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A Solvent-Free Synthesis of Coumarins Using Phosphotungstic Acid as Catalyst

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Abstract Phosphotungstic acid (PTA) is used an efficient catalyst for the von Pechmann condensation reaction of phenols and β-keto esters under solvent-free conditions. This method was compared with those of the reactions in the different solvents and catalysts. The methodology presented offers significant improvements for the synthesis of coumarins with regard to yield of products, simplicity in operation and green aspects by avoiding toxic conventional catalysts and solvents.

Keywords Coumarin · Phosphotungstic acid · Pechmann condensation · Solvent free conditions

1 Introduction

The application of clean catalytic technologies, especially those with the use of heterogeneous catalysts, is becoming increasingly important for the development of environmentally benign chemical processes [1]. In this context, catalysis by acids can be considered as one of the most important areas of catalysis. Although the acid catalysis is widely employed in chemical industry, it suffers from the traditional use of hazardous mineral acids resulting in pollution and corrosion problems [1, 2]. Heteropoly compounds are green catalysts that function in a variety of reaction fields and are efficient bifunctional catalysts, harmless to the environment with respect to corrosiveness, safety, quantity of waste and separability [3]. Among the Keggin-type Heteropolyacids are more active and possess stronger Bronsted acidity than the usual mineral acids such as H_2SO_4, HCl, HNO_3 [4] and conventional solid acids such as SiO_2–Al_2O_3, H_3PO_4–SiO_2, zeolites including HX, HY, H-ZSM-5, Amberlyst-15 and Nafion-H [5]. Among heteropoly acids, phosphotungstic acids are the most widely used catalysts [6, 7] owing to their high acid strength, thermal stabilities, and low reducibilities.

The synthesis of coumarin and their derivatives has attracted considerable attention from organic and medicinal chemists for many years as a large number of natural products contain this heterocyclic nucleus. They are widely used as additives in food, perfumes, agrochemicals, cosmetics, pharmaceuticals [8] and in the preparations of insecticides, optical brightening agents, dispersed fluorescent and tunable laser dye [9]. Coumarin and its derivatives have varied bioactivitives such as antimicrobial [10], antithrombotics [11], anticoagulants, antipsoriasis activity [12], anticancer [13], anti-HIV [14], antioxidant activity, antiproliferative activity [15], inhibitory activity on viral proteases [16], estrogen-like effects [17] and central nervous system modulating activities [18]. Coumarins also act as intermediates for the synthesis of furocoumarins, chromenes, coumarones and 2-acylresorcinols [19]. Thus, the synthesis of this heterocyclic nucleus is of much current interest.

Coumarins have been synthesized by several routes including Pechmann [20], Perkin [21], Knoevenagel [22], Reformatsky [23], Wittig reactions [24], and by flash vacuum pyrolysis [25]. Among these, the Pechmann reaction is the most widely used method, as the reaction involves the use of simple starting materials, that is, phenols and β-ketoesters, in the presence of acidic condensing agents. The use of various reagents such as H_2SO_4, P_2O_5, $FeCl_3$, $ZnCl_2$, $POCl_3$, $AlCl_3$, PPA, HCl, phosphoric acid, trifluoroacetic acid, montmorillonite and other clays are all well documented in the literature [26]. Most of these methods

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suffer from severe drawbacks including the use of a large amount of catalysts, sometimes long reaction times and very often temperatures to the extent of 150 °C. Some of the recent achievements in the efficient construction of this nucleus include the development of cation exchange resins [27], several solid acid catalysts and metal nitrates [28], heteropolyacids [29, 30] supported polyaniline catalysts, the use of microwave irradiation, the use of ionic liquids as efficient catalysts [31] and very recently the use of Pt-catalysed hydroarylation of propiolic acids with phenols [32].

The drive towards clean technology has encouraged the application of solvent-free conditions [33]. A move away from the use of solvents in organic synthesis has led in some cases to improved results and more benign synthetic procedures. Our approach reduces the use of organic solvents, which are potentially toxic, hazardous and uses simple and mild conditions, with inherently lower costs. Owing the importance of PTA and in continuation with our work on to develop environmentally friendly reactions [34], herein, we report an simple, efficient and high yielding protocol for the synthesis of coumarin derivatives using phosphotungstic acid as a catalyst under solvent-free conditions (Scheme 1).

2 Experimental

The melting points of the products were determined by open capillaries on a Buchi apparatus and are uncorrected. The IR spectra were recorded on a Nicolet Impact-410 FT-IR Spectrophotometer using KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Buckner AC-300F 300 MHz spectrometer in $CDCl_3$ using TMS as an internal standard with ^{1}H resonant frequency of 300 MHz and ^{13}C resonant frequency of 75 MHz. The Mass spectra were recorded on an Autospec EI-MS. The elemental analysis was carried out by using Heraus CHN rapid analyzer. All the compounds gave C, H and N analysis within ±0.4% of the theoretical values. The homogeneity of the compounds was described by TLC on aluminum silica gel 60 F_{254} (Merck) detected by UV light (254 nm) and iodine vapours.

2.1 Materials

Phosphotungstic acid, $H_3PW_{12}O_{40}$ (PTA hydrate), phenols and β-keto ester, were procured from Aldrich, India Ltd. Solvents was procured from M/s Loba Chemie, Mumbai with >99.9 purity.

2.2 General Experimental Procedure for the Synthesis of Coumarins

The mixture of phenols (1 mmol) and the β-keto ester (1 mmol) and Phosphotungstic acid (2 mol%) was refluxed at 90 °C with stirring for the indicated time (Table 4), and reaction monitored by TLC. After completion of reaction, the mixture got solidified within hour. The resulting solidified mixture was diluted with ethyl acetate (1 ml) and the catalyst was separated through a Büchner funnel. The filtrate obtained was washed with water (two times) and evaporated the solvent under reduced pressure yielded the crude product, which was purified by recrystallization. All synthesized coumarin derivatives were characterized using analytical techniques like IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy. Also the melting points were measured for all synthesized coumarin derivatives and were compared with the corresponding reported melting points.

2.3 The Spectral Data for Selected Products

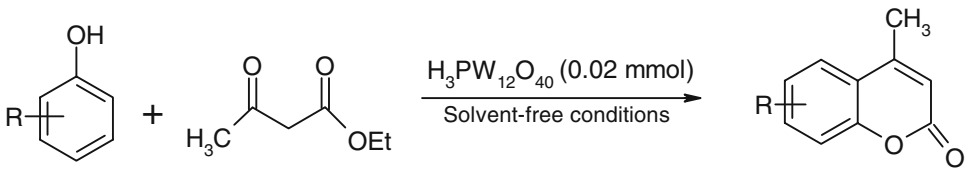
*2.3.1 4-Methyl Coumarin (**1a**)*

Colorless solid, m. p. 84–85, IR (KBr): υ 2,973, 1,685, 1,607, 1,460 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.70 (s, 3H, CH_3), 6.52 (s, 1H, C = CH), 7.20–7.7 (m, 4H, Ar–H); ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm 26.7, 113.4, 120.3, 125.7, 128.1, 152.4, 156.1,169.0; ESI-MS: 160 (M^+); Anal. Calcd for $C_{10}H_8O_2$: C, 74.99; H, 5.04; Found C, 74.80; H, 5.10.

*2.3.2 4,7-Dimethyl Coumarin (**1b**)*

Colorless solid, m. p. 131–132, IR (KBr): υ 2,973, 1,686, 1,607, 1,460 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.64 (s, 3H, CH_3), 2.82 (s, 3H, CH_3), 6.43 (s, 1H, C = CH), 7.0–7.70 (m, 3H, Ar–H), OH not observd; ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm 20.1, 23.8, 104.3, 120.0, 126.7, 135.9, 150.9, 167.0; ESI-MS: 174 (M^+); Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79; Found C, 75.87; H, 5.74.

Scheme 1 Synthesis of coumarins using phosphotungstic acid as a catalyst under solvent-free conditions



*2.3.3 7-Hydroxy–4-Methyl Coumarin (**1d**)*

Colorless solid, m. p. 186–187, IR (KBr): υ 3,467, 2,973, 1,690, 1,607, 1,460 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 2.58 (s, 3H, CH_3), 6.37 (s, 1H, C = CH), 6.8–7.78 (m, 3H, Ar–H), OH not observd; ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm 23.6, 106.7, 109.7, 121.0, 129.0, 157.4, 159.2,172.0; ESI-MS: 185 (M^+); Anal. Calcd. for $C_{11}H_8O_3$: C, 68.18; H, 4.58; Found C, 68.22; H, 4.54.

*2.3.4 5,7-Dihydroxy–4-Methyl Coumarin (**1g**)*

Colorless solid, m. p. 283–284, IR (KBr): υ 3,467, 3,160, 1,670, 1,607, 1,460 cm^{-1}; ^1H NMR (300 MHz, DMSO) δ ppm: 2.60 (s, 3H, CH_3), 6.27 (d, 1H, Ar–H), 6.32 (d, 1H, Ar–H),6.40 (s, 1H, C = CH), OH not observd; ^{13}C NMR (300 MHz, DMSO) δ ppm 23.9, 100.7, 108.8, 153.2, 156.2, 158.1,166.0; ESI-MS: 192 (M^+); Anal. Calcd. for $C_{11}H_8O_4$: C, 62.50; H, 4.21; Found C, 63.78; H, 4.31.

*2.3.5 7-Hydroxy–4,8-Dimethyl Coumarin (**1k**)*

Colorless solid, m. p. 217–218, IR (KBr): υ 3,460, 3,148, 1,685, 1,607, 1,460 cm^{-1}; ^1H NMR (300 MHz, DMSO) δ ppm: 1.90 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 6.36 (s, 1H, C = CH), 6.57 (d, 1H, Ar–H), 7.12 (d, 1H, Ar–H), OH not observd; ^{13}C NMR (300 MHz, DMSO) δ ppm 14.3, 24.6, 109.7, 112.8, 119.2, 125.0, 152.2, 155.2, 169.0; ESI-MS: 190 (M^+); Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.45; H, 5.35; Found C, 69.37; H, 5.40.

3 Results and Discussion

First, the optimization of the reaction, the effect of solvent, temperature and catalyst were carried, by selecting phenol and ethyl acetoacetate as a model. After stirring for 2–3 h, reaction did not proceed as monitored by TLC at room temperature in solvent-free conditions. Subsequently, the mixture was heated to reflux at different temperatures ranging from 60 to 120 °C, with an increment of 10 °C each time. The yield of product **1a** was increased and the reaction was raised from 60 to 90 °C (Table 1, entries 1–4). However, no significant increase in the yield of product **1a** was observed as the reaction temperature was raised from 100 to 120 °C (Table 1, entries 5–7). Therefore, 90 °C was chosen as the reaction temperature for all further reactions.

To evaluate the effect of catalyst concentration, Pechmann condensation of phenol and ethyl acetoacetate in equimolar ratio (1:1) was carried out in presence of different amounts of catalyst (1, 2, 5, 10 mol%) at 90 °C under solvent-free conditions and the isolated yields of the product were shown in Table 2. From this we concluded that 2 mol% of PTA to be optimum amount of the catalyst for this reaction. Use of higher amount of catalysts (5 and 10 mol%) neither improves the yield nor reaction time further.

After optimizing the temperature and amount of catalyst, the reaction is carried out in solvents like toluene, THF, acetonitrile 1,4-dioxane and also without solvent. It is observed that, reaction in solvents takes more time and also

Table 1 Temperature optimization for the synthesis of **1a** under solvent-free condition using PTA as a catalyst

Entry	Temperature (°C)	Time[a] (min)	Yield[b] (%)
1	60	90	82
2	70	75	86
3	80	50	86
4	90	30	95
5	100	30	88
6	110	20	84
7	120	20	84

[a] Reaction time is monitored by TLC at time interval of 10 min

[b] Reaction condition: phenol (1 mmol), ethylacetoacetate (1 mmol) and catalyst (2 mmol%) at different temperature under solvent-free conditions

Table 2 Effect of catalyst concentration for the synthesis of 4-methyl coumarin[a] (**1a**)

Entry	Catalyst concentration (% mmol)	Time (min)	Yield (%)
1	1	60	88
2	2	30	95
3	5	30	92
4	10	30	95

[a] Reaction condition: phenol (1 mmol) and ethylacetoacetate (1 mmol) at 90 °C by varying the amount of catalyst under solvent-free conditions

Table 3 PTA catalyzed one-pot synthesis of 4-methyl coumarin[a] (**1a**) with and without solvent

Entry	Solvent	Catalyst (mmol%)	Time (min)	Yield[b] (%)
1	Toluene	2	120	76
2	THF	2	120	87
3	Dioxane	2	90	69
4	Acetonitirle	2	135	77
5	None	2	45	95

[a] Reaction condition: phenol (1 mmol) and ethylacetoacetate (1 mmol) solvent (5 ml) or no solvent at 90 °C

[b] Isolated yields

Table 4 Synthesis of coumarins using phosphotungstic acid as a catalyst[a]

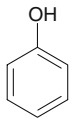
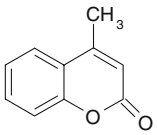
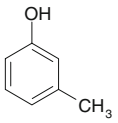
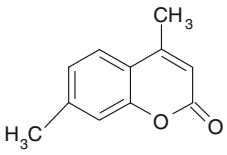
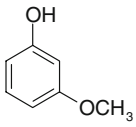
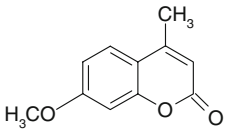
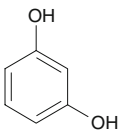
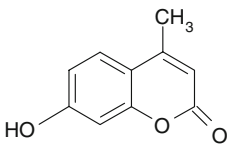
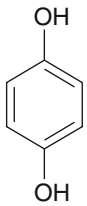
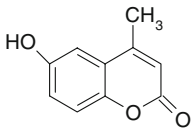
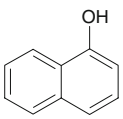
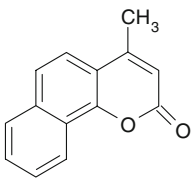
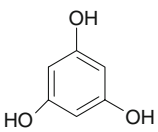
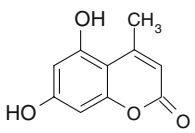
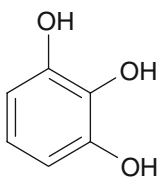
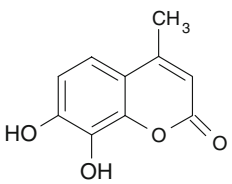
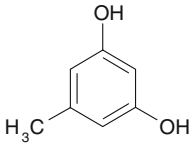
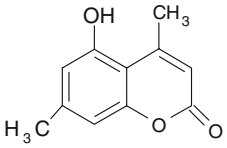
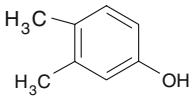
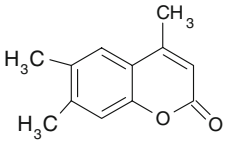
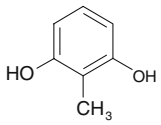
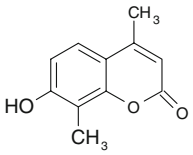
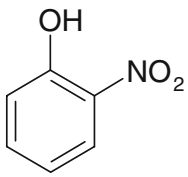
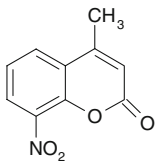
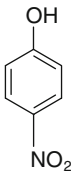
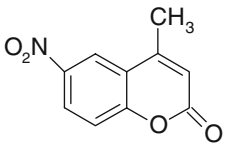
Entry	Phenol	Product[b]	Reaction time (in min)	Yield[d] (%)	Melting point[e] (°C)	
					Found	Literature (Ref)
1a			45	95	84–85	83–84 [35]
1b			30	90	131–132	131–133 [35]
1c			30	94	157–159	156–1,158 [35]
1d			30	94	186–187	185–186 [35]
1e			45	91	164–165	166–167 [36]
1f			90	60	156–158	154–155 [36]
1g			30	88	283–284	284–285 [35]
1h			30	84	243–245	244–245 [36]

Table 4 continued

Entry	Phenol	Product[b]	Reaction time (in min)	Yield[d] (%)	Melting point[e] (°C)	
					Found	Literature (Ref)
1i			30	92	255–256	258–259 [37]
1j			45	85	225–226	227–228 [38]
1k			30	89	217–218	268–269 [37]
1l			45	82	185–186	184–186 [38]
1m			45	85	149–150	150–151 [38]

[a] Reaction condition: phenols (1 mmol) and the β-keto ester(1 mmol) phosphotungstic acid (2 mmol%) at 90 °C under solvent-free conditions

[b] All products were characterized by comparison of their mp, IR, NMR, MS and elemental analysis with those of authentic samples

[c] For each 15 min monitored by TLC

[d] Isolated yields

[e] Melting points are uncorrected

the yield are low compared to the solvent-free condition (Table 3). Considering the importance of green chemistry, the solvent-free reaction conditions are the advantageous aspect of the present method, since it avoids the use of environmental hazardous and toxic solvents. The efficiency of PTA catalyst was demonstrated by synthesizing the range of coumarins using series of monohydric and polyhydric phenols and ethyl acetoacetate (Table 4). The catalyst was found to be equally effective for phenols bearing either electron-donating or electron-withdrawing substituents.

Furthermore, in order to show the excellent catalytic activity of the catalyst, we carried out the synthesis 7-hydroxy-4-methyl coumarin (entry **1d** in Table 4) catalyzed by other several catalyst under the same reaction conditions (Table 5). It shows that the yield of the desired

Table 5 Comparison of catalytic activity of PTA with several catalysts for synthesis of 7-hydroxy-4-methyl coumarin[a] (**1d**)

Entry	Catalysts (2 mol%)	Reaction time (min)	Yield[b] (%)
1	$SnCl_2{\cdot}2H2O$	150	55
2	$KAl(SO_4)_2{\cdot}12H_2O$	120	86
3	p-Toluenesulfonic acid	90	78
4	Stannic(IV) chloride	45	86
5	Iodine	240	75
6	Phosphotungstic acid	30	94
7	Vanadium(III)chloride (VCl_3)	45	90
8	$TiCl_4$	50	90

[a] Reaction condition: phenol (1 mmol), β-keto ester (1 mmol) and catalysts (2% mmol) at 90 °C under solvent-free conditions

[b] Isolated yields

product in the presence of PTA is higher than that in presence of other catalyst. From these results we concluded that, the present method was superior to reported methods regarding yields and reaction time. Also, the work-up of present method was easy and it includes the pouring of reaction mixture on ice-water to precipitate the solid, which could be collected by filtration to give the corresponding coumarin product with better yield. All the synthesized products were characterized by elemental analysis, mp, IR, ^{1}H NMR, ^{13}NMR and MS spectra.

3.1 Regeneration of Catalyst

To examine the reusability, the catalyst recovered by filtration from the reaction mixture phenol and ethylacetoacetate after dilution with ethyl acetate was reused as such for subsequent experiments (up to four cycles) under similar reaction conditions. The observed fact that yields of the product remained comparable in these experiments (Table 6), established the recyclability and reusability of the catalyst without significant loss of activity.

Table 6 Results of recyclabilty of the catalyst

Entry	Catalyst (mmol%)	Reaction time (min)	Yield (%)[a]
1[b]	–	180	–
2	2	45	95[c]
3	Cycle 1	45	95
4	Cycle 2	45	94
5	Cycle 3	45	94

Cycle 1, 2, 3 indicate the reusability of the catalyst regenerated from experiment

[a] Isolated yields

[b] Blank experiment without using catalyst

[c] Reaction conditions as in Table 4

4 Conclusions

In conclusion, we have developed an efficient, facile and environmentally acceptable synthetic methodology for the synthesis of coumarin derivatives using phosphotungstic acid as a catalyst under solvent-free condition. The attractive features of this procedure are the mild reaction conditions, high conversions, ease separation and recyclability of the catalyst, inexpensive and environmentally friendly catalyst, excellent yields, all of which make it a useful and attractive strategy for the preparation of various coumarin derivatives simply by changing different substrates.

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