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Coupled Domino Processes: Synthesis of 3,5,8-Trisubstituted Coumarins from Propargyl Vinyl Ethers

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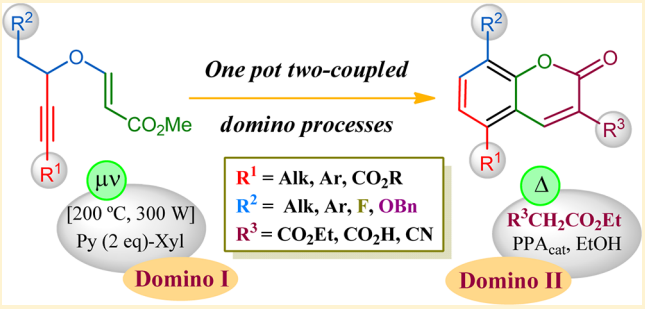
Supporting Information

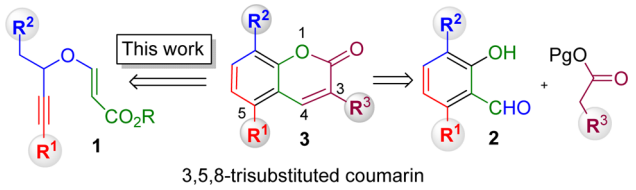
ABSTRACT: The generation of a small and representative library of 3,5,8-trisubstituted coumarins (21 compounds, 7 families, 3 groups) is described. The library was built from the corresponding propargyl vinyl ethers and three different 1,3-dicarbonyl derivatives using a one-pot coupled domino strategy. These coumarins constitute a novel chemotype defined by the presence of a chemical handle in the pyranone ring and a varied substitution pattern adorning the aromatic ring, which includes fluorine- or oxygen-containing functionalities.



Coumarins (2*H*-benzo-pyran-2-ones) comprise a large family of natural scaffolds provided with a broad spectrum of biological and pharmaceutical activities[1] and a privileged array of physicochemical properties such as a high capacity of fluorescence,[2] which has been conveniently exploited in analytical chemistry, biology, and medicine.[3] In general, the substitution pattern decorating these scaffolds largely determines their activity profiles[1] and modulates their physicochemical properties.[4] Thus, novel substitution patterns could offer novel pharmacological (therapeutic) annotations and novel biological and physicochemical properties.[3,5] From a chemical point of view, the access to novel coumarin chemotypes can be achieved either by chemical modifications of an existing one[6] or by de novo synthesis from suitable precursors. Where the first approach usually requires chemoselective manipulation of functional groups, the second one calls for a synthetic methodology capable of directly constructing the coumarin core with the appropriate substitution pattern already installed. This approach offers new opportunities for synthetic innovation and especially for the development of novel domino methodologies for use in drug discovery and development. With this idea in mind, we report herein our results in the development of a fast, operationally simple, one-pot coupled domino manifold for accessing novel 3,5,8-trisubstituted coumarins **3** from readily available propargyl vinyl ethers **1** (Scheme 1).

The substitution pattern involving the positions C_3, C_5, and C_8 (Scheme 1) is scarcely represented in the series of both natural and synthetic coumarins,[7] and its biological (therapeutic) annotation has not been conveniently studied. The main reason for this lack of information is the challenging access to this family of trisubstituted coumarins by standard synthetic methodologies. In general, coumarins are currently synthesized from the corresponding phenolic derivatives[8] conveniently functionalized (generally functionalized salicylaldehydes) by condensation with a suitable carbonyl derivative (Scheme 1).[1,8] The main limitation associated with these strategies lies on their lack of generality and efficiency; not all of the positions of the aromatic and pyranone rings can be accessed from readily obtained salicylaldehydes. This issue directly translates the problem of coumarin functionalization to the corresponding parent salicylaldehydes which are usually obtained by the direct formylation of the corresponding functionalized phenolic derivatives.[9] Recently, our group described a diversity-oriented domino synthesis of 3,6-disubstituted salicylaldehyde derivatives **2** from propargyl vinyl ethers **1** (PVEs) (Scheme 2).[10] We envisioned that these structures could serve as suitable starting materials for the synthesis of 3,5,8-trisubstituted coumarins **3** through a domino Knoevenagel condensation/lactonization reaction with an appropriated carbonyl derivative. Therefore, this strategy would allow us to perform the whole transformation in one pot directly from the PVE with good overall efficiency (Scheme 2). (**Domino I**: [3,3]-sigmatropic rearrangement−diene isomerization−enolization−6π-electrocyclization; **Domino II**: Knoevenagel condensation−lactonization.)

Scheme 1. Synthetic Access to 3,5,8-Trisubstituted Coumarins 3



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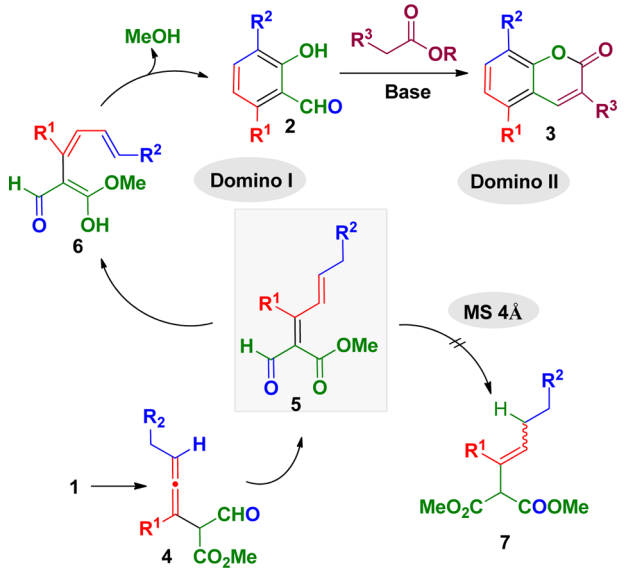
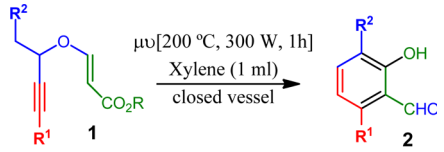
Scheme 2. Domino Coupled Synthesis of 3,6-Disubstituted Coumarins 3 from Propargyl Vinyl Ethers 1



From our previous studies on the salicylaldehyde formation reaction (Scheme 2),[10] we knew that the in situ produced methanol (1 equiv of methanol is generated in the formation of salicylaldehyde **2**) had to be removed from the reaction media to avoid the competitive formation of alkene **7**, which is generated by methanol addition on **5** and redox rearrangement of the resulting hemiacetal.[11] This redox process could be avoided by using activated powdered molecular sieves 4 Å (MS 4 Å) as an additive. A fortuitous discovery showed us that also pyridine, a nucleophilic base, inhibited the formation of the alkene.[7] It is not easy to imagine pyridine as a methanol scavenger; instead, we believe that both additives assist in the enolization of intermediate **5** to give triene **6** which is not a suitable electrophile for methanol. If intermediate **5** is quickly enolized, then its low concentration will be maintained and the formation of alkene **7** will be inhibited or severely diminished. There are precedents for the enolization of nitroalkanes aided by MS 4 Å.[12] We found that the microwave irradiation of a solution of PVE **1** in xylene (1 mmol/1 mL) [200 °C, 300 W, 1 h, closed vessel] in the presence of 2 equiv of pyridine afforded the corresponding salicylaldehydes **2** with comparable efficiency to the same process in the presence of MS 4 Å (Table 1). Whereas pyridine offers a similar or slightly lower efficiency than MS 4 Å for substrates involving an aromatic or an ester group (diene activating groups) (entries 1−4), it is the best option in the case of alkyl substitution at the terminal and propargylic positions (entry 5). It is noteworthy that in these cases pyridine offers a clear advantage over MS 4 Å in terms of instrumental simplicity (the reaction is performed under homogeneous conditions) and yields (54% versus 44%). Oxygen- and fluoride-containing derivatives can be accessed with pyridine as an additive in fairly good yields (entries 6 and 7).

Once the pyridine-assisted reaction could be standardized, we went one step further and studied the transformation of these substituted salicylaldehydes **2a−g** into coumarins **3** featuring different substituents at the C_3 position. For this transformation we explored a domino Knoevenagel condensation/lactonization protocol,[1,8] involving 1,3-dicarbonyl derivatives armed with at least one ester group and salicylaldehydes

Table 1. Effect of Additive in the Microwave-Assisted Domino Formation of Salicylaldehydes 2 from PVEs 1



Additive:
a) Py (2 mmol)
b) MS 4Å (300 mg mmol^{-1})

entry	R^1	R^2	2	Py (%)[a]	MS 4 Å (%)[a,b]
1	Ph	Et	**a**	75	76
2	Ph	Ph	**b**	80	89
3	Ph	*t*Bu	**c**	53	67
4	CO_2Me	Pr	**d**	56	70
5	Bu	Et	**e**	54	44
6	Ph	F	**f**	61	63
7	Ph	OBn	**g**	70	–

[a]Yield of isolated compounds. [b]See ref 10.

2a−g. This domino reaction can be base-catalyzed (through the formation of the enolate anion of the active methylene derivative) or iminium-catalyzed (through the formation of the corresponding iminium ion derivative of the aromatic aldehyde).[13] As a first approximation, we chose the base-catalyzed version in hopes that we would be able to connect this domino reaction with the pyridine-assisted domino formation of salicylaldehydes **2** (Scheme 2). After several experimental attempts using different malonate derivatives, bases, and reaction conditions (temperature, solvent), we were unable to run the whole process directly from the PVE: the set of experimental conditions that sparked a domino process were unfavorable for the other and vice versa. Thus, we turned our attention to a one-pot strategy. We explored this possibility using the iminium-catalyzed conditions for the Knoevenagel reaction.[13] After several experimental attempts using different catalysts and conditions, we arrived at piperidinium acetate (PPA) (5 mol %) as the best catalyst and refluxing ethanol as the more convenient reaction conditions. The one-pot process could be performed by first running the microwave-assisted formation of the salicylaldehyde intermediate **2**, and then, once the solvent and base were distilled off, the second domino reaction would proceed on the crude reaction residue.

For this study, we chose three different carbonyl derivatives, i.e. ethyl acetoacetate, Meldrum's acid, and ethyl cyanoacetate, to generate the corresponding coumarins **3** armed with an ester, acid, or nitrile group at the C_3 position. Each Knoevenagel reaction required a fine-tuning of the experimental conditions to be performed with synthetic efficiency (Scheme 3; conditions A, B, and C). Ethyl acetoacetate reacted with salicylaldehydes **2a−g** (conditions A) to afford the corresponding 3-acyl-coumarins **3ab−gb** in good overall yields (70% average yield per domino process). The more reactive Meldrum's acid required more catalyst (20 mol %) (conditions B) to be transformed into the corresponding coumarins **3ac−gc** with moderate to good efficiency (overall yields span from a modest 30% to a fairly good 57%). The less reactive and less acidic ethyl cyanoacetate required catalysis and microwave irradiation [100 °C, 300 W, 1 h, closed vessel] (conditions C) to accomplish this transformation. Under these conditions, it afforded the corresponding coumarins **3aa−ga** featuring a

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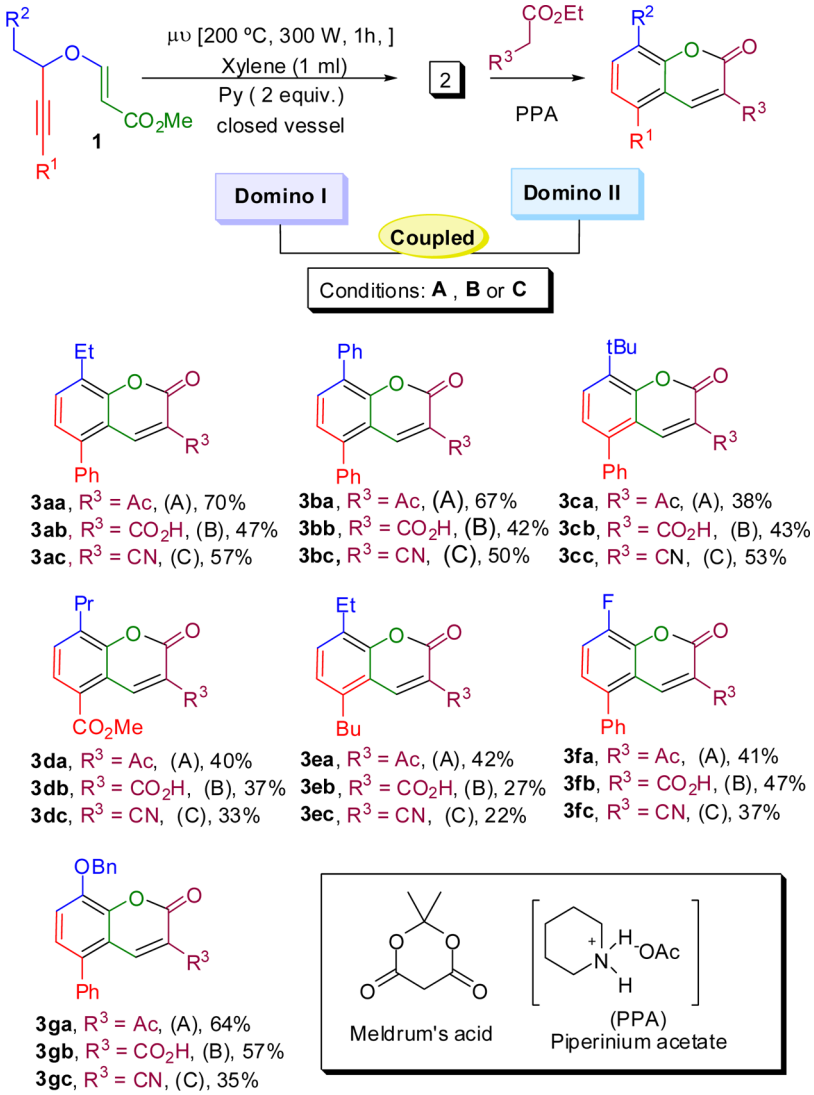
Scheme 3. Synthesis of 3,5,8-Trisubstituted Coumarins 3 from PVEs 1 by One-Pot Coupled Domino Processes[a]



[a]Conditions: (A) R^3 = Ac, EtOH (3 mL), PPA (5 mol %), reflux, 16 h. (B) Meldrum's acid, EtOH (3 mL), PPA (20 mol %), reflux, 2 h. (C) R^3 = CN, *μυ* [100 °C, 300 W], xylene (1 mL), PPA (5 mol %); 1 h, closed vessel.

chemically versatile nitrile group at C_3.[14] It should be noted that the substituents at the C_3 and C_6 positions of salicylaldehydes **2a–g** exercise an important steric impediment to these reactions, which translates to the overall yield of the process, slightly lower than those reported for salicylaldehyde derivatives with these positions free of substitution.[1,8] Last but not least, coumarins armed with a fluorine atom (**3fa–fc**) or an oxygen-containing functionality (**3ga–gc**) at the C_8 position can be generated in good overall yields under conditions A and B and with lower efficiency under conditions C.

In summary, we have generated a representative library of 21 different 3,5,8-trisubstituted coumarins grouped in 7 families of 3 members each. This representative library was built using a one-pot coupled domino process manifold. The one-pot process takes advantage of the fortuitous discovery of the pyridine-aided domino generation of salicylaldehydes **2** under microwave irradiation. This instrumentally simple coupled domino manifold allows for fast access to a novel coumarin chemotype defined by its substitution pattern at the aromatic ring (C_5,C_8-functionalization). These chemotypes feature a chemical handle in the pyranone ring (C_3-position) for further elaboration and a diverse substitution pattern at the aromatic ring, including aliphatic, aromatic, carboxylic esters, fluorine- or oxygen-containing functionalities.

EXPERIMENTAL SECTION

General Information. ^{1}H and ^{13}C NMR spectra of $CDCl_3$ solutions were recorded either at 400 and 100 MHz or at 500 and 125 MHz, respectively. Microwave reactions were conducted in sealed glass vessels (capacity 10 mL) using a microwave reactor equipped with a surface sensor for temperature measurement of the reaction mixture. FT-IR spectra were measured in chloroform solutions using an FT-IR spectrophotometer. Mass spectra (low resolution) (EI/CI) and HRMS (EI/TOF) were obtained with a gas chromatograph/mass spectrometer. Analytical thin-layer chromatography plates used UV-active silica on aluminum. Flash column chromatography was carried out with silica gel of particle size less than 0.020 mm, using appropriate mixtures of ethyl acetate and hexanes as eluents. All reactions were performed in oven-dried glassware. All materials were obtained from commercial suppliers and used as received unless otherwise noted. Propargyl vinyl ethers (PVEs) were synthesized according to literature procedures for **1a–c**, **1e–g**[15] and **1d**.[16] When not commercially available, the propargyl alcohols were prepared by addition of the

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lithium acetylides onto the appropriate aldehydes following the literature procedure.[17] All other materials were obtained from commercial suppliers and used as received. Products **1a–f** have been previously reported, and all data are in accordance with those of the literature.[10]

Synthesis of (*E*)-Methyl 3-(1-(benzyloxy)-4-phenylbut-3-yn-2-yloxy)acrylate (1g). Triethylamine (0.30 mmol) was added to a solution of methyl propiolate (3.0 mmol) and 1-(benzyloxy)-4-phenylbut-3-yn-2-ol (3.0 mmol) in dry CH_2Cl_2 (10 mL). The reaction mixture was stirred for 2 h. After removal of the solvent at reduced pressure the products were purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 90/10) to yield **1g** (959 mg; 89%) (gummy oil): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.70 (s, 3H), 3.82–3.84 (m, 2H), 4.61 (d, $^3J_{(H,H)}$ = 12.1 Hz, 1H), 4.67 (d, $^3J_{(H,H)}$ = 12.1 Hz, 1H), 4.97 (t, $^3J_{(H,H)}$ = 5.8 Hz, 1H), 5.46 (d, $^3J_{(H,H)}$ = 12.6 Hz, 1H), 7.28–7.36 (m, 8H), 7.41–7.44 (m, 2H), 7.70 (d, $^3J_{(H,H)}$ = 12.6 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 51.1, 71.9, 73.6, 82.5, 88.9, 98.9, 121.5, 127.8, 127.9, 128.4, 128.5, 129.1, 131.9, 137.5, 160.6, 167.9 ppm. FTIR ($CHCl_3$): ν = 3065.5, 3028.1, 3014.9, 2952.4, 2909.2, 2867.9, 2229.01, 1953.3, 1884.5, 1705.3, 1643.7, 1626.3, 1492.3, 1439.7 cm^{-1}. HRMS (EI-TOF) *m*/*z*: [M$^+$ + Na] Calcd for $C_{21}H_{20}O_4Na$ 359.1259. Found 359.1259.

Representative Procedure for the Microwave-Assisted Rearrangement of Propargyl Vinyl Ether 1 in the Presence of Pyridine. Synthesis of Salicylaldehydes 2. Propargyl vinyl ether **1g** (1.00 mmol), *o*-xylene (1 mL), and pyridine (2.00 mmol) were placed in a microwave-special closed vial, and the solution was irradiated for 1 h in a single-mode microwave oven (300 W, 200 °C). After removal of the solvent at reduced pressure the products were purified by flash column chromatography (silica gel, appropriate mixtures of ethyl acetate/hexane) to yield **2g** (212.8 mg; 70%). Amorphous solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.23 (s, 2H), 6.76 (d, $^3J_{(H,H)}$ = 8.3 Hz, 1H), 7.13 (d, $^3J_{(H,H)}$ = 8.33 Hz, 1H), 7.31–7.37 (m, 3H), 7.41–7.48 (m, 7H), 9.83 (s, 1H), 12.18 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 71.6, 18.3, 120.7, 120.8, 127.4, 127.9, 128.1, 128.4, 128.7, 130.2, 136.7, 137.5, 139.5, 146.7, 153.7, 197.6 ppm; FTIR ($CHCl_3$): ν = 3027.9, 2887.2, 1644.1, 1570.6, 1449.3, 1393.5 cm^{-1}; LRMS (70 eV) *m*/*z* (%): 304 (7.2) [M^+], 139 (8.2), 128 (10), 91 (100). HRMS (EI-TOF) *m*/*z*: [M]$^+$ Calcd for $C_{20}H_{16}O_3$ 304.1107; Found 304.1099.

Representative Procedure for the Synthesis of Coumarins Bearing an Acetate at the 3-Position (Conditions A). Propargyl vinyl ether **1a** (1.00 mmol), *o*-xylene (1 mL), and pyridine (2.00 mmol) were placed in a microwave-special closed vial, and the solution was irradiated for 1 h in a single-mode microwave oven (300 W, 200 °C). After the time described, the sample was cooled to room temperature, and the crude of the reaction was redissolved in 3 mL of ethanol. Ethyl acetoacetate (1.1 mmol) and piperidine (0.05 mmol) were added, and the solution was refluxed for 20 h. After that time, the solvent was removed at reduced pressure. The products were purified by flash column chromatography (silica gel, appropriate mixtures of dichloromethane/hexane) to yield **3aa** (204.4 mg; 70%).

3-Acetyl-8-ethyl-5-phenyl-2H-chromen-2-one (***3aa***). Amorphous solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.33 (t, $^3J_{(H,H)}$ = 7.6 Hz, 3H), 2.68 (s, 3H), 2.94 (q, $^3J_{(H,H)}$ = 7.58 Hz, 2H), 7.23 (d, $^3J_{(H,H)}$ = 7.6 Hz, 1H), 7.31–7.33 (m, 2H), 7.44–7.49 (m, 3H), 7.53 (d, $^3J_{(H,H)}$ = 7.6 Hz, 1H), 8.53 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0, 22.5, 30.5, 116.2, 123.9, 125.7, 128.4, 129.8, 131.1, 133.6, 137.6, 141.8, 146.4, 153.8, 159.1, 195.7 ppm. FTIR ($CHCl_3$): ν = 3025.9, 2974.9, 2877.3, 1954.9, 1905.8, 1729.9, 1688.3, 1581.5 cm^{-1}. Anal. Calcd for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found: C, 77.8; H, 5.69. LRMS (70 eV) *m*/*z* (%): 292 (90) [M^+], 277 (100), 249 (33) 235 (13), 207 (16), 193 (13), 178 (29), 165 (22), 152 (10), 84 (34).

3-Acetyl-5,8-diphenyl-2H-chromen-2-one (***3ba***). (227.8 mg; 67%). Amorphous solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.67 (s, 3H), 7.37–7.4 (m, 3H), 7.44–7.45 (m, 1H), 7.49–7.55 (m, 5H), 7.64–7.67 (m, 2H), 7.72 (t, $^3J_{(H,H)}$ = 7.83, 1H), 8.59 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 30.4, 116.8, 124.1, 125.9, 128.3, 128.6 (2C), 128.7, 128.9, 129.2, 129.5 (2C), 129.8 (2C), 134.8, 135.2, 137.4, 143.3, 146.2, 152.7, 158.6, 195.5 ppm. FTIR ($CHCl_3$): ν = 3025.3, 1736.2, 1690.0, 1584.7, 1574.8 cm^{-1}. LRMS (70 eV) *m*/*z* (%): 340 (100) [M^+], 325 (64), 297 (21), 239 (38), 230 (18), 129 (8.5), 115 (11), 83 (32). HRMS (EI-TOF) *m*/*z*: [M]$^+$ Calcd for $C_{23}H_{16}O_3$ 340.1099; Found 340.1109.

3-Acetyl-8-tert-butyl-5-phenyl-2H-chromen-2-one (***3ca***). (121.6 mg; 38%). Amorphous solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.55 (s, 9H), 2.68 (s, 3H), 7.23 (d, $^3J_{(H,H)}$ = 8.1 Hz, 1H), 7.31–7.34 (m, 2H), 7.45–7.51(m, 3H), 7.66 (d, $^3J_{(H,H)}$ = 8.1 Hz, 1H), 8.55 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 29.8, 30.5, 35.0, 116.9, 123.2, 125.5, 128.4, 128.8, 129.8, 131.5, 136.9, 137.5, 142.1, 146.7, 154.6, 158.6, 195.5 ppm. FTIR ($CHCl_3$): ν = 3694.7, 3026.5, 3013.6, 2963.9, 2928.8, 2874.8, 2857.0, 1726.4, 1688.3, 1602.3, 1574.3 cm^{-1}. LRMS (70 eV) *m*/*z* (%): 320 (45) [M^+], 305 (72), 221 (100), 189 (8.4), 165 (12). HRMS (EI-TOF) *m*/*z*: [M]$^+$ Calcd for $C_{21}H_{20}O_3$ 320.1412; Found 320.1405.

Methyl 3-Acetyl-2-oxo-8-propyl-2H-chromene-5-carboxylate (***3da***). (115.2 mg; 40%). Amorphous solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.99 (t, $^3J_{(H,H)}$ = 7.3 Hz, 3H), 1.68–1.77 (m, 2H) 2.72 (s, 3H), 2.88 (q, $^3J_{(H,H)}$ = 7.6 Hz, 2H), 3.97 (s, 3H), 7.51 (d, $^3J_{(H,H)}$ = 7.8 Hz, 1H), 7.89 (d, $^3J_{(H,H)}$ = 7.8 Hz, 1H), 9.54 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.8, 22.6, 30.3, 31.7, 52.6, 117.5, 125.5, 127.3, 127.4, 133.3, 135.6, 145.5, 153.9, 158.1, 165.8, 195.4 ppm. FTIR ($CHCl_3$): ν = 3087.2, 3027.5, 2963.8, 2874.9, 1728.1, 1693.6, 1613.9, 1585.6, 1566.4, 1480.2, 1436.0, 1415.8 cm^{-1}. LRMS (70 eV) *m*/*z* (%): 288 (43) [M^+], 273 (100), 259 (11), 217 (5.4), 189 (4.5), 115 (6.6), 102 (4.3), 77 (3.1). HRMS (EI-TOF) *m*/*z*: [M]$^+$ Calcd for $C_{16}H_{16}O_5$ 288.0998; Found 288.1000.

3-Acetyl-5-butyl-8-ethyl-2H-chromen-2-one (***3ea***). (114.2 mg; 42%). Amorphous solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.94 (t, $^3J_{(H,H)}$ = 7.3 Hz, 3H), 1.27 (t, $^3J_{(H,H)}$ = 7.6 Hz, 3H), 1.34–1.44 (m, 2H), 1.60–1.64 (m, 2H), 2.73 (s, 3H), 2.82–2.90 (m, 4H), 7.07 (d, $^3J_{(H,H)}$ = 7.6 Hz, 1H), 7.40 (d, $^3J_{(H,H)}$ = 7.8 Hz, 1H), 8.43 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.8, 13.9, 22.3, 22.4, 30.5, 30.6, 34, 116.5, 123.2, 125.0, 129.7, 133.9, 141.4, 144.7, 154.0, 159.2, 195.8 ppm. FTIR ($CHCl_3$): ν = 3027.6, 2962.2, 2935.1, 2875.1, 1725.7, 1686.7, 1586.2, 1566.8, 1481.7 cm^{-1}. LRMS (70 eV) *m*/*z* (%): 272 (93) [M^+], 257 (100), 229 (72), 215 (17), 201 (20), 187 (12), 173 (8.1), 128 (14), 115 (25), 91 (12). HRMS (EI-TOF) *m*/*z*: [M]$^+$ Calcd for $C_{17}H_{20}O_3$ 272.1411; Found 272.1412.

3-Acetyl-8-fluoro-5-phenyl-2H-chromen-2-one (***3fa***). (115.6 mg; 41%). Amorphous solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.68 (s, 3H), 7.25 (dd, $^3J_{(H,H)}$ = 8.3 Hz, 4.6, 1H), 7.31–7.33 (m, 2H), 7.42–7.50 (m, 4H), 8.47 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 30.4, 118.0, 120.0 (J_{CF} = 17.0), 125.0, 125.6 (J_{CF} = 5.7), 128.7, 128.9, 129.7, 136.7, 139.5 (J_{CF} = 4.2), 143.7 (J_{CF} = 11.3), 145.6, 148.4 (J_{CF} = 253.6), 157.6, 195.1 ppm. FTIR ($CHCl_3$): ν = 3026.9, 1887.3, 1693.2, 1604.6, 1571.3 cm^{-1}. LRMS (70 eV) *m*/*z* (%): 282 (74) [M^+], 267 (100), 238 (45), 212 (12), 183 (87), 163 (13), 157 (11), 84 (66). HRMS (EI-TOF) *m*/*z*: [M]$^+$ Calcd for $C_{17}H_{11}FO_3$ 282.0692; Found 282.0688.

3-Acetyl-8-(benzyloxy)-5-phenyl-2H-chromen-2-one (***3ga***). (236.8 mg; 64%). Amorphous solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.69 (s, 3H), 5.30 (s, 2H), 7.17–7.51 (m, 12H), 8.51 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 30.4, 71.5, 117.2, 118.1, 124.4, 125.5, 127.3, 128.1, 128.2, 128.7, 128.8, 129.8, 135.8, 136.1, 137.3, 145.2, 145.9, 146.2, 158.5, 195.6 ppm. FTIR ($CHCl_3$): ν = 3064.9, 3028.2, 3015.6, 2931.0, 1733.4, 1690.1, 1612.6, 1592.2, 1561.7 cm^{-1}. LRMS (70 eV) *m*/*z* (%): 370 (3.6) [M^+], 237 (1.9), 176 (4.9), 152 (10), 129 (22), 115 (12), 91 (100), 77 (10), 65 (16). HRMS (EI-TOF) *m*/*z*: [M]$^+$ Calcd for $C_{24}H_{18}O_4$ 370.1205; Found 370.1193.

Representative Procedure for the Synthesis of Coumarins Bearing a Carboxylic Acid at the 3-Position (Conditions B). Propargyl vinyl ether **1a** (1.00 mmol), *o*-xylene (1 mL), and pyridine (2.00 mmol) were placed in a microwave-special closed vial, and the solution was irradiated for 1 h in a single-mode microwave oven (300 W, 200 °C). After removal of the solvent at reduced pressure the products were redissolved in ethanol. Meldrum acid (1.1 mmol) and piperidinium acetate (0.2 mmol) were added. The solution was refluxed with stirring for 2 h. The solvent was removed at reduced pressure. The products were purified by flash column chromatography

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(silica gel, appropriate mixtures of dichloromethane/MeOH) to yield **3ab** (138.2 mg; 47%).

*8-Ethyl-2-oxo-5-phenyl-2H-chromene-3-carboxylic Acid (**3ab**).* Amorphous solid. ^{1}H NMR (CD_3OD, 400 MHz): δ = 1.29 (t, $^3J_{(H,H)}$ = 7.6 Hz, 3H), 2.9 (q, $^3J_{(H,H)}$ = 7.6 Hz, 2H), 7.28 (d, $^3J_{(H,H)}$ = 7.3 Hz, 1H), 7.36−7.38 (m, 2H), 7.44−7.48 (m, 3H), 7.6 (d, $^3J_{(H,H)}$ = 7.6 Hz, 1H), 8.6 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 19.4, 22.5, 116.7, 126.8, 128.7, 129.0, 129.8, 131.6, 134.7, 136.9, 142.1, 150.2, 153.0, 163.2, 163.6 ppm. FTIR ($CHCl_3$): ν = 3070.1, 2995.6, 2949.7, 2914.3, 1757.6, 1680.9, 1590.0, 1473.9 cm^{-1}. Anal. Calcd for $C_{18}H_{14}O_4$: C, 73.46; H, 4.79. Found: C, 73.56; H, 4.60. LRMS (70 eV) *m*/*z* (%): 294(100) [*M*$^+$], 279 (16), 250(71), 235 (47), 207 (37), 193 (26), 178 (43), 165 (30), 152 (20), 115 (15), 89 (13), 84 (12), 77 (11).

*2-Oxo-5,8-diphenyl-2H-chromene-3-carboxylic Acid (**3bb**).* (143.6 mg; 42%). Amorphous solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.40 (d, $^3J_{(H,H)}$ = 7.1 Hz, 2H), 7.45−7.55 (m, 7H), 7.62 (d, $^3J_{(H,H)}$ = 7.3 Hz, 2H), 7.84 (d, $^3J_{(H,H)}$ = 7.8 Hz, 1H), 9.03 (s, 1H), 12.14 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 114.3, 117.2, 127.1, 128.6, 128.8 (2C), 129.1, 129.2 (2C), 129.4 (2C), 129.7 (2C), 129.8, 134.5, 136.2, 136.7, 143.7, 150.5, 151.9, 162.5, 163.6 ppm. FTIR ($CHCl_3$): ν = 3692.4, 3063.9, 3027.8, 2962.7, 1758.9, 1682.1, 1590.8, 1471.5, 1453.8, 1397.6 cm^{-1}). LRMS (70 eV) *m*/*z* (%): 342 (100) [*M*$^+$], 298 (30), 270 (19), 256 (14), 239 (34), 133 (12),129 (28), 128 (17). HRMS (EI-TOF) *m*/*z*: [M]$^+$ Calcd for $C_{22}H_{14}O_4$ 342.0892; Found 342.0886.

*8-tert-Butyl-2-oxo-5-phenyl-2H-chromene-3-carboxylic Acid (**3cb**).* (138.5 mg; 43%). Amorphous solid. ^{1}H NMR (CD_3OD, 400 MHz): δ = 1.49 (s, 9H), 7.28 (d, $^3J_{(H,H)}$ = 7.6 Hz, 1H), 7.35−7.37 (m, 2H), 7.45−7.48 (m, 3H), 7.74 (d, $^3J_{(H,H)}$ = 7.6 Hz, 1H), 8.63 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 29.8 (3C), 35.1, 117.3, 126.6, 128.7, 128.9 (2C), 129.7 (2C), 132.8, 136.8, 137.4, 142.5, 150.7, 153.8, 163.34, 163.38 ppm. LRMS (70 eV) *m*/*z* (%): 322 (51) [*M*$^+$], 307 (67), 221 (100), 178 (12)165 (14), 84 (29). HRMS (EI-TOF) *m*/*z*: [M]$^+$ Calcd for $C_{20}H_{18}O_4$ 322.1205; Found 322.1201.

*5-(Methoxycarbonyl)-2-oxo-8-propyl-2H-chromene-3-carboxylic Acid (**3db**).* (107.3 mg; 37%). Amorphous solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.00 (t, $^3J_{(H,H)}$ = 7.3 Hz, 3H), 1.69−1.79 (m, 2H), 2.92 (q, $^3J_{(H,H)}$ = 8.1 Hz, 2H), 4.00 (s, 3H), 7.64 (d, $^3J_{(H,H)}$ = 8.09 Hz, 1H), 8.02 (d, $^3J_{(H,H)}$ = 7.83 Hz, 1H), 10.03 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.8, 22.6, 31.6, 52.9, 115.7, 117.7, 127.6, 128.5, 134.8, 136.2, 150.1, 153.2, 162.2, 163.1, 165.3 ppm. FTIR ($CHCl_3$): ν = 3030.4, 2996.9, 2957.9, 2935.3, 1757.7, 1723.0, 1686.0, 1620.9, 1588.5, 1484.4, 1437.1, 1398.6 cm^{-1}. Anal. Calcd for $C_{15}H_{14}O_6$: C, 62.07; H, 4.86. Found: C, 62.31; H, 4.83. LRMS (70 eV) *m*/*z* (%): 290 (29) [*M*$^+$], 261 (36), 246 (100), 232 (27), 217 (18), 189 (11), 161 (10), 115

*5-Butyl-8-ethyl-2-oxo-2H-chromene-3-carboxylic Acid (**3eb**).* (74 mg; 27%). Amorphous solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.95 (t, $^3J_{(H,H)}$ = 7.3 Hz, 3H), 1.29 (t, $^3J_{(H,H)}$ = 7.6 Hz, 3H), 1.34−1.45 (m, 2H), 1.58−1.66 (m, 2H), 2.86−2.95 (m, 4H), 7.20 (t, $^3J_{(H,H)}$ = 7.6 Hz, 1H), 7.52 (t, $^3J_{(H,H)}$ = 7.6 Hz, 1H), 9.14 (s, 1H), 12.42 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.8, 13.9, 22.3, 22.4, 31.6, 34.1, 113.4, 117.0, 126.3, 130.3, 135.4, 142.0, 148.7, 135.3, 163.0, 164.1 ppm. FTIR ($CHCl_3$): ν = 3029.2, 2962.1, 2934.8, 2875.7, 1753.7, 1681.1, 1593.7, 1402.8 cm^{-1}. LRMS (70 eV) *m*/*z* (%): 274 (100) [*M*$^+$], 259 (21), 230 (72), 203 (18), 187 (13), 128 (21), 115 (35), 91 (15), 84 (89), 77 (12). HRMS (EI-TOF) *m*/*z*: [M]$^+$ Calcd for $C_{16}H_{18}O_4$ 274.1202; Found 274.1205.

*8-Fluoro-2-oxo-5-phenyl-2H-chromene-3-carboxylic Acid (**3fb**).* (133.5 mg; 47%). Amorphous solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.32−7.33 (m, 2H), 7.38 (dd, $^3J_{(H,H)}$ = 8.3 Hz, 4.0, 1H), 7.52−7.60 (m, 4H), 8.93 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 115.4, 118.2, 121.3 (J_{CF} = 16.2 Hz), 126.8 (J_{CF} = 5.7 Hz), 129.1, 129.2, 129.7, 136.0, 139.9 (J_{CF} = 4.2 Hz), 142.9 (J_{CF} = 12.0 Hz), 148.5 (J_{CF} = 255 Hz), 150, 161.9, 162.5. FTIR ($CHCl_3$): ν = 3619.9, 3464.4, 3015.7, 2976.8, 2928.5, 1759.9, 1699.3, 1687.0, 1608.9, 1582.8 cm^{-1}. LRMS (70 eV) *m*/*z* (%): 284 (37) [*M*$^+$], 240 (44), 212 (33), 198 (21), 183 (100), 181 (23), 163 (17), 157 (12), 97 (15), 83 (27), 69 (37), 55 (62). HRMS (EI-TOF) *m*/*z*: [M]$^+$ Calcd for $C_{16}H_9FO_4$ 284.0485; Found 284.048.

*8-(Benzyloxy)-2-oxo-5-phenyl-2H-chromene-3-carboxylic Acid (**3gb**).* (212 mg; 57%). Amorphous solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.32 (s, 2H), 7.28−7.51 (m, 12H), 8.94 (s, 1H), 12.1 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 71.7, 114.6, 117.6, 118.9, 126.8, 127.4, 128.5, 128.6, 128.9, 129.1, 130.7, 135.6, 136.0, 136.7, 144.6, 145.5, 150.5, 162.5, 163.6 ppm. FTIR ($CHCl_3$): ν = 3694.2, 3601.2, 3029.8, 3012.2, 1756.8, 1682.5, 1598.4, 1564.3 cm^{-1}. LRMS (70 eV) *m*/*z* (%): 372 (9.3) [*M*$^+$], 333 (4.1), 282 (6.9), 181 (5.7), 152 (21), 91 (100). HRMS (EI-TOF) *m*/*z*: [M]$^+$ Calcd for $C_{23}H_{16}O_5$ 372.0998; Found 372.0992.

Representative Procedure for the Synthesis of Coumarins Bearing a Cyano Group at the 3-Position (Conditions C). Propargyl vinyl ether **1a** (1.00 mmol), *o*-xylene (1 mL), and pyridine (2.00 mmol) were placed in a microwave-special closed vial, and the solution was irradiated for 1 h in a single-mode microwave oven (300 W, 200 °C). After the time described the sample was cooled to room temperature. Ethyl cyanoacetate (1.1 mmol) and piperidine (0.05 mmol) were added, and the solution was heated to 100 °C (300 W), for 1 h. The solvent was then removed at reduced pressure. The products were purified by flash column chromatography (silica gel, appropriate mixtures of dichloromethane/hexane) to yield **3ac** (149.9 mg; 57%).

*8-Ethyl-2-oxo-5-phenyl-2H-chromene-3-carbonitrile (**3ac**).* Amorphous solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.33 (d, $^3J_{(H,H)}$ = 7.6 Hz, 3H), 2.92 (q, $^3J_{(H,H)}$ = 7.6 Hz, 2H), 7.29−7.32 (m, 3H), 7.49−7.55 (m, 3H), 7.60 (d, $^3J_{(H,H)}$ = 7.8 Hz, 1H), 8.28 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9, 22.4, 102.4, 113.9, 115.4, 126.3, 128.8, 129.0, 129.7, 131.9, 134.8, 136.8, 140.9, 151.0, 153.1, 156.4 ppm. FTIR ($CHCl_3$): ν = 3064.1, 3026.8, 2973.9, 2934.1, 2876.7, 2236.1, 1906.8, 1743.0, 1588.6, 1473.5, 1215.9 cm^{-1}. Anal. Calcd for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.58; H, 4.76; N, 5.16. LRMS (70 eV) *m*/*z* (%): 275 (100) [*M*$^+$], 260 (90), 193 (18), 165 (17).

*2-Oxo-5,8-diphenyl-2H-chromene-3-carbonitrile (**3bc**).* (161.5 mg; 50%). Amorphous solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.36−7.61 (m, 11H), 7.7 (d, $^3J_{(H,H)}$ = 7.8 Hz, 1H), 8.34 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 102.7, 113.8, 115.9, 126.5, 128.5, 128.7 (2C), 129.0, 129.1 (2C), 129.4 (2C), 129.7 (2C), 129.9, 134.5, 136.1, 136.6, 142.7, 150.9, 151.9, 155.8 ppm. FTIR ($CHCl_3$): ν = 3692.0, 3026.3, 2928.2, 2855.6, 2239.6, 1745.6, 1589.9, 1470.4 cm^{-1}. LRMS (70 eV) *m*/*z* (%): 323 (100) [*M*$^+$], 294 (12), 266 (13), 239 (11), 190 (6.80), 164 (3.30), 128 (8.10), 119 (4.60), 63 (3.90). HRMS (EI-TOF) *m*/*z*: [M]$^+$ Calcd for $C_{22}H_{13}NO_2$ 323.0946; Found 323.0937.

*8-tert-Butyl-2-oxo-5-phenyl-2H-chromene-3-carbonitrile (**3cc**).* (160.6 mg; 53%). Amorphous solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.53 (s, 9H), 7.28 (d, $^3J_{(H,H)}$ = 8.1 Hz, 1H), 7.30−7.32 (m, 2H), 7.51−7.53 (m, 3H), 7.72 (d, $^3J_{(H,H)}$ = 8.1 Hz, 1H), 8.28 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 29.8, 35.1, 101.8, 113.9, 116.0, 126.0, 128.8, 129.0, 129.7, 132.7, 136.8, 137.7, 141.3, 151.3, 153.9, 155.8 ppm. FTIR ($CHCl_3$): ν = 3692.6, 3063.7, 3025.1, 2963.8, 2876.3, 2237.4, 1742.5, 1618.5, 1582.9 cm^{-1}. LRMS (70 eV) *m*/*z* (%): 303 (26) [*M*$^+$], 288 (94), 259 (16), 229 (38), 221 (42), 197 (66), 187 (17), 175 (18), 170 (11), 142 (20), 131 (31), 103 (11), 88 (11), 84 (100), 77 (11), 57 (51). HRMS (EI-TOF) *m*/*z*: [M]$^+$ Calcd for $C_{20}H_{17}NO_2$ 303.1259; Found 303.1257.

*Methyl 3-Cyano-2-oxo-8-propyl-2H-chromene-5-carboxylate (**3dc**).* (89.4 mg; 33%). Amorphous solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.98 (t, $^3J_{(H,H)}$ = 7.3 Hz, 3H) 1.66−01.75 (m, 2H), 2.86 (t, $^3J_{(H,H)}$ = 7.8 Hz, 2H) 3.98 (s, 3H), 7.58 (d, $^3J_{(H,H)}$ = 7.8 Hz, 1H), 7.98 (t, $^3J_{(H,H)}$ = 7.8 Hz, 1H), 9.59 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.8, 22.6, 31.6, 52.9, 104.4, 113.6, 116.6, 125.9, 128.1, 134.7, 136.6, 150.5, 153.4, 155.5, 165.4 ppm. FTIR ($CHCl_3$): ν = 3092.7, 3028.0, 3001.9, 2961.4, 2934.6, 2875.3, 2237.3, 1742.9, 1720.9, 1618.7, 1586.8, 1482.3, 1436.3 cm^{-1}. LRMS (70 eV) *m*/*z* (%): 271 (71) [*M*$^+$], 242 (100), 212 (9.8), 155 (6.5), 127 (7.10), 84 (27), 55 (7.2). HRMS (EI-TOF) *m*/*z*: [M]$^+$ Calcd for $C_{15}H_{13}NO_4$ 271.0845; Found 271.0837.

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*5-Butyl-8-ethyl-2-oxo-2H-chromene-3-carbonitrile (**3ec**).* (56.1 mg; 22%). Amorphous solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.95 (t, $^3J_{(H,H)}$ = 7.1 Hz, 3H), 1.25 (t, $^3J_{(H,H)}$ = 7.6 Hz, 3H), 1.36−1.45 (m, 2H), 1.55−1.63 (m, 2H), 2.81−2.85 (m, 4H), 7.13 (d, $^3J_{(H,H)}$ = 7.6 Hz, 1H), 7.46 (d, $^3J_{(H,H)}$ = 7.8 Hz, 1H), 8.45 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.8, 13.9, 22.2, 22.5, 31.7, 34.1, 101.9, 114.1, 115.6, 125.8, 130.5, 135.2, 140.5, 149.2, 153.3, 156.5 ppm. FTIR ($CHCl_3$): ν = 3026.2, 2962.9, 2935.4, 2875.6, 2234.7, 1910.8, 1880.2, 1739.7, 1591.8, 1483.8, 1463.1, 1438.0 cm^{-1}. LRMS (70 eV) *m*/*z* (%): 255 (65) [*M*$^+$], 240 (30), 212 (100), 184 (28), 140 (13), 115 (15), 83 (22). HRMS (EI-TOF) *m*/*z*: [M]$^+$ Calcd for $C_{16}H_{17}NO_2$ 255.1259; Found 255.1252.

*8-Fluoro-2-oxo-5-phenyl-2H-chromene-3-carbonitrile (**3fc**).* (98.1 mg; 37%). Amorphous solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.30−7.33 (m, 3H), 7.50−7.55 (m, 4H), 8.25 (d, $^3J_{(H,H)}$ = 1.3 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 103.8, 113.3, 116.9, 121.6 (J_{CF} = 17.7 Hz), 126.3 (J_{CF} = 6.4), 129.1, 129.2, 129.7, 135.9, 138.7 ($J_{C\,F}$= 4.2 Hz), 143.0 (J_{CF} = 12.7 Hz), 148.5 (J_{CF} = 255 Hz), 150.4, 154.7 ppm. FTIR ($CHCl_3$): ν = 3692.5, 3066.1, 3024.3, 2241.4, 1890.7, 1607.9, 1578.6 cm^{-1}. LRMS (70 eV) *m*/*z* (%): 265 (100) [*M*$^+$], 237 (35), 208 (47), 199 (19), 170 (24), 84 (51). HRMS (EI-TOF) *m*/*z*: [M]$^+$ Calcd for $C_{16}H_8FNO_2$ 265.0539; Found 265.0540.

*8-(Benzyloxy)-2-oxo-5-phenyl-2H-chromene-3-carbonitrile (**3gc**).* (123.6 mg; 35%). Amorphous solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.23 (s, 2H), 7.16−7.45 (m, 12H), 8.20 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 71.6, 103.1, 113.8, 116.2, 119.1, 126.1, 127.4, 128.4, 128.6, 128.8, 129.0, 129.8, 134.8, 135.7, 136.6, 145.2, 145.6, 150.9, 155.8 ppm. FTIR ($CHCl_3$): ν = 3694.5, 3592.2, 3065.8, 3025.2, 228.2, 1746.5, 1596.9, 1564.2 cm^{-1}. LRMS (70 eV) *m*/*z* (%): 353 (1.8) [*M*$^+$], 263 (1.7), 177 (4.4), 151 (3.0), 91 (100). HRMS (EI-TOF) *m*/*z*: [M]$^+$ Calcd for $C_{23}H_{15}NO_3$ 353.1052; Found 353.1064.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **1g**, **2g**, and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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