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Phosphotungstic acid an efficient catalyst for the synthesis of Bis(4-Hydroxycoumarine)derivatives under ultrasound irradiation

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Abstract: An efficient and simple one pot domino Knoevenagel typecondensation /Michael reaction of aromatic, heteroaromaticand aliphatic aldehydes with 4-hydroxycoumarine under ultrasound irradiation were usingphosphotungstic acid as an efficient and recyclable catalyst gives high yield in short time.

Keywords: Heteropolyacids, Heterogeneous catalysis, Bis-coumarine, Aromatic aldehydes.

Introduction:

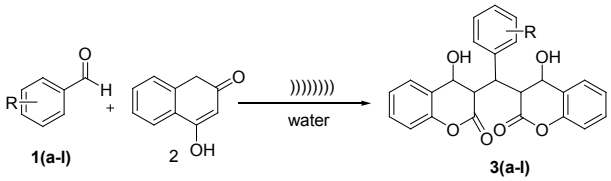
Coumarine derivatives are biologically active chemical compounds found in highconcentration in the tonica bean, woodruff and bison grass.7,7-Dihydroxy-6,6-dimethyoxy-3,3'biscoumarine was isolated from Erycibe obtusifolia[1].4-Hydroxycoumarine derivatives are used as antibacterial, antifungal and antitoxic agent [2-4]Coumarine derivatives have recently revealed new biological activities with interesting potential in therapeutic application besides their traditional employment as anticoagulant and sustaining agents [5]. Among the systems studied, the 3,3'-benzylidene bis(4-hydroxycoumarin-3-yl)toluene has been tested as a HIV integrase inhibitor and has shown significant activity [4,6].Thus the introduction of efficient new methods based on several green methodologyused for the synthesis ofbis-coumarine in aqueous media have been reported despite effectiveness and eco-friendliness of these methods,use different types of catalyst such as TEBA,I_2[7-8],Heteropolyacids,TBAB,SDS, [9-13],Lewis acids[14 -18], Phase transfer catalys[19 -23], Phosphorus pentoxide [24], $ZrCl_4$ [25], $TiCl_4$ [26],Nafion-H [27], zeolite H-BEA, modified zirconia [28] Amberlyst 15 [29] montmorillonite clay [30] Bis-coumarine could be obtained even without catalyst by simple heating at 60-70^{0}C but the reported protocol suffer from various disadventages such

as low yield more reaction time therefore we developed newmethod for the synthesis ofbis-coumarine.

In present work,we use phosphotungstic acid as a catalyst. In recent years, the use of solid acids as heterogeneous catalysts has received considerable attention in different organic synthesis. The various heterogeneous catalysts, heteropolyacids (HPAs) are commerciallyvaluable, easy to handle, low toxicity, environmentally friendly and economically low cost, they have high Bronsted acidity, they constitute a mobile ionic structure and absorbpolar molecules easily in the bulk, forming a 'pseudo liquid phase' as a result, both the surfaceprotons and the bulk protons participate in their catalytic activity, which help toenhances the reaction rate. The most known HPAs are the Keggin HPAs, $H_{8-}nXM_{12}O_{40}$, where X is thecentral atom (Si^{4+}, P^{5+}etc.), n is the oxidation state of X and M is the metal ion (W^{6+} or Mo^{6+}). Ofthese, phosphomolybdic acid, and silicotungstic acid, has beenused in recent years for the synthesis of various heterocycles [31-36]. Therefore, the introduction of a novel and inexpensive heterogeneous catalyst, which can beeasily separated, reused, and does not become contaminated by the products. We herein report the use of phosphotungstic acid as a catalyst in the synthesis of bis-coumarine derivatives with excellent yields bythe reaction of a variety of aromatic aldehydes and 4-hydroxycoumarineunder ultra-sound irradiation has been increasingly used because the method is more convenient and it gives large yield in short time so we use the method for synthesis of bis-coumarine without using harmful solvent reaction proceeds withwater as a solventwhich is reported below**(**scheme**1).**

In recent years, synthetic chemists are challenged to consider more environmentally friendly methods for synthesis of the desired target molecules. Because of the toxic and volatile nature of many organic solvents, water as a reaction medium was considered a very promising resulting in less expensive, lessdangerous, and environmentally friendly and attractive substitute for volatile organic solvents and was widely used in the green chemistry area.

The catalysti.e., phosphotungstic acid was recovered reused in subsequent runs with any loss of activity using simple filtration method. The reusilibility of the catalyst is one of the advantages of this method.



Scheme-1. Synthesis of bis (4-Hydroxy-coumarine**)**

Result and discussion

A green methodology is developed for the synthesis of biscoumarin by coupling of 4-hydroxycoumarine and aromatic aldehydes in water under ultrasonic irradiation. Inourinitial efforts to synthesize biscoumarin derivative we chose model reaction by coupling of benzaldehyde(1mmol), 4-hydroxycoumarine (2 mmol) usingdifferent acid as a catalyst (entry table-1).We investigated the reaction we found that phosphotungstic acid was better suited as a catalyst for better yield in short time. To establish reaction condition for MCRs the scope and generality of the new protocol for various aromatic and heteroaromatic aldehydes containing electron-windrawing and electron-donating group shows smooth transformation to bis-coumarin without formation of side product give high yield in short time.

The various concentration of $H_3PW_{12}O_{40}$was employed and reaction carried out in ultrasonic irradiaton. Initially in model reaction carried out with 2 mol% catalyst which gave 50% yield

Table 1 Screening of the different catalysts for the model reaction[a]

Entry	Catalyst	Solnvents	Time in min	Yield (%)
1	HBF_4	Neat	90	25
		ethanol	50	65
		CH_2CN	46	62
		CH_2Cl_2	40	65
		water	10	72
2	CCl_3COOH	Neat	90	22
		ethanol	50	65
		CH_2CN	46	59
		CH_2Cl_2	40	68
		water	10	78
3	Sulfamic acid	Neat	90	38
		ethanol	50	73
		CH_2CN	46	66
		CH_2Cl_2	40	75
		water	10	80
4	**Phosphotungstic acid**	Neat	90	40
		ethanol	50	65
		CH_2CN	46	68
		CH_2Cl_2	40	78
		water	**10**	**98**

[a]Reactionconditions:Ultrasonic power: 100 watts; reaction at ambient temperature.

even after 40 min of stirring, while another set of reaction with 5 mol% of the catalyst furnished the desired product in 62% yield. We observed that the catalyst concentration increases there is an increase in the product yield and decrease in the time required with maximum yield at 15 mol% of catalyst. Further increase in the concentration of catalyst up to 20 mol% was not increase the yield of product (Table. 2).

Table 2: Optimization amount of catalyst for preparation of bis(4-hydroxycoumarin) derivatives[a]

Entry	Catalyst	Amount of catalyst, mol %	Time in Min	Yield[b]
1	$H_3PW_{12}O_{40}$	2	15	50
2	$H_3PW_{12}O_{40}$	5	15	62
3	$H_3PW_{12}O_{40}$	7	15	68
4	$H_3PW_{12}O_{40}$	10	15	85
5	$H_3PW_{12}O_{40}$	15	15	98

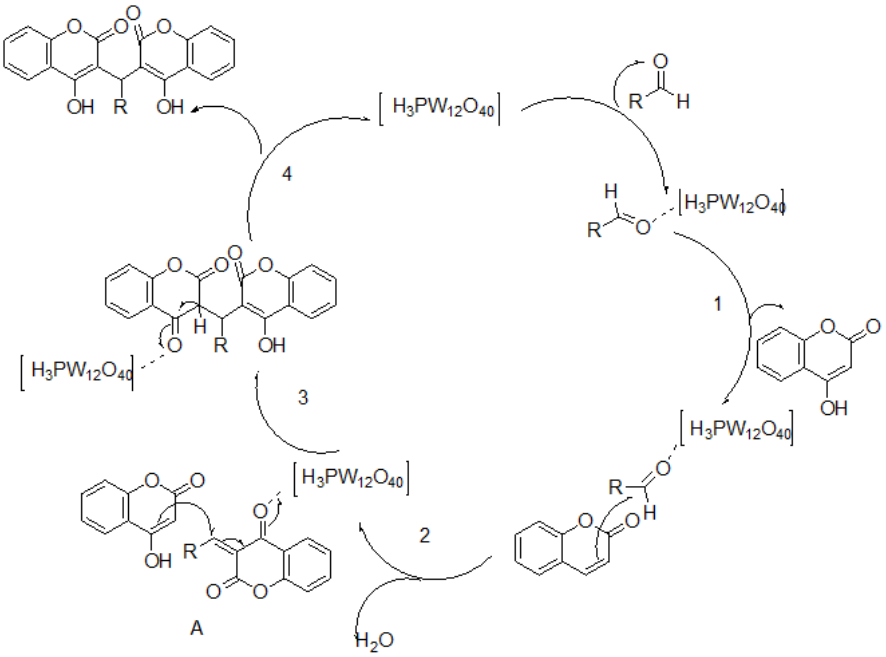
[a]Reactionconditions:4-hydroxy-coumarine (2 mmol), aromatic aldehyde 5a-m (1 mmol),) and phosphotungstic acidcatalyst (15mol %). [b]Isolated yield

The $H_3PW_{12}O_{40}$is a heterogeneous acid catalyst and could easily be separated from the reaction mixture by simple filtration. The recovered catalyst was used for successive runs to investigate its reusability (Table 3). It was observed that the catalyst could be reused at least four times with a slight decrease in the rate of the reaction and yield of the product (Table 3, entries 1-4).

Table 3:Reusability study[a]

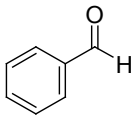
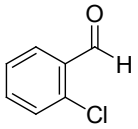
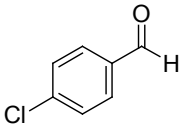
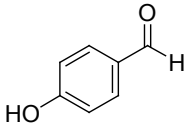
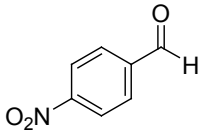
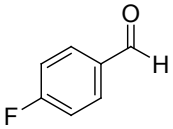
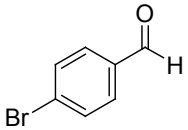
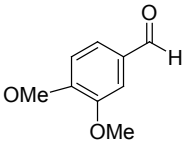
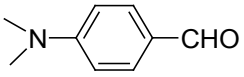
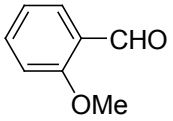
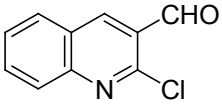
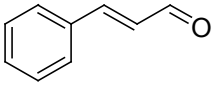
Run	Yield[b](%
1	92
2	91
3	90
4	89

[a]Reactionconditions:4-hydroxy-coumarine (2 mmol), aromatic aldehyde 5a-m (1 mmol),) and phosphotungstic acidcatalyst (15mol %). [b]Isolated yield



Scheme 2. Proposed mechanism for phosphotungstic acid catalyzed synthesis of bis-coumarine

Table 3: Phosphotungstic acid catalyzed synthesis of bis (4-hydroxycoumarine) derivatives[a]

Entry	R(aldehyde)	Product	Time (min)	Yield[b]	M. P (Found)	MP(lit) (Reported)
1		1a	10	90	228-230	227-228[10]
2		1b	12	95	224-226	225-226[37]
3		1c	12	94	252-254	254-256[13]
4		1d	15	94	222-224	221-223[10]
5		1e	10	85	232-234	234-236[10]
6		1f	10	80	213-14	212-214[11]
7		1g	10	91	265-266	266-268[13]
8		1h	12	89	263-265	264-265[10]
9		1i	10	90	221-222	220-221
10		1j	9	9	258-260	259-260
11		1k	12	96	225-227	---------
12		1l	10	94	181-184	-------

[a]Reactionconditions:4-hydroxy-coumarine (2 mmol), aromatic aldehyde 5a-m (1mmol),) and phosphotungstic acidcatalyst (15mol %). Ultrasonic power: 100 watts; reaction at ambient temperature. [b]Isolated yield

A proposed mechanism for condensation of aldehydes and 4-hydroxycoumarine ratenlize formation of product is exhibited in scheme-2. As shown the nucleophile shows the attack on 4-hydroxycoumarine to activated aldehyde (by phosphotungstic acid.) followed by H_2O elimination provides intermediate "A" which activated by phosphotungstic acid undergoes second attack of nucleophile by another 4-hydroxycoumarine form the desired productbis (4-hydroxycoumarine**).**

Experimental

All chemicals were purchased from Sigma-Aldrich, SD fine chemicals companies and used without further purification. Electric Supply:203 V A.C.50Hz, 1Phase Ultrasonic frequency: 36 ± KHz. Ultrasonic power: 100watts. The progress of reaction was followed by thin layer chromatography (TLC). The uncorrected melting points of compounds were taken in an open capillary in a paraffin bath and uncorrected.^{1}H NMR spectra were recorded on a Bruker Advance 400 and ^{13}C NMR was recorded on a Bruker DRX-300 instrument using TMS as an internal reference. Mass spectra were recorded on waters UPLC-TQD Mass spectrometer using electrospray ionization technique..

General procedurefor the synthesis of bis (4-hydroxycoumarine)3(a-l):

A mixture of aromatic aldehyde(1mmole) and 4-hydroxycoumarine (2mmole) water(5ml),Catalyst(0.5mmol) were taken in 25ml round bottom flask.The mixture was irradiated in the water bath of an ultra sonication for appropriate time. The progress of reaction monitored by thin layer chromatography (eluent: EtOAc-hexane, 1:9), the mixture was cooled. The solid product was filtered washed with water and dried. The crude product was recrystalised from ethanol to yield pure product.

Physical and spectroscopic data of some representative compounds

Whitesolid;**M.P**.-180-185°C;**1l**;**^{1}HNMR**(300 ,MHz,CDCl3,δ):3.86(s,1H),6.07(s,2H),6.71-7.65(m,13H),11.28(s,1H,OH),11.51(s,1H,OH); **^{13}CNMR**(300MHz,CDCl3):35.96,56.08,56.30, 104.43,106.02,110.62,111.47,116.83,119.12,12 4.125,125.08,127.75,133.02,148.27,149.33,152 .63,165.73;**Mass** EI-MS: m/z (%) = 441 (M+1).

Yellow-solid;**M.P**-225-227°C;**1k**; **^{1}HNMR**(300,MHz,$CDCl_3$)δ:5.11(s,1H),6.89-8.27(m,13H),11.28(s,1H,OH),11.51 (s,1H,OH); **^{13}CNMR**(300MHz, CDCl3):33.14,48.03,55.08, 65.3,104.04,106.12,112.47,117.02,119.13,125. 55,127.25, 128.09,134.08,148.24,149.35,165.8 0;**Mass** EI-MS: m/z (%) = 497.4, 498.4 (M+1).

Conclusion

Afacileandenvironmentallybenignmethodology for the synthesis of 4-hydroxycoumarine and aromatic/heteroaromatic aldehydes. This method gives catalyst is inexpensive and easily available. Moreover, mild reaction conditions, simple procedure, short reaction times, easy workup and excellent yields.

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