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Phospho sulfonic acid: a versatile and efficient solid acid catalyst for facile synthesis of bis-(4-hydroxycoumarin-3-yl) methanes under solvent-free conditions

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Abstract Biscoumarin derivatives are synthesized via a simple, one-pot, pseudo three-component reaction between various arylaldehydes and 4-hydroxycoumarin using phospho sulfonic acid as a reaction mediator under solvent-free neat conditions in good to excellent yields. High yields, short reaction time, easy work-up, elimination of solvents and environmentally benign milder reaction conditions are the advantages of this procedure.

Keywords: Bis-(4-hydroxycoumarin-3-yl) methanes · Biscoumarin · Multicomponent reaction · Solvent-free · Phospho sulfonic acid

Introduction

Multi-component reactions (MCRs), are a promising and vital field of chemistry because by the synthesis of complicated molecules can be achieved in a very fast, efficient and time saving manner without the isolation of any intermediate [1–3]. On the other hands, the use of heterogeneous catalytic methods for synthesis of fine chemicals is a promising field of research with potential application in pharmaceutical and related fine chemical industries [4]. Therefore, the possibility of performing multicomponent reactions under solvent-free conditions with a heterogeneous catalyst could enhance their efficiency from an economic as well as ecological point of view.

Biscoumarins have received considerable attention of synthetic and medicinal chemists because of their broad spectrum of biological and pharmaceutical activities [5–7]. A number of biscoumarins have also been found to be urease inhibitors [8]. Although some types of these compounds could be isolated from plants [9], attempts

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have been made to use alternative catalysts for biscoumarin synthesis. A literature search revealed that a number of catalytic methods have been developed for the synthesis of biologically important biscoumarin derivatives, specially the bridge substituted dimers of 4-hydroxycoumarin, by the reaction of 4- hydroxycoumarin and various aldehydes [10–15]. However, each of the methods has its own disadvantages, such as long reaction time, harsh reaction conditions, the use of large excess of reagents, low yield and the use of toxic, corrosive, expensive, or non-reusable catalysts.

This finding prompted us towards further investigation in search for a new catalyst, which will carry out the synthesis of biscoumarins under simpler experimental set up and eco-friendly conditions. Therefore, we now wish to explore a straightforward convergent one-pot synthesis of bis-(4-hydroxycoumarin-3-yl) methanes using phospho sulfonic acid as an efficient solid acid catalyst under solvent-free conditions through domino Knoevenagel condensation/Michael addition sequence (Scheme 1).

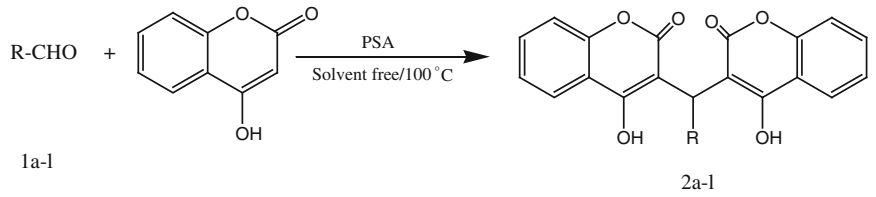
Experimental section

General

All commercially available chemicals were purchased from Fluka and Merck companies and used without further purification. IR spectra were recorded on a BOMEM MB-Series 1998 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Advanced DPX 400 MHz FT-NMR spectrometer using TMS as internal standard. Reaction monitoring was accomplished by TLC on silica gel polygram SILG/UV 254 plates.

Preparation of phospho sulfonic acid

A 50 mL suction flask was equipped with a constant pressure dropping funnel. The gas outlet was connected to a vacuum system through an adsorbing solution of alkali trap. Diammonium hydrogen phosphate (2 g, 15 mmol) was charged in the flask and chlorosulfonic acid (5.24 g, ca. 3 mL, 45 mmol) in CH_2Cl_2 (10 mL) was added dropwise over a period of 30 min at room temperature. After completion of the addition, the mixture was shaken for 2 h, while the residual HCl was eliminated by suction. Then the mixture was washed with excess dried CH_2Cl_2. Finally, a white solid powder (4.2 g) was obtained.



Scheme 1 Synthesis of biscoumarins

General procedure

A mixture of benzaldehyde (1 mmol), 4-hydroxycoumarin (2 mmol) and PSA (0.05 g) was heated at 100 °C. Completion of the reaction was indicated by TLC [ethyl acetate/n-hexane (1:2)]. After completion of the reaction the insoluble crude product was dissolved in hot ethyl acetate and phospho sulfunic acid was filtered. The crude product was purified by recrystallization in ethanol to afford the pure product.

Selected spectral data

Product (**2a**): 3,3-(Benzylidene)-bis-(4-hydroxycoumarin): white crystal, melting point (228–230), IR (KBr, cm^{-1}): 1098, 1347, 1493, 1605, 1657, 3084.57; ^{1}H NMR: ($CDCl_3$): 6.12 (s, 1H), 7.25–8.21 (m, 13H), 11.33 (s, 1H), 11.56 (s, 1H); ^{13}C NMR: ($CDCl_3$): 36.17, 103.89–152.54 (C_{aromat}), 164.62 (C–OH),165.84 (C–OH),166.90 (CO),169.34 (CO).

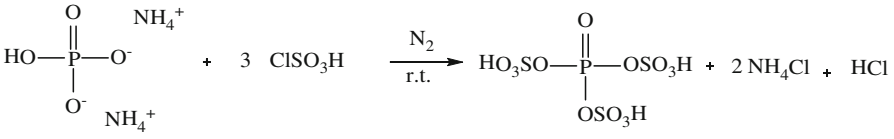
Product (**2b**): 3,3-(4-Ethoxybenzylidene)-bis-(4-hydroxycoumarin): red crystal, melting point (229–231), IR (KBr, cm^{-1}): 1087, 1345.53, 1448.4, 1609.39, 1667, 3072.64; ^{1}H NMR: (CDCl3): 2.8 (t, 3H), 5.2 (q, 2H), 5.56 (s, 1H), 6.48–7.8 (m, 12H), 10.49 (s, 1H), 10.62 (s, 1H); ^{13}C NMR: (CDCl3): 31.1, 98.1–152.2 (C_{aromat}), 152.5, 162.3, (C–OH), 163.9 (C–OH), 189.9 (CO), 191.1(CO).

Product (**2c**): 3,3-(4-Nitrobenzylidene)-bis-(4-hydroxycoumarin): yellow crystal, melting point (227–229), IR (KBr, cm^{-1}): 1100.18, 1357.81, 1493.17, 1608.91, 1660.48, 3087.35; ^{1}H NMR: (CDCl3): 6.13 (s, 1H), 7.41–8.21 (m, 12H), 11.40 (s, 1H), 11.59 (s, 1H); 13C NMR: (CDCl3): 36.52, 103.27–152.57 (C_{aromat}), 146.86, 164.86 (C–OH),166.46 (C–OH), 167.02 (CO), 169.14 (CO).

Product (**2e**): 3,3-(4-Triflurobenzylidene)-bis-(4-hydroxycoumarin): white crystal, melting point(266–268), IR(KBr, cm^{-1}): 1112.8, 1324.79, 1483.52, 1609.17, 1664.88, 3074.72; ^{1}H NMR: (CDCl3): 5.6 (s, 1H), 6.8–7.9 (m, 12H), 9.68 (s, 1H), 10.6 (s, 1H); ^{13}C NMR: (CDCl3): 32.3,73.1, 97.7–148.2 (C_{aromat}), 162.3 (C–OH), 164 (C–OH), 190.1 (CO), 191.3(CO).

Results and discussion

Phospho sulfonic acid, PSA, was easily prepared by simple mixing of diammonium hydrogen phosphate and chlorosulfonic acid in CH_2Cl_2 at room temperature (Scheme 2).



Scheme 2 Preparation of the PSA

The presence of sulfonyl group in PSA is confirmed by FT-IR analysis. The FT-IR spectrum of the catalyst (KBr disk), showed O=S=O asymmetric and symmetric stretching peaks in 1124 and 1075 cm^{-1}, respectively, and the S–O stretching peak in 678 cm^{-1}, which strictly confirms the sulfonic group linkage. The sulfonic acid loading of PSA was calculated based on titration of the proton-exchanged brine solution and shown the loading of 11 mmol SO_3H g^{-1} of acidic catalyst.

In order to carry out the synthesis of biscoumarin under environmentally benign conditions, Initially, the synthesis of 3,3'-(benzylidene)-bis(4-hydroxycoumarin) was selected as a model reaction to optimize the reaction conditions. The reaction was carried out by heating a mixture of benzaldehyde (1 mmol) and 4-hydroxycoumarin (2 mmol) in the presence of various amount of PSA at different temperatures under solvent free conditions. As can be seen from Table 1, the

Table 1 Optimum conditions for the condensation reaction of benzaldehyde (1 mmol), and 4-hydroxycoumarin (2 mmol) under solvent-free conditions

Entry	Catalyst (g)	Temp. (°C)	Time (min)	TLC analysis
1	0.05	25	200	Not completed
2	0.05	60	30	completed
3	0.05	80	20	completed
4	0.05	100	15	completed
5	0.02	100	200	Not completed
6	0.1	100	200	Not completed

Table 2 Synthesis of bis-(4-hydroxycoumarin-3-yl) methanes by condensation of aldehydes, 4-hydroxycoumarin using PSA (0.05 g) as catalyst under solvent free conditions

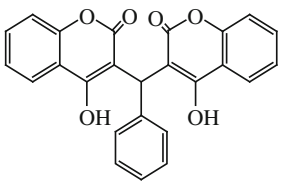
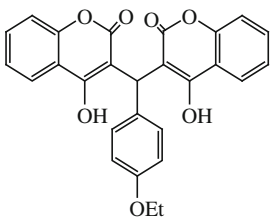
Entry	Ar	Product	Time (Min)	Yield (%)	Melting point(Experimental) (°C)	Melting point(Reported) (°C)
1(**2a**)	C_6H_5		15	81	228–230	228–230 [9]
2(**2b**)	4-OEt C_6H_4		90	63	229–231	–

Table 2 continued

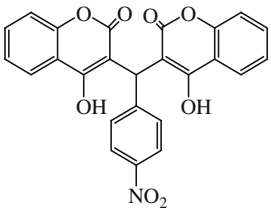
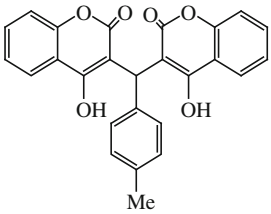
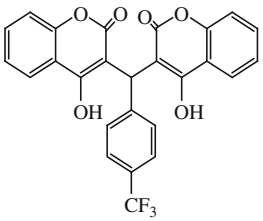
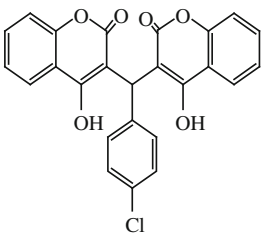
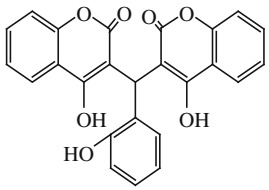
Entry	Ar	Product	Time (Min)	Yield (%)	Melting point(Experimental) (°C)	Melting point(Reported) (°C)
3(**2c**)	4-NO_2 C_6H_4		45	96	227–231	232–234 [9]
4(**2d**)	4-Me C_6H_4		40	80	266–268	266–268 [9]
5(**2e**)	4-CF_3 C_6H_4		65	80	266–268	–
6(**2f**)	4-Cl C_6H_4		20	87	246–248	246–248 [9]
7(**2g**)	2-OH C_6H_4		20	80	250–252	254–256 [9]

Table 2 continued

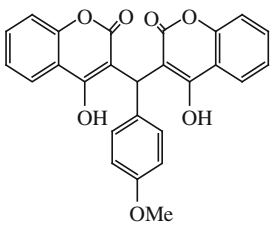
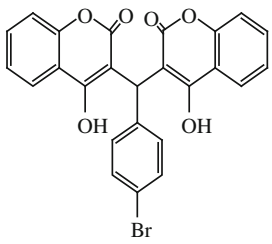
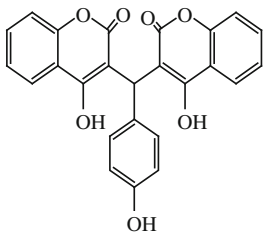
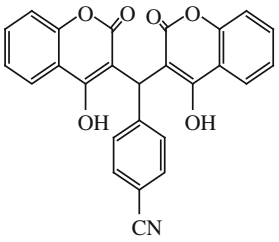
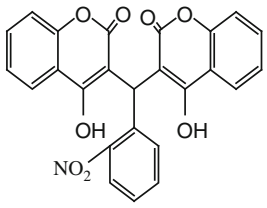
Entry	Ar	Product	Time (Min)	Yield (%)	Melting point(Experimental) (°C)	Melting point(Reported) (°C)
8(**2h**)	4-OMe C_6H_4		70	88	244–246	242–244 [9]
9(**2i**)	4-Br C_6H_4		30	88	263–265	266–268 [9]
10(**2j**)	4-OH C_6H_4		40	85	222–224	222–224 [9]
11(**2k**)	4-CN C_6H_4		55	86	234–236	240–242 [9]
12(**2l**)	2-NO_2 C_6H_4		35	94	194–196	190–192 [16]

Table 3 Comparative study on the present method with the reported methods

Entry	Catalyst	Amount of catalyst	Time (Min)	Solvent	Yeild (%)
1	Piperidine [7]	–	240	EtOH	89
2	Heteropoly acids [17]	3 mol%	900	EtOH/Water	70
3	$RuCl_3 \cdot nH_2O$ [16]	5 mol%	25	Water	84
4	TiO_2/SO_4^{2-} [18]	15 mol%	15	Water	92
5	SDS [5]	20 mol%	150	Water	90
6	TBAB [10]	10 mol%	30	Water	88
7	Phospho sulfonic acid	0.05 g	15	Solvent-free	81

shortest time and best yield was achieved in the presence of 0.05 g of catalyst at 100 °C (Entry 4).

Encouraged by this result, a wide variety of aromatic aldehydes, containing both electron withdrawing and donating substitutes were treated under the optimized conditions and afforded the corresponding biscoumarin (Table 2) in good to excellent yields and short reaction times. With regard to the substituents, both aldehydes with electron withdrawing and electron donating groups participated in the reaction, but the former were better. The structure of the products was established from their IR spectral data and comparison of their melting points with those of authentic samples. Also, the structure of some products was confirmed by ^1H and ^{13}C NMR spectral data.

To compare the advantage of the use of PSA over the reported catalysts, the model reaction of, benzaldehyde (1 mmol) and 4-hydroxycoumarin (2 mmol) was considered as a representative example (Table 3). These results clearly demonstrate that PSA is an equally or more efficient catalyst for this three-component reaction.

Conclusion

In conclusion, we have reported an easy, efficient and green protocol for the synthesis of biscoumarins from the one-pot pseudo three-component condensation reaction of various arylaldehydes and 4-hydroxycoumarin using phospho sulfonic acid as a novel environmentally safe heterogeneous solid acid catalyst under solvent-free conditions. The method offers marked improvement with its operational simplicity, low reaction time and high yields of pure products.

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