35	80
3	10	H <sub>2</sub> O	80	28	95
<b>4</b>	<b>15</b>	<b>H<sub>2</sub>O</b>	<b>80</b>	<b>20</b>	<b>95</b>
5	20	H <sub>2</sub> O	80	20	92
6	25	H <sub>2</sub> O	80	20	90
7	15	C <sub>2</sub> H <sub>5</sub> OH	80	38	88
8	15	C <sub>2</sub> H <sub>5</sub> OH:H <sub>2</sub> O	80	30	93
9	15	CH <sub>3</sub> OH	80	45	87
10	15	CH <sub>3</sub> CN	80	120	70
11	15	H <sub>2</sub> O	25	180	< 10
12	15	H <sub>2</sub> O	40	70	46
13	15	H <sub>2</sub> O	60	40	78
14	15	H <sub>2</sub> O	100	20	89

<sup>a</sup>Reaction conditions: benzaldehyde (1 mmol), 4-Hydroxycoumarin (2 mmol), solvent (15 ml).

<sup>b</sup>Isolated yield.

It should be mentioned that our efforts for the synthesis of biscoumarins using aliphatic aldehydes were unsuccessful. The problem with alkyl aldehydes is likely due to their enolization during the reaction. In order to show the superiority, efficiency and novelty of our introduced method, the results of the presented protocol in comparison with the different available catalysts in condensation reaction of benzaldehyde with 4-Hydroxycoumarin are shown in Table 2. The information of this table show that MTSA presented better results in comparison with the other methods in this condensation reaction and probably, this is due to existing of three acidulous functions in the structure of MTSA. Despite the other methods are clean and efficient strategies, but sometimes it is not possible to establish everywhere.

The results of this synthetic method are presented in Table 3. As shown in this table, all aromatic aldehydes reacted with 4-Hydroxycoumarin to afford 3,3'-(arylmethylene)-bis-(4-hydroxy-2*H*-chromene-2-ones) in excellent yields. On the other hand, benzaldehydes with electron-donating groups such as 4b, 4j, and 4p or electron-withdrawing groups such as 4f, 4l, and 4t were condensed into the corresponding 3,3'-(arylmethylene)-bis-(4-hydroxy-2*H*-chromene-2-ones) in high yields.

The proposed mechanism for the synthesis of biscoumarin is shown in Scheme 4. As shown in Scheme 4, at first proton activates carbonyl group of aromatic aldehyde to give intermediate 7 and thus increases the electrophilicity carbonyl carbon of aldehyde. Nucleophilic addition of 4-hydroxycoumarin to 7 to give intermediate 8 and followed by loss of H<sub>2</sub>O from 8 to afford intermediate 9, which is further activated by proton. Another molecule of 4-hydroxycoumarin is added to intermediate 9 to give intermediate 10 which loss molecular MTSA to give bis-coumarin 6. The reusability of catalyst is important for the large scale operation and industrial point of view. Therefore, the possibility of recycling the catalyst was examined using the reaction of benzaldehyde and 4-Hydroxycoumarin under the optimized conditions. Upon completion of reaction, catalyst was separated by filtration. The recovered catalyst was washed with diethyl ether, dried, and reused for subsequent runs. The recycled catalyst could be reused seven times without any additional treatment (Fig. 1).

#### 4. Conclusions

In conclusion, we have prepared some 3,3'-(arylmethylene)-bis-(4-hydroxy-2*H*-chromene-2-ones) by a tandem condensation reaction of aromatic aldehydes with 2 equivalents of 4-Hydroxy coumarin

in the presence of melamine trisulfonic acid in water as solvent and at 80 °C. This catalyst synthetic method seems facile, short times for reaction, good to high yields, workup procedure is easy and gives pure target compounds containing several potential centers for further modification. Moreover, the catalyst can be easily recovered by filtration and used at least seven times with only slight reduction in its catalytic activity.

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**Table 2.** Condensation reaction of benzaldehyde with 4-Hydroxycoumarin in the presence of different catalysts<sup>a</sup>.

Entry	Catalyst	Catalyst loading		Time (min)	Yield (%) <sup>a</sup>	Ref.
		gr	mol%			
1	MTSA	0.05	15	20	95 <sup>b</sup>	This Work
2	SDS <sup>c</sup>	0.06	20	150	90	[16]
3	TBAB <sup>d</sup>	0.03	10	25	92	[11]
4	[TBA] <sub>2</sub> [W <sub>6</sub> O <sub>19</sub> ]	0.15	8	5	91	[15]
5	H <sub>14</sub> [NaP <sub>5</sub> W <sub>30</sub> O <sub>110</sub> ]/SiO <sub>2</sub>	0.02	0.3	30	92	[17]
6	H <sub>14</sub> [NaP <sub>5</sub> W <sub>30</sub> O <sub>110</sub> ]	0.02	0.3	40	88	[17]
7	[MIM(CH <sub>2</sub> ) <sub>4</sub> SO <sub>3</sub> H][HSO <sub>4</sub> ]	0.04	0.15	30	92	[19]
8	NaHSO <sub>4</sub> /SiO <sub>2</sub>	0.15	-	30	89	[20]
9	Indione 190 resin	0.15	-	30	92	[20]
10	SiO <sub>2</sub>	0.05	-	60	95	[21]

<sup>a</sup>Isolated yield.

<sup>b</sup>This work.

<sup>c</sup>Sodium dodecyl sulfate.

<sup>d</sup>Tetra butyl ammonium bromide.

**Table 3.** Synthesis of biscoumarin derivatives catalyzed by MTSA in water at 80 °C conditions.<sup>a</sup>

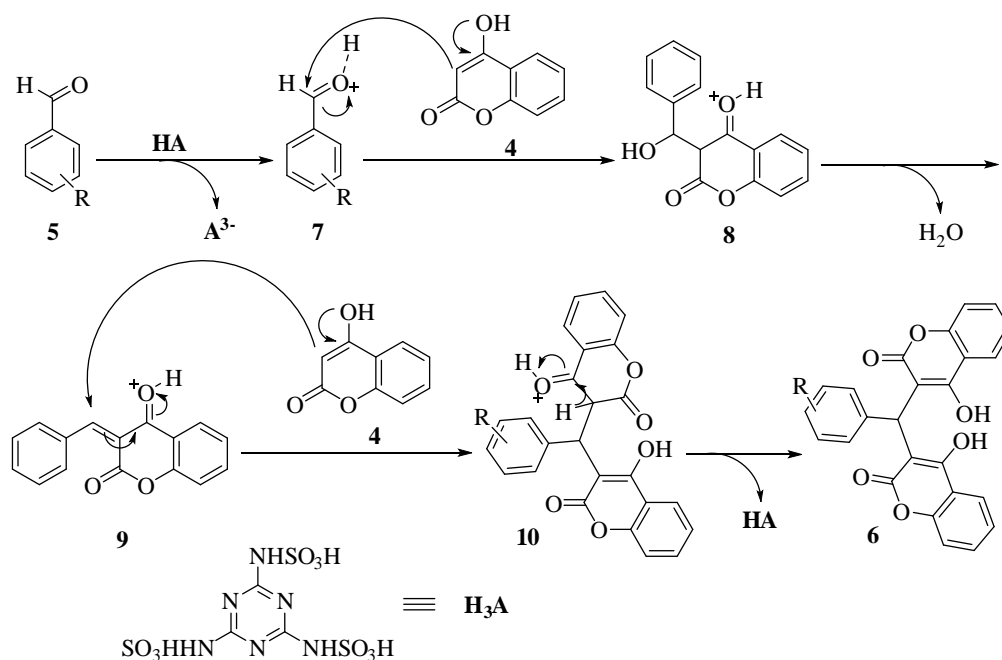
Entry	[R <sup>b</sup> and/or Ar <sup>c</sup> ] (5)	Product (6)	Time (min)	Yield <sup>d</sup> (%)	m.p. (°C)		Ref.
					Found	Reported	
1	C <sub>6</sub> H <sub>5</sub> -	6a	20	95	227-230	228-230	[20]
2	4-Me-C <sub>6</sub> H <sub>4</sub> -	6b	35	84	268-270	269-270	[20]
3	4-Cl-C <sub>6</sub> H <sub>4</sub> -	6c	23	90	259-261	258-259	[15]
4	2-Cl-C <sub>6</sub> H <sub>4</sub> -	6d	30	85	200-202	198-199	[15]
5	2,4-(Cl) <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> -	6e	40	83	262-264	-	-
6	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> -	6f	12	97	230-233	232-234	[20]
7	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> -	6g	24	88	214-216	212-215	[15]
8	4-OH-C <sub>6</sub> H <sub>4</sub> -	6h	28	83	221-223	222-224	[20]
9	3-OH-C <sub>6</sub> H <sub>4</sub> -	6i	33	77	210-213	-	-
10	3,4-(MeO) <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> -	6j	46	94	266-268	264-266	[16]
11	4-MeS-C <sub>6</sub> H <sub>4</sub> -	6k	38	86	238-241	-	-
12	4-CN-C <sub>6</sub> H <sub>4</sub> -	6l	25	91	260-263	-	-
13	2-OH-C <sub>6</sub> H <sub>4</sub> -	6m	22	78	229-231	230-232	[17]
14	4-F-C <sub>6</sub> H <sub>4</sub> -	6n	35	82	217-219	213-215	[16]
15	4- <sup>i</sup> Pr-C <sub>6</sub> H <sub>4</sub> -	6o	42	75	244-247	245-247	[14]
16	4-MeO-C <sub>6</sub> H <sub>4</sub> -	6p	30	89	242-245	249-250	[20]
17	2-Br-C <sub>6</sub> H <sub>4</sub> -	6q	36	85	259-261	258	[20]
18	4-Br-C <sub>6</sub> H <sub>4</sub> -	6r	45	80	264-267	266-268	[20]
19	4-[N(Me) <sub>2</sub> ]-C <sub>6</sub> H <sub>4</sub> -	6s	25	92	219-220	222-224	[20]
20	4-Cl-3-NO <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> -	6t	36	88	264-268	265-267	[6]
21	3,4,5-(MeO) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub> -	6u	40	80	239-240	243-245	[6]
22	C <sub>6</sub> H <sub>5</sub> -CH=CH-	6v	30	88	261-264	-	-
23	S-Naphthyl	6w	29	83	283-287	-	-

<sup>a</sup>Reaction conditions: aldehyde (1 mmol), 4-Hydroxycoumarin (2 mmol), MTSA (15 mol %), H<sub>2</sub>O (15 ml), 80 °C.

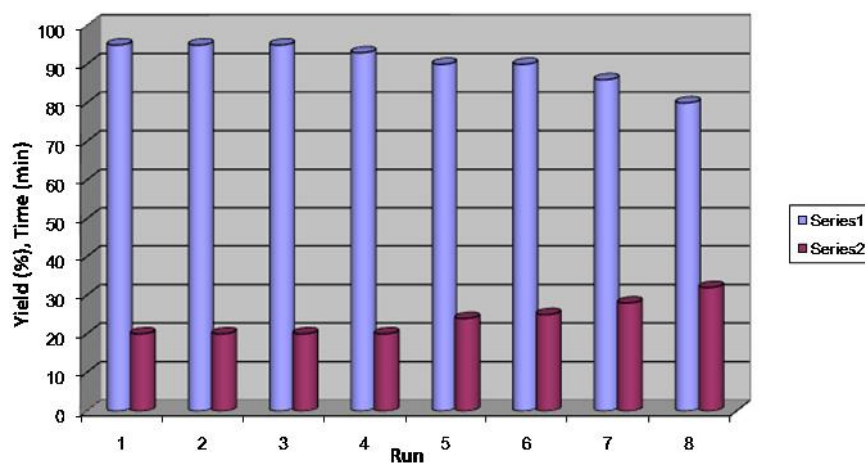
<sup>b</sup>For aldehydes 5a-5u.

<sup>c</sup>For aldehydes 5v and 5w.

<sup>d</sup>Isolated yield.



**Scheme 4.** Proposed mechanism for the synthesis of biscoumarin derivatives catalyzed by MTSA.



**Fig. 1.** Recyclability of MTSA (15 mol %, 0.05 gr) in the reaction of benzaldehyde (1 mmol) and 4-Hydroxy coumarin (2 mmol) in H<sub>2</sub>O (15 ml), at 80 °C. Series 1: Yield (%), Series 2: Time (min).

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