



## ULTRASOUND ASSISTED CATALYST-FREE ONE -POT SYNTHESIS OF BIS-COUMARINS IN NEAT WATER

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### ABSTRACT

An efficient and simple catalyst-free one pot synthesis of biscoumarins by condensing 4-hydroxycoumarin with aromatic aldehydes in water under ultrasound irradiations at ambient temperature with excellent yield of the desired products in shorter reaction time is described.

**Key words:** Green synthesis, Biscoumarins, Catalyst free, Sonochemistry.

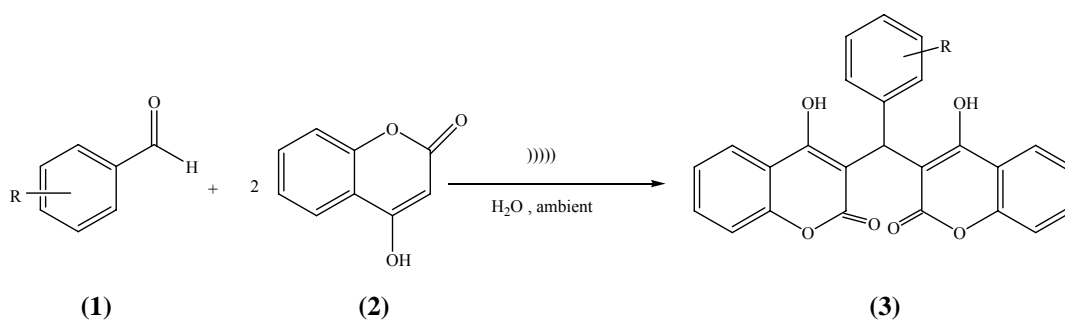
### INTRODUCTION

Coumarin derivatives are biologically active chemical compounds found in many plants, notably in high concentration in the tonka bean, woodruff and bison grass<sup>1</sup> and they have various biological activities such as anticoagulant, insecticidal, antihelminthic, hypnotic, antifungal, phytoalexin and as HIV protease inhibitors<sup>2-4</sup>. Several biscoumarins were isolated from plants<sup>5-11</sup>. Dimeric coumarin derivatives (phebalin, thamnosin, toddasin) were also identified from Rutacea and synthesized through expedite method<sup>12</sup>. Other interesting dimeric compounds were isolated and synthesized, namely those described in the review of Estévez-Braun and González<sup>13</sup>. However, Bis-coumarins were usually prepared by the condensation of carbonyl compounds with 4-hydroxycoumarin in organic solvents<sup>14,15</sup>, which employs large amounts of hazardous and toxic solvents associated with catalysts. With the increasing public concern over environmental awareness, the use of environmentally benign solvents like water represent very powerful green chemical technology procedures from both the economical and synthetic points of view. Recently, several methods of synthesis using 4-hydroxycoumarin for preparation of Bis-coumarins in aqueous media have been reported. Despite effectiveness and eco-friendliness of these methods, they use

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catalysts such as TEBA<sup>16</sup> and I<sub>2</sub><sup>17</sup> and have long reaction times. Thus, the introduction of efficient new methods based on green methodology is still in great demand. Ultrasound irradiation has been increasingly used in organic synthesis in last three decades. Comparing with traditional methods, this method is more conveniently and easily controlled. A large number of organic reactions have been carried out in higher yield with shorter reaction time and milder reaction condition under ultrasound irradiation<sup>18-20</sup>. In all reactions, organic solvents were always being used. Recently organic reactions in water without use of harmful organic solvents have drawn much more attention, because water is a cheap, safe and environmentally benign solvent<sup>21-22</sup>. In the course of our investigation to developed new green synthetic method, we have reported ultrasound assisted catalyst free synthesis of biscoumarins in water (**Scheme 1**).



**Scheme 1: Synthesis of Bis-coumarins**

## EXPERIMENTAL

All reagents were purchased from Merck and Loba and used without further purification. Melting points were measured in open capillary and are uncorrected. The products were characterized by IR spectra and <sup>1</sup>H NMR. IR spectra were recorded on Perkin–Elmer FT-IR-1710 instrument. <sup>1</sup>H NMR was recorded on Bruker AC-200 MHz and Bruker MSL-300 MHz instrument using TMS as an internal standard. Elemental analyses were determined by an elemental analyzer (CHNS-O, EA 1108-elemental analyzer, Carlo Erba instruments). For ultrasound assisted organic reactions, ultrasonicator was used with the following technical specifications.

Electric supply: 230 V A.C. 50 Hz, 1phase.

Ultrasonic frequency: 36 ± 3 KHz.

Ultrasonic power: 100 watts.

### General procedure

A aromatic aldehyde (1 mmol) and 4-hydroxycoumarin (2 mmol) were taken in 25 mL round bottom flask followed by addition of water (5 mL). The mixture was irradiated in the water bath of an ultrasonic cleaner for appropriate time (Table 1). After completion of the reaction monitored by TLC, the solid product was filtered, washed by water and dried under vacuum. The crude product was recrystallized by methanol.

#### **3-((phenyl) (4-hydroxy-2-oxo-2H-chromen-3-yl) methyl)-4-hydroxy-2H-chromen-2-one (3a)**

M.P.: 226-228°C; IR (KBr) 3057, 1676, 1608, 1568, 1492, 1350, 759  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  (ppm) = 11.53 (s, 1H, OH), 11.32 (s, 1H, OH), 8.09-7.24 (m, 13H, 13  $\times$  CH), 6.11 (s, 1H, CH).

#### **3-((4-chloro-phenyl) (4-hydroxy-2-oxo-2H-chromen-3-yl) methyl)-4-hydroxy-2H-chromen-2-one (3b)**

M.P.: 254-256 °C; IR (KBr) 3076, 1668, 1602, 1566, 1491, 1450, 1350, 1270, 1215, 767  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  (ppm) = 11.54 (s, 1H, OH), 11.32 (s, 1H, OH), 8.09-7.17 (m, 12H, 12  $\times$  CH), 6.04 (s, 1H, CH).

#### **3-((2-chloro-phenyl) (4-hydroxy-2-oxo-2H-chromen-3-yl) methyl)-4-hydroxy-2H-chromen-2-one (3c)**

M.P.: 224-226°C; IR (KBr) 3057, 2719, 1660, 1568, 1494, 1437, 1352, 1309, 758  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  (ppm) = 11.63 (s, 1H, OH), 10.93 (s, 1H, OH), 8.03-7.22 (m, 12H, 12  $\times$  CH), 6.14 (s, 1H, CH).

#### **3-((4-methoxy-phenyl) (4-hydroxy-2-oxo-2H-chromen-3-yl) methyl)-4-hydroxy-2H-chromen-2-one (3d)**

M.P.: 244-246°C; IR (KBr) 3070, 3001, 1668, 1604, 1466, 1510, 1452, 1352, 1309, 1259, 769  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  (ppm) = 11.5 (s, 1H, OH), 11.29 (s, 1H, OH), 8.05-6.87 (m, 12H, 12  $\times$  CH), 6.05 (s, 1H, CH), 3.80 (s, 3H,  $\text{CH}_3\text{O}$ ).

#### **3-((2-methoxy-phenyl) (4-hydroxy-2-oxo-2H-chromen-3-yl) methyl)-4-hydroxy-2H-chromen-2-one (3e)**

M.P.: 258-260°C; IR (KBr) 3076, 1666, 1604, 1568, 1487, 1454, 1350, 763  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  (ppm) = 11.58 (s, 1H, OH), 11.28 (s, 1H, OH), 8.05-6.77 (m, 12H, 12  $\times$  CH), 6.08 (s, 1H, CH), 3.75 (s, 3H,  $\text{CH}_3\text{O}$ ).

**3-((4-nitro-phenyl) (4-hydroxy-2-oxo-2H-chromen-3-yl) methyl)-4-hydroxy-2H-chromen- 2-one (3f)**

M.P.: 236-237°C; IR (KBr) 3080, 1660, 1616, 1600, 1566, 1518, 1450, 1348, 765  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  (ppm) = 11.57 (s, 1H, OH), 11.37 (s, 1H, OH), 8.22-7.26 (m, 12H,  $12 \times \text{CH}$ ), 6.13 (s, 1H, CH).

**3-((4-hydroxy-phenyl) (4-hydroxy-2-oxo-2H-chromen-3-yl) methyl)-4-hydroxy-2H-chromen-2-one (3g).**

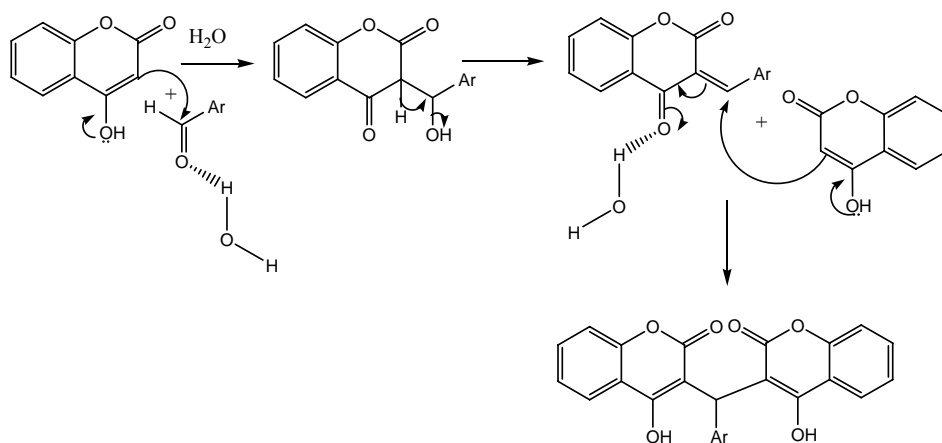
M.P.: 220-224°C; IR (KBr) 3452, 3072, 1668, 1608, 1566, 1514, 1433, 1348, 1307, 763  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  (ppm) = 11.49 (s, 1H, OH), 11.29 (s, 1H, OH), 8.05-6.77 (m, 12H,  $12 \times \text{CH}$ ), 6.04 (s, 1H, CH), 3.73 (q, 3H, OH)

**3-((3,4,5-trimethoxy-phenyl)(4-hydroxy-2-oxo-2H-chromen-3-yl)methyl)-4-hydroxy-2H-chromen-2-one (3h).**

M.P.: 240-242°C; IR (KBr) 3072, 3003, 1662, 1618, 1602, 1566, 1508, 1450, 1348, 1126, 761  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  (ppm) = 11.55 (s, 1H, OH), 11.28 (s, 1H, OH), 8.04-6.42 (m, 10H,  $10 \times \text{CH}$ ), 6.07 (s, 1H, CH), 3.85-3.72 (s, 9H,  $3 \times \text{CH}_3\text{O}$ ).

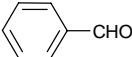
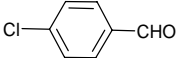
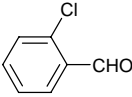
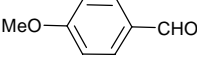
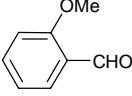
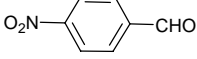
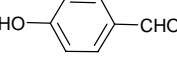
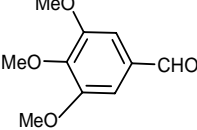
## RESULTS AND DISCUSSION

A green methodology is developed for the synthesis of biscoumarins by the coupling of 4-hydroxycoumarin and aromatic aldehydes in water under ultrasound irradiations. The desired products were obtained in excellent yields. The mechanism of the reaction is depicted in Scheme 2 and results are shown in Table 1.



**Scheme 2: Mechanism of reaction**

**Table 1: Catalyst-free synthesis of bis (4-hydroxycoumarin-3-yl) methanes in aqueous media under ultrasound irradiation**

Entry	Aldehydes	Time (min) <sup>a</sup>	Product	Yield (%)	M.P (°C)	
					Found	Lit.
		5	3a	98	226-228	228-230 <sup>23</sup>
		5	3b	98	254-256	252-254 <sup>22</sup>
		10	3c	90	224-226	224-226 <sup>23</sup>
		5	3d	85	244-246	242-244 <sup>23</sup>
		15	3e	92	258-260	--
		10	3f	83	236-237	232-234 <sup>23</sup>
		15	3g	95	220-224	222-224 <sup>23</sup>
		15	3h	85	240-242	--

<sup>a</sup>Ultrasonic power: 100 watts; reaction at ambient temperature<sup>b</sup>Yields of the isolated products

All the aforementioned reactions (Table 1) delivered excellent product yields and accommodated a wide range of aromatic aldehydes bearing both electron donating and electron withdrawing substituent. It is postulated that the ultrasound role is to accelerate the coupling reaction and thus promotes the formation of products and it is catalyst-free reaction at ambient temperature, needs only 5-10 minutes for completion of the reaction. Workup of the reaction is only filtration to get the crude product followed by crystallization to furnish the pure product.

## CONCLUSION

A highly efficient and environmentally benign methodology for the synthesis of Bis-Coumrins have been developed, which offers several advantages such as it is a catalyst free reaction in aqueous medium under ultrasound irradiation at ambient temperature with easy workup, short reaction time and excellent yields of the desired products.

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