

A Highly Efficient and Fast Method for the Synthesis of Biscoumarins Using Tetrabutylammonium Hexatungstate [TBA]₂[W₆O₁₉] as Green and Reusable Heterogeneous Catalyst

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A novel catalytic synthesis of biscoumarins from 4-hydroxycoumarin and aromatic aldehydes has been developed. The reaction occurs in ethanol in the presence of tetrabutylammonium hexatungstate [TBA]₂[W₆O₁₉] 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 three times with only slight reduction in its catalytic activity.

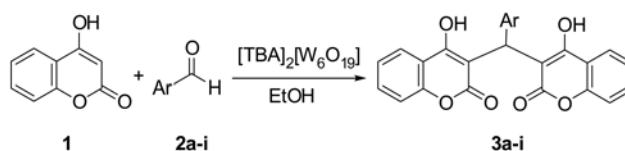
Key Words : Aromatic aldehydes, Biscoumarins, 4-Hydroxycoumarin, Tetrabutylammonium hexatungstate [TBA]₂[W₆O₁₉]

Introduction

4-Hydroxycoumarin and its derivatives are known for their various biological activities such as anticoagulant, insecticidal, antihelminthic, hypnotic, antifungal, phytoalexin, and HIV protease inhibition.¹⁻³ Biscoumarins, the bridge substituted dimers of 4-hydroxycoumarin, have enormous potential as anticoagulants.^{4,5} A number of biscoumarins have also been found to be urease inhibitors.⁶ Recently, a number of methods have been reported for the synthesis of biscoumarins by reaction of 4-hydroxycoumarin and various aldehydes.⁷⁻¹¹ Although these methods may be effective, some of them have relatively long reaction times, and unsatisfactory yields. These findings 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.

Polyoxometalates (POMs), constituting a large class of metal oxide molecules, are known to have a variety of sizes, structures, electrochemical properties, and chemical reactivities.¹² POMs has been extensively studied because they have many practical applications such as catalysis,^{13,14} molecular materials,¹⁵ and corrosion inhibition.¹⁶ In recent decades, uses of some POMs as catalysts for fine organic synthetic processes have been developed and are important for industries related with fine chemicals,¹⁷ including flavors, pharmaceuticals and food industries.¹⁸ Furthermore, the Lindqvist-type metal-oxygen clusters, M₆O₁₉²⁻ (M = W, Mo), and their functionalized compounds have fascinating chemical properties, photophysical properties, and diverse practical applications.¹⁹⁻²³

Prompted by these findings and interest on the development of novel synthetic methodologies in organic reactions,²⁴⁻²⁷ in this paper for the first time a highly efficient and fast method for the synthesis of biscoumarins by reaction of 4-hydroxycoumarin with aromatic aldehydes using tetrabutyl-



Scheme 1. Synthesis of biscoumarins catalyzed by [TBA]₂[W₆O₁₉].

ammonium hexatungstate [TBA]₂[W₆O₁₉], an isopolytungstate, as heterogeneous catalyst is reported (Scheme 1).

Experimental

All chemicals were available commercially and used without additional purification. Melting points were recorded on a Stuart SMP3 melting point apparatus. The IR spectra were obtained using a Tensor 27 Bruker spectrophotometer as KBr disks. The ¹H NMR (500 MHz) spectra were recorded with a Bruker DRX500 spectrometer.

Synthesis of Tetrabutylammonium hexatungstate [TBA]₂[W₆O₁₉]. A mixture of sodium tungstate dihydrate, Na₂WO₄·2H₂O, (99%, 0.1 mol, 33 g), acetic anhydride (40 mL) and *N,N*-dimethylformamide (30 mL) is heated at 100 °C for 3 h to obtain a white cream. Then a solution of acetic anhydride (20 mL) and HCl (12 N, 18 mL) in DMF (50 mL) is added with stirring, and the resulting mixture is filtered off to eliminate the undissolved white solid. A solution of tetrabutylammonium bromide (0.047 mol, 15.1 g) in methanol (50 mL) is added with rapid stirring to give a white precipitate. This suspension is stirred for 5 min and the product is filtered. Recrystallization from a minimum amount of hot DMSO gives colorless diamond-shaped crystals.²⁸

General Procedure for the Synthesis of Biscoumarins 3a-i Catalyzed by [TBA]₂[W₆O₁₉]. A mixture of 4-hydroxycoumarin **1** (4 mmol), aromatic aldehyde **2a-i** (2 mmol), [TBA]₂[W₆O₁₉] (0.15 g, 0.08 mmol) as catalyst in ethanol (7 mL) was heated under reflux for the appropriate time. The

reaction was monitored by TLC. At the end of reaction, catalyst was removed by filtration. The product was collected from the filtrate after cooling to room temperature and recrystallized from ethanol to give compounds **3a-i** in high yields.

Recycling and Reusing of the Catalyst. Due to the fact that the catalyst was insoluble in hot ethanol, it could therefore be recycled by a simple filtration. The separated catalyst was washed with cold ethanol, dried at 60 °C under vacuum for 1 h and reused in another reaction. The results show that there is not any significant loss of activity in using recycled catalyst after three times in the reactions.

Selected ¹H NMR and FT-IR Data.

Compound 3a: ¹H NMR (500 MHz, CDCl₃) δ 6.14 (s, 1H, CH), 7.26 (d, 2H, *J* = 7.9 Hz, arom-H), 7.31 (t, 1H, *J* = 5.8 Hz, arom-H), 7.36 (t, 2H, *J* = 7.7 Hz, arom-H), 7.38-7.50 (m, 4H, arom-H), 7.66 (t, 2H, *J* = 7.7 Hz, arom-H), 8.00-8.15 (m, 2H, arom-H), 11.33 (s, 1H, OH), 11.56 (s, 1H, OH); FT-IR (KBr disc, v/cm⁻¹): 3421, 3059, 1673, 1605, 1562, 1492, 1352, 1098, 760.

Compound 3d: ¹H NMR (500 MHz, DMSO) δ 6.35 (s, 1H, CH), 7.25 (t, 2H, *J* = 7.7 Hz, arom-H), 7.29 (d, 2H, *J* = 8.2 Hz, arom-H), 7.36 (d, 2H, *J* = 8.3 Hz, arom-H), 7.53 (t, 2H, *J* = 8.4 Hz, arom-H), 7.82 (d, 2H, *J* = 7.8 Hz, arom-H), 8.06 (d, 2H, *J* = 8.8 Hz, arom-H), 11.28 (s, 1H, OH), 11.53 (s, 1H, OH); FT-IR (KBr disc, v/cm⁻¹): 3413, 3072, 1668, 1618, 1563, 1491, 1351, 1094, 766.

Compound 3i: ¹H NMR (500 MHz, CDCl₃) δ 3.83 (s, 3H, OCH₃), 6.08 (s, 1H, CH), 6.88 (d, 2H, *J* = 8.6 Hz, arom-H), 7.16 (d, 2H, *J* = 8.6 Hz, arom-H), 7.35-7.55 (m, 4H, arom-H), 7.66 (t, 2H, *J* = 7.6 Hz, arom-H), 8.00-8.15 (m, 2H, arom-H), 11.32 (s, 1H, OH), 11.54 (s, 1H, OH); FT-IR (KBr

Table 1. Effect of [TBA]₂[W₆O₁₉] amount, solvent and temperature in the synthesis of compound **3a**^a

Entry	Catalyst (mol %)	Solvent	T (°C)	Time (min)	Yield (%) ^b
1	None	EtOH	78	240	29
2	None	Solvent-free	100	240	12
3	2.6	EtOH	78	10	82
4	4.0	EtOH	50	30	76
5	4.0	EtOH	78	5	91
6	5.3	EtOH	78	5	92
7	4.0	MeOH	64	5	68
8	5.3	MeOH	64	5	70
9	4.0	CHCl ₃	61	10	59
10	5.3	CHCl ₃	61	10	62
11	4.0	CH ₃ CN	81	10	63
12	5.3	CH ₃ CN	81	10	64
13	4.0	Solvent-free	100	30	69
14	5.3	Solvent-free	120	30	72

^a4 mmol 4-hydroxycoumarin, and 2 mmol benzaldehyde. ^bThe yields were calculated based on 4-hydroxycoumarin and refer to the pure isolated product.

disc, v/cm⁻¹): 3429, 3063, 1671, 1605, 1564, 1510, 1353, 1259, 1094, 769.

Results and Discussion

The catalyst, [TBA]₂[W₆O₁₉] was prepared according to the Fournier's method.³⁹ First, the synthesis of compound **3a** was selected as a model reaction to determine suitable reaction conditions. The reaction was carried out by heating a mixture of 4-hydroxycoumarin, and benzaldehyde in the

Table 2. [TBA]₂[W₆O₁₉] catalyzed synthesis of biscoumarins^a

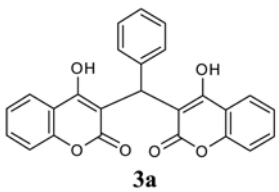
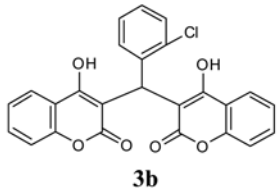
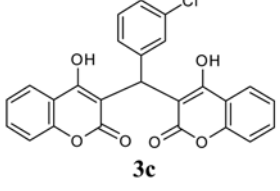
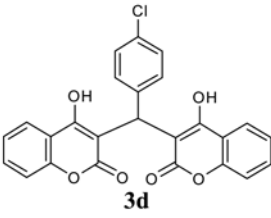
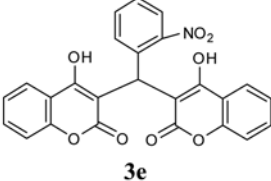
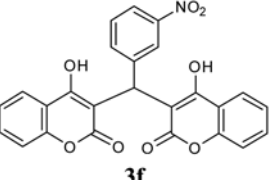
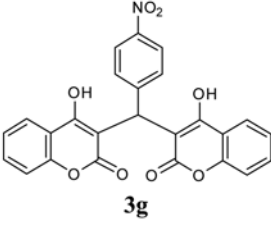
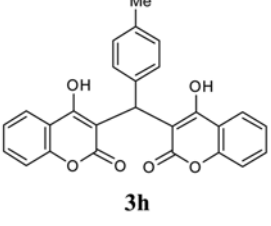
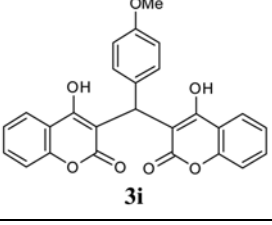
Entry	Ar	Products ^b	Time (min)	Yield (%) ^c	mp °C		Ref.
					Found	Reported	
1	C ₆ H ₅		5	91	229-230	228-230	8
2	2-ClC ₆ H ₄		10	86	200-203	198-199	10
3	3-ClC ₆ H ₄		5	88	219-221	222-224	10

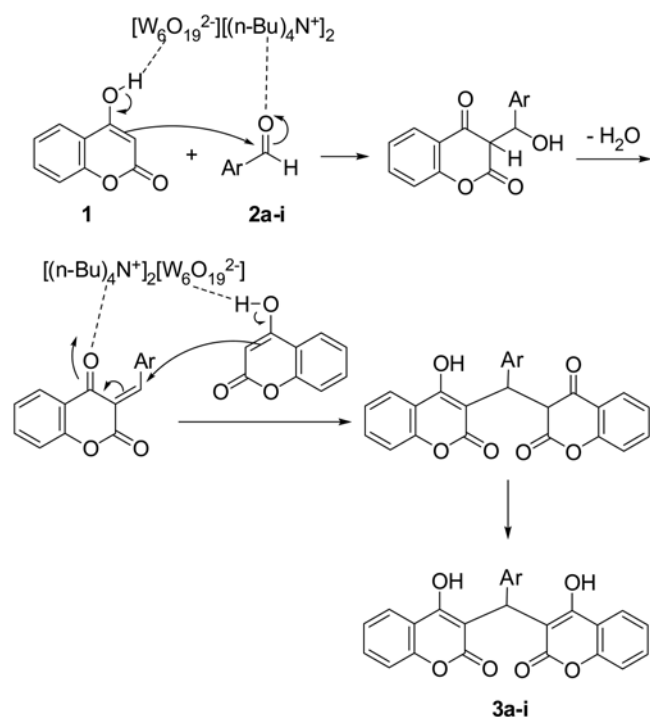
Table 2. Continued

Entry	Ar	Products ^b	Time (min)	Yield (%) ^c	mp °C		Ref.
					Found	Reported	
4	4-ClC ₆ H ₄	 3d	5	90	257-259	258-259	11
5	2-O ₂ NC ₆ H ₄	 3e	7	85	196-198	200-202	10
6	3-O ₂ NC ₆ H ₄	 3f	7	89	214-216	212-215	10
7	4-O ₂ NC ₆ H ₄	 3g	10	92	232-233	232-234	8
8	4-MeC ₆ H ₄	 3h	7	89	271-273	269-270	11
9	4-MeOC ₆ H ₄	 3i	5	88	251-253	249-250	11

^a4 mmol 4-hydroxycoumarin, 2 mmol aromatic aldehyde, 0.08 mmol (4.0 mol % based on aromatic aldehyde) [TBA]₂[W₆O₁₉] in ethanol under reflux.
^bAll the products were characterized by IR spectral data and comparison of their melting points with those of authentic samples. Also, the structures of some products were confirmed by ¹H NMR spectral data. ^cThe yields were calculated based on 4-hydroxycoumarin and refer to the pure isolated product.

presence of [TBA]₂[W₆O₁₉] in different solvents and under solvent-free conditions (Table 1). As can be seen from Table 1, the compound **3a** was obtained in high yield in refluxing EtOH but in moderate yields in MeOH, CHCl₃, CH₃CN, and also in solvent-free conditions. The efficiency of the reaction is affected mainly by the amount of the

catalyst. The product was obtained in low yield in the absence of the catalyst (entries 1 and 2) indicating that the catalyst is necessary for the reaction. Increasing the amount of the catalyst increased the yield of the product **3a**. The optimal amount of [TBA]₂[W₆O₁₉] was 0.15 g (4.0 mol % based on benzaldehyde) (entry 5); increasing the amount of



Scheme 2. Plausible mechanism for the synthesis of biscoumarins in the presence of $[TBA]_2[W_6O_{19}]$ as catalyst.

the catalyst beyond this value did not increase the yield significantly.

Encouraged by this success, the reaction of 4-hydroxycoumarin with a range of other aromatic aldehydes under the optimized reaction conditions was extended. In all cases the expected products were obtained in high yields in short reaction times. The results are summarized in Table 2. As shown, aromatic aldehydes with substituents carrying either electron-donating or electron-withdrawing groups reacted successfully and gave the products in high yields. The kind of aldehyde has no significant effect on the formation of final product.

The principle advantage of the use of heterogeneous catalysts in organic transformations is their reusability. Hence, the catalytic activity of recycled $[TBA]_2[W_6O_{19}]$ in the synthesis of compound **3a** under the optimized conditions was studied. After the completion of the reaction, the catalyst was filtered under hot condition, washed with cold ethanol, dried at 60 °C under vacuum for 1 h, and reused for the similar reaction. The catalyst could be used at least three times with only slight reduction in the catalytic activity (91% for 1st use; 90% for 2nd use; 88% for 3rd use).

Although the reaction mechanism was not investigated, based on Kantevari's suggestion,²⁹ it is proposed that the tetrabutylammonium ion $[(n-Bu)_4N^+]$ induces polarization of carbonyl group in aldehydes. On the other hands, Reinheimer and co-workers³⁰ reported that terminal oxygen atoms or the bridging oxygen atom in polyoxometalate anion, $W_6O_{19}^{2-}$, are slightly basic and therefore can promote the reactions. Therefore, a plausible mechanism may proceed as depicted in Scheme 2.

Conclusion

In summary, in this paper a highly efficient, fast and green method for the synthesis of biscoumarins through the reaction of 4-hydroxycoumarin with aromatic aldehydes in ethanol using $[TBA]_2[W_6O_{19}]$ as catalyst has been reported. Some attractive features of this protocol are high yields, simple procedure, short reaction times, easy work-up, high catalytic activity and recyclability and reusability of the catalyst. The catalyst can be used at least three times without substantial reduction in its catalytic activity. Therefore, this applicability of $[TBA]_2[W_6O_{19}]$ with mentioned advantages makes this method superior over other reported methods to synthesis of biscoumarins.

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