

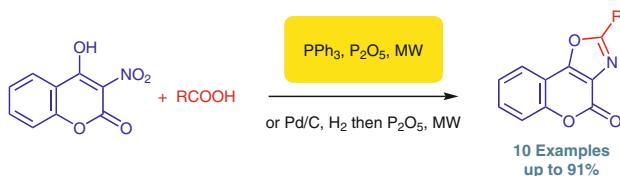
One-pot Synthesis of 2-Substituted 4H-Chromeno[3,4-d]oxazol-4-ones from 4-Hydroxy-3-nitrocoumarin and Acids in the Presence of Triphenylphosphine and Phosphorus Pentoxide under Microwave Irradiation

T. D. Balalas^aG. Stratidis^aD. Papatheodorou^aE.-E. Vlachou^aC. Gabriel^bD. J. Hadjipavlou-Litina^cK. 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

^c Department of Pharmaceutical Chemistry, School of Pharmacy, Aristotle University of Thessaloniki, Thessaloniki 54124, Greece



Received: 31.01.2018

Accepted after revision: 13.03.2018

Published online: 17.04.2018

DOI: 10.1055/s-0036-1591977; Art ID: so-2018-d0015-op

License terms:

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 PPh_3 and P_2O_5 under microwave irradiation or by one-pot two-step reactions in the presence of Pd/C and hydrogen and then P_2O_5 under microwave irradiation. The fused oxazolocoumarins were also synthesized from 3-amido-4-hydroxycoumarins and P_2O_5 under microwave irradiation. The 3-amido-4-hydroxycoumarins are obtained almost quantitatively from 4-hydroxy-3-nitrocoumarin, acids and PPh_3 under microwave irradiation, or in the presence of Pd/C and H_2 on heating. Preliminary biological tests indicate significant inhibition of soybean lipoxygenase and antilipid peroxidation for both oxazolocoumarins and o-hydroxyamidocoumarins.

Key words oxazolocoumarins, PPh_3 , reduction, phosphorus pentoxide, microwaves, Pd/C

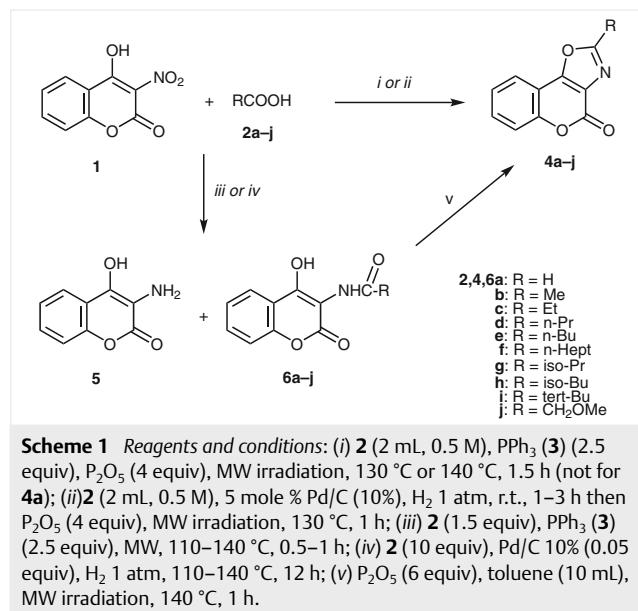
Coumarins are a class of compounds that are widely distributed in natural products and in synthetic biologically active derivatives¹ with interesting biological properties, such as anticoagulant, antibiotic, anti-inflammatory, anti-HIV, and anticancer activity. Fused coumarins are also biologically active agents. In particular, fused oxazolocoumarins have been examined for antibacterial,² anti-inflammatory,^{2,3} antimicrobial,⁴ and photosensitizing⁵ activities and as agonists/antagonists⁶ of benzodiazepine receptors. Recently, such derivatives have been used as photolabile pro-

tecting groups, forming conjugates with active compounds as prodrugs, for the photorelease and controlled delivery of the active molecules.⁷ 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 benzoxazoles and oxazoles, there are usually two approaches. One is the condensation of *o*-aminophenols¹³ with aldehydes, orthoesters, acids, acid derivatives, alcohols or β -diketones catalyzed by metal derivatives. The other is the intramolecular cyclization of *o*-hydroxyamides,¹⁴ or the metal-catalyzed cyclization of *o*-haloamides,¹⁵ enamides,¹⁶ and amides.¹⁷ Benzoxazoles have also been prepared by a one-pot multistep procedure, from *o*-nitrophenols with alcohols in the presence of Au nanoparticles/ TiO_2 ,¹⁸ Cu-Pd nanoparticles/ $\gamma\text{-Al}_2\text{O}_3$,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,^{2,4,6,12,22} acids^{6,22} or anhydrides,^{2,12} or by condensation of *o*-amidohydroxycoumarins with anhydrides,²³ POCl_3 ,²⁴ or P_2O_5 .²⁵ 2-Methyl-4*H*-[1]benzopyrano[3,4-*d*]oxazol-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-chromenedione in CH₃CN in the presence of Rh₂(OAc)₄ as catalyst.²⁷ 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.²⁸ The formation of oxazolocoumarins 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 methyl-arenes, or arylacetic esters.³⁰ Very recently, we have synthesized oxazolocoumarins 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



Triphenylphosphine (PPh₃) is a versatile reagent for the reduction of a range of substrates including azides³² (Staudinger reaction), disulfides,³³ sulfonyl chloride,³⁴ peroxides,³⁵ ozonides,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 oxazolocoumarin derivatives,^{1d,30,31} we would like to present, herein, the use of PPh₃ for the one-pot synthesis of fused oxazolocoumarins 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-nitrocoumarin⁴⁰ (**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.⁴¹ In contrast to expectations, only the amides **6a** and **6b**^{23b} 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**²⁶ 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 oxazolocoumarin **4c**^{23a} 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 P₂O₅.⁴³

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). 3-Amino-

Table 1 One-Pot Synthesis of 2-Substituted 4*H*-Chromeno[3,4-*d*]oxazol-4-ones **4b–j** from 4-Hydroxy-3-nitrocoumarin (**1**) and Acids **2a–j**

Entry	Acid RCOOH 2a–j (R)	Conditions	Temp. (°C)	Time (h)	Product (yield, %) ^a
1	2a (H) ^b	SnCl ₂ ·2H ₂ O, MW	100	45 min	6a (48), 1 (40)
2	2b (CH ₃)	SnCl ₂ ·2H ₂ O, MW	120	2.5	6b (42), 1 (40)
3	2b (CH ₃)	PPh ₃ (3), P ₂ O ₅ , MW (Method A)	130	1.5	4b (89)
4	2b (CH ₃)	Pd/C, H ₂ , then P ₂ O ₅ , MW (Method B)	r.t. then 130	1 then 1	4b (87)
5	2c (CH ₂ CH ₃)	Method A	130	1.5	4c (89)
6	2c (CH ₂ CH ₃)	Method B	r.t. then 140	1 then 1	4c (86)
7	2d (CH ₂ CH ₂ CH ₃)	Method A	140	1.5	4d (89)
8	2d (CH ₂ CH ₂ CH ₃)	Method B	r.t. then 140	2 then 1.5	4d (84)
9	2e (CH ₂ CH ₂ CH ₂ CH ₃)	Method A	140	1.5	4e (89)
10	2e (CH ₂ CH ₂ CH ₂ CH ₃)	Method B	150	3 then 1.5	4e (85)
11	2f [CH ₂ (CH ₂) ₅ CH ₃]	Method A	140	1.5	4f (90)
13	2g (i-Pr)	Method A	140	1.5	4g (89)
14	2h (i-Bu)	Method A	140	1.5	4h (90)
15	2i (t-Bu)	Method A	140	2.5	4i (91)
16	2j (CH ₂ OCH ₃)	Method A	140	1.5	4j (7)
17	2j (CH ₂ OCH ₃)	Method B	r.t. then 130	1 then 1	4j (7)

^a Isolated yield.^b Formic acid not tested with P₂O₅ because they react violently under CO production.⁴²

4-hydroxycoumarin (**5**), 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.^{23a} 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**⁴⁴ or propionamidocoumarin **6c**,^{23a} 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**⁴⁴ or **6e**⁴⁴ (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 POCl₃ in refluxing CHCl₃, as expected for the analogous benzoxazole synthesis.^{14b} This led to **4b** in refluxing acetic anhydride^{23b} for 10 min, quantitatively (99%). Oxazolocoumarin **4b** was also obtained quantitatively from a toluene solution of **6b** in the presence of P₂O₅²⁵ under reflux for 6 h or microwave irradiation at 140 °C for 1 h. An effort to get oxazolocoumarin **4a**

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

Entry	Acid RCOOH 2a–j (R)	Conditions	Temp. (°C)	Time (h)	Product (yield, %)
1	2a (H)	PPh ₃ (3), MW (Method C)	110	30 min	6a (98), 5 (trace)
2	2a (H)	Pd/C, H ₂ , heating (Method D)	100	12	6a (96), 5 (trace)
3	2b (CH ₃)	Method C	130	1	6b (94), 5 (trace)
4	2b (CH ₃)	Method D	120	12	6b (94), 5 (trace)
5	2c (CH ₂ CH ₃)	Method C	130	1	6c (96), 5 (trace)
6	2c (CH ₂ CH ₃)	Method D	120	12	6c (94), 5 (trace)
7	2d (CH ₂ CH ₂ CH ₃)	Method C	140	1	6d (94), 5 (trace)
8	2d (CH ₂ CH ₂ CH ₃)	Method D	130	12	6d (91), 5 (trace)
9	2e (CH ₂ CH ₂ CH ₂ CH ₃)	Method C	140	1	6e (93), 5 (trace)
10	2e (CH ₂ CH ₂ CH ₂ CH ₃)	Method D	140	12	6e (91), 5 (trace)
11	2f [CH ₂ (CH ₂) ₅ CH ₃]	Method C	140	1.5	6f (89), 5 (trace)
12	2f [CH ₂ (CH ₂) ₅ CH ₃]	Method D	140	12	6f (85), 5 (trace)
13	2g (i-Pr)	Method C	130	1.5	6g (95), 5 (trace)
14	2g (i-Pr)	Method D	130	12	6g (92), 5 (trace)
15	2h (i-Bu)	Method C	140	1.5	6h (95), 5 (trace)
16	2h (i-Bu)	Method D	140	12	6h (92), 5 (trace)
17	2i (t-Bu)	Method C	140	1.5	6i (25), 5 (67)
18	2i (t-Bu)	Method D	140	12	6i (39), 5 (56)
19	2j (CH ₂ OCH ₃)	Method C	130	45 min	6j (95), 5 (trace)
20	2j (CH ₂ OCH ₃)	Method D	120	12	6j (93), 5 (trace)

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,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-amidinopropane) dihydrochloride (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-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.

Table 3 Inhibition (%) of Lipid Peroxidation (AAPH%): *in vitro* Inhibition of Soybean Lipoxygenase (%LOX) /IC₅₀ μM

Entry	Compounds	Anti-LP% @ 100 μM (±SD) ^a	IC ₅₀ μM or %LOX Inh. @ 100 μM (±SD) ^a
1	4a	53±0.7	74±1.4
2	4b	100±3	53.5±0.4
3	4c	74±1.1	74±1.1
4	4d	95±1.8	30±1
5	4e	95±0.8	32.5±0.6
6	4f	100±2	75±2.3
7	4g	95±0.6	49±1
8	4h	100±1.2	56±1.7
9	4i	56±1.7 μM	60±1.4
10	4j	57±0.6	70±1
11	6a	83±1.8	61.5±0.7
12	6b	79±2	64±1.3
13	6c	100±3.1	48±1%
14	6d	54±0.5	NA ^b
15	6e	100±2.8	59±0.9
16	6f	67±0.5	62±1.2
17	6g	79±1.3	70±0.3
18	6h	45±0.4	45±0.9
19	6i	79±1.1	62±1.1
20	6j	67±0.8	53±1
21	NDGA		93%/0.55 μM (±0.1)
22	Trolox	88±1	

^a Values are means ±SD of three or four different determinations.^b NA: no activity under the reported experimental conditions.

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 an Agilent 500/54 (DD2) (500 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 No. 60, Merck A.G. was used for column chromatography. The MW experiment was performed in a scientific focused microwave reactor (Biotage Initiator 2.0) in a 2 mL tube or in a 20 mL tube for the larger scale reaction. 4-Hydroxy-3-nitrocoumarin were prepared according to a reported procedure.⁴⁰

2-Methyl-4H-chromeno[3,4-d]oxazol-4-one (**4b**); Typical Procedures

Method A: 4-Hydroxy-3-nitrocoumarin (**1**; 0.1035 g, 0.5 mmol), acetic acid (**2b**; 1 mL, 0.5 M), PPh₃ (**3**; 0.328 g, 1.25 mmol) and P₂O₅ (0.284 g, 2 mmol) were added to a flask for the MW oven. The mixture was irradiated at 130 °C (ca. 2 bar, ca. 48 W) for 1.5 h. After cool-

ing, the liquid mixture was poured in a separation funnel. The remaining solid in the reaction flask was treated alternately with EtOAc (10 × 2 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). The combined organic layers were dried over anhydrous Na₂SO₄ and separated by column chromatography [silica gel; hexane/EtOAc, 3:1] to afford compound **4b** (90 mg, 89%).

When the same reaction was performed in larger scale by using **1** (1.035 g, 5 mmol), **2b** (10 mL), **3** (3.28 g, 12.5 mmol) and P₂O₅ (2.84 g, 20 mmol) under irradiation 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 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. 2 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%).

Method E: 3-Acetamido-4-hydroxycoumarin (**6b**; 0.11 g, 0.5 mmol), P₂O₅ (0.426 g, 3 mmol) and toluene (5 mL) were added to a flask for a MW oven. 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%).

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. EtOAc (20 mL) was added and the mixture was washed with water (3 × 10 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered and evaporated to give **4b** (0.1 g, 99%).

Compound **4b**

White solid; m.p. 198–200 °C (toluene/hexane) (lit.²⁶ 196–197 °C).

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

¹H NMR (CDCl₃, 500 MHz): δ = 7.80 (d, J = 7.9 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 = 163.7, 156.0, 155.7, 153.0, 131.6, 124.95, 124.9, 121.4, 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, EtOAc (20 mL) was added and the mixture was washed with water (3 × 10 mL). The

organic layer was dried over anhydrous Na_2SO_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): 3134, 1752, 1630, 1599, 1510 cm^{-1} .

^1H NMR (CDCl_3 , 500 MHz): δ = 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): δ = 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 $\text{C}_{10}\text{H}_6\text{NO}_3$: for 188.0342; found: 188.0343.

2-Ethyl-4*H*-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, 2995, 2879, 1754, 1640, 1599, 1584 cm^{-1} .

^1H NMR (CDCl_3 , 500 MHz): δ = 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): 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.

MS (ESI): m/z = 216 [M + H]⁺, 238 [M + Na]⁺.

2-Propyl-4*H*-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 (CDCl_3 , 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), 2.96 (t, J = 7.5 Hz, 2 H), 1.98–1.91 (m, 2 H), 1.07 (t, J = 7.4 Hz, 3 H).

^{13}C NMR (CDCl_3 , 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.

MS (ESI): m/z = 230 [M + H]⁺, 252 [M + Na]⁺.

HRMS (ESI-MS): m/z [M + H]⁺ calcd for $\text{C}_{13}\text{H}_{12}\text{NO}_3$: 230.0812; found: 230.0812.

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

Yield (Method A, 140 °C): 0.108 g (89%); (Method B, 3 h then 1.5 h): 0.103 g (85%); (Method E, 150 °C): 0.120 g (99%); white solid; m.p. 113–114 °C (toluene/hexane).

IR (KBr): 3085, 2952, 2930, 2870, 1750, 1642, 1600, 1583, 1500 cm^{-1} .

^1H NMR (CDCl_3 , 500 MHz): δ = 7.80 (d, J = 7.8 Hz, 1 H), 7.56 (t, J = 7.8 Hz, 1 H), 7.46 (d, J = 8.4 Hz, 1 H), 7.38 (t, J = 7.6 Hz, 1 H), 2.98 (t, J = 7.6 Hz, 2 H), 1.91–1.86 (m, 2 H), 1.49–1.44 (m, 2 H), 0.97 (t, J = 7.4 Hz, 3 H).

^{13}C NMR (CDCl_3 , 126 MHz): δ = 167.4, 156.2, 155.4, 152.9, 131.5, 124.9, 124.8, 121.4, 117.7, 111.7, 28.8, 28.1, 22.3, 13.7.

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

HRMS (ESI-MS): m/z [M + Na]⁺ calcd for $\text{C}_{14}\text{H}_{13}\text{NNaO}_3$: 266.0793; found: 266.0767.

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

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, 2921, 2849, 1748, 1640, 1582, 1558, 1499 cm^{-1} .

^1H NMR (CDCl_3 , 500 MHz): δ = 7.81 (d, J = 7.8 Hz, 1 H), 7.55–7.60 (m, 1 H), 7.48 (d, J = 8.4 Hz, 1 H), 7.39 (t, J = 7.6 Hz, 1 H), 2.98 (t, J = 7.6 Hz, 2 H), 1.94–1.85 (m, 2 H), 1.45–1.40 (m, 2 H), 1.39–1.34 (m, 2 H), 1.32–1.26 (m, 4 H), 0.88 (t, J = 6.8 Hz, 3 H).

^{13}C NMR (CDCl_3 , 126 MHz): δ = 167.4, 156.2, 155.5, 153.0, 131.5, 124.9, 124.8, 121.5, 117.8, 111.8, 31.7, 29.1, 28.9, 28.5, 26.9, 22.7, 14.2.

MS (ESI): m/z = 286 [M + H]⁺, 308 [M + Na]⁺.

HRMS (ESI-MS): m/z [M + H]⁺ calcd for $\text{C}_{17}\text{H}_{20}\text{NO}_3$: 286.1443; found: 286.1439.

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

Yield: (Method A, 140 °C): 0.102 g (89%); (Method E, 150 °C): 0.113 g (99%); white solid; m.p. 125–126 °C (toluene/hexane).

IR (KBr): 3064, 2981, 2946, 2910, 2879, 1753, 1637, 1598, 1575 cm^{-1} .

^1H NMR (CDCl_3 , 500 MHz): δ = 7.83 (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), 3.35–3.26 (m, 1 H), 1.49 (d, J = 7.0 Hz, 6 H).

^{13}C NMR (CDCl_3 , 126 MHz): δ = 171.4, 156.3, 155.4, 153.0, 131.5, 124.9, 124.7, 121.5, 117.7, 111.8, 29.0, 20.4.

MS (ESI): m/z = 230 [M + H]⁺, 252 [M + Na]⁺.

HRMS (ESI-MS): m/z [M + H]⁺ calcd for $\text{C}_{13}\text{H}_{12}\text{NO}_3$: 230.0812; found: 230.0811.

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

Yield: (Method A, 140 °C): 0.109 g (90%); (Method E, 150 °C): 0.12 g (99%); white solid; m.p. 117–119 °C (toluene/hexane).

IR (KBr): 3086, 2936, 2961, 2898, 2876, 1753, 1640, 1601, 1579 cm^{-1} .

^1H NMR (CDCl_3 , 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).

^{13}C NMR (CDCl_3 , 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 $\text{C}_{14}\text{H}_{14}\text{NO}_3$: 244.0968; found: 244.0972.

2-(tert-Butyl)-4*H*-chromeno[3,4-*d*]oxazol-4-one (4i)

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 (CDCl_3 , 500 MHz): δ = 7.84 (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).

^{13}C NMR (CDCl_3 , 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 $\text{C}_{14}\text{H}_{14}\text{NO}_3$: 244.0968; found: 244.0963.

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): 3088, 2937, 2907, 2829, 1748, 1641, 1596, 1500 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 C₁₂H₉NNaO₄: 254.0424; found: 254.0420.

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, 0.138 g, 3 mmol), and PPh₃ (**3**; 0.656 g, 2.5 mmol) 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 cooling, CH₂Cl₂ (10 mL) was added and the solution was evaporated and the mixture was separated by column chromatography (silica gel, hexane/EtOAc, 2:1 to 1:10) to give compound **6a** (0.2 g, 98%) followed by 3-amino-3-hydroxycoumarin **5** (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 **5** (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), 7.43–7.38 (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, 116.15, 102.8.

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, 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)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 = 13.62 (brs, 1 H), 8.18 (brs, 1 H), 7.98 (d, J = 7.9 Hz, 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): 3281, 3217, 3054, 2961, 2934, 2874, 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 = 7.9 Hz, 1 H), 7.56–7.52 (m, 1 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)pentanamide (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): 3279, 3209, 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), 8.18 (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), 1.77–1.72 (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)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, 3966, 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), 2.78–2.72 (m, 1 H), 1.30 (d, J = 6.9 Hz, 6 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.

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, 126 MHz): δ = 174.2, 161.1, 153.0, 150.6, 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 C₁₄H₁₆NO₄: 262.1074; found: 262.1072.

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

Yield (Method C, 140 °C, 1.5 h, ca. 57 W): 65 mg (25%); (Method D, 140 °C): 0.101 g (39%); white solid; m.p. 149–151 °C (hexane).

IR (KBr): 3370, 3065, 2969, 2874, 1687, 1637, 1607, 1533 cm⁻¹.

¹H NMR (CDCl₃, 500 MHz): δ = 13.87 (brs, 1 H), 8.41 (brs, 1 H), 7.98 (dd, J₁ = 7.9, J₂ = 1.0 Hz, 1 H), 7.55–7.51 (m, 1 H), 7.36–7.31 (m, 2 H), 1.37 (s, 9 H).

¹³C NMR (CDCl₃, 126 MHz): δ = 180.2, 161.3, 152.8, 150.6, 131.7, 124.8, 124.5, 117.3, 116.3, 104.7, 39.8, 27.7.

MS (ESI): *m/z* = 260 [M – H]⁻.

HRMS (ESI-MS): *m/z* [M + H]⁺ calcd for C₁₄H₁₆NO₄: 262.1074; found: 262.1075.

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

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.

MS (ESI): *m/z* = 248 [M – H]⁻.

HRMS (ESI-MS): *m/z* [M + H]⁺ calcd for C₁₂H₁₂NO₅: 250.0710; found: 250.0711.

Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0036-1591977>.

References

- (a) Murray, D. H.; Mendez, J.; Brown, S. A. *The Natural Coumarins: Occurrence, Chemistry and Biochemistry*; J. Wiley: New York, **1982**. (b) O'Kennedy, R.; Thornes, R. D. *Coumarins: Biology, Applications and Mode of Action*; Wiley: Chichester, **1997**. (c) Yu, D. L.; Suzuki, M.; Xie, L.; Morris-Natsche, S. L.; Lee, K. H. *Med. Res. Rev.* **2003**, *23*, 322. (d) Fylaktakidou, K. C.; Hadjipavlou-Litina, D. J.; Litinas, K. E.; Nicolaides, D. N. *Curr. Pharm. Des.* **2004**, *10*, 3813. (e) Santana, L.; Uriarte, E.; Roleira, F.; Milhazes, N.; Borges, F. *Curr. Med. Chem.* **2004**, *11*, 3239. (f) Lacy, A.; O'Kennedy, R. *Curr. Pharm. Des.* **2004**, *10*, 3797. (g) Zhang, X.-S.; Li, Z.-W.; Shi, Z.-J. *Org. Chem. Front.* **2014**, *1*, 44. (h) Medina, F. G.; Marrero, J. G.; Alonso, M. M.; González, M. C.; Córdova-Guerrero, I.; García, A. G. T.; Osegueda-Robles, S. *Nat. Prod. Rep.* **2015**, *32*, 1472.
- Sahoo, S. S.; Shukla, S.; Nandy, S.; Sahoo, H. B. *Eur. J. Exp. Biol.* **2012**, *2*, 899.
- Kontogiorgis, C.; Hadjipavlou-Litina, D. *J. Enzyme Inhib. Med. Chem.* **2003**, *18*, 63.
- Prasanna, B.; Sandeep, A.; Revathi, T. *World J. Pharm. Pharm. Sci.* **2014**, *3*, 404.
- Pathak, M. A.; Fellman, J. H.; Kaufman, K. D. *J. Invest. Dermatol.* **1960**, *35*, 165.
- Colotta, V.; Catarzi, D.; Varano, F.; Cecchi, L.; Filacchioni, G.; Martini, C.; Giusti, L.; Lucacchini, A. *Il Farmaco* **1998**, *53*, 375.
- (a) Soares, A. M. S.; Hungeford, G.; Goncalves, M. S. T.; Costa, S. P. G. *New J. Chem.* **2017**, *41*, 2997. (b) Soares, A. M. S.; Hungeford, G.; Costa, S. P. G.; Goncalves, M. S. T. *Dyes Pigm.* **2017**, *137*, 91. (c) Soares, A. M. S.; Piloto, A. M.; Hungeford, G.; Costa, S. P. G.; Goncalves, M. S. T. *Eur. J. Org. Chem.* **2012**, 922. (d) Soares, A. M. S.; Costa, S. P. G.; Goncalves, M. S. T. *Tetrahedron* **2010**, *66*, 8189.
- Matos, M. J.; Gaspar, A.; Kachler, S.; Klotz, K.-N.; Borges, F.; Santana, L.; Uriarte, E. *J. Pharm. Pharmacol.* **2013**, *65*, 30.
- Danis, O.; Yuce-Dursun, B.; Gunduz, C.; Ogan, A.; Sener, G.; Bulut, M.; Yarat, A. *Arzneim. Forsch.* **2010**, *60*, 617.
- Radanyi, C.; Le Bras, G.; Messaoudi, S.; Bouclier, C.; Peyrat, J.-F.; Brion, J.-D.; Marsaud, V.; Renoir, J.-M.; Alami, M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2495.
- Patonay, T.; Litkei, G. Y.; Bognar, R.; Erdei, J.; Miszti, C. *Pharmazie* **1984**, *39*, 86.
- Nofal, Z. M.; El-Zahar, M. I.; Abd El-Karim, S. S. *Molecules* **2000**, *5*, 99.
- (a) Sharma, H.; Singh, N.; Jang, D. O. *Green Chem.* **2014**, *16*, 4922. (b) Mohammadpoor-Baltork, I.; Khosropour, A. R.; Hojati, S. F. *Monatsh. Chem.* **2007**, *138*, 663. (c) Yamamoto, K.; Watanabe, H. *Chem. Lett.* **1982**, *11*, 1225. (d) Maleki, B.; Baghayeri, M.; Vahdat, S. M.; Mohammadzadeh, A.; Akhoondi, S. *RSC Adv.* **2015**, *5*, 46545. (e) Khalafi-Nezhad, A.; Panahi, F. *ACS Catal.* **2014**, *4*, 1686. (f) Mayo, M. S.; Yu, X.; Zhou, X.; Feng, X.; Yamamoto, Y.; Bao, M. *J. Org. Chem.* **2014**, *79*, 6310.
- (a) Rambabu, D.; Murthi, P. R. K.; Dulla, b.; Rao, M. V. B.; Pal, M. *Synth. Commun.* **2013**, *43*, 3083. (b) Li, K.-L.; Du, Z.-B.; Guo, C.-C.; Chen, Q.-Y. *J. Org. Chem.* **2009**, *74*, 3286. (c) Doeller, W. *Ber. Dtsch. Chem. Ges. B.* **1939**, *72*, 2148. (d) Phillips, M. A. *J. Chem. Soc.* **1930**, 2685.

- (15) (a) Jadhav, J.; Gaikwad, V.; Kurane, R.; Salunkhe, R.; Rashinkar, G. *Tetrahedron* **2013**, *69*, 2920. (b) Saha, P.; Ramana, T.; Purkait, N.; Ali, M. A.; Paul, r.; Punniyamurthy, T. *J. Org. Chem.* **2009**, *74*, 8719. (c) Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802. (d) Altenhoff, G.; Glorius, F. *Adv. Synth. Catal.* **2004**, *346*, 1661.
- (16) Cheung, C. W.; Buchwald, S. L. *J. Org. Chem.* **2012**, *77*, 7526.
- (17) Ueda, S.; Nagasawa, H. *J. Org. Chem.* **2009**, *74*, 4272.
- (18) Tang, L.; Guo, X.; Yang, Y.; Zha, Z.; Wang, Z. *Chem. Commun.* **2014**, *6145*.
- (19) Feng, F.; Ye, J.; Cheng, Z.; Xu, X.; Zhang, Q.; Ma, L.; Lu, C.; Li, X. *RSC Adv.* **2016**, *6*, 72750.
- (20) Lee, J. J.; Kim, J.; Jun, J. M.; Lee, B. M.; Kim, B. H. *Tetrahedron* **2009**, *65*, 8821.
- (21) Ryuzaburo, N.; Watanabe, H.; Kuwata, S.; Yokoyama, S. *Yakugaku Zasshi* **1959**, *79*, 1378; *Chem. Abstr.* **1960**, *10936*.
- (22) Reddy, S. *J. Indian Chem. Soc.* **1981**, *58*, 599.
- (23) (a) Dallacker, F.; Kratzer, P.; Lipp, M. *Justus Liebigs Ann. Chem.* **1961**, *643*, 97. (b) Stammer, C. H. *J. Org. Chem.* **1960**, *25*, 460. (c) Hinman, J. W.; Caron, E. L.; Hoeksema, H. *J. Am. Chem. Soc.* **1957**, *79*, 3789.
- (24) Gammon, D. W.; Hunter, R.; Wilson, S. A. *Tetrahedron* **2005**, *61*, 10683.
- (25) Saikachi, H.; Ichikawa, M. *Chem. Pharm. Bull.* **1966**, *14*, 1162.
- (26) Chantegrel, B.; Nadi, A. I.; Gelin, S. *J. Org. Chem.* **1984**, *49*, 4424.
- (27) Lee, Y. R.; Suk, J. Y.; Kim, B. S. *Tetrahedron Lett.* **1999**, *40*, 6603.
- (28) Kaufman, K. D.; McBride, D. W.; Eaton, D. C. *J. Org. Chem.* **1965**, *30*, 4344.
- (29) Abdelghani, S.; Abd El-Aal, A.; Shehab, W.; El-Mobayed, M. *Synthesis* **2003**, *1373*.
- (30) Bezergiannidou-Balouctsi, C.; Litinas, K. E.; Malamidou-Xenikaki, E.; Nicolaides, D. N.; Mentzasos, D.; Terzis, A. *Tetrahedron* **1993**, *49*, 9127.
- (31) Vlachou, E.-E. N.; Armatas, G. S.; Litinas, K. E. *J. Heterocycl. Chem.* **2017**, *54*, 2447.
- (32) (a) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635. (b) Pal, B.; Jaisankar, P.; Giri, V. S. *Synth. Commun.* **2004**, *34*, 1317.
- (33) Humphrey, R. E.; McGrary, A. L.; Webb, R. M. *Talanta* **1965**, *12*, 727.
- (34) Bellale, E. V.; Chaudhari, M. K.; Akamanchi, K. G. *Synthesis* **2009**, *3211*.
- (35) Erden, I.; Gartner, C.; Azimi, M. S. *Org. Lett.* **2009**, *11*, 3986.
- (36) Carles, J.; Fliszar, S. *Can. J. Chem.* **1969**, *47*, 1113.
- (37) (a) Mustafa, A. H.; Malakar, C. C.; Ajaar, N.; Merisor, E.; Conrad, J.; Beifuss, U. *Synlett* **2013**, *24*, 1573. (b) Creencia, E. C.; Kosaka, M.; Muramatsu, T.; Kobayashi, M.; Oizuka, T.; Horaguchi, T. *J. Heterocycl. Chem.* **2009**, *46*, 1309. (c) Sanz, R.; Escribano, J.; Pedrosa, M. R.; Aguado, R.; Arnaiz, F. J. *Adv. Synth. Catal.* **2007**, *349*, 713. (d) Freeman, A. W.; Urvoy, M.; Criswell, M. E. *J. Org. Chem.* **2005**, *70*, 5014. (e) Scott, P. H.; Smith, C. P.; Kober, E.; Churchill, J. W. *Tetrahedron Lett.* **1970**, *1153*. (f) Cadogan, J. I. G.; Cameron-Wood, M.; Mackie, R. K.; Searle, R. J. G. *J. Chem. Soc.* **1965**, *4831*.
- (38) Odum, R. A.; Brenner, M. *J. Am. Chem. Soc.* **1966**, *88*, 2074.
- (39) Kaneko, C.; Yamamori, M.; Yamamoto, A.; Hayashi, R. *Tetrahedron Lett.* **1978**, *31*, 2799.
- (40) Iaroshenko, V. O.; Mkrtchyan, S.; Gevorgyan, A.; Vilches-Herrera, M.; Sevenard, D. V.; Villinger, A.; Ghochikyan, T. V.; Saghiyan, A.; Sosnovskikh, V. Y.; Lange, P. *Tetrahedron* **2012**, *68*, 2532.
- (41) VanVliet, D. S.; Gillespie, P.; Scicinski, J. J. *Tetrahedron Lett.* **2005**, *46*, 6741.
- (42) <http://www.inchem.org/documents/icsc/icsc/eics0485.htm>.
- (43) Kameda, A.; Nishimori, H.; Omura, S.; Koike, M.; Hino, T.; Jobashi, T.; Maeyama, K.; Yonezawa, N. *Nippon Kagaku Kaishi* **2002**, *211*.
- (44) Reppel, L.; Schmollak, W. *Arch. Pharm.* **1964**, *297*, 45.
- (45) Balalas, T.; Abdul-Sada, A.; Hadjipavlou-Litina, D. J.; Litinas, K. E. *Synthesis* **2017**, *49*, 2575.
- (46) <https://pubchem.ncbi.nlm.nih.gov/compound/54738232#section>.
- (47) Wang, Z.-M.; Xie, S.-S.; Li, X.-M.; Wu, J.-J.; Wang, X.-B.; Kong, L.-Y. *RSC Adv.* **2015**, *5*, 70395.