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CARBON-BASED SOLID ACID AS A HIGHLY EFFICIENT RECYCLABLE CATALYST FOR THE SYNTHESIS OF BISCOUMARINS IN WATER

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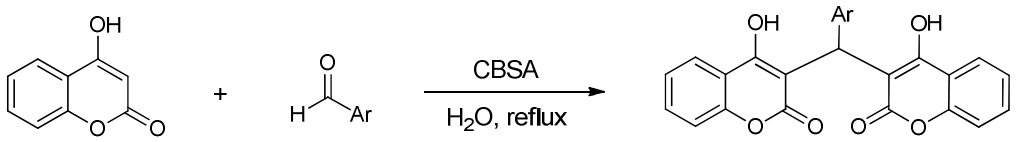
ABSTRACT
A novel catalytic synthesis of biscoumarins from 4-hydroxycoumarin and aromatic aldehydes has been developed. The reaction occurs in water in the presence of carbon-based solid acid as catalyst to give the corresponding products in high yields. This new approach has short reaction times, clean reaction profiles, and simple experimental and workup procedures. Moreover, the catalyst can be easily recovered by filtration and used at least four times with only slight reduction in its catalytic activity.

KEYWORDS: Carbon-based solid acid; biscoumarins; Fast synthesis;Green solvent.

INTRODUCTION
Coumarins are a large group of heterocycles with diverse and interesting biological activities. These compoundsare reported to possess significant anticoagulant, insecticidal, antihelminthic, hypnotic, antifungal, and HIV protease inhibition activities[i]. Biscoumarins, the bridge substituted dimers of 4-hydroxycoumarin, have enormous potential as anticoagulants[ii]. A number of biscoumarins have also been found to be urease inhibitors[iii]. The synthesis of biscoumarins is succeeded *via* a domino Knoevenagel−Michael reaction between 4-hydroxycoumarin and aromatic aldehydes, and various procedures involving different solvents and catalysts such as some Brønsted-acidic ionic liquids[iv-vi],TiO_2-SO_3H[vii], $[TBA]_2[W_6O_{19}]$[viii], $RuCl_3{\cdot}nH_2O$[ix], I_2[x], RHA-SO_3H[xi], Alum $[KAl(SO_4)_2{\cdot}12H_2O]$[xii], and Mo_{132}[xiii]. Most of these methodologies suffer from disadvantages such as unsatisfactory yields, toxic organic solvents, harsh reaction conditions, long reaction times, and the use of relatively expensive reagents. These findings prompted us to perform investigations to find new method for the synthesis of biscoumarin derivatives.
The current presentation is the development of our earlier studies of reusable catalysts for the synthesis of organic compounds[xiii-xxiv]. We report here Carbon-based solid acid (CBSA) as a green catalyst for the synthesis of biscoumarins byone-pot reaction between 4-hydroxycoumarin **1** and various aromatic aldehydes **2a–2h**, in water upon refluxing(Scheme 1).



1 **2a-2h** **3a-3h**

Scheme 1.CBSAcatalyzed synthesis of biscoumarins.

RESULTS AND DISCUSSION

Characterization of the catalyst

The CBSA was characterized by FT-IR, X-ray diffraction (XRD), and pH analysis.The FT-IR spectrum of the CBSA catalyst shows the SO_2 symmetric and asymmetric stretching modes in 1100–1250 cm^{-1}. The spectrum also shows a broad OH stretching absorption around 2500–3600 cm^{-1} (Figure 2 (a)). The XRD pattern exhibits two broad, weak diffraction peaks (2h = 13–30,35–50) attributable to amorphous carbon (Figure3). The density of the SO_3H group was measured using NaOH (0.01 mol/L) as titrant by acid-base potentiometric titration. The amount of SO_3H attached to the polycyclic aromatic carbon was 4.37 mmol/g.

Evaluation of catalytic activity of CBSAin the synthesis of biscoumarin derivatives.

At the beginning of this study, 4-chlorobenzaldehyde **2e** was employed as the model aldehyde and reacted with 4-hydroxycoumarin **1**. In order to get the effective reaction conditions, the reaction was optimized in terms of various parameters such as catalyst amount, effect of solvent and influence of temperature (Table 1). Low yields of the product **3e** were obtained in the presence of the catalyst under solvent-free conditions at high temperatures (entry 3), or in the absence of the catalyst in the presence of the solvent under reflux condition (entries 4-12), indicating that the catalyst and solvent are necessary for the reaction. Among the tested solvents such as H_2O, EtOH, MeOH, CH_2Cl_2, CH_3CN, and also solvent-free conditions and various amounts of the catalyst, the reaction was more facile and proceeded to give the highest yield, using 0.08 g of CBSA in H_2O at reflux temperature (entry 16). All subsequent reactions were carried out in these optimized conditions.

Table 1. Optimization of reaction conditions for synthesis of compound**3e**catalyzed by CBSA[a].

Entry	Catalyst (g)	Solvent	T (°C)	Time (min)	Isolated yield (%)
1	-----	-----	90	150	11
2	-----	-----	110	150	13
3	0.08	-----	110	150	91
4	-----	CH_2Cl_2	Reflux	150	16
5	-----	$CHCl_3$	Reflux	150	21
6	-----	MeCN	Reflux	150	35
9	-----	MeOH	Reflux	150	37
10	-----	EtOH	Reflux	150	41
11	-----	EtOH	Reflux	150	19
12	-----	H_2O	Reflux	150	23
13	0.08	H_2O	r.t.	37	62
14	0.08	H_2O	60	23	59
15	0.1	H_2O	Reflux	25	94
16	**0.08**	**H_2O**	**Reflux**	**24**	**93**

17	0.06	H_2O	Reflux	33	92
18	0.04	H_2O	Reflux	43	90
19	0.08	EtOH	Reflux	35	88
20	0.06	EtOH	Reflux	45	82

[a]Reaction conditions: 4-hydroxycoumarin **1** (2 mmol) and 4-cholorobenzaldehyde **2e** (1 mmol).

Encouraged by this success, and in order to evaluate the generality of this model reaction, we extended the reaction 4-hydroxycoumarinwith a range of other aromatic aldehydes under the optimized reaction conditions (Table 2). The CBSA efficiently catalyzed the reactions, giving the products **3a-3h** in high yields over relatively short reaction times. Easy separation of obtained products from the catalyst makes this method useful for the synthesis of biscoumarins.Purity checks with melting points, TLC and the ^{1}H NMR spectroscopic data reveal that only one product is formed in all cases and no undesirable side-products are observed. The structures of all known products **3a-3h** were deduced from their ^{1}H NMR and FT-IR spectral data and a comparison of their melting points with those of authentic samples.

Table 2. CBSA catalyzed synthesis of biscoumarinderivatives[a].

Entry	Ar	Product[b]	Time /min	Isolated Yield/%	m.p. (°C) Found	Reported
1	Ph	**3a**	17	90	229-231	229-230[viii]
2	4-$MeOC_6H_4$	**3b**	19	94	250-252	251-253[viii]
3	4-MeC_6H_4	**3c**	15	92	270-272	269-271[xxiv]
4	4-$O_2NC_6H_4$	**3d**	12	95	233-235	232-234[xxiv]
5	4-ClC_6H_4	**3e**	13	93	255-257	253-255[xxiv]
6	2-ClC_6H_4	**3f**	13	88	203-205	204-205[xxiv]
7	3-BrC_6H_4	**3g**	16	89	233-235	233-236[xxiv]
8	4-FC_6H_4	**3h**	14	94	211-213	213-214[xxiv]

[a]Reaction conditions: 4-hydroxycoumarin **1** (2 mmol), aldehyde **2a–h**(1 mmol), CBSA (0.08 g), water (5 mL), reflux.
[b]All the products were characterized by their FT-IR and ^{1}H NMR spectral data and by comparison of their melting points with those of authentic samples.

We also used the model reaction under optimized reaction conditions to evaluate the reusability of the catalyst CBSA. After completion of the reaction, the catalyst was recovered as described in the experimental section. The separated catalyst was washed with hot ethanol and subsequently dried at 50 °C under vacuum for 1 h before being reused in a similar reaction. We found that the catalyst could be used at least four times with only a slight reduction in activity (Figure 1). Furthermore, the FT-IR spectra of the recovered catalysts (Figure2(b)–(d)) were almost identical to the spectrum of the fresh catalyst (Figure2(a)), indicating that the structure of the catalyst was unchanged by the reaction.

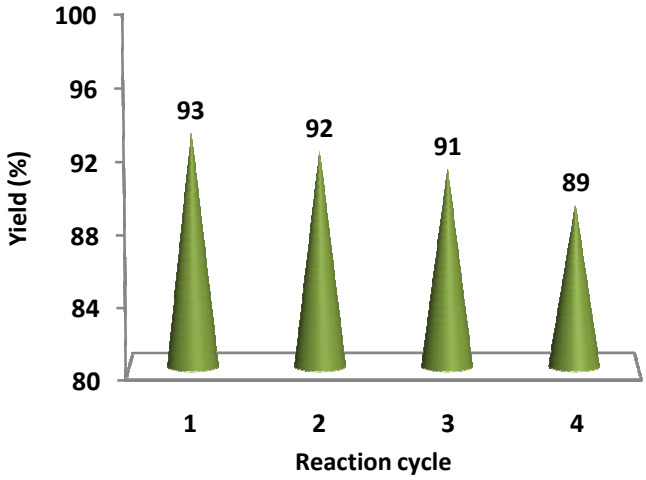


Figure 1. Effect of recycling on the catalytic performance of CBSA in the synthesis of **3e**.

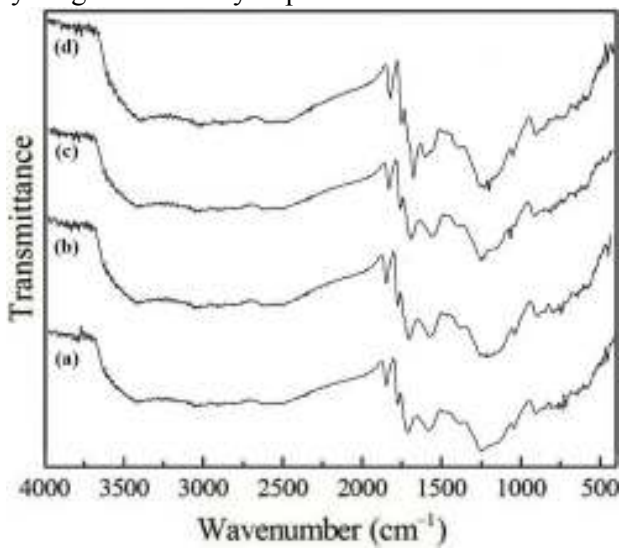


Figure2.FT-IR spectra of fresh catalyst CBSA ((a), first run), and recovered catalysts ((b-d), second to forth runs, respectively) for the synthesis of compound **3e**in model reaction.

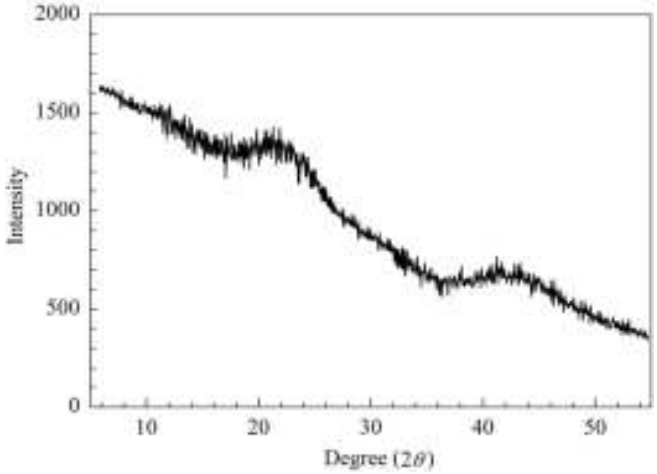
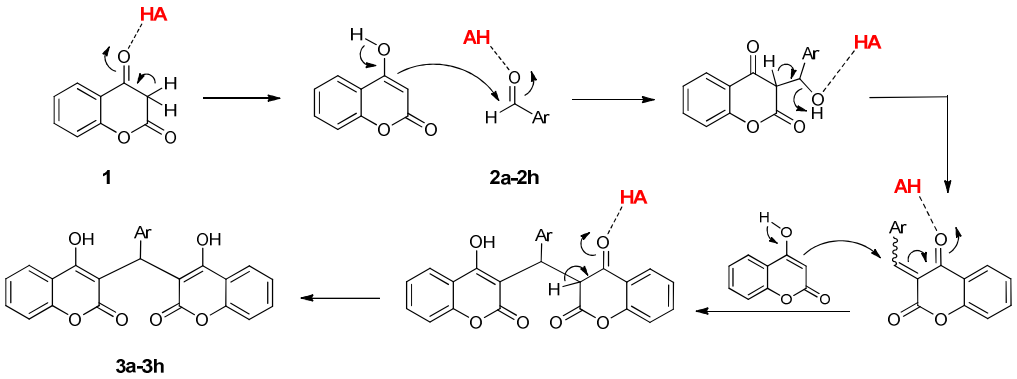


Figure 3.XRD pattern of CBSA.

Although we did not investigate the reaction mechanism, the CBSAcould acts as Brönsted acid related to the $–SO_3H$ groups and therefore promote the necessary reactions. The catalyst would play a significant role in increasing the electrophilic character of the electrophiles in the reaction.



Scheme 2. Plausible mechanism for the CBSA (HA)catalyzed formation of biscoumarins.

EXPERIMENTAL

Chemicals and Apparatus

All chemicals were available commercially and used without additional purification. The catalyst was synthesized according to the literature[xxv]. Melting points were recorded using a Stuart SMP3 melting point apparatus. The FT-IR spectra of the products were obtained with KBr disks, using a Tensor 27 Bruker spectrophotometer. The ^{1}H NMR spectra were recorded using Bruker300 spectrometers.

3.2. General experimental procedure for the synthesisof3a-3h catalyzed by CBSA

A mixture of 4-hydroxycoumarin (2 mmol), aromatic aldehydes (1 mmol) and CBSA (0.08 g) as catalyst in water was heated under reflux condition. The reaction was monitored by TLC. Upon completion of the transformation, the catalyst was removed by filtration under hot conditions. The catalyst was washed with a small portion of hot ethanol. After cooling, the combined filtrate was allowed to stand at room temperature. The precipitated solid was collected by filtration, and recrystallized from ethanol to give compounds 3a-3h in high yields.

^{1}H NMR and FT-IR data:

3,3'-(phenylmethylene)bis(4-hydroxy-2H-chromen-2-one) (3a) FT-IR (KBr disc, ν/cm^{-1}): 3437, 3023, 1659, 1601, 1557, 1488, 1359, 1093, 764; ^{1}H NMR ($CDCl_3$): δ 6.15 (s, 1H, CH), 7.24 (d, 2H, *J* = 7.4 Hz, arom-H), 7.31 (t, 1H, *J* = 5.3 Hz, arom-H), 7.35 (t, 2H, *J* = 7.2 Hz, arom-H), 7.35-7.47 (m, 4H, arom-H), 7.64 (t, 2H, *J* = 7.2 Hz, arom-H), 8.05- 8.20 (m, 2H, arom-H), 11.31 (s, 1H, OH), 11.53 (s, 1H, OH).

3,3'-((4-methoxyphenyl)methylene)bis(4-hydroxy-2H-chromen-2-one) (3b) FT-IR (KBr disc, ν/cm^{-1}): 3431, 3074, 1666, 1600, 1562, 1518, 1358, 1262, 1088, 779; ^{1}H NMR ($CDCl_3$): δ 3.85 (s, 3H, OCH_3), 6.12 (s, 1H, CH), 6.84 (d, 2H, *J* = 8.4 Hz, arom-H), 7.13 (d, 2H, *J* = 8.4 Hz, arom-H), 7.33-7.52 (m, 4H, arom- H), 7.64 (t, 2H, *J* = 7.5 Hz, arom-H), 8.00-8.15 (m, 2H, arom-H), 11.35 (s, 1H, OH), 11.56 (s, 1H, OH).

3,3′-((4-Methylphenyl)methylene)bis(4-hydroxy-2H-chromen-2-one) (3c)FT-IR (KBr disc, ν/cm^{-1}): 3427, 3043, 2991, 1669, 1603, 1571, 1483,1356, 1311, 1075, 772 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.33 (s, 3H, CH_3), 6.12 (s, 1H, CH), 7.12(q, *J* = 8.2 Hz, 4H, arom-H), 7.35–

7.43 (m, 4H, arom-H),7.61 (td, *J* = 8.4, 1.4 Hz, 2H, arom-H), 8.08 (d, *J* = 7.4 Hz,1H, arom-H), 8.13 (d, *J* = 7.4 Hz, 1H, arom-H), 11.35 (s,1H, OH), 11.55 (s, 1H, OH).

3,3′-((4-Nitrophenyl)methylene)bis(4-hydroxy-2H-chromen-2-one) (3d)FT-IR (KBr disc, ν/cm^{-1}): 3422, 3057, 1653, 1601, 1566, 1531, 1497,1456, 1354, 1321, 1100, 788 cm^{-1}; 1H NMR ($CDCl_3$): δ 6.16 (s, 1H, CH), 7.43–7.50 (m, 6H, arom-H), 7.68 (t, *J* = 7.4 Hz, 2H, arom-H), 8.09 (d, *J* = 7.4 Hz, 1H,arom-H), 8.17 (d, *J* = 8.2 Hz, 1H, arom-H), 8.25 (d, *J* = 8.5Hz, 2H, arom-H), 11.42 (s, 1H, OH), 11.63 (s, 1H, OH).

3,3′-((4-Chlorophenyl)methylene)bis(4-hydroxy-2H-chromen-2-one) (3e)FT-IR (KBr disc, ν/cm^{-1}): 3432, 3076, 1672, 1621, 1565, 1493, 1456, 1348, 1315, 1089, 762 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.07 (s, 1H, CH), 7.12 (dd, *J* = 8.6, 0.8 Hz, 2H, arom-H), 7.33 (d, *J* = 8.6 Hz, 2H, arom-H), 7.35–7.45 (m, 4H, arom-H), 7.60–7.67 (m, 2H, arom-H), 7.97 (d, *J* = 7.4 Hz, 1H, arom-H), 8.11 (d, *J* = 7.4 Hz, 1H, arom-H), 11.38 (s br, 1H, OH), 11.58 (s br, 1H, OH).

3,3′-((2-Chlorophenyl)methylene)bis(4-hydroxy-2H-chromen-2-one) (3f)FT-IR (KBr disc, ν/cm^{-1}): 3432, 3084, 1653, 1562, 1496, 1471, 1452,1349, 1303, 1270, 1100, 761 cm^{-1};^{1}H NMR ($CDCl_3$): δ 6.15 (s, 1H, CH), 7.25–7.45 (m, 7H, arom-H),7.44 (d, *J* = 7.2 Hz, 1H, arom-H), 7.65 (td, *J* = 7.6, 1.2 Hz, 2H,arom-H), 8.00–8.15 (m, 2H, arom-H), 10.94 (br, 1H, OH),11.62 (s br, 1H, OH).

3,3′-((3-Bromophenyl)methylene)bis(4-hydroxy-2H-chromen-2-one) (3g)FT-IR (KBr disc, ν/cm^{-1}): 3433, 3071, 1663, 1616, 1555, 1492, 1473, 1353, 1319, 1090, 773 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.11 (s, 1H, CH), 7.17–7.47 (m, 9H, arom-H), 7.65– 7.75 (m, 2H, arom-H), 8.05 (d, *J* = 8.2 Hz, 1H, arom-H), 8.13 (d, *J* = 8.2 Hz, 1H, arom-H), 11.35 (s, 1H, OH), 11.65 (s, 1H, OH).

3,3′-((4-Fluorophenyl)methylene)bis(4-hydroxy-2H-chromen-2-one) (3h)FT-IR (KBr disc, ν/cm^{-1}): 3456, 3062, 1678, 1558, 1512, 1451, 1358,1311, 1101, 769 cm^{-1};^{1}H NMR ($CDCl_3$): δ 6.09 (s, 1H, CH), 7.08 (t, *J* = 8.2 Hz, 2H, arom-H),7.18–7.24 (m, 2H, arom-H), 7.40–7.50 (m, 4H, arom-H), 7.64(td, *J* = 8.1, 1.2 Hz, 2H, arom-H), 8.05 (d, *J* = 7.4 Hz, 1H,arom-H), 8.13 (d, *J* = 7.4 Hz, 1H, arom-H), 11.34 (s, 1H, OH),11.56 (s, 1H, OH).

CONCLUSION

In summary, we showed that CBSA,efficiently catalyzed the synthesis of biscoumarins derivatives by one-pot, two-component reaction of4-hydroxycoumarin, and aryl aldehyde inwater under reflux conditions. The method was relatively fast and high yielding, and the work-up was easy. The catalyst can be recycled after simple handling, and used at least four times without any substantial reduction in its catalytic activity. The procedure is also advantageous in the sense that it is a fast reaction and therefore operates under environmentally friendly conditions.

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