

(Diacetoxyiodo)benzene (DIB) catalyzed green and efficient synthesis of biscoumarin derivatives in aqueous media

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ABSTRACT

(Diacetoxyiodo)benzene has been used as an efficient catalyst for an improved and rapid one-pot synthesis of biscoumarin derivatives in excellent yield under reflux condition using water as an environmentally benign reaction medium. This aqua mediated Knoevenagel condensation of various aromatic and hetero-aromatic aldehydes with 4-hydroxycoumarin using catalytic amount of (diacetoxyiodo)benzene devoid the route of expensive, corrosive reagents and toxic solvents. Along with the routine aldehydes, the aldehydes like aryl-sulphonyloxybenzaldehyde, aryl-carbonyloxybenzaldehyde also leads to the product under the reaction conditions. High yields, shorter reaction times, one pot condensation, operational simplicity, easy work-up, and purification of products by non-chromatographic methods are some additional features of this method.

Keywords: Biscoumarin; Hypervalent iodine; Aromatic aldehydes; Water; Condensation reaction.

1. Introduction

Coumarins form an important group of organic compounds. 4-hydroxy-coumarin and its derivatives are known for their biological activities like anticoagulant [1], spasmolytic [2], antibacterial and antifungal activities [3]. In addition, certain derivatives have also found applications against diseases such as cancer [4] and HIV [5]. Coumarin also shows diverse applications as agrochemicals [6] as well as analytical reagents [7]. Biscoumarins, the bridge substituted dimers of 4-hydroxycoumarin, have been enormous potential as anticoagulants [8, 9]. 3, 3'-methylene-bis-(4-hydroxycoumarin), commonly known as dicoumarol, occurs naturally in moldy clover [10]. It is the haemorrhagic agent responsible for the sweet clover disease of cattle and has also been employed for the prevention and treatment of thrombosis [11]. Dicoumarol is also a starting material for the synthesis of various furocoumarins and benzopyrans [12]. A number of biscoumarin have been found to be ureases inhibitors [13]. Biscoumarins have generally been synthesized by refluxing 4-hydroxycoumarin and various aldehydes in acetic acid or ethanol for several

hours [14]. Biscoumarins have also been synthesized under microwave [15] and ultrasound [16] irradiations. Recently, some condensations have been introduced for the synthesis of biscoumarins using molecular iodine [17], piperidine [18], DBU [19], DBSA [20], LiClO₄ [21], SDS [22], Zn(Proline)₂ [23], TBAB [24], ionic liquids [25] and nanoparticles [26]. Each of the above methods has its own merit, with at least one of the limitations of low yields, difficulty to obtain reagents, long reaction times, effluent pollution, harsh reaction conditions and tedious work-up procedures. The concept of green chemistry [27] has been widely adopted to meet the fundamental scientific challenges of protecting human health and environment wide simultaneously achieving the commercial viability. One of thrust area for achieving this target is to explore alternative reaction conditions and reaction media to accomplish the desired products and waste generation as well as eliminating the use of volatile and toxic organic solvents [28]. It is therefore of almost important to develop simple and effective methodology for the synthesis of coumarin and its derivatives that cover the concept of green chemistry. The uses of environmentally benign solvents like water represent green solvent, being economical and eco-friendly for synthetic transformations [29,30].

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(Diacetoxyiodo)benzene has been known for a long time [31]. They are often used as mild oxidizing agents [32]. In addition, it has been used in several other useful transformations including α -functionalization of carbonyl compounds, carbon-carbon bond forming reactions [33], cyclizations [34]. In continuation of our interest of the application of DIB as a catalyst [35], here we wish to report a highly efficient procedure for the preparation of biscoumarin derivatives by Knoevenagel condensation reaction using (diacetoxyiodo) benzene (DIB) as a catalyst in aqueous media under refluxing conditions (Scheme 1).

2. Experimental

2.1. General

All chemicals were purchased from s d fine & Qualigens and used without further purification. All yields were referred to isolated products after purification. Melting points were determined by open capillary method and are uncorrected. IR spectra were recorded on KBr discs on a FT IR Jasco - 4100 type A and the values are expressed as ν_{\max} cm^{-1} , ^1H NMR and ^{13}C NMR spectra were recorded on a Varian mercury YH-300 and Bruker advance II 400 NMR spectrophotometer using tetramethylsilane (TMS) as an internal standard. The chemical shift values are recorded on δ scale and the coupling constants (J) are in hertz. All products are known compounds and were characterized by comparison of their spectral and physical data with literature values. The progress of the reaction was monitored by TLC using aluminium plates with silica gel 60 F254 (Merck).

2.2. General procedure for the synthesis of biscoumarins

A mixture of 4-hydroxycoumarin (2 mmol), aromatic aldehydes (1 mmol) and (diacetoxyiodo)benzene (5 mol%) in 10 ml of water was refluxed for the appropriate time mentioned in Table 3. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with cold water. The solid crude products, which separated out, were filtered, washed with water and dried. The crude product was further purified by recrystallization with ethanol to afford pure product 3.

Selected spectral data

3,3'-(Benzylidene)-bis-(4-hydroxycoumarin) (3a):

White solid. m.p.= 218–220°C. FT-IR (KBr): $\bar{\nu}$ = 2360, 1674, 1608, 1565, 1493, 1351, 1109 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ = 6.10 (s, 1H), 7.13–8.05 (m, 13H), 11.30 (s, 1H), 11.52 (s, 1H) ppm. ^{13}C NMR (CDCl_3 , 100MHz): δ = 36.04, 103.74, 105.46, 116.50, 117.91, 124.23, 124.75, 126.33, 126.72, 128.48, 132.74, 135.06, 151.21, 164.44, 165.66, 166.76, 169.11 ppm.

3,3'-(4-Chlorobenzylidene)-bis-(4-hydroxycoumarin) (3c):

White solid. m.p.= 256–258°C. FT-IR (KBr): $\bar{\nu}$ = 2608, 1671, 1563, 1492, 1306 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ = 6.08 (s, 1H), 7.10–8.08 (m, 12H), 11.01 (s, 1H), 11.54 (s, 1H) ppm. ^{13}C NMR ($\text{DMSO}-d_6$, 100MHz): δ = 35.20, 108.97, 115.89, 116.60, 123.69, 123.89, 127.89, 128.21, 130.79, 132.22, 136.90, 151.91, 164.15, 165.18 ppm.

3,3'-(2-Nitrobenzylidene)-bis-(4-hydroxycoumarin) (3d):

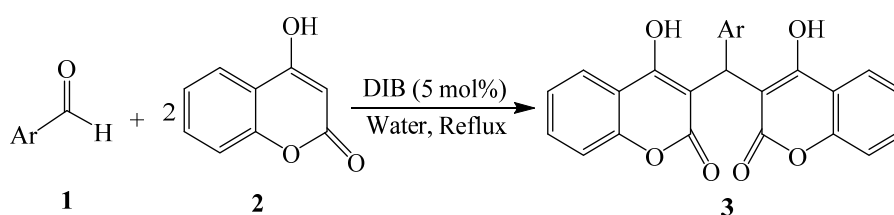
Yellow solid. m.p.= 204–206°C. FT-IR (KBr): $\bar{\nu}$ = 2600, 1658, 1610, 1523, 1357, 1308 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ = 6.13 (s, 1H), 7.26–8.15 (m, 12H), 11.52 (s, 1H), 11.58 (s, 1H) ppm. ^{13}C NMR ($\text{DMSO}-d_6$, 100MHz): δ = 33.82, 103.65, 116.28, 116.45, 124.30, 124.56, 124.62, 127.94, 129.43, 131.06, 132.16, 132.81, 149.69, 152.34, 164.87, 166.47 ppm.

3,3'-(4-Methoxybenzylidene)-bis-(4-hydroxycoumarin) (3f):

White solid. m.p.= 238–240°C. FT-IR (KBr): $\bar{\nu}$ = 2625, 1670, 1563, 1509, 1350, 1258 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ = 3.61 (s, 6H), 6.08 (s, 1H, CH), 7.10–8.08 (m, 12H), 11.01(s, 1H), 11.54 (s, 1H) ppm. ^{13}C NMR (CDCl_3 , 100MHz): δ = 26.89, 28.21, 31.47, 34.57, 49.96, 127.81, 128.39, 129.31, 131.28, 141.66, 158.06, 161.51, 186.71, 195.29 ppm.

3. Results and Discussion

In our interest in green chemistry and in particular the development of nonhazardous methods using DIB as a catalyst, we report a very simple and efficient DIB catalyzed synthesis of biscoumarin derivatives in aqueous media. Initially, benzaldehyde was selected as a probe aldehyde to optimize the reaction conditions. The formation of the 3a did not proceed in absence of the (diacetoxyiodo)benzene even after refluxing the reaction mixture for 2 hrs in water. The effect of the amount of catalyst was studied and it was found that use of 5 mol% DIB was sufficient for the reaction to proceed to completion. Further increase in the amounts of the catalyst did not have any significant effect on the reaction. After optimizing the amount of catalyst, the reaction was carried out in ethanol and water and comparable results were achieved in the two solvents. The results are summarized in Table 1. With these results in hand, other aromatic aldehydes were reacted with 4-hydroxycoumarin in water and the results are listed in Table 2. Benzaldehyde and other aromatic aldehydes containing groups such as Cl, Br, NO_2 , OH, OCH_3 , etc. and heterocyclic moieties were employed and reacted well to give the corresponding biscoumarin derivatives in good to excellent yields.



Scheme 1. Synthesis of bis-coumarin derivatives catalysed by DIB.

Table 1. Optimization of solvent and amount of catalyst for the synthesis of (3a).^a

Entry	Solvent	Catalyst (mol %)	Time (min.)	Yield (%) ^b
1	Ethanol	--	120	trace
2	Water	---	120	trace
3	Ethanol	2.5	30	56
4	Water	2.5	30	62
5	Ethanol	5.0	20	82
6	Water	5.0	20	85
7	Ethanol	7.5	20	82
8	Water	7.5	20	85

^aAll reactions were carried out at reflux.

^bIsolated yields.

Table 2. Condensation of aromatic aldehydes and 4-hydroxycoumarin in water in the presence of 5 mol% DIB as a catalyst.

Entry	Aldehyde	Product	Time (min.)	Yield(%) ^a	m.p.(°C)		Ref.
					Found	Reported	
1			20	85	218-220	215	[15 a]
2			15	86	208-210	212-215	[15 a]
3			15	85	256-258	252-258	[17]
4			10	80	204-206	200-202	[15a]

Table 2. (Continued).

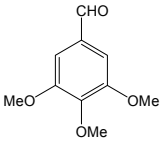
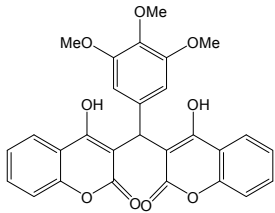
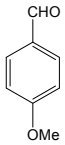
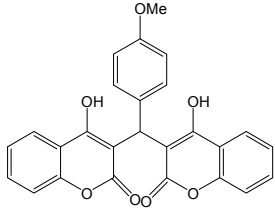
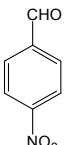
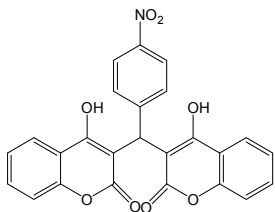
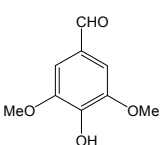
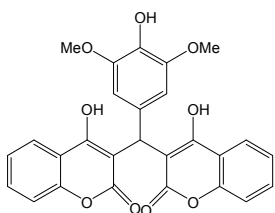
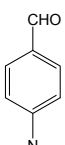
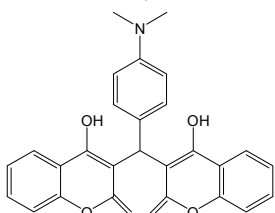
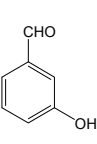
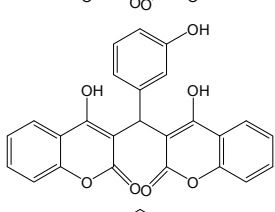
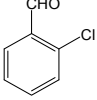
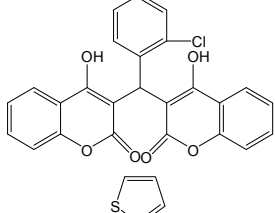
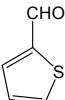
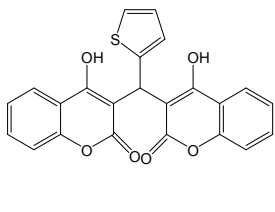
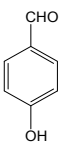
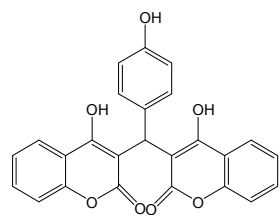
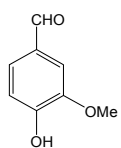
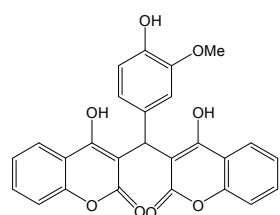
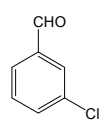
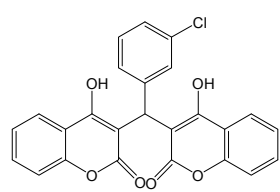
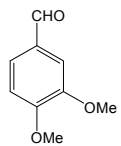
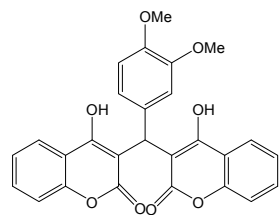
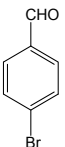
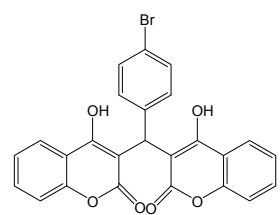
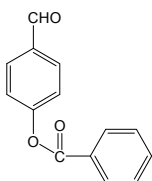
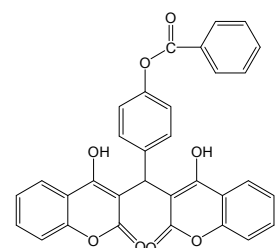
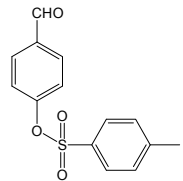
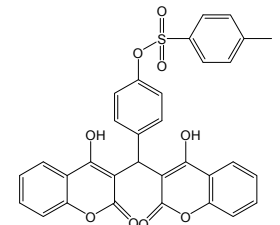
5			10	94	244-246	240-245	[20]
6			20	91	238-240	238-240	[15a]
7			15	95	230-232	232-234	[17]
8			20	90	200-202	188-189	[9]
9			15	90	220-222	222-224	[22]
10			15	93	212-214	210.5	[13]
11			20	90	218-220	221-223	[26 b]
12			20	95	210-212	210	[17]

Table 2. (Continued).

13			20	82	218-220	222-224	[17]
14			20	94	208-210	213-215	[12]
15			20	94	218-220	222-224	[15 a]
16			15	95	260-262	263-265	[22]
17			15	95	262-264	265-267	[22]
18 ^b			120	90	192-194	200-201	[5 a]
19 ^b			120	91	240-242	240-241	[5 a]

^aIsolated yields.^bThe reaction was conducted in aqueous ethanol (1:1).

Table 3. Catalytic activity and reaction conditions comparison of DIB with other reported catalysts.

Entry	Catalyst	Reaction conditions	Time	Yield (%)	Ref.
1	Piperidine	Ethanol/reflux	4:00 h	89-97	[18]
2	Glacial acetic acid	Glacial acetic acid/reflux	3min.-18 h	50-91	[9]
3	SDS (20 mol%)	H ₂ O/60°C	2:30-3:00 h	84-98	[22]
4	I ₂ (10 mol%)	H ₂ O/100°C	20-34 min	91-99	[17]
5	Ionic Liquids	IL/40°C	3:00 h	43-97	[25 b]
6	No catalyst	Ethanol/reflux	24:00 h	63-84	[14 a]
7	DBSA (25 mol%)	H ₂ O:Ethanol/ 80°C	45-130 min	60-90	[20]
8	DIB (5 mol%)	H ₂ O/100°C	10-120 min	80-95	This work

Due to low solubility of aryl-sulphonyloxy benzaldehyde and aryl-carbonyloxybenzaldehyde in aqueous medium, reactions do not proceed smoothly hence these two reactions are carried out in aqueous ethanol. The bulkier structure reacts slowly so takes extended time as compared with earlier entries to complete the reactions.

The structures of these compounds were deduced from their physical and spectroscopic data. The IR spectra of these compounds shows a strong absorption near about 1670 cm⁻¹, due to the C=O group. All the products exhibited a singlet in ¹H NMR spectra at about δ = 6.01–6.13 ppm for H-11 (in case of 3n it is observed at 5.06 δ ppm) and also peaks at about δ = 11.01-11.64 ppm for OH groups.

To show the advantage of the present method a comparison of the efficiency of catalytic activity of the DIB with several methods is presented in table 3. It is observed that the present method is better to some of the earlier methods reported in terms of catalyst amount, yield and reaction time.

4. Conclusions

We have developed a simple, rapid and most efficient green protocol for the synthesis of biscoumarin derivatives using catalytic amount (diacetoxyiodo)benzene in aqueous medium. The short reaction time, simple work-up in isolation of the products, good yields with high purity, and mild reaction conditions are features of the present procedure.

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