

Original article

Propane-1,2,3-triyl tris(hydrogen sulfate): A mild and efficient recyclable catalyst for the synthesis of biscoumarin derivatives in water and solvent-free conditions

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ABSTRACT

A simple, efficient, and ecofriendly procedure has been developed using propane-1,2,3-triyl tris(hydrogen sulfate) as a catalyst for the synthesis of biscoumarin derivatives in water and solvent-free conditions. The significant features of the present protocol are simplicity, environmentally benign, high yields, no chromatographic separation, and recyclability of the catalyst.

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1. Introduction

α,α' -(Benzylidene)-bis-(4-hydroxycoumarin), commonly known as biscoumarin, and its derivatives are of considerable interest due to their biological activities, e.g., anticoagulant activity [1], prevention and treatment of thrombosis [2], urease inhibitors [3]. Also, a number of coumarin derivatives showed HIV inhibitory activity [4]. To date, available synthesis methods of biscoumarins include Pechmann, Perkin, Knoevenagel, Reformatsky, and Wittig reactions. Among these, the Knoevenagel reaction is the most commonly applied one, in which different types of acid catalysts such as sulfuric acid, phosphorus pentoxide, aluminum chloride, iodine, and trifluoroacetic acid are employed [5–7]. Other procedures use microwaves [8] and ultrasound [9]. Given the importance of this reaction, many attempts to reduce its environmental impact have been made by using catalysts such as molecular iodine [10], 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) [11], MnCl_2 [12], POCl_3 in dry dimethylformamide (DMF) [13], Et_2AlCl_3 [14], SO_3H functionalized ionic liquids [15], [bmim][BF_4] [16], tetrabutylammonium bromide (TBAB) [17], $\text{Zn}(\text{Proline})_2$ [18], sodium dodecyl sulfate (SDS) [19], tris(hydrogensulfato) boron [20], and sulfated titania [21].

Glycerol is a non-toxic, biodegradable, and recyclable liquid that is highly inert, stable and also able to dissolve organic compounds that are poorly miscible in water. It combines the advantages of water (low toxicity, low price, and wide availability) and ionic liquids (highly boiling point and low vapor pressure). These advantages make it ideal for use as a sustainable solvent in organic synthesis [22,23]. Chemically modified glycerols are generally made by treating glycerol with agents that can react with hydroxyl groups. Such glycerols have physicochemical properties that differ significantly from the parent glycerol, thus widening their usefulness in many applications such as in biodiesel industries [24] and other industrial processes, so some reviews have appeared recently dealing with the use of glycerol as a source of commodity chemicals [25].

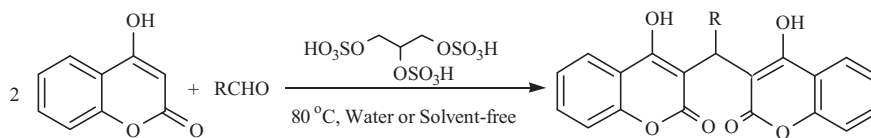
We report herein a green approach for the synthesis of some biscoumarin derivatives from aldehydes and 4-hydroxycoumarin catalyzed by propane-1,2,3-triyl tris(hydrogen sulfate) [PTTH] in water and solvent-free conditions for the first time (Scheme 1).

2. Experimental

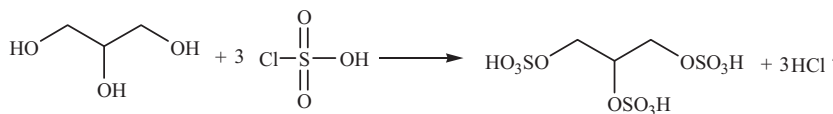
All chemicals and analytical grade solvents were purchased from Merck or Fluka. Melting points of all products were determined in open glass capillaries on a Mettler 9100 melting point apparatus. Infrared (IR) spectra were recorded using a 4300 Shimadzu FT-IR spectrometer. ^1H NMR spectra were recorded on a

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Scheme 1. Synthesis of biscoumarin.



Scheme 2. Synthesis of propane-1,2,3-triyl tris(hydrogen sulfate).

Bruker 400 MHz spectrometer. Elemental analysis was performed on a Horeaus CHN Rapid analyzer. All products were characterized by comparison of their melting points, IR, and ^1H NMR spectra with those of authentic samples.

2.1. Preparation of propane-1,2,3-triyl tris(hydrogen sulfate)

A 250 mL suction flask charged with glycerol (8.30 g, 90.22 mmol) was equipped with a gas inlet tube for conducting HCl gas over an adsorbing solution *i.e.* water. Chlorosulfonic acid (~20.0 mL, ~300 mmol) was added in small portions over a period of 30 min at 0 °C. HCl gas evolved from the reaction vessel immediately (Scheme 2). After completion of the addition of chlorosulfonic acid, the mixture was shaken for 30 min; meanwhile, the residual HCl was exhausted by suction. Then, the mixture was concentrated under vacuum, washed with ether (10 mL) three times, and dried under vacuum. PTTH (8.77 g, 26.40 mmol) was obtained as yellow oil, which was stored in a capped bottle. IR: 3374, 2944, 1657, 1510, 1110, 1043 cm^{-1} . According to the results, the efficiency of the coupling of glycerol was estimated to be ~88% *via* spectrophotometric analysis. Also, according to the Boehm back-titration analysis, the percentage of three sulfur atom presented in the propane-1,2,3-triyl tris(hydrogen sulfate), as the proposed catalyst synthesized according to the recommended procedure, was estimated to be 87.67%.

2.2. General procedure for the synthesis of biscoumarin derivatives

Method A: A mixture of 4-hydroxycoumarin (2.0 mmol), aldehyde (1.0 mmol), PTTH (0.1 g, 0.03 mol%), and 5 mL of water was stirred magnetically at 80 °C for the appropriate time as

mentioned in Table 1. After completion of the reaction as monitored by TLC, the reaction mixture was extracted with ethyl acetate (10 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. A crude solid was obtained. The pure product was obtained through crystallization from ethanol.

Method B: In another procedure, the components as mentioned above were mixed thoroughly and heated in an oil bath maintained at 80 °C under solvent-free conditions for the appropriate time. After completion of the reaction as monitored by TLC, ethyl acetate (10 mL) and water (5 mL) were added to the mixture and the reaction was worked up as described in method A.

In order to recover the catalyst totally, the separated aqueous layer (after extraction of the reaction mixture with EtOAc) containing the catalyst was washed with diethyl ether (3×5 mL) and concentrated under vacuum conditions.

The structures of all products **3a–l** were confirmed by IR, ^1H NMR and elemental analysis.

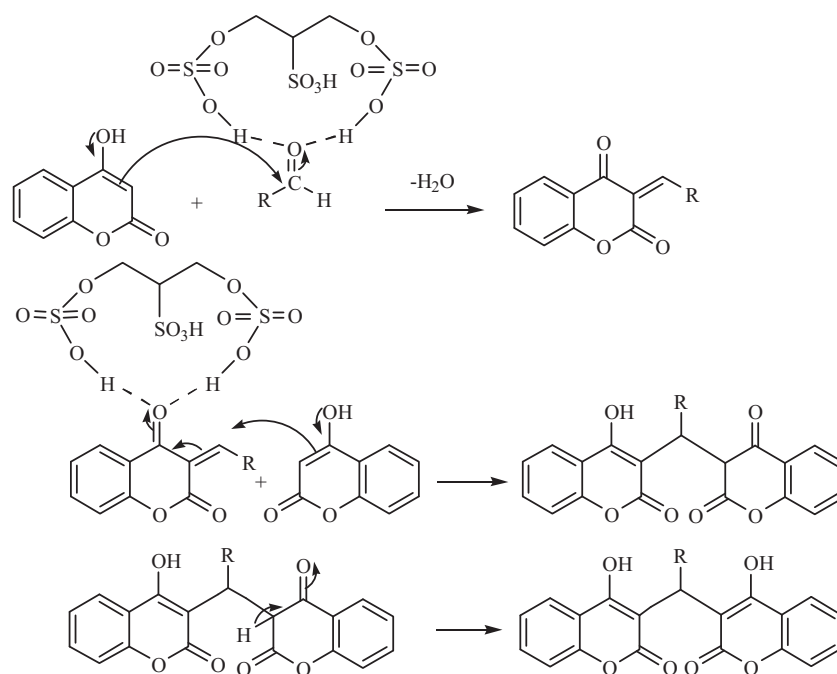
α,α' -(4-Chlorobenzylidene)-bis-(4-hydroxycoumarin) (entry 2): IR (KBr, cm^{-1}): 3427, 3030, 1670, 1605, 1563, 1351, 765; ^1H NMR (400 MHz, DMSO- d_6): δ 6.40 (s, 1H, CH), 7.32–8.40 (m, 12H, ArH), 11.33 (s, 1H, OH), 11.57 (s, 1H, OH), Anal. Calcd. for $\text{C}_{25}\text{H}_{15}\text{ClO}_6$ (445.68): C, 67.20; H, 3.38. Found: C, 67.0; H, 3.30.

α,α' -(2-Chlorobenzylidene)-bis-(4-hydroxycoumarin) (entry 3): IR (KBr, cm^{-1}): 3435, 2925, 1651, 1618, 1060, 762; ^1H NMR (400 MHz, DMSO- d_6): δ 6.14 (s, 1H, CH), 7.24–8.03 (m, 12H, ArH), 10.92 (s, 1H, OH), 11.63 (s, 1H, OH), Anal. Calcd. for $\text{C}_{25}\text{H}_{15}\text{ClO}_6$ (445.68): C, 67.20; H, 3.38. Found: C, 67.15; H, 3.35.

α,α' -(3-Nitrobenzylidene)-bis-(4-hydroxycoumarin) (entry 5): IR (KBr, cm^{-1}): 3420, 2926, 1656, 1616, 1346, 760; ^1H NMR (400 MHz, DMSO- d_6): δ 6.13 (s, 1H, CH), 7.26–8.17 (m, 12H,

Table 1
Synthesis of biscoumarin.

Entry	R	Product	Method A		Method B		Mp (°C)	
			Time (min)	Yield (%)	Time (min)	Yield (%)	Found	Reported [9,19,20]
1	C ₆ H ₅	3a	10	90	8	90	228–230	233–234
2	4-ClC ₆ H ₄	3b	7	90	5	80	254–25	258–259
3	2-ClC ₆ H ₄	3c	10	85	7	80	218–220	–
4	4-NO ₂ C ₆ H ₄	3d	8	95	5	90	232–234	238–240
5	3-NO ₂ C ₆ H ₄	3e	8	95	5	90	122–124	128–130
6	4-CH ₃ OC ₆ H ₄	3f	10	85	7	80	242–244	249–250
7	4-CH ₃ C ₆ H ₄	3g	8	90	5	80	266–268	270–272
8	4-HOC ₆ H ₄	3h	10	85	8	80	218–220	222–224
9	–CH=CH–C ₆ H ₄	3i	10	85	8	80	228–230	230–232
10	3,4-(CH ₃ O) ₂ C ₆ H ₃	3j	10	85	7	80	260–262	265–267
11	H	3k	8	80	–	–	290–292	–
12	2-Furanyl	3l	10	80	8	75	198–200	202



Scheme 3. Proposed mechanism.

ArH), 11.58 (s, 2H, OH), Anal. Calcd. for $C_{25}H_{15}NO_8$ (458.43): C, 65.65; H, 3.31; N, 3.06. Found: C, 65.69; H, 3.30; N, 2.90.

$\alpha,\alpha'-(2\text{-Styrylpropane-1,3-diyl})\text{-bis-(4-hydroxycoumarin)}$ (entry 9): IR (KBr, cm^{-1}): 3325, 3025, 1725, 1670, 1614, 760; ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 6.56 (d, 1H, CH), 6.68 (d, 1H, CH=), 6.75 (d, 1H, CH=), 7.14–8.05 (m, 12H, $12 \times \text{CH}$); 11.42 (s, 1H, OH), 11.58 (s, 1H, OH); Anal. Calcd. for $C_{27}H_{18}O_6$ (437.55): C, 73.97; H, 4.14. Found: C, 73.78; H, 4.08.

$\alpha,\alpha'-(\text{Methylene})\text{-bis-(4-hydroxycoumarin)}$ (entry 11): IR (KBr, cm^{-1}): 3443, 2926, 1650, 1600, 1567, 1308, 1347, 762; ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 3.85 (s, 2H, CH_2), 7.26–8.01 (m, 8H, ArH), 11.32 (s, 2H, OH). Anal. Calcd. for $C_{19}H_{12}O_6$ (336.29): C, 67.86; H, 3.60. Found: C, 67.82; H, 3.63.

3. Results and discussion

PTTH was readily prepared by addition of chlorosulfonic acid to glycerol while keeping the temperature at 0°C . The reaction is easy and clean, and needs no special work-up procedure because HCl gas is evolved from the reaction vessel immediately. This liquid catalyst is safe and easy to handle (Scheme 2).

Initially, benzaldehyde and 4-hydroxycoumarin were chosen as model substrates to optimize the reaction conditions. The reaction was investigated in different conditions; according to the data the best conversion was obtained by carrying out the reaction with a 1:2 mol ratio of benzaldehyde and 4-hydroxycoumarin in the presence of 0.1 g (0.03 mol%) of PTTH as the catalyst in water at

80°C . Ninety percent yield of $\alpha,\alpha'-(\text{benzylidene})\text{-bis-(4-hydroxycoumarin)}$ **3a** was obtained by simple recrystallization from ethanol. Reaction with 0.05 g of catalyst required longer reaction time, while reaction with 0.025 g of catalyst was incomplete even after 5 h and only 30% of the product was obtained. To investigate the effect of solvent, the model reaction was carried out in the various solvents (water, ethanol, CH_3CN and THF) at different reflux temperatures; water was found to be the best medium for this reaction.

Subsequently, the condensation of a series of aromatic and aliphatic aldehydes with 4-hydroxycoumarin was carried out using PTTH as a catalyst under the conditions outlined above. As can be seen from Table 1, aromatic aldehydes having electron-donating as well as electron-withdrawing groups were transformed into the corresponding biscoumarins in high to excellent yields within 5–10 min (Table 1, entries 1–10). Additionally, aliphatic aldehydes such as formaldehyde were also investigated, and the corresponding biscoumarin was isolated in 80% yield (Table 1, entry 11). In the case of aliphatic aldehydes, reactions were not performed under solvent-free conditions because of the low boiling point of the aldehydes. A comparison of aqua mediated synthesis with those performed under solvent-free conditions is drawn in Table 1. It can be inferred from Table 1 that high yields of biscoumarins were obtained by both methods, though, the reaction times were slightly shortened in solvent-free conditions, and the yields were also slightly lower.

Regarding the mechanism, the transformation involves a Knoevenagel condensation of 4-hydroxycoumarin with the

Table 2
Comparison results of PTTH with other catalysts reported in the literature.

Entry	Conditions	Catalyst	Time (min)	Yield (%)	Reference
1	H_2O , MW	–	8–10	76–95	[8]
2	H_2O , reflux	I_2 (10 mol%),	20–32	91–99	[10]
3	Solvent-free, $60\text{--}70^\circ\text{C}$	[bmim][BF_4] (4 mmol)	120–180	77–91	[16]
4	H_2O , reflux	TBAB (10 mol%)	20–40	77–95	[17]
5	H_2O , 60°C	SDS (20 mol%)	150–180	78–96	[19]
6	$\text{H}_2\text{O}:\text{EtOH}$ (1:1), 70°C	$\text{B}(\text{HSO}_4)_3$ (0.3 mmol)	3–6	81–98	[20]
7	H_2O , 80°C	$\text{TiO}_2/\text{SO}_4^{2-}$ (10 mol%)	12–30	82–96	[21]
8	Water/solvent-free, 80°C	PTTH (0.03 mol%)	5–12	75–95	This work

aldehydes followed by a Michael addition with another molecule of 4-hydroxycoumarin. The highly solving action of PTTH on the reactants makes them readily available to interact, and the carbonyl carbon of the aldehyde will be activated because of the intermolecular hydrogen bonding with the hydroxyl groups of PTTH. In addition, the formed intermediates could be stabilized by several types of complexations and hydrogen bonding with the hydroxyl groups of PTTH (Scheme 3).

To show the merit of this work, we compared our results with those from synthesis of α,α' -(benzylidene)-bis-(4-hydroxycoumarin) derivatives by use of previously reported catalysts (Table 2). As it is clear from Table 2, the present method is more efficient when all terms, including yields, reaction times, conditions, and catalyst are taken into account.

4. Conclusion

We have developed an efficient and environmentally benign strategy for the synthesis of biscoumarin derivatives using PTTH as a catalyst. This method offers several advantages, including high yield of products, short reaction time, low cost, cleaner reaction profile, ease of preparation of catalyst, and ease of product isolation. Also the catalyst was successfully recovered and recycled for at least three runs without significant loss in activity.

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