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

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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 lipoxygenase and antilipid 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 photolabile 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 (Ars),8 as anticoagulants,9 as potent inhibitors of heat-shock protein 90 (hsp90),10 for antibacterial and antifungal activities,11 as well as for antitumor activity.12

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,13 or the metal-catalyzed cyclization of o-haloamides,15 enamides,16 and amides.17 Benzoazoles have also been prepared by a one-pot multistep procedure, from o-nitrophenols with alcohols in the presence of Au nanoparticles/TiO2,18 Cu-Pd nanoparticles/γ-Al2O3,19 with orthoesters and In as catalyst,20 or with acetic anhydride and hydrogenation over Ni.21

Several methodologies are available for the synthesis of fused oxazolocoumarins. These have been prepared by condensation of o-aminohydroxycoumarins with aldehydes, acids,24-22 or anhydrides 2,12 or by condensation of o-aminohydroxycoumarins with anhydrides,23 POCl3,24 or P2O5.25 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,26 by the reduction of 4-hydroxy-3-nitrosocoumarin in acetic anhydride in the presence of Pd/C,26 or by heating 3-diazo-2,4-chromene-3-dione in CH3CN in the presence of Rh2(OAc)4 as catalyst.27 Heating a mixture of 6-hydroxy-4-methyl-5-nitrocumarin acetate with iron powder, CH3COONa, and (CH3CO)2O in CH3COOH leads to the corresponding oxazolocumarins.28

The formation of oxazolocumarins has likewise been reported by the anodic oxidation29 of 7-hydroxycoumarin in a solution of MeCN and LiClO4 and by condensation of 7-methoxyimino-4-methylchromen-2,8-dione with methylenes or arylacetic esters.30 Very recently, we have synthesized oxazolocumarins by one-pot tandem reactions of o-hydroxynitrocoumarins with benzyl alcohol in toluene under catalysis with gold nanoparticles supported on TiO2, by FeCl3 or by silver nanoparticles supported on TiO2.31

Reagents and conditions: (i) 2 (2 mL, 0.5 M), PPh3 (3) (2.5 equiv), P2O5 (4 equiv), MW irradiation, 130 °C or 140 °C, 1.5 h (not for 4a); (ii) 2 (2 mL, 0.5 M), 5 mol% Pd/C (10%), H2 1 atm, r.t., 1–3 h then P2O5 (4 equiv), MW irradiation, 130 °C, 1 h; (iii) 2 (1.5 equiv), PPh3 (3) (2.5 equiv), MW, 110–140 °C, 0.5–1 h; (iv) 2 (10 equiv), Pd/C 10% (0.05 equiv), H2 1 atm, 110–140 °C, 12 h; (v) P2O5 (6 equiv), toluene (10 mL), MW irradiation, 140 °C, 1 h.

Scheme 1 Reagents and conditions: (i) 2 (2 mL, 0.5 M), PPh3 (3) (2.5 equiv), P2O5 (4 equiv), MW irradiation, 130 °C or 140 °C, 1.5 h (not for 4a); (ii) 2 (2 mL, 0.5 M), 5 mol% Pd/C (10%), H2 1 atm, r.t., 1–3 h then P2O5 (4 equiv), MW irradiation, 130 °C, 1 h; (iii) 2 (1.5 equiv), PPh3 (3) (2.5 equiv), MW, 110–140 °C, 0.5–1 h; (iv) 2 (10 equiv), Pd/C 10% (0.05 equiv), H2 1 atm, 110–140 °C, 12 h; (v) P2O5 (6 equiv), toluene (10 mL), MW irradiation, 140 °C, 1 h.

Triphenylphosphine (PPh3) is a versatile reagent for the reduction of a range of substrates including azides (Staudinger reaction), disulfides,33 sulfonyl chloride,34 peroxides,35 oxazides,36 nitro compounds (for the Cadogan type reductive cyclization),37 nitroso compounds,38 and N-oxides.39 In a continuation of our studies on fused oxazolocumarin derivatives,10,30,31 we would like to present, here-in, the use of PPh3 for the one-pot synthesis of fused oxazolocumarins from o-hydroxynitrocoumarin in the presence of acid and phosphorus pentoxide. The PPh3 is utilized for the first time to our knowledge for the synthesis of oxazoles. 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-nitrocumarin20 (1) to the fused oxazolocumarins 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.41 In contrast to expectations, only the amides 6a and 6b23a 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 oxazolocumarins 4. The reaction of 1 with 2b under MW irradiation resulted in formation of oxazolocumarin 4b38 in excellent yield (89%) (entry 3), better than all the former methods.23,26,27 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.42 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 oxazolocumarin 4c23a in excellent yields (Table 1, entries 5 and 6). The 3-propyl and 2-butyl substituted oxazolocumarins 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 oxazolocumarin derivatives 4f–i in 89–91% yield, with the more steric hindered compounds requiring 2.5 h (Table 1, entries 11–15). The above oxazolocumarins 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 oxazolocumarin 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 P2O5.43

We examined, in parallel, the reactions of 4-hydroxy-3-nitrocumarin 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). 3-Amino-
4-hydroxy-3-methoxyacetamidocoumarin (6b), as representative reactant, failed to react with POCl₃ in refluxing CHCl₃, as expected for the analogous benzoxazole synthesis.¹⁴b This led to 4b in refluxing acetic anhydride for 10 min, quantitatively (99%). Oxazolocoumarin 4b was also obtained quantitatively 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 P₂O₅ in refluxing CHCl₃, as expected for the analogous benzoxazole synthesis.¹⁴b 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 P₂O₅,²⁵ 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 oxazolocoumarin 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 oxazolocoumarins 4.

Preliminary biological experiments were then performed in vitro. The compounds were tested as inhibitors of soybean lipoxygenase, 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) dihydrochloride (AAPH) protocol, 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-amido-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.
All the chemicals were procured 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 were recorded with a Varian Gemini 300 spectrometer (300 MHz) and 125 MHz for 1H and 13C respectively using CDCl3 as solvent and TMS as an internal standard. J values are reported in Hz. Mass spectra were determined with a LCMS-2010 EV Instrument (Shimadzu) under electrospray ionization (ESI) conditions. HRMS (ESI-MS) were recorded with a ThermoFisher Scientific model LTQ Orbitrap Discovery MS. Silica gel, hexane/EtOAc, 3:1 to afford compound 4b (0.884 g, 88%) was isolated, as described above.

**Method B:** 4-Hydroxy-3-nitrocoumarin (1; 0.1035 g, 0.5 mmol), acetic acid (2b; 1 mL, 0.5 M) and Pd/C 10% (26 mg, 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. 4 bar, ca. 45 W) for 1.5 h, the compound 4b (0.884 g, 88%) was isolated, as described above.

**Method E:** 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. 4 bar, ca. 48 W) for 1 h. After cooling, EtOAc (15 mL) was added and the solid was filtered and washed with EtOAc (15 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%).

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

3-Acetamido-4-hydroxycoumarin (6b; 0.11 g, 0.5 mmol) and acetic anhydride (1 mL) were heated at reflux for 10 min. The mixture was poured in a separation funnel. The remaining solid in the reaction flask was treated alternately with CH2Cl2 (3 × 20 mL) and saturated solution Na2CO3 (10 × 2 mL) and poured in the funnel. The separated organic layer was washed with saturated solution Na2CO3 (2 × 10 mL) and water (10 mL) and 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 compound 4b (0.884 g, 88%).

**Compound 4b**

White solid; m.p. 198–200 °C (toluene/hexane) (lit. 196–197 °C).

IR (KBr): 3086, 2928, 2856, 1747, 1641, 1599, 1585 cm⁻¹. 

1H NMR (CDCl3, 500 MHz): δ = 7.80 (d, J = 8.2 Hz, 1 H), 7.57 (t, J = 7.9 Hz, 1 H), 7.48 (d, J = 8.4 Hz, 1 H), 7.38 (t, J = 7.6 Hz, 1 H), 2.70 (s, 3 H).

13C NMR (CDCl3, 126 MHz): δ = 156.3, 150.5, 155.7, 153.0, 131.6, 124.9, 124.9, 124.1, 117.8, 111.7, 14.4.

MS (ESI); m/z = 202 [M + H]⁺, 224 [M + Na]⁺.

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

Yield (Method E): 93 mg (99%); white solid; m.p. 196–198 °C (toluene/hexane).

**Synthesis of 4a from 6a and Acetic Anhydride**

3-Formamido-4-hydroxycoumarin (6a; 0.1025 g, 0.5 mmol) and acetic anhydride (1 mL) were heated at reflux for 10 min. The mixture was poured in a separation funnel. The remaining solid in the reaction flask was treated alternately with CH2Cl2 (3 × 20 mL) and saturated solution Na2CO3 (10 × 2 mL) and poured in the funnel. The separated organic layer was washed with saturated solution Na2CO3 (2 × 10 mL) and water (10 mL). The aqueous layers were extracted with CH2Cl2 (3 × 20 mL) and the combined organic layers were dried over anhydrous Na2SO4 and separated by column chromatography [silica gel; hexane/EtOAc, 3:1] to afford 4a (90 mg, 89%).
organic layer was dried over anhydrous Na$_2$SO$_4$, 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$^{-1}$.

1$^H$ NMR (CDCl$_3$, 500 MHz): $\delta$ = 8.15 (s, 1 H), 7.87 (dd, $J$$_{1}$ = 7.8, $J$$_{2}$ = 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).

13$^C$ NMR (CDCl$_3$, 126 MHz): $\delta$ = 155.9, 155.6, 153.2, 152.0, 132.3, 125.1, 124.3, 121.8, 117.8, 111.5.

MS (ESI): $m/z$ = 188 [M + H]$^+$, 210 [M + Na]$^+$. HRMS (ESI-MS): $m/z$ [M + H]$^+$ calcd for C$_8$H$_{13}$NO$_2$: 188.0342; found: 188.0343.

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

Yield: (Method A, 140 °C): 0.106 g (99%); (Method B, 2 h then 1.5 h): 96 mg (84%); (Method E, 150 °C): 0.113 g (99%); white solid; m.p. 151–153 °C (toluene/hexane) (lit.$^{15a}$ 147 °C).

IR (KBr): 3085, 2955, 2897, 1754, 1640, 1599, 1584 cm$^{-1}$.

1$^H$ NMR (CDCl$_3$, 500 MHz): $\delta$ = 7.81 (d, $J$ = 7.9 Hz, 1 H), 7.57 (t, $J$ = 7.9 Hz, 1 H), 7.47 (d, $J$ = 8.4 Hz, 1 H), 7.38 (t, $J$ = 7.6 Hz, 1 H), 3.02 (q, $J$ = 7.6 Hz, 2 H), 1.48 (t, $J$ = 7.6 Hz, 3 H).

13$^C$ NMR (CDCl$_3$, 126 MHz): $\delta$ = 168.1, 156.2, 155.5, 153.0, 131.5, 124.9, 124.8, 121.4, 117.8, 111.7, 22.1, 110.

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

Yield: (Method A, 140 °C): 9 mg (7%); (Method B): 9 mg (7%); (Method E): 0.114 g (99%); white solid; m.p. 142–144 °C (toluene/hexane).

IR (KBr): 3298, 3239, 3046, 2955, 2858, 1675, 1629, 1601, 1545 cm⁻¹.

1H NMR (CDCl₃, 500 MHz): δ = 7.87 (d, J = 7.9 Hz, 1 H), 7.61 (t, J = 7.9 Hz, 1 H), 7.50 (d, J = 8.4 Hz, 1 H), 7.41 (t, J = 7.6 Hz, 1 H), 4.74 (s, 2 H), 3.53 (s, 3 H).

13C NMR (CDCl₃, 126 MHz): δ = 162.5, 156.3, 155.9, 153.2, 132.2, 125.1, 124.7, 121.8, 117.9, 111.5, 66.4, 59.4.

MS (ESI): m/z = 232 [M + H]⁺, 254 [M + Na⁺].

HRMS (ESI-MS): m/z [M + Na⁺] calcd for C₁₇H₁₆NO₅: 304.1424; found: 304.0420.

N-(4-Hydroxy-2-oxo-2H-chromen-3-yl)formamide (6a); Typical Procedures

Method C: 4-Hydroxy-3-nitrocoumarin (1: 0.207 g, 1 mmol), formic acid (2a: 0.114 ml, 1.38 g, 3 mmol), and Pd/C 10% (0.224 g, 98%) were added to a flask for a MW oven. The mixture was irradiated at 100 °C (ca. 1 bar, ca. 44 W) for 30 min. After evacuating, CH₂Cl₂ (10 ml) was added and the solution was evaporated and the mixture was separated by column chromatography (silica gel; hexane/EtOAc, 3:1) to afford 6a (0.2 g, 97%) followed by 3-amino-3-hydroxy-2(1H)-chromen-3-yl)formamide (7a) (2 mg, 2%).

Method D: A mixture of 4-hydroxy-3-nitrocoumarin (1: 0.207 g, 1 mmol), formic acid (2a: 0.38 ml, 0.46 g, 10 mmol) and Pd/C 10% (51 mg, 0.05 mmol) was heated in an oil bath at 100 °C under 1 atm hydrogen and stirring for 12 h. The hydrogen was removed, EtOAc (5 ml) was added to the hot mixture (without further heating) and the mixture was filtered. The solid was washed with hot EtOAc (8 × 5 ml) and the solution was evaporated and purified by column chromatography (silica gel: hexane/EtOAc, 1:1) to afford 6a (0.197 g, 96%) followed by derivative 5a (2 mg, 2%).

Compound 6a

White solid; m.p. 233–234 °C (chloroform).

IR (KBr): 3299, 3239, 3046, 2955, 2858, 1675, 1629, 1601, 1545 cm⁻¹.

1H NMR (CDCl₃, 500 MHz): δ = 12.62 (brs, 1 H), 9.95 (brs, 1 H), 8.17 (d, J = 1.9 Hz, 1 H), 7.89 (dd, J₁ = 7.8, J₂ = 1.0 Hz, 1 H), 7.65 (t, J = 7.8 Hz, 1 H), 7.43–7.30 (m, 2 H).

13C NMR (CDCl₃, 126 MHz): δ = 162.2, 159.7, 155.8, 150.9, 132.2, 124.5, 123.7, 116.2, 115.1, 108.2.

MS (ESI): m/z = 204 [M + H]⁺ (MS-GC-MS lit.46).

Compound 5

White solid; m.p. 220–222 °C (ethanol) (lit.47 220–222 °C).

N-(4-Hydroxy-2-oxo-2H-chromen-3-yl)acetamide (6b)

Yield: (Method C, 130 °C, 1 h): 0.205 g (94%); (Method D, 120 °C): 0.205 g (94%); white solid; m.p. 230–231 °C (chloroform/hexane) (lit.44 228–230 °C).

IR (KBr): 3288, 3059, 2938, 2867, 1687, 1628, 1600, 1572 cm⁻¹.

1H NMR (CDCl₃, 500 MHz): δ = 12.31 (brs, 1 H), 9.48 (brs, 1 H), 7.88 (d, J = 7.7 Hz, 1 H), 7.64 (d, J = 7.7 Hz, 1 H), 7.42–7.36 (m, 2 H), 2.11 (s, 3 H).

13C NMR (CDCl₃, 126 MHz): δ = 171.1, 160.1, 157.1, 151.1, 132.1, 124.4, 123.6, 116.3, 116.1, 103.6, 22.7.

MS (ESI): m/z = 218 [M + H]⁺.
N-(4-Hydroxy-2-oxo-2H-chromen-3-yl)isobutyramide (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, 3060, 2966, 2934, 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), 2.38–2.72 (m, 1 H), 1.30 (d, J = 6.9 Hz, 6 H).

13C NMR (CDCl₃, 150 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.

MS (ESI): m/z = 246 [M + H]⁺.

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

Yield (Method C, 140 °C, ca. 57 W, 1.5 h): 0.239 g (95%); (Method D, 140 °C): 0.232 g (92%); white solid; m.p. 154–155 °C (hexane).

IR (KBr): 3293, 3055, 2964, 2953, 2872, 1682, 1635, 1603, 1571, 1537 cm⁻¹.

1H NMR (CDCl₃, 500 MHz): δ = 13.64 (brs, 1 H), 8.19 (brs, 1 H), 7.97 (d, J = 7.9 Hz, 1 H), 7.55–7.50 (m, 1 H), 7.35–7.29 (m, 2 H), 2.39 (d, J = 7.2 Hz, 2 H), 2.27–2.16 (m, 1 H), 1.04 (t, J = 6.6 Hz, 3 H).

13C NMR (CDCl₃, 150 MHz): δ = 164.1, 152.6, 150.4, 131.8, 124.8, 124.5, 117.2, 116.3, 104.8, 45.8, 26.7, 22.4.

MS (ESI): m/z = 260 [M + H]⁺.

HRMS (ESI-MS): m/z [M + H]⁺ calcd for C₁₄H₁₆NO₅: 263.0775; found: 262.0725.

Supporting Information

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References


(34) Bellale, E. V.; Choudhary, M. K.; Akamanchi, K. G. Synthesis 2009, 3211.