

Ammonium Metavanadate: A Mild and Efficient Catalyst for the Synthesis of Coumarins

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A mild and efficient method has been developed for condensation of substituted phenol with β -ketoester in the presence of catalytic amount of ammonium metavanadate (10 mol%) at ambient temperature to afford the corresponding substituted 4-methyl-2*H*-chromen-2-one in high yields under mild conditions. Utilization of commercially available inexpensive catalyst makes this manipulation very interesting from an economic perspective.

Key Words: Ammonium metavanadate, 4-Methyl-2*H*-chromen-2-one, β -Ketoester Pechmann condensation

Introduction

Coumarin and its derivatives have been proved as useful precursors for the synthesis of variety of medicinal agents. The heterocycles derived from these intermediates have also been tested for their potential as anti-HIV,¹ anti-inflammatory,² anti-convulsant,³ anti-viral,⁴ anti-coagulant,⁵ antioxidant,⁶ antibacterial,⁷ antifungal,⁸ anti-carcinogenic material⁹ and antihistamine.¹⁰ Apart from this, it is attracting considerable attention of chemists as it is widely used in fragrances, pharmaceuticals,¹¹ optical brighteners¹² and molecular photonic devices.¹³ despite the importance of these intermediates, the methodologies available for the synthesis were generally target specific and restrictive in their scope. Several routes are used for the synthesis of Coumarins including Pechmann,¹⁴ Perkin,¹⁵ Knoevenagel,¹⁶ Reformatsky¹⁷ and Wittig reaction.¹⁸

However, it is noticed that all these methods involve various disadvantages such as low yields, prolonged reaction times and the use of toxic organic reagents such as conc. H₂SO₄,¹⁹ PPA,²⁰ TFA,²¹ In addition to this, harsh catalyst are used such as InCl₃,²² ZrCl₄,²³ Yb(OTf)₃,²⁴ *p*-TsOH,²⁵ sulfated Zirconia,²⁶ and cellulose sulphuric acid.²⁷ Hence, it is imperative to develop a convenient, efficient and user friendly method for the synthesis of substituted 4-methyl-2*H*-chromen-2-one.

Experimental

Melting point was recorded in open capillary in liquid paraffin bath. IR spectra were recorded on a Perkin-Elmer FTIR using KBr discs. ¹H NMR spectra were recorded on Mercury Plus Varian in CDCl₃ at 400 MHz using TMS as an internal standard. Mass spectra were recorded on Micro mass Quattro II using Electrospray Ionization technique, showing (m + 1) peak as a base peak.

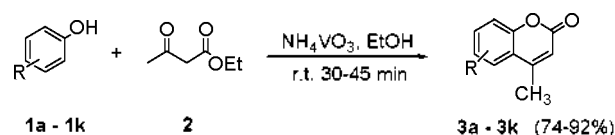
General Procedure. A mixture of substituted phenol (1.0 eq.) and ethyl acetoacetate (1.0 eq.) in ethanol (10 mL), ammonium metavanadate (10 mol%) was added. The mixture was stirred at room temperature for 30 - 45 min. The progress of reaction was monitored on TLC. After completion, the reaction mixture was filtered and the filtrate was concentrated under

vacuum, water was added to the residue and extracted with ethyl acetate (25 × 2 mL), which was then dried and concentrated. The residue was subjected to column chromatography (60-120 mesh size silica gel, eluted with hexane-acetone) to obtain the pure product of coumarin.

Result and Discussion

As a contribution of our research work devoted to the development of useful synthetic methodologies,²⁸⁻³⁰ we herein report an eco-friendly, facile and efficient methodology for the synthesis of 4-methyl-2*H*-chromen-2-ones. This method involves the efficient synthesis of substituted Coumarins by treatment of ethyl acetoacetate and substituted phenol using catalyst ammonium metavanadate in ethanol at room temperature for 30 - 45 min (Scheme 1). Consequently several aromatic phenols with different substituents on the aromatic ring were subjected to the cyclo condensation reaction. The reaction conditions are mild and workup procedure is simple. The physical characteristic of ammonium metavanadate is slightly acidic to neutral. We have used ammonium metavanadate for the synthesis of 4-methyl-2*H*-chromen-2-one. The products were isolated in high yields (74 - 92%). Some of the compounds were purified by recrystallization techniques in acetone: hexane. In some cases by using 60 - 120 mesh size silica gel for column chromatography with acetone in hexane. The structures of the products were determined from their spectral (¹H NMR, IR and MS) data.

In the present study, the commercially available catalyst ammonium metavanadate is used as a catalyst but its scope has not been fully explored. Ammonium metavanadate was used as cyclo condensing agent and water is removed azeotropically. Along with this, by the proposed mechanism we reco-



Scheme 1


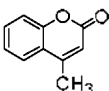

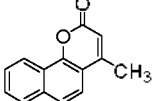
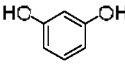
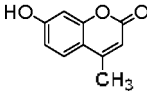
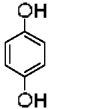
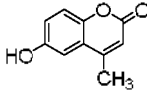
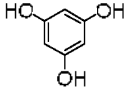
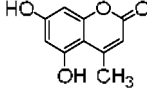
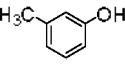
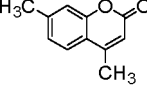

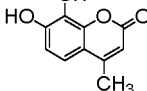
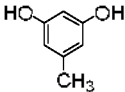
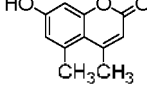
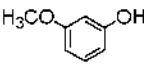
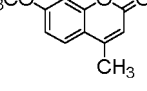
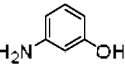
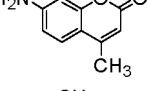
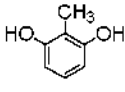
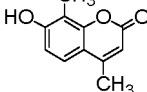
Table 1. Ratio of ammonium metavanadate for the synthesis of 4-methyl-2H-chromen-2-ones

Entry	Ammonium Metavanadate (mol%)	Time (min)	Yield ^a
1	0	45	trace
2	5	45	69
3	10	45	81
4	15	45	79
5	20	45	79

^aIsolated yield.**Table 2.** Effect of solvent in condensation of ethyl acetoacetate with phenol

Entry	Solvent	Condition		Yield ^a
		Temp. (°C)	Time (min)	
1	Methanol ^b	25 - 30	40 min	< 50
2	Ethanol	25 - 30	40 min	82
3	Aq. ethanol ^b	25 - 30	40 min	45
4	Water ^b	25 - 30	40 min	-
5	Toluene ^c	25 - 30	40 min	-
6	Acetonitrile ^c	25 - 30	40 min	-

^aIsolated yield; ^bReaction incomplete, unreacted ethyl acetoacetate; ^cReaction did not proceed at all.**Table 3.** Characterization data of compounds (3a-3k) from the reaction of substitute phenol and ethyl acetoacetate

Entry	Reactant	Product	Time (min)	Isolated yield ^a	mp (°C) found	Lit. ^b (reported)
3a			32	81	77 - 79	79 - 81 ³⁶
3b			40	87	152 - 154	153 - 155 ²³
3c			30	92	185 - 186	182 - 184 ³⁴
3d			44	79	242 - 244	241 - 242 ³⁶
3e			36	74	282 - 284	280 - 281 ²³
3f			35	78	130 - 131	130 - 131 ³⁵
3g			33	89	234 - 237	234 - 235 ³⁴
3h			37	76	260 - 262	250 - 252 ³⁴
3i			31	91	160 - 161	158 - 160 ³⁴
3j			48	80	221 - 223	220 - 224 ³⁷
3k			43	77	265 - 267	264 - 266 ³⁴

^aAll the products were characterized by ¹H NMR and MS spectral data and were compared with the reference compounds.²⁰⁻²² ^bThe products were characterized by comparison of their spectroscopic and physical data with reference samples synthesized by reported procedure.

vered the catalyst and reused for further reactions. The catalyst was recovered by filtration and washed with diethyl ether and dried at 60 - 70 °C.

In order to establish the optimum condition on this reaction, various ratios of ammonium metavanadate were examined using ethyl acetoacetate and phenol as a model reaction. ammonium metavanadate was added in various ratio in ethanol at room temperature. As shown in (Table 1), very little of the desired products was obtained in the absence of ammonium metavanadate and the excellent yields were obtained with 10 mol% ammonium metavanadate. Next we tested the reaction of ethyl acetoacetate and phenol as a simple model reaction in different solvents, namely methanol, ethanol, aq. ethanol, water, toluene and acetonitrile. The results are shown in (Table 2). It was found that ethanol stands out as the solvent of choice, with its fast conversion, high yield and low toxicity. Using optimized reaction parameters, a number of 4-methyl-2H-chromen-2-ones, (**3a-3k**). (Scheme 1) were synthesized. To the best of our knowledge, there are no earlier reports on the preparation of 4-methyl-2H-chromen-2-ones using ammonium metavanadate as a catalyst.

The reaction of aminophenol with ethyl acetoacetate can lead to the formation of mixtures of coumarins and quinolines in contrast to von Pechmann's procedure which provides primarily coumarins. While the reaction is regioselective in that ring formation is ortho to the reacting functional group and para to the second giving 7-substituted products and not the 5-substituted products, it is nonselective with respect to the functional groups. But when the same reaction is carried out in the presence of (10% mol) ammonium metavanadate and ethanol as solvent the major product formed is 7-amino-4-methyl-2H-chromen-2-one and a trace amount of the isomeric 7-hydroxy-4-methylquinolin-2(1H)-one was formed, which was separated by column chromatography (60 - 120 mesh size silica gel, eluted with hexane-acetone) to obtain the pure 7-amino-4-methyl-2H-chromen-2-one formed.

In summary, novel approaches for the synthesis of 4-methyl-2H-chromen-2-ones (Table 3) have been explored by using ammonium metavanadate as an acid catalyst in ethanol, which showed several advantages: mild reaction conditions (at ambient temperature), shorter span, operational and experimental simplicity, leading to a useful and attractive process for the preparation of coumarins.

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- Compound **3a**: 4-Methyl-2H-chromen-2-one: ¹H NMR (400MHz, CDCl₃) δ 2.42 (s, 3H), 6.32 (s, 1H), 7.15-7.42 (m, 3H), 7.48 (d, J = 6.0 Hz, 1H); IR (KBr) 1064, 1238, 1543, 1705, 3020 cm⁻¹. MS: m/z 160.9 (M+1). Compound **3b**: 4-Methyl-2H-benzo[h]chromen-2-one: ¹H NMR (400MHz, CDCl₃) δ 2.45 (s, 3H), 6.32 (s, 1H), 7.32-7.60 (m, 4H), 7.9 (d, J = 9.0 Hz, 1H), 8.54 (d, J = 9.0

Hz, 1H), IR (KBr) 1044, 1235, 1572, 1710, 3012 cm^{-1} . MS: *m/z* 211.1 (M+1) Compound **3c**: 7-Hydroxy-4-methyl-2H-chromen-2-one: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 2.48 (s, 3H), 6.52 (s, 1H), 7.45-7.68 (m, 4H), 7.79 (d, $J = 9.0$ Hz, 1H), 8.57 (d, $J = 9.0$ Hz, 1H); IR (KBr) 1048, 1225, 1570, 1701, 3016 cm^{-1} . MS: *m/z* 177.1 (M+1). Compound **3d**: 6-Hydroxy-4-methyl-2H-chromen-2-one: $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ 2.42 (s, 3H), 6.33 (s, 1H), 6.72 (d, $J = 8.4$ Hz, 1H), 6.74 (d, $J = 8.4$ Hz, 1H), 7.05 (s, 1H); IR (KBr) 1055, 1225, 1565, 1693, 3010, 3412 cm^{-1} . MS: *m/z* 177.1 (M+1). Compound **3e**: 5,7-Dihydroxy-4-methyl-2H-chromen-2-one: $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ 2.44 (s, 3H), 3.90-4.30 (s, 2H), 5.90 (s, 1H), 6.25 (d, $J = 1.8$ Hz, 1H), 6.35 (d, $J = 1.8$ Hz, 1H); IR (KBr) 1064, 1232, 1587, 1703, 3024, 3385 cm^{-1} . MS: *m/z* 193.1 (M+1). Compound **3f**: 4,7-Dimethyl-2H-chromen-2-one: $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ 2.31 (s, 3H), 2.10 (s, 3H), 4.17 (s, 1H), 6.71-7.29 (m, 3H); IR (KBr) 1070, 1146, 1212, 1248, 1378, 1579, 1636, 1704, 2920, 2970 cm^{-1} . MS: *m/z* 175.1 (M+1). Compound **3g**: 7,8-Dihydroxy-4-methyl-2H-chromen-2-one: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 2.37 (s, 3H), 6.10 (s, 1H), 6.80 (d, $J = 8.8$ Hz, 1H), 7.10

(d, $J = 8.0$ Hz, 1H), 9.30 (s, 1H), 10.04 (s, 1H); IR (KBr): 468, 629, 722, 1006, 1062, 1186, 1388, 1440, 1512, 1596, 1652, 2925, 3240, 3419 cm^{-1} . MS: *m/z* 193.2 (M+1). Compound **3h**: 7-Hydroxy-4,5-dimethyl-2H-chromen-2-one: $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ 2.27 (s, 3H), 2.54 (d, $J = 1.2$ Hz, 3H), 6.05 (d, $J = 1.2$ Hz, 1H), 6.57 (d, $J = 1.2$, 1H), 6.62 (d, $J = 1.2$, 1H), 10.52 (s, 1H); IR (KBr) 724, 1025, 1685, 1709, 3106 cm^{-1} . MS: *m/z* 191.1 (M+1). Compound **3i**: 7-Methoxy-4-methyl-2H-chromen-2-one: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 2.32 (s, 3H), 3.75 (s, 3H), 6.15 (s, 1H), 6.74 (s, 2H), 7.62 (d, $J = 8.7$ Hz, 1H); IR (KBr) 1078, 1216, 1552, 1700, 3054 cm^{-1} . MS: *m/z* 191.1 (M+1). Compound **3j**: 7-Amino-4-methyl-2H-chromen-2-one: $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ 2.30 (s, 3H), 5.90 (s, 1H), 6.40 (s, 1H), 6.55 (d, $J = 8.7$ Hz, 1H), 7.40 (d, $J = 8.7$ Hz, 1H); IR (KBr) 1052, 1238, 1570, 1688, 3012, 3312, 3468 cm^{-1} . MS: *m/z* 176.1 (M+1). Compound **3k**: 7-Hydroxy-4,8-dimethyl-2H-chromen-2-one: $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ 2.15 (s, 3H), 2.36 (d, $J = 1.2$ Hz, 3H), 6.12 (d, $J = 1.2$ Hz, 1H), 6.86 (d, $J = 8.8$ Hz, 1H), 7.45 (d, $J = 8.8$ Hz, 1H), 10.40 (s, 1H); IR (KBr) 1460, 1607, 1685, 3148, 3460 cm^{-1} . MS: *m/z* 191.0 (M+1).