Zirconyl Chloride: A Useful Catalyst in the Pechmann Coumarin Synthesis

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Abstract: Coumarin derivatives were prepared using zirconyl chloride octahydrate (1%) as a Pechmann catalyst, either neat or in some cases employing small volumes of ethanol as solvent. As result of this work, coumarins were obtained in moderate to good yields.

Key words: coumarins, zirconyl chloride, Pechmann reaction

For a number of years, coumarins have received attention from researchers due to their biological activity. The classical Pechmann synthesis of such compounds involves the reaction of phenols with β-ketoesters, and requires significant quantities of sulfuric acid as both catalyst and solvent. Since this procedure inherently leads to large quantities of acidic waste, alternative, environmentally friendly reagents and catalysts have been sought in order to reduce the amount of acidic effluent that has to be treated, thus diminishing the total cost of the process.2

We wish to report that catalytic amounts (1%) of zirconyl chloride octahydrate in either neat reagent or in concentrated alcoholic solution enables coumarins to be prepared in good yields without the need for acidic solvent (Scheme 1).

Scheme 1 Where X and Y are either H or Cl. a) Ethyl acetoacetate; b) Ethyl 2-chloroacetoacetate; c) Ethyl 4-chloroacetoacetate.

The reagents were purchased from Acros Organics. Thin-layer chromatography (TLC) was carried out using silica gel plates Alugram Sil G/UV 254 (CHCl3–EtOAc–AcOH, 8:6:1). The 1H and 13C NMR spectra were recorded on an AC Bruker 250 MHz spectrometer using DMSO-d6 as both solvent and internal standard. The chemical shifts are reported in ppm and coupling constants (J) in Hz. Melting points were determined on a Stuart Scientific SMP 3 capillary melting point apparatus and are uncorrected. Mass spectra were recorded on a HRMS Micromass Autospec 3F.

Coumarin Synthesis; General Procedure

With unhalogenated acetoacetyl ester: Zirconyl chloride (1 mol%) was added to an equimolar mixture of phenol and acetoacetyl ester and stirred at 80 °C for 24 h. When all the starting material was consumed (TLC), and while still hot, the mixture was poured into vigorously stirred cold water (20 mL/g of starting phenol). The precipitate was filtered, washed with cold water and dried at 50 °C overnight, yielding the coumarin. All reactions were performed on a 5-g scale with respect to starting phenol.

With halogenated acetoacetyl ester: Zirconyl chloride (1 mol%) was added to an equimolar mixture of phenol and acetoacetyl ester and stirred at 60–65 °C for 2 h before EtOH (1 mL/g of phenol) was added.
added. The reaction was stirred for an additional 22 h. When all the starting material was consumed (TLC), the reaction was diluted with EtOH (1 mL/g of phenol) and poured into vigorously stirred cold water (20 mL/g of starting phenol). The precipitate was filtered, washed with cold water and dried at 50 °C overnight, yielding the coumarin. All reactions were performed on a 5-g scale with respect to starting phenol.

### 7-Hydroxy-4-methylcoumarin (4-Methylumbelliferone) (1)

Yield: 7.25 g.

**Mp** 186–189 °C (Lit.3 185 °C).

**1H NMR:**
\[ \delta = 10.53 \text{ (s, 1 H, OH), 7.59 (d, } J_{8-6} = 8.73 \text{ Hz, 1 H, H-8), 6.81 (dd, } J_{6-5} = 2.03 \text{ Hz, } J_{6-6} = 2.3 \text{ Hz, 1 H, H-6), 6.71 (d, } J_{6-6} = 2.22 \text{ Hz, 1 H, H-5), 6.13 (s, 1 H, H-3), 2.37 \text{ (s, 3 H, CH}_3) . \]

**13C NMR:**
\[ \delta = 161.33, 160.47, 155.01, 153.72, 126.8, 113.03, 112.20, 110.43, 102.37, 18.3. \]

### 3-Chloro-7-hydroxy-4-methylcoumarin (3-Chloro-4-methylumbelliferone) (2)

Yield: 9.4 g.

**Mp** 236–240 °C (Lit.4 242–243 °C).

**1H NMR:**
\[ \delta = 7.65 \text{ (d, } J_{6-6} = 9.15 \text{ Hz, 1 H, H-5), 6.84 (dd, } J_{6-6} = 2.45 \text{ Hz, } J_{6-6} = 2.43 \text{ Hz, 1 H, H-6), 6.72 (d, } J_{6-6} = 1.83 \text{ Hz, 1 H, H-8), 2.51 (s, 3 H, CH}_3) . \]

### 7,8-Dihydroxy-4-methylcoumarin (4-Methyldaphnetin) (3)

Yield: 4.87 g.

**Mp** 242–244 °C (Lit.2a 241–243 °C, Lit.5 234–235 °C).

**1H NMR:**
\[ \delta = 7.09 \text{ (d, } J_{6-6} = 8.6 \text{ Hz, 1 H, H-6), 6.82 (d, } J_{6-6} = 2.3 \text{ Hz, 1 H, H-5), 6.13 (s, 1 H, H-3), 2.37 \text{ (s, 3 H, CH}_3) . \]

### 3-Chloro-7,8-dihydroxy-4-methylcoumarin (3-Chloro-4-methyldaphnetin) (4)

Yield: 7.70 g.

**Mp** 267–268 °C (dec.) (Lit.6 265 °C).

**1H NMR:**
\[ \delta = 7.17 \text{ (d, } J_{6-6} = 8.75 \text{ Hz, 1 H, H-6), 6.86 (d, } J_{6-6} = 8.63 \text{ Hz, 1 H, H-5), 6.13 (s, 1 H, H-3), 2.49 (s, 3 H, CH}_3) . \]

### 4-Chloromethyl-7,8-dihydroxycoumarin (4-Chloromethyl-daphnetin) (5)

Yield: 8.23 g.

**Mp** 200–301 °C (Lit.7 198–199 °C).

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**Table 1** Synthesis of Coumarins Catalyzed by ZrOCl₂·8H₂O (1%)

<table>
<thead>
<tr>
<th>Phenol (β-ketoester) a</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Phenol (β-ketoester) a</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>1</td>
<td>91</td>
<td>a</td>
<td>3</td>
<td>86</td>
</tr>
<tr>
<td>b</td>
<td>2</td>
<td>98</td>
<td>b</td>
<td>4</td>
<td>48</td>
</tr>
<tr>
<td>c</td>
<td>5</td>
<td>92</td>
<td>c</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>a</td>
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<td>58</td>
<td>b</td>
<td>8</td>
<td>77</td>
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<td>a</td>
<td>9</td>
<td>64</td>
<td>c</td>
<td>10</td>
<td>48</td>
</tr>
</tbody>
</table>

a The applied acetoacetate is indicated by a, b, or c (see also Scheme 1).

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**Scheme 1**

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PRACTICAL SYNTHETIC PROCEDURES

Zirconyl Chloride Catalysed Coumarin Synthesis

1H NMR: δ = 7.18 (d, J6–5 = 8.65 Hz, 1 H, H-6); 6.86 (d, J5–6 = 8.78 Hz, 1 H, H-5); 6.42 (s, 1 H, H-3). 4.94 (s, 2 H, CH2Cl).

13C NMR: δ = 160.37, 151.64, 150.02, 143.93, 132.73, 115.72, 112.59, 110.38, 41.75.

6-Methoxy-4-methylcoumarin (6)
Yield: 1.00 g.
Mp 163–165 °C (Lit. 8 169 °C).
1H NMR: δ = 7.31 (d, J8–7 = 12.8 Hz, 1 H, H-8), 7.23 (d, J5–7 = 3.05 Hz, 1 H, H-5), 7.17 (d, J7–6 = 2.43 Hz, 1 H, H-7), 6.4 (s, 1 H, H-3), 3.84 (s, 3 H, CH3O), 2.44 (s, 3 H, CH3).

8-Carboxy-7-hydroxy-4-methylcoumarin (8-Carboxy-4-methylumbelliferone) (7)
Yield: 4.16 g.
Mp 266–268 °C.
1H NMR: δ = 7.67 (d, J5–6 = 8.77 Hz, 1 H, H-5), 6.92 (d, J6–5 = 8.84 Hz, 1 H, H-6), 6.24 (s, 1 H, H-3), 2.38 (s, 3 H, CH3).
13C NMR: δ = 169.3, 166.7, 159.97, 159.31, 127.8, 113.15, 112.2, 110.9, 110.6, 18.5.


5,7-Dihydroxy-4-methylcoumarin (5-Hydroxy-4-methylumbelliferone) (8)
Yield: 2.82 g.
Mp 289–290 °C (dec.) (Lit. 9 292–293 °C).
1H NMR: δ = 10.53 (s, 1 H, OH), 10.31 (s, 1 H, OH), 6.26 (d, J8–6 = 1.82 Hz, 1 H, H-8), 6.16 (d, J6–8 = 2.45 Hz, 1 H, H-6), 5.85 (s, 1 H, H-3), 2.48 (s, 3 H, CH3).
13C NMR: δ = 161.33, 160.38, 158.20, 156.76, 155.24, 109.08, 102.35, 99.34, 94.77, 23.70.

3-Chloro-5,7-dihydroxy-4-methylcoumarin (3-Chloro-5-hydroxy-4-methylumbelliferone) (9)
Yield: 5.38 g.
Mp 317–319 °C (Lit. 10 206–308 °C).
1H NMR: δ = 10.79 (s, 1 H, OH), 10.46 (s, 1 H, OH), 6.32 (d, J8–6 = 2.42 Hz, 1 H, H-8), 6.21 (d, J6–8 = 1.82 Hz, 1 H, H-6), 2.70 (s, 3 H, CH3).

4-Chloromethyl-5,7-dihydroxycoumarin (4-Chloromethyl-5-hydroxyumbelliferone) (10)
Yield: 6.56 g.
1H NMR: δ = 10.94 (s, 1 H, OH), 10.42 (s, 1 H, OH), 6.28 (d, J8–6 = 2.42 Hz, 1 H, H-6), 6.22–6.21 (m, 2 H, H-6 and H-3), 5.03 (s, 2 H, CH2), 2.48 (s, 3 H, CH3).
13C NMR: δ = 161.72, 160.33, 157.34, 156.69, 152.22, 108.94, 100.02, 99.46, 95.02, 45.21.

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