Research Article

Cobalt(II) Chloride Hexahydrate as an Efficient and Inexpensive Catalyst for the Preparation of Biscoumarin Derivatives

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Cobalt(II) chloride hexahydrate ($\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$) has been found to be an efficient catalyst for the one-pot synthesis of biscoumarin derivatives through a combination of aromatic aldehydes and 4-hydroxycoumarin in aqueous media at 70°C . Several types of aromatic aldehyde, containing electron-withdrawing groups as well as electron-donating groups, were used in the reaction and in all cases the desired products were synthesized successfully. The present approach offers remarkable advantages such as short reaction times, excellent yields, straightforward procedure, easy purification, environment friendliness, and low catalyst loading.

1. Introduction

Coumarin derivatives, especially biscoumarins, are important compounds in organic synthesis due to their wide spectrum of pharmacological properties such as antifungal, anti-HIV, anticancer, anticoagulant, antithrombotic, antimicrobial, and antioxidant [1–5]. These compounds are also utilized as urease inhibitors [6].

A number of methods have been reported for the synthesis of these compounds in the presence of various catalysts like molecular iodine [7], sodium dodecyl sulfate (SDS) [8], tetrabutylammonium bromide (TBAB) [9], $[(\text{MIM}(\text{CH}_2)_4\text{SO}_3\text{H})[\text{HSO}_4]]$ [10], tetrabutylammonium hexatungstate $[(\text{TBA})_2[\text{W}_6\text{O}_{19}]]$ [11], sulfated titania ($\text{TiO}_2/\text{SO}_4^{2-}$) [12], ruthenium(III) chloride hydrate ($\text{RuCl}_3 \cdot n\text{H}_2\text{O}$) [13], n-dodecylbenzene sulfonic acid (DBSA) [14], and silica chloride nanoparticles (nano SiO_2Cl) [15]. However, these methods suffer from one or more disadvantages such as low yields of products, long reaction times, use of expensive catalyst, toxic solvents, or harsh reaction conditions. Therefore, introducing a clean procedure by the use of green and environmentally friendly catalyst with high catalytic activity, moderate temperature, and short reaction time accompanied with excellent yield for the production of biscoumarin derivatives is needed.

We hoped to develop a more general protocol for the efficient synthesis of biscoumarin derivatives via $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$, which have recently attracted much attention as catalyst to organic synthesis due to their low toxicity and easy availability [16–18].

2. Results and Discussion

We herein present efficient and eco-friendly procedure for the synthesis of biscoumarin derivatives (3 a–m) by three-component condensation of 4-hydroxycoumarin (1) and aromatic aldehyde (2) catalyzed by $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ in water-ethanol solvent system 70°C (Scheme 1).

For this study, a reaction between 4-hydroxycoumarin (2 mmol) and 3-nitrobenzaldehyde (1 mmol) was examined as the model reaction. Initial studies showed that better results could be obtained in the presence of (10 mol%) $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ in aqueous ethanol (1 : 1, H_2O : EtOH) at 70°C .

To optimize the mol% of catalyst, the above reaction was performed with different mol% of $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ such as 5, 10, 15, 20, and 25 mol%. The results are summarised in Table 1 which shows that the reaction catalysed by about 10 mol% $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ results in the highest yield (Table 1, entry 2). In the presence of less than this amount, the yield decreased

SCHEME 1: Synthesis of biscoumarins.

TABLE 1: Optimization of the catalysed model reaction for synthesis of 3,3'-(3-nitrobenzylidene)-bis-(4-hydroxycoumarin).

Entry	Catalyst	Amount of catalyst (mol%)	Time (min)	Yield (%) ^a
1	CoCl ₂ ·6H ₂ O	5	8	89
2	CoCl ₂ ·6H ₂ O	10	2	98
3	CoCl ₂ ·6H ₂ O	15	2	98
4	CoCl ₂ ·6H ₂ O	20	2	98
5	CoCl ₂ ·6H ₂ O	25	2	96

All reactions were carried out in aqueous ethanol at 70°C.

^aIsolated yields.

(Table 1, entry 1). When the amount of CoCl₂·6H₂O was increased over 10 mol%, neither the yield nor the reaction time was improved (Table 1, entry 3).

To study the effect of temperature on this synthesis, we also performed four experiments in aqueous ethanol at room temperature, 50, and 70 (Celsius degrees) and under reflux condition (Table 2). It was observed that the yield of the product is maximum at 70°C (Table 2, entry 3).

During the optimization of the reaction condition, various solvents were also screened to test their efficiency and the results are summarized in Table 3. The highest reaction activity was achieved in the system using aqueous ethanol (1:1, H₂O:EtOH) as a solvent in comparison to other solvents under similar reaction conditions (Table 3, entry 5).

With these encouraging results in hand, the generality of this reaction was examined using various aromatic aldehydes containing electron-donating as well as electron-withdrawing groups. In all cases, the reactions gave the corresponding products in good yields and short reaction times without formation of any byproducts (Table 4). Substituents on the aromatic ring had no obvious effect on yield or reaction time under the above optimal conditions.

In order to assess the efficiency of this methodology, the obtained result from the reaction of 3-nitrobenzaldehyde with 4-hydroxycoumarin by this method has been compared with those of the previously reported methods. As demonstrated in Table 5, the use of CoCl₂·6H₂O leads to an improved protocol in terms of compatibility with environment, reaction time, yield of the product, and amount of the catalyst when compared with other catalysts.

3. Experimental

3.1. Materials and Methods. All reagents were purchased from Fluka, Merck, and Aldrich with high-grade quality and used without any purification. The reactions were monitored by TLC. Visualisation of the developed chromatogram was

performed by UV light (254 nm). All yields refer to isolated products after purification. Products were characterized by comparison with authentic samples and by spectroscopy data (IR, ¹H NMR spectra). IR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27. ¹H NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer using TMS as an internal standard (DMSO-d₆ solution). Melting points were measured by using the capillary tube method with IA 9000 series thermal analyser.

3.2. General Procedure for the Synthesis of Biscoumarin Derivatives. A mixture of the 4-hydroxycoumarin (2 mmol), aromatic aldehyde (1 mmol), and CoCl₂·6H₂O (10 mol%) was stirred in 5 mL aqueous ethanol (1:1, H₂O:EtOH) 70°C for the appropriate time. Completion of the reaction was indicated by TLC. After the completion, the reaction mixture was filtered off and washed with n-hexane (2×5 mL) to obtain pure products. As the catalyst is completely soluble in distilled water, it was easily separated from the reaction mixture. All of the products are known compounds and were characterized by IR and ¹H NMR spectroscopic data and their melting points are compared with reported values.

3.3. Selected Spectral Data

3.3.1. 3,3'-(4-Chlorobenzylidene)-bis-(4-hydroxycoumarin) (Table 4, Entry 7): IR(KBr). 3420 (OH), 2923 (C–H stretching), 1668 (–C=O stretching of –COOR group), 1606 (–C=C stretching), 1563, 1490 (C=C– stretching of aromatic ring), 765 (C–H out of plane bending) cm^{–1}; ¹H NMR (400 MHz, DMSO-d₆): δ 6.63 (s, 1H, CH), 7.16–7.90 (m, 12H, ArH), 7.90–9 (m, 2H, OH).

3.3.2. 3,3'-(3-Nitrobenzylidene)-bis-(4-hydroxycoumarin) (Table 4, Entry 9): IR(KBr). 3424 (OH), 2925 (C–H stretching), 1655 (–C=O stretching of –COOR group), 1616 (–C=C stretching), 1564, 1494 (C=C– stretching of aromatic ring),

TABLE 2: Optimisation of temperature for synthesis of 3,3'-(3-nitrobenzylidene)-bis-(4-hydroxycoumarin) using $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ (10 mol%) as catalyst in aqueous ethanol.

Entry	Catalyst	Temperature °C	Time (min)	Yields (%)
1	$\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$	Room temperature	4	85
2	$\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$	Reflux	2	98
3	$\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$	70	2	98
4	$\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$	50	4	95

Isolated yield of the pure compound.

TABLE 3: Effect of solvents in reaction of 3-nitrobenzaldehyde and 4-hydroxycoumarin catalyzed by $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$.

Entry	Catalyst	Solvent	Time (min)	Yields (%) ^a
1	$\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$	EtOH	4	95
2	$\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$	H_2O	3	97
3	$\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$	$\text{H}_2\text{O} : \text{EtOH}$ (1 : 2)	4	96
4	$\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$	$\text{H}_2\text{O} : \text{EtOH}$ (2 : 1)	3	98
5	$\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$	$\text{H}_2\text{O} : \text{EtOH}$ (1 : 1)	2	98
6	$\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$	Solvent free	2 h	Trace

All reactions were catalyzed by $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ at 70 °C.^aIsolated yields.TABLE 4: $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ catalyzed synthesis of biscoumarin derivatives^a.

Entry	Ar	Product	Time (min)	Yield ^b (%)	mp (°C)	
					Reported [ref]	This work
1	C_6H_5	3a	2	92	229–231 [10]	230–232
2	4- FC_6H_4	3b	2	97	212–214 [15]	211–212
3	4- BrC_6H_4	3c	5	96	266–268 [15]	264–266
4	4- CNC_6H_4	3d	5	96	240–242 [13]	240–242
5	2- ClC_6H_4	3e	3	93	201–203 [10]	200–202
6	3- ClC_6H_4	3f	3	94	221–223 [10]	221–223
7	4- ClC_6H_4	3g	1	97	261–263 [10]	256–258
8	2- $\text{O}_2\text{NC}_6\text{H}_4$	3h	3	94	198–200 [10]	195–197
9	3- $\text{O}_2\text{NC}_6\text{H}_4$	3i	1	98	235 [19]	234–236
10	4- $\text{O}_2\text{NC}_6\text{H}_4$	3j	1	98	232–234 [20]	238–239
11	4- $\text{CH}_3\text{C}_6\text{H}_4$	3k	5	92	271–273 [11]	266–268
12	4- $\text{CH}_3\text{OC}_6\text{H}_4$	3l	4	94	251–253 [11]	246–248
13	3- $\text{CH}_3\text{OC}_6\text{H}_4$	3m	5	92	238 [21]	238–240
14	CH_3CHO	—	120	—		

^a Reaction conditions: 4-hydroxycoumarin (2 mmol), aromatic aldehyde (1 mmol), $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ (10 mol%), and aqueous ethanol (5 mL), at 70 °C.^bYields refer to isolated products.TABLE 5: Comparison of the efficiency of $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ with other reported catalysts in the synthesis of 3,3'-(3-nitrobenzylidene)-bis-(4-hydroxycoumarin).

Entry	Catalyst	Conditions	Time	Yield (%) [ref]
1	$[\text{P}_4\text{VPy-BuSO}_3\text{H}]\text{Cl-X}(\text{AlCl}_3)$, 0.07 mmol	Toluene, 90 °C	0.5 (h)	96 [22]
2	SBPPSP, 0.06 g	EtOH/ H_2O , reflux	15 (min)	94 [20]
3	SDS, 20 mol%	H_2O , 60 °C	2.15 (h)	95 [8]
4	Nano- SiO_2Cl , 75 mg	CH_2Cl_2 , 40 °C	3.5 (h)	90 [15]
5	$[\text{TBA}]_2[\text{W}_6\text{O}_{19}]$, 0.08 mmol	EtOH, reflux	7 (min)	85 [11]
6	$\text{NaHSO}_4 \cdot \text{SiO}_2$ or Indion 190 resin, 150 mg	Toluene, 100 °C	30 (min)	90 [19]
7	$\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$, 10 mol%	EtOH/ H_2O , 70 °C	2 (min)	98 [present work]

762 (C–H out of plane bending) cm^{-1} ; ^1H NMR (400 MHz, DMSO-d_6): δ 6.39 (s, 1H, CH), 7.28–8.04 (m, 12H, ArH), 8.04–9.52 (m, 2H, OH).

3.3.3. 3,3'-(4-Methoxybenzylidene)-bis-(4-hydroxycoumarin) (Table 4, Entry 12). IR(KBr): 3443 (OH), 2926 (C–H stretching), 1668 (C=O stretching of –COOR group), 1606 (C=C stretching), 1563, 1510 (C=C stretching of aromatic ring), 767 (C–H out of plane bending) cm^{-1} ; ^1H NMR (400 MHz, DMSO-d_6): δ 3.71 (s, 3H, CH_3O), 6.31 (s, 1H, CH), 6.80–7.93 (m, 12H, ArH), 8.16–8.78 (m, 2H, OH).

4. Conclusion

In conclusion, we have developed a green, practical, and facile approach for the preparation of biscoumarin derivatives through the three-component reaction of 4-hydroxycoumarin and aromatic aldehydes using a catalytic amount of $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ as an efficient and inexpensive catalyst. The distinguished advantages of this procedure are (i) simple experimental procedure, (ii) mild reaction conditions, (iii) high to excellent yields of products, (iv) short reaction times, (v) and utilization of an inexpensive and readily available catalyst.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

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