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

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A mild and efficient method has been developed for condensation of substituted phenol with \( \beta \)-ketoester in the presence of catalytic amount of ammonium metavanadate (10 mol%) at ambient temperature to afford the corresponding substituted 4-methyl-2/3-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-2/3-chromen-2-one, \( \beta \)-Ketoester Pechmann condensation

Introduction

Coumarins 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, anti-inflammatory, anti-convulsant, anti-viral, anti-coagulant, antioxidant, antibacterial, anti-hypertensive material and antihistamine. Apart from this, it is attracting considerable attention of chemists as it is widely used in fragrances, pharmaceuticals, optical brighteners and molecular photonic devices. 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, Perkin, knevenagel, Reformatsky and Wittig reaction.

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. H\( \cdot \)SO\(_4\), PPA, Varian and Conc. TFA. In addition to this, harsh catalyst are used such as InCl\(_3\), ZrCl\(_4\), Yb(OTf)\(_3\), p-TsOH, sulfated Zirconia and cellulose sulphuric acid. Hence, it is imperative to develop a convenient and user friendly method for the synthesis of substituted 4-methyl-2/3-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. \(^1\)H NMR spectra were recorded on Mercury Plus Varian in CDCl\(_3\) at 400 MHz using TMS as an internal standard. Mass spectra were recorded on Micro mass Quatttr 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 x 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, here we herein report an eco-friendly, facile and efficient methodology for the synthesis of 4-methyl-2/3-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 cyclocondensation 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-2/3-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 (\(^1\)H 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 aceto- tropically. Along with this, by the proposed mechanism we reco...
Table 1. Ratio of ammonium metavanadate for the synthesis of 4-methyl-2H-chromen-2-ones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ammonium Metavanadate (mol%)</th>
<th>Time (min)</th>
<th>Yield</th>
<th>Isolated yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>45</td>
<td>trace</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>45</td>
<td>69</td>
<td>69</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>45</td>
<td>81</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>45</td>
<td>79</td>
<td>79</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>45</td>
<td>79</td>
<td>79</td>
</tr>
</tbody>
</table>

Isolated yield.

Table 2. Effect of solvent in condensation of ethyl acetoacetate with phenol

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Condition</th>
<th>Yield</th>
<th>Isolated yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Methanol</td>
<td>25 - 30</td>
<td>40 min</td>
<td>&lt; 50</td>
</tr>
<tr>
<td>2</td>
<td>Ethanol</td>
<td>25 - 30</td>
<td>40 min</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>Aq. ethanol</td>
<td>25 - 30</td>
<td>40 min</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>Water</td>
<td>25 - 30</td>
<td>40 min</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Toluene</td>
<td>25 - 30</td>
<td>40 min</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Acetonitrile</td>
<td>25 - 30</td>
<td>40 min</td>
<td>-</td>
</tr>
</tbody>
</table>

Isolated yield. Reaction incomplete, unreacted ethyl acetoacetate. Reaction did not proceed at all.

Table 3. Characterization data of compounds (3a-3k) from the reaction of substitute phenol and ethyl acetoacetate

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reactant</th>
<th>Product</th>
<th>Time (min)</th>
<th>Isolated yield</th>
<th>mp (°C) found</th>
<th>Lit (reported)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>OH</td>
<td><img src="image" alt="3a" /></td>
<td>32</td>
<td>81</td>
<td>77 - 79</td>
<td>79 - 8119</td>
</tr>
<tr>
<td>3b</td>
<td>OH</td>
<td><img src="image" alt="3b" /></td>
<td>40</td>
<td>87</td>
<td>152 - 154</td>
<td>153 - 15520</td>
</tr>
<tr>
<td>3c</td>
<td>HO</td>
<td><img src="image" alt="3c" /></td>
<td>30</td>
<td>92</td>
<td>185 - 186</td>
<td>182 - 18421</td>
</tr>
<tr>
<td>3d</td>
<td>HO</td>
<td><img src="image" alt="3d" /></td>
<td>44</td>
<td>79</td>
<td>242 - 244</td>
<td>241 - 24222</td>
</tr>
<tr>
<td>3e</td>
<td>Ho</td>
<td><img src="image" alt="3e" /></td>
<td>36</td>
<td>74</td>
<td>282 - 284</td>
<td>280 - 28123</td>
</tr>
<tr>
<td>3f</td>
<td>OH</td>
<td><img src="image" alt="3f" /></td>
<td>35</td>
<td>78</td>
<td>130 - 131</td>
<td>130 - 13124</td>
</tr>
<tr>
<td>3g</td>
<td>OH</td>
<td><img src="image" alt="3g" /></td>
<td>33</td>
<td>89</td>
<td>234 - 237</td>
<td>234 - 23525</td>
</tr>
<tr>
<td>3h</td>
<td>OH</td>
<td><img src="image" alt="3h" /></td>
<td>37</td>
<td>76</td>
<td>260 - 262</td>
<td>250 - 25226</td>
</tr>
<tr>
<td>3i</td>
<td>H2CO</td>
<td><img src="image" alt="3i" /></td>
<td>31</td>
<td>91</td>
<td>160 - 161</td>
<td>158 - 16027</td>
</tr>
<tr>
<td>3j</td>
<td>H2N</td>
<td><img src="image" alt="3j" /></td>
<td>48</td>
<td>80</td>
<td>221 - 223</td>
<td>220 - 22428</td>
</tr>
<tr>
<td>3k</td>
<td>OH</td>
<td><img src="image" alt="3k" /></td>
<td>43</td>
<td>77</td>
<td>265 - 267</td>
<td>264 - 26629</td>
</tr>
</tbody>
</table>

All the products were characterized by 1H NMR and MS spectral data and were compared with the reference compounds. The products were characterized by comparison of their spectroscopic and physical data with reference samples synthesized by reported procedure.
verified 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 acetate and ethanol as a model reaction. Ammonium metavanadate was added in various ratios in ethanol at room temperature. As shown in (Table 1), very little of the desired product 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 acetate and ethanol as a simple model reaction in different solvents, namely methanol, ethanol, acetaldehyde, water, toluene and acetone. 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 3-amino phenol with ethyl acetate 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 (ambient temperature), shorter span, operational and experimental simplicity, leading to a useful and attractive process for the preparation of coumarins.

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References

18. (a) Pechmann, V. H.; Duisberg, C. Chem Ber. 1883, 16, 2119.
(b) Pechmann, V. H.; Duisberg, C. Chem Ber. 1884, 17, 7929.
37. Compound 3a: 4-Methyl-2H-chromene-2-one: HNMR (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), 1H (KBr) 1064, 1238, 1543, 1765, 3202 cm⁻¹.
38. Compound 3b: 4-Methyl-2H-benzof[b] chromene-2-one: HNMR (400MHz, CDCl3) δ 2.45 (s, 3H), 6.32 (s, 1H), 7.2-7.60 (m, 4H), 7.5 (d, J = 9.0 Hz, 1H), 8.54 (d, J = 9.0 Hz, 1H).
Hz, 1H), IR (KBr) 1044, 1235, 1572, 1710, 3012 cm⁻¹. MS: m/z 211.1 (M+1). Compound 3e: 7-Hydroxy-4-methyl-2H-chromen-2-one. 1H NMR (400 MHz, CDCl₃) δ 8.24 (s, 1H), 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 3f: 6-Hydroxy-4-methyl-2H-chromen-2-one. 1H NMR (400 MHz, DMSO-d₆) δ 5.24 (s, 3H), 1.63 (d, J = 3.7 Hz, 3H), 7.05 (d, J = 8.4 Hz, 1H), IR (KBr) 1055, 1225, 1565, 1693, 3010, 3412 cm⁻¹. MS: m/z 177.1 (M+1). Compound 3g: 5,7-Dihydroxy-4-methyl-2H-chromen-2-one. 1H NMR (400 MHz, DMSO-d₆) δ 8.24 (s, 1H), 3.90-4.30 (m, 4H), 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 3h: 4,7-Dimethoxy-2H-chromen-2-one. 1H NMR (400 MHz, DMSO-d₆) δ 8.24 (s, 1H), 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 3i: 7,8-Dihydroxy-4-methyl-2H-chromen-2-one. 1H NMR (400 MHz, CDCl₃) δ 8.23 (s, 1H), 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, 1052, 1186, 1388, 1440, 1512, 1596, 1652, 2925, 3240, 3419 cm⁻¹. MS: m/z 193.2 (M+1). Compound 3j: 7-Hydroxy-4,5-dimethyl-2H-chromen-2-one. 1H NMR (400 MHz, DMSO-d₆) 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 Hz, 1H), 6.62 (d, J = 1.2, 1H), 10.52 (s, 1H), IR (KBr) 724, 1025, 1685, 1700, 3120 cm⁻¹. MS: m/z 191.1 (M+1). Compound 3k: 7-Methoxy-4-methyl-2H-chromen-2-one. 1H NMR (400 MHz, DMSO-d₆) 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, 3034 cm⁻¹. MS: m/z 191.1 (M+1). Compound 3l: 7-Amino-4-methyl-2H-chromen-2-one. 1H NMR (400 MHz, DMSO-d₆) 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, 1226, 1370, 1689, 3012, 3312, 3568 cm⁻¹. MS: m/z 197.1 (M+1). Compound 3m: 7-Hydroxy-4,8-dimethyl-2H-chromen-2-one. 1H NMR (400 MHz, DMSO-d₆) δ 2.15 (s, 3H), 2.30 (d, J = 1.2 Hz, 3H), 6.12 (d, J = 1.2 Hz, 1H), 6.80 (d, J = 8.8 Hz, 1H), 7.45 (d, J = 8.8 Hz, 1H), 10.40 (s, 1H), IR (KBr) 1460, 1607, 1688, 3148, 3460 cm⁻¹. MS: m/z 191.0 (M+1).