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$H_3PW_{12}O_{40}$ catalyzed efficient synthesis of 4-substituted coumarins

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Phosphotungstic acid is commercially available and environmentally benign catalyst to promote the Pechmann condensation of various phenols with β-Ketoesters afford 4-substituted coumarins **3a-g** in very good yields. This method is practical and provides several advantages.

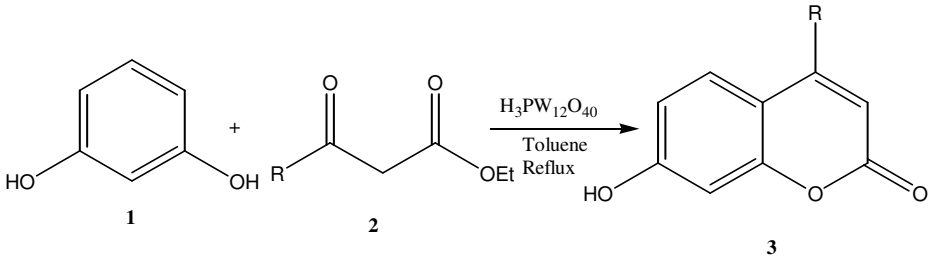
Keywords: Pechmann reaction, 4-substituted coumarins, phenols, β-ketoesters, phosphotungstic acid

Coumarin and its derivatives are biologically active[1] compounds and widely occur in nature. The coumarin heterocyclic ring is a common feature of various bioactive compounds such as calanolides[2], lipid-lowering agents[3]. Recent studies have revealed that coumarin and its derivatives exhibit several other medicinal applications[4] such as anticoagulants, antifungal, insecticidal, anthelminths, hypnotics, phytoalexins, HIV protease inhibitors and AChE inhibitors[5]. Coumarins act as intermediates for the synthesis of various biologically active molecules such as coumarones, chromenes, and fluorocoumarins. Thus the synthesis of coumarins is of continuing interest.

Many synthetic methods for coumarins have been reported including Perkin[6], Knoevenegel[7], Reformetsky[8], Wittig[9] and Pechmann[10]. 4-Methylcoumarins were obtained by Pechmann condensation, which involves condensation of phenol with β-ketoesters using different catalysts such as Ionic liquids[11], $InCl_3$ (Ref.12), $ZrCl_4$ (Ref.13), $BiCl_3$ (Ref.14), $TiCl_4$ (Ref.15), $ZnCl_2$ (Ref.16), ZnI_2 (Ref.17), $Sm(NO_3)_3$ (Ref.18) $Bi(NO_3)_3$ (Ref.19), *p*-TsOH (Ref.20), $KHSO_4$ (Ref.21), NH_2SO_3H (Ref.22), Zeolites (Ref.23), Zr-TMS (Ref.24), sulfated zirconia (Ref.25), alum (Ref. 26), montmorillonite K-10 (Ref.27) and Pd(0) catalyst (Ref.28). Even though a number of modified methods under improved conditions have been reported, many of them suffer from drawbacks such as unsatisfactory yields, longer reaction times and corrosive reagents. Thus, the development of an efficient and versatile method for the synthesis of coumarins is an active ongoing research and there is a scope for further improvement toward milder reaction conditions and yields.

Phosphotungstic acid ($H_3PW_{12}O_{40}$) is a heteropolyacid[29], grayish in colour, non-toxic, commercially available and widely used heterogeneous catalyst. Phosphotungstic acid is the strongest acid[30] of the heteropolyacids; the heteropoly anion ($PW_{12}O_{40}$-3, Keggin unit) represents the structure of HPW, which then forms a bulk structure by coordinating to acidic protons. Keggin[30] types of heteropolyacids have been widely investigated because of their high structural and thermal studies with well defined acidic properties. Tungstophosphoric acid (HPW) has been investigated by Jalil. *et al*[31] using different spectroscopic and chemical techniques such as X-ray diffraction (XRD) and infrared (IR) spectroscopy indicated the acid stability and Izumi *et al*[29] reported HPW molecule is highly stable up to 600°C. Heteropoly acids are stronger than the usual mineral acids[32] such as HCl, H_2SO_4 and HNO_3. Solid heteropoly acids are stronger than conventional solid acids[33] such as SiO_2/Al_2O_3, H_3PO_4/SiO_2 and HY zeolites. $H_3PW_{12}O_{40}$ has been utilized for several organic transformations such as β-acetamido ketones[34], 3,4-dihydropyrimidines[35], pyrazolo pyrimidine[36], reductive amination with $NaBH_4$[37], Michael addition[38] and thioacetalization[39]. Generally the heteropolyacids are reusable catalysts[38], as a continuation of our studies on heteropolyacid[40] and on synthetic methodologies[41]; herein we report an efficient Pechman synthesis of 4-substituted coumarins (**Scheme I**) in very good yields.

Condensation of resorcinol **1a** (1 mole) with ethyl acetoacetate **2** (1 mole) in presence of catalytic amount of phosphotungstic acid (1 mole %) under reflux conditions in toluene (20 min, TLC) resulted in the formation of 7-hydroxy-4-methylcoumarin **3a** in 96% yield. Under similar conditions 4-chloromethyl and 4-phenyl coumarins were prepared in 78-80% yield. Similarly other substituted phenols **1b-g** were also reacted with ethyl acetoacetate to give coumarins **3b-g** in very good yield and the results were summarized in **Table I**. All the reactions were clean,



Scheme I

efficient and the products were obtained within 20-60 mins. All the products were characterized by ^{1}H NMR, IR and mass spectra and known compounds were compared with those reported in the literature. The reaction of 7-hydroxycoumarin and 4-hydroxy coumarin with ethyl acetoacetate under similar conditions were also taken up but the reaction was not preceded, even under high temp. and longer reaction times.

In conclusion, an efficient method is developed for the synthesis of coumarins using $H_3PW_{12}O_{40}$ as an inexpensive, commercially available, easy to handle, environmentally benign and non-corrosive catalyst. The advantages of present protocols are the shorter reaction times, milder reaction conditions, high yields. The present improved modification is convenient and attractive to the existing methods for the synthesis of 4-substituted coumarins.

Experimental Section

Phosphotungstic acid was obtained from S.D. Fine Chemicals Ltd. ^{1}H NMR spectra were recorded on Varian 200 and Gemini 300 MHz instrument in $CDCl_3$, MeOH-d_4 and TMS as the internal standard. The mass spectra were recorded on VG Micro mass 7070 H mass spectrometer. The IR spectra were recorded on Nicolet 740 FT IR spectrometer. Melting points were measured on Buchi-510 apparatus and are uncorrected.

Typical experimental procedure

Resorcinol **1a**, (0.5 g, 4.5 mmole), ethyl acetoacetate **2,** (0.59 g, 4.5 mmole) and phosphotungstic acid (1 mol%) were refluxed in toluene (10 mL) for 20 min. The reaction-mixture was cooled; the solid precipitated was extracted with ethyl acetate and the solvent removed under reduced pressure to give the 7-hydroxy-4-methyl-2*H*-1-benzopyran-2-one **3a** in 96% yield. Similarly other coumarins were also prepared according to this procedure.

Spectral data

7-Hydroxy-4-methyl-2*H*-2-chromenone 3a: Solid, m.p.184-86°C. ^{1}H NMR (300 MHz, $CDCl_3$ + MeOH-d_4): δ 2.32 (s, 3H, CH_3), 5.99 (s, 1H, CH), 6.60 (d, 1H), 6.71 (dd, 1H, *J* = 8.7, 2.4 Hz, aromatic), 7.49 (d, 1H, *J* = 8.7 Hz, aromatic). Mass: (EI-MS): *m/e* 176 M^+.

5,7-dihydroxy-4-methyl-2*H*-2-chromenone 3b: Solid, m.p.281-83°C. ^{1}H NMR (300 MHz, $CDCl_3$ + MeOH-d_4): δ 2.12 (s, 3H, CH_3), 5.70 (s, 1H, CH), 6.17 (d, *J* = 7.0 Hz, 1H), 6.24 (d, 1H, *J* = 7.2 Hz, aromatic), 9.70 (brs, 1H), 9.90 (brs, 1H). Mass: (EI-MS): *m/e* 192 M^+.

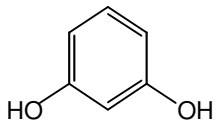
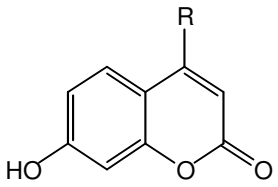
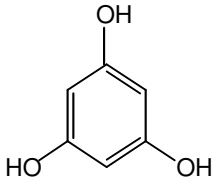
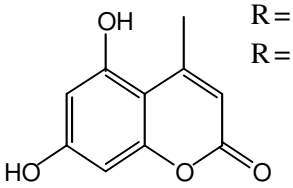
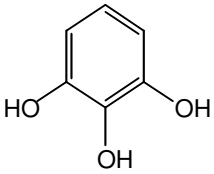
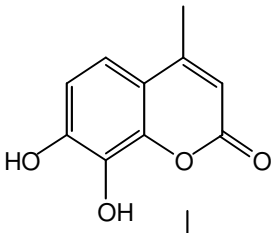
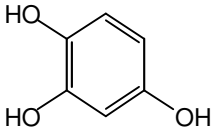
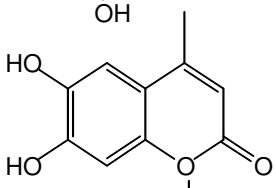
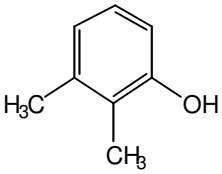
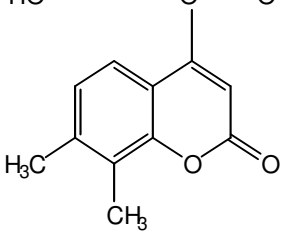
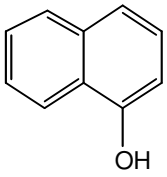
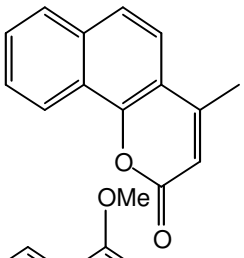
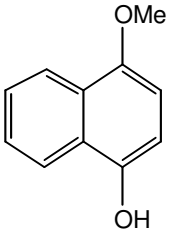
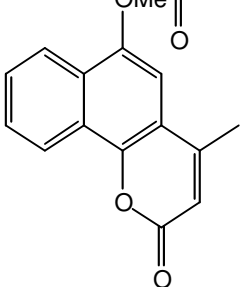
7,8-dihydroxy-4-methyl-2*H*-2-chromenone 3c: Solid, m.p.236-38°C. ^{1}H NMR (300 MHz, $CDCl_3$ + MeOH-d_4): δ 2.38 (s, 3H, CH_3), 5.98 (s, 1H, CH), 6.90 (d, *J* = 7.6 Hz, 1H), 6.99 (d, 1H, *J* = 7.8 Hz, aromatic), 9.12 (brs, 1H), 9.40 (brs, 1H). Mass: (EI-MS): *m/e* 192 M^+.

6,7-dihydroxy-4-methyl-2*H*-2-chromenone 3d: Solid, m.p.272-74°C. ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 2.34 (s, 3H, CH_3), 5.92 (s, 1H, H-3), 6.68 (s, 1H, aromatic), 6.94 (s, 1H, aromatic). Mass: (EI-MS): *m/e* 192 M^+.

4,7,8-Trimethyl-2*H*-2-chromenone 3e: Solid, m.p.138-40°C. ^{1}H NMR (300 MHz, $CDCl_3$ + MeOH-d_4): δ 2.38 (s, 3H, CH_3), 2.42 (s, 6H, $2CH_3$), 6.20 (s, 1H, H-3), 7.04 (d, 1H, *J* = 8.6 Hz, aromatic), 7.30 (d, *J* = 8.7 Hz, 1H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$ + MeOH-d_4): δ 161.41, 153.11, 141.27, 125.47, 124.38, 121.10, 117.49, 113.07, 29.44, 19.91 & 18.26. IR (KBr): 1710, 1600, 1450, 1240 & 1180 cm^{-1}, Mass: (EI-MS): *m/e* 188 M^+.

4-Methyl-2*H*-benzo[*h*]-chromen-2-one 3f: Solid, m.p.153-55°C. ^{1}H NMR (300 MHz, $CDCl_3$ + MeOH-d_4): δ 2.48 (s, 3H, CH_3), 6.46 (s, 1H), 7.66-7.82 (m, 4H, aromatic), 7.95-8.16 (m, 1H, aromatic), 8.32-8.36 (m, 1H, aromatic). IR (KBr): 3024, 1710, 1575, 1238 & 1046 cm^{-1}; Mass: (EI-MS): *m/e* 210 M^+.

Table I — $H_3PW_{12}O_{40}$ catalyzed synthesis of 4-substituted coumarins

S. No.	Substrate **1**	Time (min) **2**	Product **3**	Yield (%)[a]
a		20		96
			$R = CH_3$,	
			$R = CH_2Cl$,	80
			$R = Ph$	78
b		25		94
c		30		94
d		40		88
e		40		88
f		60		82
g		60		80

a) All the products were characterized by ^1H NMR, IR & MS and compared with authentic compounds

6-Methoxy-4-methyl-2*H*-benzo[*h*[chromen-2-one 3g: Brown solid, m.p.: 135-38°C; IR (KBr): 1724 (C = O), 1595, 1453, 1242, 1109 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.48 (s, 3H, CH_3), 4.06 (s, 3H, OMe), 6.40 (s, 1H, H-3), 6.78 (s, 1H, Ar), 7.60-7.70 (m, 2H), 8.36 (d, 1H, *J* = 4 Hz, Ar), 8.60 (d, 1H, *J* = 4 Hz, Ar), ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.20, 158.62, 145.24, 146.10, 131.22, 126.46, 128.20, 124.82, 122.64, 123.22, 115.00, 115.02, 56.42, and 20.24. EI-MS: *m/z* 240 [M^+]. Anal.Calcd..For $C_{15}H_{12}O_3$: C, 75.00; H, 5.00. Found: C, 75.03; H, 4.97%.

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