One-pot Synthesis of 2-Substituted 4H-Chromeno[3,4-d]oxazol-4-ones from 4-Hydroxy-3-nitrocoumarin and Acids in the Presence of Triphenylphosphine and Phosphorus Pentoxide under Microwave Irradiation

T. D. Balalas a
G. Stratidisa
D. Papatheodorou a
E.-E. Vlachou a
C. Gabriels b
D. J. Hadjipavlou-Litanas a
K. E. Litinas a

a Laboratory of Organic Chemistry, Department of Chemistry, Aristotle University of Thessaloniki, University Campus, Thessaloniki 54124, Greece
klitinas@chem.auth.gr
b Center for Research of the Structure of Matter, Magnetic Resonance Laboratory, Department of Chemical Engineering, Aristotle University of Thessaloniki, University Campus, Thessaloniki 54124, Greece

Abstract 2-Substituted 4H-chromeno[3,4-d]oxazol-4-ones are prepared from 4-hydroxy-3-nitrocoumarin and acids by one-pot reaction in the presence of PPh3 and P2O5 under microwave irradiation or by one-pot two-step reactions in the presence of Pd/C and hydrogen and then P2O5 under microwave irradiation. The fused oxazolocoumarins were also synthesized from 3-amido-4-hydroxycoumarins and P2O5 under microwave irradiation. The 3-amido-4-hydroxycoumarins are obtained almost quantitatively from 4-hydroxy-3-nitrocoumarin, acids and PPh3 under microwave irradiation, or in the presence of Pd/C and H2 on heating. Preliminary biological tests indicate significant inhibition of soybean lipoxigenase and antioxidant peroxidation for both oxazolocoumarins and o-hydroxyamidocoumarins.

Key words oxazolocoumarins, PPh3, reduction, phosphorus pentoxide, microwaves, Pd/C

Coumarins are a class of compounds that are widely distributed in natural products and in synthetic biologically active derivatives with interesting biological properties, such as anticoagulant, antibiotic, anti-inflammatory, anti-HIV, and anticancer activity. Fused coumarins are also biologically active agents. In particular, fused oxazolocoumarins have been examined for antibacterial, anti-inflammatory, antimicrobial, and photosensitizing activities and as agonists/antagonists of benzodiazepine receptors. Recently, such derivatives have been used as photoaffine protecting groups, forming conjugates with active compounds as prodrugs, for the photorelease and controlled delivery of the active molecules. 3-Acylamino-4-hydroxycoumarins and 3-amino-4-hydroxycoumarin, the usual precursors of oxazolocoumarins, also exhibit significant biological activities. They have been studied for their influence on the binding affinity and selectivity against adenosine receptors (Ar.s), as anticoagulants, as potent inhibitors of heat-shock protein 90 (hsp90), for antibacterial and antifungal activities, as well as for antitumor activity.

Among the many reported methods for the synthesis of benzoazoles and oxazoles, there are usually two approaches. One is the condensation of o-aminophenols with aldehydes, orthoesters, acids, acid derivatives, alcohols or β-diketones catalyzed by metal derivatives. The other is the intramolecular cyclization of o-hydroxyamides, or the metal-catalyzed cyclization of o-haloamides, enamides, and amides. Benzoxazoles have also been prepared by a one-pot multistep procedure, from o-nitrophenols with alcohols in the presence of Au nanoparticles/TiO2, Cu-Pd nanoparticles/γ-Al2O3, with orthoesters and In as catalysts, or with acetic anhydride and hydrogenation over Ni.

Several methodologies are available for the synthesis of fused oxazolocoumarins. These have been prepared by condensation of o-aminohydroxycoumarins with aldehydes, acids or anhydrides or by condensation of o-amidohydroxycoumarins with anhydrides, or PC1324 or P2O5. 2-Methyl-4H-[1]benzopyran-3,4-dioxazol-4-one
has also been formed by Beckmann rearrangement of the oxime of 3-acetyl-4-hydroxycoumarin, by the reduction of 4-hydroxy-3-nitrosocoumarin in acetic anhydride in the presence of Pd/C, or by heating 3-diazoo-2,4-chromene-dione in CH3CN in the presence of Rh6(OAc)3 as catalyst. Heating a mixture of 6-hydroxy-4-methyl-5-nitrocoumarin acetate with iron powder, CH3COONa, and (CH3CO)2O in CH3COOH leads to the corresponding oxazolocoumarin.

The formation of oxazolocoumarins has likewise been reported by the anodic oxidation of 7-hydroxycoumarin in a solution of MeCN and LiClO4 and by condensation of 7-methoxyimino-4-methylchromen-2,8-dione with methylacetate with iron powder, CH3COONa, and (CH3CO)2O in CH3COOH leads to the corresponding oxazolocoumarin.

Oxides. The reactions studied and the products obtained are depicted in Scheme 1.

We investigated suitable conditions for the one-pot transformation of 4-hydroxy-3-nitrosocoumarin (1) to the fused oxazolocoumarins 4 by using formic acid (2a) and acetic acid (2b) as representative reactants. At first, the reactions of 1 with 2a and 2b was performed in the presence of tin(II) chloride under microwave conditions by analogy with the reported one-pot transformation of o-nitroanilines to benzimidazoles. In contrast to expectations, only the amides 6a and 6b were isolated, with a significant amount (40%) of the starting material being recovered (Table 1, entries 1 and 2). Next, we tried PPh3 as the reducing agent in the presence of P2O5 (Method A) as condensation agent for the one-pot synthesis of oxazolocoumarins 4. The reaction of 1 with 2b under MW irradiation resulted in formation of oxazolocoumarin 4b in excellent yield (89%) (entry 3), better than all the former methods. The yield of this reaction remained almost unchanged (88%) on repeating the reaction at larger scale (10 fold). Another one-pot, but two step, reaction was also tested between 1 and 2b in the presence of Pd/C and H2 as reducing agent and subsequent addition of P2O5 (Method B) under MW conditions and longer reaction time and this approach gave 4b in similar yield (entry 4). It must be mentioned that formic acid was not investigated because it reacts violently with strong acids. Method A was used mainly in the following efforts as more convenient procedure.

The reaction of o-hydroxynitrocoumarin 1 with propionic acid (2c) with both Methods A and B (140 °C) resulted in the 2-ethyl substituted oxazolocoumarin 4c in excellent yields (Table 1, entries 5 and 6). The 3-propyl and 2-butyl substituted oxazolocoumarins 4d and 4e isolated also by both Methods A and B from the reactions of starting compound 1 with butyric (2d) and pentanoic (2e) acids, respectively, with the latter required higher temperature and longer reaction time (entries 7–10).

The one-pot reactions of 1 with the acids 2f–i by Method A also led to the corresponding oxazolocoumarin derivatives 4f–i in 89–91% yield, with the more steric hindered compounds requiring 2.5 h (Table 1, entries 11–15). The above oxazolocoumarins 4d–i are new compounds.

In the case of the reaction of o-hydroxynitrocoumarin 1 with methoxyacetic acid (2j) by both Methods A and B, the expected new oxazolocoumarin 4j was obtained in only 7% yield (Table 1, entries 16 and 17) after chromatographic separation of the tar reaction mixture. During the microwave irradiation, a rapid increase in the pressure of the reaction vessel was observed in the first seconds of both procedures (18–20 bar for temperature >45 °C). The complication of methoxyacetic acid (2j) could be attributed to the possibility of Friedel–Crafts reaction products and decarboxylative formation of diarylmethanes during the treatment of this acid with arenes in the presence of P2O5.

We examined, in parallel, the reactions of 4-hydroxy-3-nitrocoumarin (1) with the acids 2a–j in the absence of P2O5 (Scheme 1). The reaction of 1 with formic acid (2a) with PPh3 (3), as reducing agent, under microwave irradiation (Method C) led to 3-formamido-4-hydroxycoumarin (6a) in almost quantitative yield (Table 2, entry 1).
4-hydroxycoumarin (1), the reduction product, was also isolated in trace amounts after separation by column chromatography. This kind of reaction was performed for the first time to our knowledge.

Some 3-amido-4-hydroxycoumarins had been prepared by the reaction of 1 with anhydrides under Raney-nickel reduction. We tested the Pd/C and hydrogen for the reaction of 1 with formic acid (2a) under heating (Method D) at 100 °C for 12 h and the formamidocoumarin 6a was formed in excellent yield (Table 2, entry 2).

The reactions of 1 with the acetic acid (2b) or propionic acid (2c) under Method C and MW conditions at 130 °C for 1 h resulted in the formation of the known acetamidocoumarin 6b or propionamidocoumarin 6c respectively (Table 2, entries 3 and 5). The same products were also obtained in excellent yields by Method D and heating at 120 °C for 12 h (entries 4 and 6). The analogous reactions of 1 with butanoic acid (2d) or pentanoic acid (2e) at higher temperature under both Methods C and D led to the known coumarin derivatives 6d or 6e (entries 7–10). The new 4-hydroxy-3-octanamidocoumarin (6f) was isolated from the reaction of 1 with octanoic acid (2f) by both Methods C and D (entries 11 and 12). The known amidocoumarin derivative 6g was obtained from the reaction of 1 with 2-methylpropanoic acid (2g) under either microwave irradiation (Method C) or thermal heating (Method D) (entries 13 and 14).

The more steric hindered acids 3-methylbutanoic acid (2h) and 2,2-dimethylpropanoic acid (2i) reacted with 1 at higher temperature and longer reaction time under Method C to give the new amidocoumarins 2h and 2i (Table 2, entries 15 and 17). The same derivatives were also obtained at higher temperature by using Method D (entries 16 and 18). Product 6i formed in lower yield, but was isolated in reasonable amount from 3-amino-4-hydroxycoumarin (5) (entries 17 and 18). In the case of methoxyacetic acid, the new 4-hydroxy-3-methoxyacetamidocoumarin (6j) was obtained at lower temperature and with less irradiation time by Method C or at lower temperature by Method D (entries 19 and 20).

The condensation of 3-amido-4-hydroxycoumarins 6 was then tested for the formation of oxazolocoumarins 4. The 3-acetamido-4-hydroxycoumarin (6b), as representative reactant, failed to react with POCI₃ in refluxing CHCl₃, as expected for the analogous benzoxazole synthesis. This led to 4b in refluxing acetic anhydride for 10 min, quantitatively (99%). Oxazolocoumarin 4b was also obtained quantitatively from a toluene solution of 6b in the presence of P₂O₅ under reflux for 6 h or microwave irradiation at 140 °C for 1 h. An effort to get oxazolocoumarin 4a...
by refluxing a solution of 3-formamido-4-hydroxycoumarin (6a) in acetic anhydride for 10 min led to only 15% 4a along with 80% 4b. So, the condensation of 3-amido-4-hydroxycoumarins 6a–i was performed in the presence of P2O5 in toluene under MW conditions at 140 °C for 1 h, quantitatively (99%) (Method E; Scheme 1).

As revealed from the above procedures, for the mechanism of one-pot o xoazolocoumarin formation, the reactions of 4-hydroxy-3-nitrocoumarin (1) with the acids 2 proceed through reduction of the nitro group to the amino group and formation of 3-amino-4-hydroxycoumarin (5). Acylation of the latter to amido-derivatives 6, followed by condensation–cyclization in the presence of P2O5, resulted to o xoazolocoumarins 4.

Preliminary biological experiments were then performed in vitro. The compounds were tested as inhibitors of soybean lipoxygenase,45 which is an enzyme that is implicated in arachidonic acid cascade and inflammation and constitutes an attractive biological target for drug design (Table 3). The tests showed that compounds 4d and 4e (IC50 = 30 and 32 μM) (entries 4 and 5) are the most active within the set, whereas compound 6d is inactive under the reported experimental conditions (entry 14) and 6c presents very low activity (48% at 100 μM) (entry 13). Considering the anti-lipid peroxidation behavior of the compounds, as tested by the 2,2′-azobis(2-aminopropane) dialkylchloride (AAPH) protocol,45 we found that all derivatives 4 and 6 showed significant inhibition of lipid peroxidation (anti-LP) (42–100%). In our studies, AAPH was used as a free radical initiator to follow oxidative changes of linoleic acid to conjugated diene hydroperoxide. Our results indicated that LOX inhibition is accompanied and correlated with anti-lipid peroxidation. Judging overall the structural characteristics, the derivatives of series 4 are more potent than the molecules of series 6. The main difference within the two sets is the presence of the condensed heterocyclic ring in positions 3 and 4 of the coumarin ring. Thus, the combination of the coumarin with the heterocyclic moiety offers anti-LOX and anti-lipid peroxidation activities.

In conclusion, 2-substituted [3,4]-fused oxazolocoumarins were synthesized in excellent yields from 4-hydroxy-3-nitrocoumarin and acids through the one-pot reaction, for the first time, in the presence of PPh3 and P2O5 under microwave irradiation or through one-pot, two-step reaction under reduction in Pd/C and hydrogen and then microwave irradiation in the presence of P2O5. The fused oxazolocoumarins were also obtained quantitatively from the 3-amido-4-hydroxycoumarins and P2O5 in microwaves. The 3-ami do-4-hydroxycoumarins were prepared from 4-hydroxy-3-nitrocoumarin, acids and PPh3 under microwave conditions. The compounds present interesting antioxidant and inhibitory activity of lipoxygenase; especially, derivatives 4d and 4e could be used as lead compounds for the design of agents with biological interest.

### Table 2 Synthesis of 3-Amido-4-hydroxycoumarins 6a–j from 4-Hydroxy-3-nitrocoumarin (1) and Acids 2a–j

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid RCOOH 2a–j (R)</th>
<th>Conditions</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Product (yield, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a (H)</td>
<td>PPh3 (3), MW (Method C)</td>
<td>110</td>
<td>30 min</td>
<td>6a (98), 5 (trace)</td>
</tr>
<tr>
<td>2</td>
<td>2a (H)</td>
<td>Pd/C, H2, heating (Method D)</td>
<td>100</td>
<td>12</td>
<td>6a (96), 5 (trace)</td>
</tr>
<tr>
<td>3</td>
<td>2b (CH3)</td>
<td>Method C</td>
<td>130</td>
<td>1</td>
<td>6b (94), 5 (trace)</td>
</tr>
<tr>
<td>4</td>
<td>2b (CH3)</td>
<td>Method D</td>
<td>120</td>
<td>12</td>
<td>6b (94), 5 (trace)</td>
</tr>
<tr>
<td>5</td>
<td>2c (CH2CH3)</td>
<td>Method C</td>
<td>130</td>
<td>1</td>
<td>6c (96), 5 (trace)</td>
</tr>
<tr>
<td>6</td>
<td>2c (CH2CH3)</td>
<td>Method D</td>
<td>120</td>
<td>12</td>
<td>6c (94), 5 (trace)</td>
</tr>
<tr>
<td>7</td>
<td>2d (CH2CH2CH3)</td>
<td>Method C</td>
<td>140</td>
<td>1</td>
<td>6d (94), 5 (trace)</td>
</tr>
<tr>
<td>8</td>
<td>2d (CH2CH2CH2CH3)</td>
<td>Method D</td>
<td>130</td>
<td>12</td>
<td>6d (91), 5 (trace)</td>
</tr>
<tr>
<td>9</td>
<td>2e (CH2CH2CH2CH3)</td>
<td>Method C</td>
<td>140</td>
<td>1</td>
<td>6e (93), 5 (trace)</td>
</tr>
<tr>
<td>10</td>
<td>2e (CH2CH2CH2CH3)</td>
<td>Method D</td>
<td>140</td>
<td>12</td>
<td>6e (91), 5 (trace)</td>
</tr>
<tr>
<td>11</td>
<td>2f (CH2CH2CH2CH3)</td>
<td>Method C</td>
<td>140</td>
<td>1.5</td>
<td>6f (89), 5 (trace)</td>
</tr>
<tr>
<td>12</td>
<td>2f (CH2CH2CH2CH3)</td>
<td>Method D</td>
<td>140</td>
<td>12</td>
<td>6f (85), 5 (trace)</td>
</tr>
<tr>
<td>13</td>
<td>2g (t-Pr)</td>
<td>Method C</td>
<td>130</td>
<td>1.5</td>
<td>6g (95), 5 (trace)</td>
</tr>
<tr>
<td>14</td>
<td>2g (t-Pr)</td>
<td>Method D</td>
<td>130</td>
<td>12</td>
<td>6g (92), 5 (trace)</td>
</tr>
<tr>
<td>15</td>
<td>2h (t-Bu)</td>
<td>Method C</td>
<td>140</td>
<td>1.5</td>
<td>6h (95), 5 (trace)</td>
</tr>
<tr>
<td>16</td>
<td>2h (t-Bu)</td>
<td>Method D</td>
<td>140</td>
<td>12</td>
<td>6h (92), 5 (trace)</td>
</tr>
<tr>
<td>17</td>
<td>2i (t-Bu)</td>
<td>Method C</td>
<td>140</td>
<td>1.5</td>
<td>6i (25), 5 (67)</td>
</tr>
<tr>
<td>18</td>
<td>2i (t-Bu)</td>
<td>Method D</td>
<td>140</td>
<td>12</td>
<td>6i (39), 5 (56)</td>
</tr>
<tr>
<td>19</td>
<td>2j (CH2OCH3)</td>
<td>Method C</td>
<td>130</td>
<td>45 min</td>
<td>6j (95), 5 (trace)</td>
</tr>
<tr>
<td>20</td>
<td>2j (CH2OCH3)</td>
<td>Method D</td>
<td>120</td>
<td>12</td>
<td>6j (93), 5 (trace)</td>
</tr>
</tbody>
</table>
The chemical reactions were performed from either Sigma–Aldrich Co. or Merck & Co., Inc. Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. IR spectra were obtained with a Perkin–Elmer 1310 spectrophotometer as KBr pellets. NMR spectra (1H and 13C respectively) using CDCl 3 as solvent and TMS as an internal standard were recorded with an Agilent 500/54 (DD2) (500 MHz and 125 MHz respectively) spectrometer. Mass spectra were determined with a ThermoFisher Scientific model LTQ Orbitrap Discovery MS. Silica gel, hexane/EtOAc, 3:1 afforded compound 4b (87 mg, 87%).

### Method B: 4-Hydroxy-3-nitrocoumarin

1. 4-Hydroxy-3-nitrocoumarin (1; 0.1035 g, 0.5 mmol), acetate acid (2b; 1 mL, 0.5 M) and Pd/C 10% (0.025 mmol) were added to a flask for a MW oven under 1 atm of hydrogen. The mixture was stirred at r.t. for 1 h until 1 was consumed as indicated by TLC. The hydrogen was removed, P2O5 (0.284 g, 2 mmol) was added and the flask was irradiated in the MW oven at 130 °C (ca. 2 bar, ca. 45 W) for 1 h. After cooling, the mixture was treated alternately with EtOAc and water (3 × 10 mL). The filtrate was washed with saturated solution Na2CO3 (2 × 10 mL) and water (10 mL), dried over anhydrous Na2SO4 and separated by column chromatography [silica gel; hexane/EtOAc, 3:1] to afford 4b (87 mg, 87%).

### Method E: 3-Acetamido-4-hydroxycoumarin

1. 3-Acetamido-4-hydroxycoumarin (6b; 0.11 g, 0.5 mmol) and toluene (5 mL) were added to a flask for a MW oven under 1 atm of hydrogen. The mixture was irradiated at 130 °C (ca. 2 bar, ca. 45 W) for 1 h. After cooling, the toluene solution was removed. The remaining solid was diluted with water (20 mL) and extracted with CH2Cl2 (5 × 10 mL). The organic layer was combined with the toluene solution, dried over anhydrous Na2SO4, filtered and evaporated to give 4b (0.1 g, 99%).

### Synthesis of 4b from 6b and Acetic Anhydride

1. 3-Acetamido-4-hydroxycoumarin (6b; 0.11 g, 0.5 mmol) and acetic anhydride (1 mL, 0.5 M) were added to a flask for a MW oven under 1 atm of hydrogen. The mixture was irradiated at 140 °C (ca. 2 bar, ca. 53 W) for 1 h. After cooling, the toluene solution was removed. The remaining solid was diluted with water (20 mL) and extracted with CH2Cl2 (5 × 10 mL). The organic layer was combined with the toluene solution, dried over anhydrous Na2SO4, filtered and evaporated to give 4b (0.1 g, 99%).

### Compound 4b

2. IR (KBr): 3086, 2928, 2856, 1747, 1641, 1599, 1585 cm⁻¹.
3. 1H NMR (CDCl 3, 500 MHz): δ = 8.4 Hz, 1 H), 7.57 (t, J = 7.9 Hz, 1 H), 7.38 (d, J = 8.4 Hz, 1 H), 7.38 (t, J = 7.6 Hz, 1 H), 2.70 (s, 3 H).
4. 13C NMR (CDCl 3, 126 MHz): δ = 163.7, 156.0, 155.7, 153.0, 131.6, 124.95, 124.9, 121.4, 117.8, 111.7, 14.4.
5. MS (ESI); m/z = 202 [M + H]+, 224 [M + Na]+.

### 4H-Chromeno[3,4-d]oxazol-4-one (4a)

2. IR (KBr): 3066, 2928, 2856, 1747, 1641, 1599, 1585 cm⁻¹.
3. 1H NMR (CDCl 3, 500 MHz): δ = 8.4 Hz, 1 H), 7.57 (t, J = 7.9 Hz, 1 H), 7.38 (d, J = 8.4 Hz, 1 H), 7.38 (t, J = 7.6 Hz, 1 H), 2.70 (s, 3 H).
4. 13C NMR (CDCl 3, 126 MHz): δ = 163.7, 156.0, 155.7, 153.0, 131.6, 124.95, 124.9, 121.4, 117.8, 111.7, 14.4.
5. MS (ESI); m/z = 202 [M + H]+, 224 [M + Na]+.
organic layer was dried over anhydrous Na₂SO₄, filtered, evaporated and separated by column chromatography [silica gel; hexane/EtOAc, 3:1] to give 4a (14 mg, 15%) followed by 4b (80 mg, 80%).

IR (KBr): 3085, 2952, 2930, 2870, 1750, 1642, 1600, 1583, 1500 cm⁻¹.

Yield (Method A, 140 °C): 0.116 g (90%); (Method E, 150 °C): 0.140 g (98%); white solid; m.p. 99–101 °C (toluene/hexane).

IR (KBr): 3084, 2955, 2849, 1748, 1640, 1582, 1558, 1499 cm⁻¹.

1H NMR (CDCl₃, 500 MHz): δ = 8.15 (s, 1 H), 7.87 (dd, J₁ = 7.8, J₂ = 1.1 Hz, 1 H), 7.64–7.60 (m, 1 H), 7.51 (d, J = 8.5 Hz, 1 H), 7.42 (t, J = 7.8 Hz, 1 H).

13C NMR (CDCl₃, 126 MHz): δ = 155.9, 155.6, 153.2, 152.0, 132.3, 125.1, 124.3, 121.8, 117.8, 111.5.


HRMS (ESI-MS): m/z [M + H]⁺ calcd for C₁₀H₈NO₃: 188.0342; found: 188.0343.

2-Ethyl-4H-chromeno[3,4-d]oxazol-4-one (4c)

Yield (Method A): 96 mg (89%); (Method B): 92 mg (86%); (Method E): 0.106 g (99%); white solid; m.p. 151–153 °C (toluene/hexane) (lit.²³a 147 °C).

IR (KBr): 3058, 2985, 2879, 1754, 1640, 1599, 1584 cm⁻¹.

1H NMR (CDCl₃, 500 MHz): δ = 7.81 (d, J = 7.9 Hz, 1 H), 7.57 (t, J = 7.6 Hz, 1 H), 7.47 (d, J = 8.4 Hz, 1 H), 7.38 (t, J = 7.6 Hz, 1 H), 7.26 (q, J = 7.6 Hz, 2 H), 1.48 (t, J = 7.6 Hz, 3 H).

13C NMR (CDCl₃, 126 MHz): δ = 168.1, 156.2, 155.5, 153.0, 131.5, 124.9, 124.8, 121.4, 117.8, 111.7, 22.1, 11.0.


2-Propyl-4H-chromeno[3,4-d]oxazol-4-one (4d)

Yield (Method A, 140 °C): 0.101 g (89%); (Method B, 2 h then 1.5 h): 96 mg (84%); (Method E, 150 °C): 0.113 g (99%); white solid; m.p. 119–121 °C (toluene/hexane).

IR (KBr): 3080, 2963, 2929, 2924, 2871, 1753, 1641, 1600, 1584 cm⁻¹.

1H NMR (CDCl₃, 500 MHz): δ = 7.81 (d, J = 7.8 Hz, 1 H), 7.57 (t, J = 7.8 Hz, 1 H), 7.48 (d, J = 8.4 Hz, 1 H), 7.38 (t, J = 7.5 Hz, 1 H), 7.26 (q, J = 7.5 Hz, 2 H), 1.98–1.91 (m, 2 H), 1.07 (t, J = 7.4 Hz, 3 H).

13C NMR (CDCl₃, 126 MHz): δ = 167.2, 156.1, 155.4, 152.8, 131.5, 124.9, 124.7, 121.4, 117.6, 111.6, 30.2, 20.3, 13.7.


HRMS (ESI-MS): m/z [M + H]⁺ calcd for C₁₇H₂₀NO₃: 286.1443; found: 286.1439.

2-Isopropyl-4H-chromeno[3,4-d]oxazol-4-one (4e)

Yield: (Method A, 140 °C): 0.109 g (90%); (Method E, 150 °C): 0.113 g (99%); white solid; m.p. 117–119 °C (toluene/hexane).

IR (KBr): 3086, 2936, 2961, 2988, 2876, 1753, 1640, 1601, 1579 cm⁻¹.

1H NMR (CDCl₃, 500 MHz): δ = 7.81 (d, J = 7.7 Hz, 1 H), 7.59–7.55 (m, 1 H), 7.47 (d, J = 8.4 Hz, 1 H), 7.38 (t, J = 7.6 Hz, 1 H), 2.86 (d, J = 7.1 Hz, 2 H), 2.36–2.28 (m, 1 H), 1.06 (d, J = 6.7 Hz, 6 H).

13C NMR (CDCl₃, 126 MHz): δ = 166.7, 156.2, 155.5, 152.9, 131.5, 124.9, 124.8, 121.5, 117.7, 111.8, 37.3, 27.6, 22.5.

MS (ESI): m/z = 244 [M + H]⁺, 266 [M + Na]⁺.

HRMS (ESI-MS): m/z [M + H]⁺ calcd for C₁₉H₂₀NO₃: 288.1468; found: 288.1466.

2-Isobutyl-4H-chromeno[3,4-d]oxazol-4-one (4f)

Yield: (Method A, 140 °C): 0.111 g (91%); (Method E, 150 °C): 0.12 g (99%); white solid; m.p. 218–219 °C (toluene/hexane).

IR (KBr): 3083, 2970, 2939, 2876, 1755, 1638, 1601, 1574 cm⁻¹.

1H NMR (CDCl₃, 500 MHz): δ = 7.81 (d, J = 7.8 Hz, 1 H), 7.57 (t, J = 7.8 Hz, 1 H), 7.47 (d, J = 8.4 Hz, 1 H), 7.39 (t, J = 7.6 Hz, 1 H), 1.52 (s, 9 H).

13C NMR (CDCl₃, 126 MHz): δ = 173.7, 156.4, 155.4, 153.0, 131.5, 124.8, 124.6, 121.5, 117.7, 111.8, 34.7, 28.6.

MS (ESI): m/z = 244 [M + H]⁺, 266 [M + Na]⁺.

HRMS (ESI-MS): m/z [M + H]⁺ calcd for C₁₉H₂₀NO₃: 286.1443; found: 286.1439.
N-(4-Hydroxy-2-oxo-2H-chromen-3-yl)propionamide (6c)
Yield (Method C, 130 °C, 1 h): 0.222 g (96%); (Method D, 120 °C): 0.218 g (94%); white solid; m.p. 150–152 °C (hexane) (lit.44 154–155 °C).
IR (KBr): 3287, 3231, 3063, 2975, 2940, 2878, 1692, 1636, 1604, 1573 cm⁻¹.
1H NMR (CDCl₃, 500 MHz): δ = 7.63 (s, 1 H), 7.56–7.51 (m, 1 H), 7.36–7.30 (m, 2 H), 2.56 (q, J = 7.6 Hz, 2 H), 1.30 (t, J = 7.6 Hz, 3 H).
13C NMR (CDCl₃, 126 MHz): δ = 175.3, 161.1, 152.8, 150.6, 131.8, 124.8, 124.5, 117.2, 116.3, 104.7, 30.0, 9.9.
MS (ESI): m/z = 232 [M + H].

N-(4-Hydroxy-2-oxo-2H-chromen-3-yl)butyramide (6d)
Yield (Method C, 140 °C, 1 h): 0.231 g (94%); (Method D, 130 °C): 0.224 g (91%); white solid; m.p. 169–171 °C (hexane) (lit.44 173–174 °C).
IR (KBr): 3287, 3231, 3063, 2975, 2940, 2878, 1690, 1634, 1606, 1571 cm⁻¹.
1H NMR (CDCl₃, 500 MHz): δ = 13.65 (brs, 1 H), 8.15 (brs, 1 H), 7.98 (d, J = 7.6 Hz, 2 H), 7.36–7.31 (m, 2 H), 2.50 (q, J = 7.5 Hz, 2 H), 1.83–1.76 (m, 2 H), 1.04 (t, J = 7.4 Hz, 3 H).
13C NMR (CDCl₃, 126 MHz): δ = 174.6, 161.1, 152.9, 150.6, 131.8, 124.8, 124.5, 117.2, 116.3, 104.8, 38.7, 19.3, 13.7.
MS (ESI): m/z = 246 [M – H].

N-(4-Hydroxy-2-oxo-2H-chromen-3-yl)penatanamide (6e)
Yield (Method C, 140 °C, 1 h): 0.243 g (93%); (Method D, 140 °C): 0.237 g (91%); white solid; m.p. 139–141 °C (hexane) (lit.44 132.5–133.5 °C).
IR (KBr): 3287, 3231, 3071, 3039, 2951, 2930, 2868, 1693, 1623, 1602, 1570, 1549 cm⁻¹.
1H NMR (CDCl₃, 500 MHz): δ = 13.65 (brs, 1 H), 8.16 (brs, 1 H), 7.98 (dd, J₁ = 7.9, J₂ = 1.1 Hz, 1 H), 7.56–7.51 (m, 1 H), 7.36–7.30 (m, 2 H), 2.52 (q, J = 7.6 Hz, 2 H), 1.77–1.71 (m, 2 H), 1.47–1.40 (m, 2 H), 0.97 (t, J = 7.4 Hz, 3 H).
13C NMR (CDCl₃, 126 MHz): δ = 174.8, 161.1, 152.9, 150.6, 131.8, 124.8, 124.5, 117.2, 116.3, 104.8, 36.6, 27.9, 22.4, 13.8.
MS (ESI): m/z = 260 [M – H].

N-(4-Hydroxy-2-oxo-2H-chromen-3-yl)octanamide (6f)
Yield (Method C, 140 °C, 1.5 h): 0.27 g (89%); (Method D, 140 °C): 0.279 g (85%); white solid; m.p. 122–123 °C (hexane).
IR (KBr): 3281, 3217, 3040, 2952, 2929, 2854, 2868, 1693, 1623, 1603, 1571 cm⁻¹.
1H NMR (CDCl₃, 500 MHz): δ = 13.65 (brs, 1 H), 8.16 (brs, 1 H), 7.97 (d, J = 7.9, 1 H), 7.53 (t, J = 7.8 Hz, 1 H), 7.36–7.29 (m, 2 H), 2.51 (q, J = 7.6 Hz, 2 H), 1.83–1.71 (m, 2 H), 1.41–1.26 (m, 8 H), 0.88 (t, J = 6.8 Hz, 3 H).
13C NMR (CDCl₃, 126 MHz): δ = 174.8, 161.1, 152.8, 150.6, 131.8, 124.8, 124.5, 117.2, 116.3, 104.8, 36.8, 31.7, 29.1, 29.0, 25.8, 22.7, 14.2.
MS (ESI): m/z = 302 [M – H].
HRMS (ESI-MS): m/z [M + H⁺] calcd for C₁₇H₂₂NO₄: 304.1549; found: 304.1547.
N-(4-Hydroxy-2-oxo-2H-chromen-3-yl)-isobutryramide (6g)

Yield (Method C, 130 °C, 1.5 h): 0.233 g (95%); (Method D, 130 °C): 0.226 g (92%); white solid; m.p. 140–141 °C (hexane) (lit. 11 164–166 °C).

IR (KBr): 3297, 2927, 2879, 1679, 1635, 1606, 1572, 1537 cm⁻¹.

1H NMR (CDCl₃, 500 MHz): δ = 13.74 (brs, 1 H), 8.22 (brs, 1 H), 7.97 (d, J = 7.9 Hz, 1 H), 7.52 (t, J = 7.8 Hz, 1 H), 7.35–7.29 (m, 2 H), 2.78–2.72 (m, 1 H), 1.30 (d, J = 6.9 Hz, 3 H).

13C NMR (CDCl₃, 126 MHz): δ = 178.5, 161.1, 152.8, 150.6, 131.7, 124.8, 124.5, 117.2, 116.3, 104.7, 36.1, 19.7.


N-(4-Hydroxy-2-oxo-2H-chromen-3-yl)-3-methylbutanamide (6h)

Yield (Method C, 140 °C, ca. 57 W, 1.5 h): 0.236 g (95%); (Method D, 140 °C, 1.5 h, ca. 57 W): 0.239 g (95%); white solid; m.p. 140–141 °C (hexane) (lit. 11 164–165 °C).

IR (KBr): 3293, 3055, 2964, 2953, 2872, 1682, 1635, 1603, 1571 cm⁻¹.

1H NMR (CDCl₃, 500 MHz): δ = 13.87 (brs, 1 H), 8.41 (brs, 1 H), 7.98 (d, J = 7.8 Hz, 1 H), 7.36–7.31 (m, 2 H), 4.11 (s, 2 H), 1.37 (s, 9 H).

13C NMR (CDCl₃, 126 MHz): δ = 178.5, 161.1, 152.8, 150.6, 131.7, 124.8, 124.5, 117.2, 116.3, 104.7, 45.8, 26.7, 22.4.

MS (ESI): m/z = 260 [M + H]⁺.

HRMS (ESI-MS): m/z [M + H]⁺ calcd for C₁₄H₁₆NO₄: 262.1074; found: 262.1072.

N-(4-Hydroxy-2-oxo-2H-chromen-3-yl) pivalamide (6i)

Yield (Method C, 130 °C, 45 min): 0.236 g (95%); (Method D, 120 °C): 0.231 g (93%); white solid; m.p. 165–166 °C (hexane).

IR (KBr): 3312, 3020, 2971, 2945, 2907, 2840, 1701, 1645, 1605, 1542 cm⁻¹.

1H NMR (CDCl₃, 500 MHz): δ = 13.38 (brs, 1 H), 9.15 (brs, 1 H), 7.98 (d, J = 7.9 Hz, 1 H), 7.55 (t, J = 7.8 Hz, 1 H), 7.36–7.31 (m, 2 H), 4.11 (s, 2 H), 3.56 (s, 3 H).

13C NMR (CDCl₃, 126 MHz): δ = 170.6, 160.7, 153.0, 150.8, 131.9, 124.8, 124.5, 117.1, 116.4, 104.2, 71.1, 59.7.


HRMS (ESI-MS): m/z [M + H]⁺ calcd for C₁₄H₁₃NO₄: 250.0710; found: 250.0711.

N-(4-Hydroxy-2-oxo-2H-chromen-3-yl)-2-methoxyacetamide (6j)

Yield (Method C, 140 °C, 1.5 h): 0.226 g (92%); white solid; m.p. 140–141 °C (hexane).