One-Pot Synthesis of 3-Carboxycoumarins via Consecutive Knoevenagel and Pinner Reactions in Water

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Abstract: Chloro-, hydroxy-, methoxy-, and tert-butyl-substituted 3-carboxycoumarins have been prepared by one-pot procedure by reaction of suitably substituted salicylaldehydes with malononitrile in water. The over-all yields are high and the protocol does not require organic solvents. Key words: aldol reactions, cyclizations, hydrolyses, 3-carboxycoumarins, water

Coumarins are an important class of natural and synthetic compounds which display a wide variety of properties. They are active as drugs, found in perfumes and cosmetics, and used in laser dyes, insecticides, photographic sensitizers and solar collectors, and are employed as fluorescent markers in biochemistry. Coumarins are also exploited as intermediates and building blocks in organic synthesis.

Recently, there has been great interest in 3-carboxycoumarins that have been used to synthesize modified cephalosporins, penicillins, oxygen-bridged tetrahydropridines, isoureas, esters and amides which exhibit specific inhibitors of α-chymotripsin and human leukocyte elastase, and polymeric compounds. Consequently, syntheses specifically aimed at 3-carboxycoumarins have appeared in the literature. Most of them are based on a Knoevenagel reaction between a suitably substituted salicylaldehyde and Meldrum’s acid carried out under various reaction conditions. Alternative procedures include a solid-phase synthesis between diethyl malonate bound to the Wang resin and the condensation of salicylaldehyde and Meldrum’s acid in the presence of clay KFS. These procedures are easy, and, in some cases, environmentally friendly.

The 3-carboxycoumarins are usually prepared in water, in good yields, but, when highly hydrophobic substituents, such as one or two tert-butyl groups are present in the aromatic ring of the molecule, the reaction does not work in aqueous medium.

Continuing our work in organic synthesis performed in water, we decided to investigate the use of coumarins as building blocks. Recently, we reported a one-pot synthesis under neat conditions and in aqueous medium of chromene derivatives starting from 3-nitrocoumarins. Here we report a new approach for synthesizing 3-carboxycoumarins in water that is also operative when highly hydrophobic groups such as tert-butyl groups are present in the aromatic moiety.

Salicylaldehydes 1 reacted with malononitrile (2) at room temperature in aqueous basic heterogeneous medium (pH 8.3–13.3) to give the cyanoimino ethers 4 via Knoevenagel (1 + 2 → 3) and Pinner (3 → 4) reactions (Scheme 1). Acid hydrolysis in situ of 4 at 90 °C produced the 3-cyanocoumarins 5 in high yields. These compounds could then be isolated by simple filtration or, without interruption, hydrolyzed at 90 °C under basic conditions. Final acidification of the reaction mixture allowed the isolation of 3-carboxycoumarins 6 by filtration in excellent over-all yields without using an organic solvent.

The results are illustrated in Table 1. If the process is stopped after the Knoevenagel and Pinner reactions, the iminoethers 4 can be isolated by filtration. As an example we report the isolation of 3-cyano-7-hydroxy-2-iminoethers 4d. The procedure is clean, environmentally friendly and takes advantage of two as-
Table 1  Synthesis of 3-Cyano- and 3-Carboxycoumarins in Water

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde 1</th>
<th>3-Cyanoacoumarin 5</th>
<th>3-Carboxycoumarin 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>t1 (h)a</td>
<td>t2 (h)b</td>
<td>Yield (%)c</td>
</tr>
<tr>
<td>a</td>
<td>H</td>
<td>2</td>
<td>2.5</td>
</tr>
<tr>
<td>b</td>
<td>6-Cl</td>
<td>4f</td>
<td>2</td>
</tr>
<tr>
<td>c</td>
<td>6-OH</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>d</td>
<td>7-OH</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>e</td>
<td>7-OMe</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>f</td>
<td>8-OH</td>
<td>2.5</td>
<td>2</td>
</tr>
<tr>
<td>g</td>
<td>8-tert-Bu</td>
<td>1e</td>
<td>1.5</td>
</tr>
<tr>
<td>h</td>
<td>5,7-(OMe)2</td>
<td>4f</td>
<td>2</td>
</tr>
<tr>
<td>i</td>
<td>6,8-(tert-Bu)2</td>
<td></td>
<td>1.5</td>
</tr>
</tbody>
</table>

a At r.t. and pH 8.3.
b At 90 °C and under basic conditions.
c Yield of isolated compound.
d At 90 °C and pH 8.3 followed by acidification.
e Overall yield of isolated compound.
f At pH 12.4.
g At pH 13.3.
h At pH 13.3 and in H2O-MeOH (9:1).
i At pH 9.0.

pects of using aqueous medium: (i) several reactions can be performed in sequence by simply changing the pH of the reaction medium and (ii) the desired products 4, 5 and 6 can be isolated by filtration without having to use any organic solvent.

All of the compounds prepared were characterized by 1H NMR, IR and GC-MS analyses and are described in the experimental section.

The coumarins 5g, 6g, 5i and 6i and the iminocoumarin 4d are new compounds. The 3-cyanocoumarins 5a, 5b, 5c, 5d, 5e, 5f, 5g and 5h and the 3-carboxycoumarins 6a, 6b, 6c, 6d, 6e, 6f, 6g and 6h are known compounds, but since their spectroscopic data are often missing, all of the coumarins prepared are described here. The IR spectra were recorded with a FT Perkin-Elmer RXI spectrometer in KBr and with a FT Bruker IFS 113V spectrometer. The IR spectra were recorded with a FT Perkin-Elmer RXI spectrometer in KBr and with a FT Bruker IFS 113V spectrometer. The IR spectra were recorded with a FT Perkin-Elmer RXI spectrometer in KBr and with a FT Bruker IFS 113V spectrometer.

3-Carboxycoumarins 6 and Their Precurors 4 and 5
A suitable salicylaldehyde (10 mmol), malononitrile (2) (0.80 g, 12.5 mmol) and 0.05 M aq NaHCO₃ solution (pH 8.3, 50 mL) or 0.025 M aq NaOH solution (pH 12.4, 50 mL) or 0.2 M aq NaOH solution (pH 13.3, 50 mL) were vigorously stirred at r.t. in a 100 mL round-bottom flask fitted with a mechanical or magnetic stirrer and reflux condenser for the time (t₁) reported in Table 1. 3-Cyano-2-iminocoumarins 4 were separated by vacuum filtration or conc. HCl (1.25–2.0 mL) was added and the heterogeneous mixture was heated at 90 °C under stirring for 1–2.5 h (t₂ of Table 1). After cooling, 3-cyanocoumarins 5 were separated by vacuum filtration or 1 M aq NaHCO₃ solution (20 mL) or 1.5 M aq NaOH solution (20 mL) was added and the mixture was heated at 90 °C under stirring for the time (t₃) reported in Table 1. The sodium salts of 3-carboxycoumarins are soluble in H₂O. The final solution, cooled to r.t., was acidified with conc HCl to pH ≤ 2 under stirring and refrigerated at 0–5 °C. 3-Carboxycoumarins 6 were separated from the aqueous medium by vacuum-filtration using a Büchner funnel under reduced pressure and then dried (yield 60–95%). The crude coumarins had a purity higher than 98% which could be further purified by recrystalization.

3-Cyanocoumarin (5a)₁¹
Mp 180–182 °C (EtOH).
IR (KBr): 2220 (C=O), 1730 (C=O), 1615 cm⁻¹ (C=C).

3-Carboxycoumarin (6a)₁⁵
Mp 186–188 °C (EtOAc).
IR (KBr): 2150 (C=O), 1600 cm⁻¹ (C=C).

6-Chloro-3-cyanocoumarin (5b)₁⁴
Mp 191–192 °C (EtOH).
IR (KBr): 2242 (C=O), 1735 (C=O), 1614 cm⁻¹ (C=C).

3-Carboxy-6-chlorocoumarin (6b)₁⁷
Mp 240 °C (dec.).
IR (KBr): 3189 (OH), 1743 (C=O), 1678 (C=O), 1620 cm⁻¹ (C=C).

3-Cyano-6-hydroxycoumarin (5c)₁³
Mp 237–238 °C (H₂O–EtOH).
IR (KBr): 3213 (OH), 2236 (C≡N), 1719 (C=O), 1615 cm⁻¹ (C=C).

3-Carboxy-6-hydroxycoumarin (6c)₁⁶
Mp 283 °C (EtOH).
IR (KBr): 3149 (OH), 1728 (C=O), 1650 cm⁻¹ (C=C).

3-Cyano-7-hydroxy-2-iminocoumarin (4d)
Mp 250 °C (dec.) (DMF–H₂O, 9:1).
IR (CsI pellet): 3261 (NH), 3094 (OH), 3049 (C=C–H), 2230 (C≡N), 1720 (C=O), 1615 cm⁻¹ (C=C).

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3-Carboxy-7-hydroxy coumarin (6d)\textsuperscript{18}

Mp 248–250 °C (dec.) \( (\text{H}_2\text{O}–\text{AcOH}, 8:2) \).

IR (CsI pellet): 3216 (OH), 2230 (C≡N), 1716 (C=O), 1610 cm \(^{-1} \) (C=C).

1\(^{13}\)C NMR 200 MHz \( (\text{DMSO-d}_6) \): \( \delta = 30.0, 31.4, 35.3, 35.7, 102.4, 114.9, 118.6, 125.3, 131.4, 138.0, 148.5, 152.3, 154.8, 157.2.

MS: \( m/z \) (%) = 72 (12), 77 (4), 91 (1), 115 (3), 127 (3), 212 (12), 224 (2), 240 (23), 268 (100), 269 (29), 283 (M\(^+\), 24).

Anal. Calcd for C\(_{14}\)H\(_{13}\)O\(_2\): C, 73.90; H, 5.79; N, 6.17. Found: C, 73.90; H, 5.79; N, 6.17.

3-Cyano-5,7-dimethoxycoumarin (5f)\textsuperscript{11}

Mp 233–235 °C (acetone).

IR (KBr): 3350 (OH), 1740 (C=O), 1690 (C=O), 1615 cm \(^{-1} \) (C=C).

1\(^{13}\)C NMR 200 MHz \( (\text{DMSO-d}_6) \): \( \delta = 30.0, 31.4, 35.3, 35.7, 102.4, 114.9, 118.6, 125.3, 131.4, 138.0, 148.5, 152.3, 154.8, 157.2.

MS: \( m/z \) (%) = 57 (12), 77 (4), 91 (1), 115 (3), 127 (3), 212 (12), 224 (2), 240 (23), 268 (100), 269 (29), 283 (M\(^+\), 24).

Anal. Calcd for C\(_{14}\)H\(_{14}\)O\(_4\): C, 68.28; H, 5.73. Found: C, 68.31; H, 5.76.

8-tert-Butyl-3-cyanocoumarin (5i)\textsuperscript{11}

Mp 143–144 °C (EtOH).

IR (KBr): 3350 (OH), 1740 (C=O), 1690 (C=O), 1615 cm \(^{-1} \) (C=C).

1\(^{13}\)C NMR 200 MHz \( (\text{DMSO-d}_6) \): \( \delta = 30.0, 31.4, 35.3, 35.7, 102.4, 114.9, 118.6, 125.3, 131.4, 138.0, 148.5, 152.3, 154.8, 157.2.

MS: \( m/z \) (%) = 57 (12), 77 (4), 91 (1), 115 (3), 127 (3), 212 (12), 224 (2), 240 (23), 268 (100), 269 (29), 283 (M\(^+\), 24).

Anal. Calcd for C\(_{14}\)H\(_{14}\)NO\(_2\): C, 76.29; H, 7.46; N, 4.94. Found: C, 76.35; H, 7.46; N, 4.96.

8-tert-Butyl-3-cyanocoumarin (6i)

Mp 268–270 °C (dec.).

IR (KBr): 3418 (OH), 1734 (C=O), 1710 (C=O), 1620 cm \(^{-1} \) (C=C).

1\(^{13}\)C NMR 200 MHz \( (\text{DMSO-d}_6) \): \( \delta = 30.0, 31.4, 35.3, 35.7, 102.4, 114.9, 118.6, 125.3, 131.4, 138.0, 148.5, 152.3, 154.8, 157.2.

MS: \( m/z \) (%) = 57 (7), 77 (1), 91 (1), 115 (3), 128 (4), 187 (3), 213 (9), 243 (4), 258 (3), 269 (12), 287 (100), 288 (20), 302 (M\(^+\), 20).

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Anal. Calcd for C_{18}H_{22}O_{4}: C, 71.50; H, 7.33. Found: C, 71.58; H, 7.29.

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