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Assembly of 3-Substituted Isocoumarins via a CuI-Catalyzed Domino Coupling/Addition/Deacylation Process

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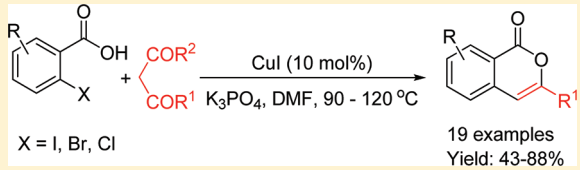
Supporting Information

ABSTRACT: An efficient strategy for the synthesis of a variety of 3-substituted isocoumarins has been developed. The reaction proceeded from *o*-halobenzoic acids and 1,3-diketones via a copper(I)-catalyzed domino reaction in DMF under the action of K_3PO_4 at 90−120 °C without a ligand to afford the corresponding 3-substituted isocoumarin derivatives in good to excellent yields. *o*-Halobenzoic acids could be *o*-iodobenzoic acid, *o*-bromobenzoic acid, and *o*-chlorobenzoic acid derivatives. 1,3-Diketones could be alkyl- and aryl-substituted 1,3-diketones.



INTRODUCTION

Isocoumarins are an important class of heterocyclic scaffolds that exhibit a wide range of biological activities, such as antifungal, antibacterial, and antidiabetic effects.[1] Among various substituted isocoumarins, the 3-substituted isocoumarins with no substituent at the 4-position have a great influence on their biological activities.[1d,e,2] For example, coriandrin (**I**),[3] compound 185322 (**II**),[4] thunberginol A (**III**),[5] and thunberginol B (**IV**)[6] have been employed in the design of pharmaceuticals and related compounds, such as inhibitor of microtubule assembly anti-HIV, antiallergic, and antiviral agents (Figure 1). In addition, 3-substituted isocoumarins are useful

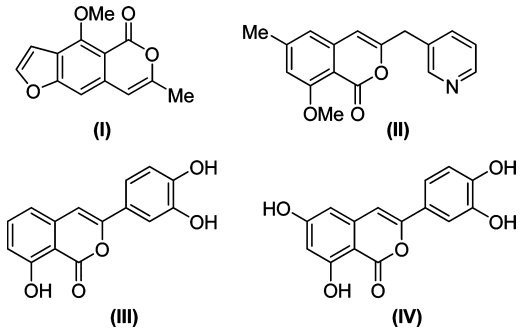


Figure 1. Structures of pharmacologically important 3-substituted isocoumarins.

intermediates[7] for the synthesis of various natural products, such as canesin, α- and β-sorigenin methyl ethers, and 3-alkylisocoumarins as well as some isoquinoline alkaloids.[8]

Although the 3-substituted isocoumarins play an important role from both the biological and the synthetic points of view, the available synthetic strategies that lead to these compounds are limited. The classical methods for the assembly of these molecules involved multistep reaction sequences and harsh conditions.[9] In an attempt to circumvent these restrictions, a metal-based formation of 2-alkenyl or 2-allylbenzoic acids and a subsequent annulation toward the 3-substituted isocoumarins were reported.[10] These methods still suffered from either multistep reactions or the requirement for a stoichiometric amount of palladium. Later, palladium-catalyzed cyclization of *o*-haloaromatic acids with π-components has been recognized as an efficient method for synthesis of isocoumarins.[11] However, in those reactions, a preactivated coupling partner, C-M reagent, or an additive is used as a starting material to construct isocoumarin derivatives. In some cases, the reaction led to contamination by byproduct. Recently, the oxidative cyclization of aromatic acids with alkynes in the presence of rhodium catalyst provided an atom-economical method for construction of 3,4-disubstituted isocoumarin derivatives.[12] Herein, we would like to report a highly efficient domino process for the construction of various 3-substituted isocoumarins by a copper-catalyzed reaction of 2-halobenzoic acid and 1,3-diketones in one pot.[13]

A recent advance in Ullmann-type reactions provided the opportunity for the development of new methodologies to assemble heterocycles.[14] For example, Ma et al and Fu et al had developed useful Cu-catalyzed domino processes for elaboration of heterocycles, such as indoles,[14e,m] isoquinolines,[14p] and isoquinolin-1(2*H*)-one.[14q] Our group has recently established some domino processes for the elaboration of heterocycles via Cu-catalyzed addition/cyclization or coupling/cyclization reactions, which included formation of 2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one,[15] 2-aminobenzimidazoles,[16] thiophenes[17] and pyrroles.[18] Continuing our efforts in this area, we became interested in the coupling reaction of 2-halobenzoic acids with 1,3-diketones, which

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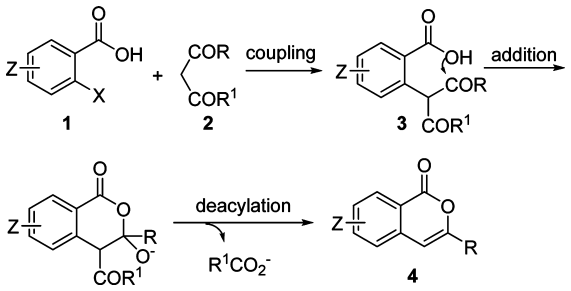
are inexpensive and available starting materials. We envisioned that, if the copper-catalyzed coupling between aryl halides **1** and these activated methylene compounds **2** proceeded smoothly,[19a] the resulting coupling products **3** would undergo an intramolecular addition, followed by deacylation[14e] to afford 3-substituted isocoumarins **4** (Scheme 1). This reaction includes new C−C and

Scheme 1. Design of Synthesis of 3-Substituted Isocoumarins by a Domino Reaction

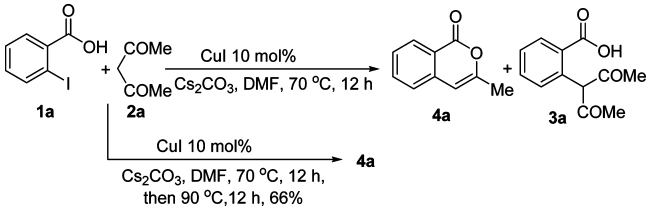


C−O bond-forming as well as C−C and C−O bond-cleaving events to occur in one sequence, which greatly enhances the synthetic efficiency.

RESULTS AND DISCUSSION

With the above idea in mind, we investigated the reaction of 2-iodobenzoic acid **1a** and pentane-2,4-dione **2a** under the catalysis of 10 mol % CuI in *N*,*N*-dimethylformamide (DMF) with Cs_2CO_3 as a base (Scheme 2). We are pleased to find that,

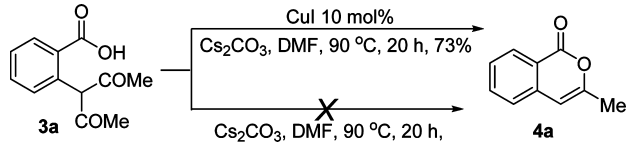
Scheme 2. CuI-Catalyzed Coupling of 1a and 2a



after 12 h at 70 °C, a mixture of **3a** (isolated 8%) and **4a** (isolated 48%) was obtained. We then tried to transform **3a** into **4a** in a one-pot reaction and found that **4a** formed exclusively when the coupling reaction mixture was heated at 90 °C for 12 h.

In addition, compound **3a**, the coupling product of **1a** and **2a** at 30 °C, was isolated and subsequently treated with Cs_2CO_3 in DMF at 90 °C. It was found that, in the presence of 10 mol % CuI, compound **4a** had formed in 73% isolated yield, whereas no **4a** could be detected in the absence of CuI (Scheme 3).

Scheme 3. Transformation of the Intermediate

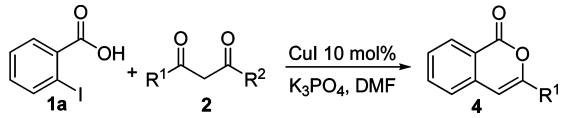


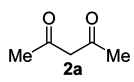
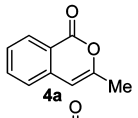
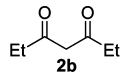
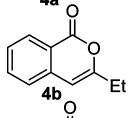
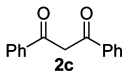
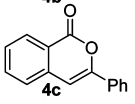
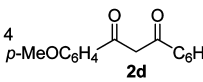
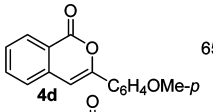
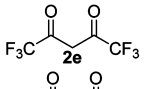
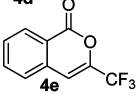
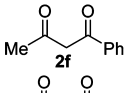
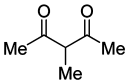
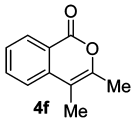
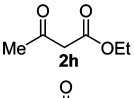
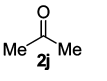
This result demonstrated that copper as a catalyst in the cyclization also plays a crucial role for transformation into 3-methylisocoumarie.

We next tried to optimize the reaction conditions. It was found that all bases examined, Cs_2CO_3, K_3PO_4, ^{t}BuONa, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and 1,4-diazobicyclo-[2.2.2]octane (DABCO), are effective. We chose less-expensive and less-toxic K_3PO_4 as a base for this reaction. We next tested the reaction in different solvents. DMF and DMSO were superior to MeCN and toluene. We are pleased to find that the reaction did not need addition of any ligand or additive. On the basis of above investigations, the optimal condition involved the following parameters: 10 mol % CuI as a catalyst, K_3PO_4 as a base, DMF as a solvent, and a reaction temperature at 90 °C and ligand-free.

Encouraged by the above results, we examined the scope and limitation of 2-halobenzoic acid derivatives and 1,3-diketones for the synthesis of 3-substituted isocoumarins. First, reaction of 2-iodobenzoic acid **1a** with various 1,3-diketones was investigated, and results are summarized in Table 1. When **2a**

Table 1. Synthesis of 3-Substituted Isocoumarins from 2-Iodobenzoic Acid[a]



entry	1,3-diketone	temp (°C)	time (h)	product	yield(%)[b]
1	 **2a**	90	24	 **4a**	76
2	 **2b**	90	24	 **4b**	75
3	 **2c**	100	36	 **4c**	68
4	 **2d**	100	36	 **4d**	65
5	 **2e**	90	36	 **4e**	trace
6	 **2f**	90	24	**4c + 4a**	73[c]
7	 **2g**	120	36	 **4f**	36
8	 **2h**	120	36	**4a**	18
9	 **2i**	120	36	-	-
10	 **2j**	120	36	-	-

[a]Unless otherwise noted, the reactions were performed in a sealed tube with 2-iodobenzoic acid (0.5 mmol), 1,3-diketone (0.5 mmol), and K_3PO_4 (1.0 mmol) in DMF (1 mL). [b]Isolated yields. [c]Combined yield with a ratio of **4c**/**4a** = 3.5/1.

or heptane-3,5-dione **2b** was employed as the substrate, the desired products were formed in excellent yield (entries 1 and 2).

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When 1,3-diphenylpropane-1,3-dione **2c** or 1,3-bis(4-methoxyphenyl)propane-1,3-dione **2d** was employed, the corresponding product formed in good yield (entries 3 and 4). In these cases, benzoic acid and 4-methoxybenzoic acid were also obtained, respectively. The results indicated that deacylation unambiguously occurred in the reaction. The reaction of **1a** with hexafluoropentane-2,4-dione **2e** did not proceed (entry 5). When unsymmetrical 1,3-diketone **2f** was engaged in the system, the reaction gave a mixture of two isomeric products in a 3.5:1 ratio within a 73% combined yield (entry 6). The 3-phenylisocoumarin **4c** is major. When 3-methylpentane-2,4-dione **2g** was used, the corresponding product **4f** was obtained in 36% yield (entry 7). When β-keto ester **2h** was employed as a substrate, the product was obtained in low yield (entry 8), most of the β-keto ester remained. Monoketones were also examined in the reaction. Unfortunately, the reaction did not proceed and starting materials remained (entries 9 and 10).

2-Bromobenzoic acid **1b** and its derivatives were then applied under the optimized condition. To our delight, the reaction with 2-bromobenzoic acid derivatives could proceed smoothly and the products were obtained in satisfactory yields, as shown in Table 2. However, in comparison with the aryl iodides, slightly higher temperatures were required to complete the reaction. For example, when **1b** was treated with **2a** under the optimized condition, the desired product was obtained in 71% yield at 100 °C (entry 1). The reaction of monosubstituted 2-bromobenzoic acids with **2** proceeded always in good yields regardless of electron-donating or electron-withdrawing groups linked on the benzene ring (entries 2−12). In general, electron-donating substituents on the 2-bromobenzoic acid ring (entries 2−7) are superior to electron-withdrawing substituents (entries 8−12) to afford 3-substituted isocoumarins. A substrate with two substituents situated para and meta to the carboxyl group also afforded an excellent yield of the corresponding 3-substituted isocoumarin derivatives **4** (entries 13 and 14).

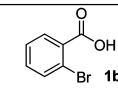
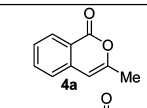
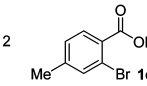
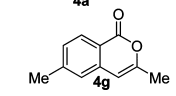
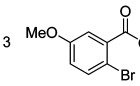
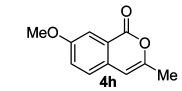
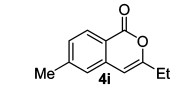
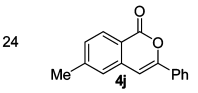
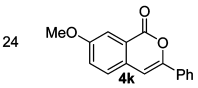
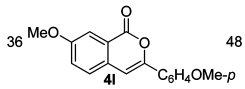
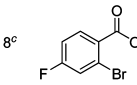
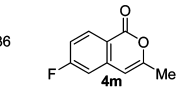
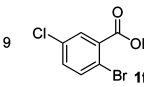
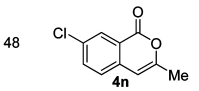
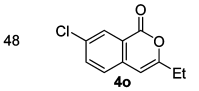
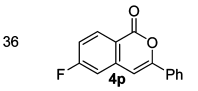
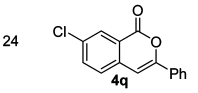
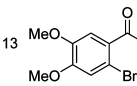
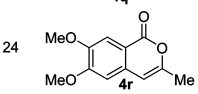
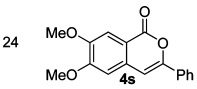
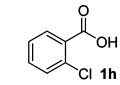
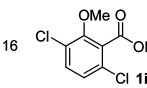
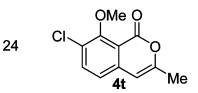
To further demonstrate the scope of this reaction, we examined the reaction with 2-chlorobenzoic acids, and the corresponding products were also obtained in moderate yield at 120 °C (Table 2, entries 15 and 16). Since chlorobenzene did not couple with 1,3-diketones under the same reaction condition, the formation of **4a** and **4t** in our reaction demonstrated that the *ortho*-COOH group may promote the coupling reaction. Subsequently, 2-fluorobenzoic acid was tested under the optimized condition. In this case, the desired product was not obtained even when the reaction temperature was raised to 140 °C. For the 2-halobenzoic acids, their relative reactivity was in the order of aryl iodides > aryl bromides > aryl chlorides > aryl fluorides.

On the basis of the above results, we propose the following reaction mechanism for this cascade sequence (Scheme 4). After initial formation of coupling compound **3′** by the Hurtley reaction,[19,20] the carboxylate ion could attack the carbonyl group of the 1,3-diketone moiety to produce intermediate **5**.[21,19c] Next, the alkoxy anion in **5** would attack another keto moiety to form an intermediate **6** with a four-membered ring,[14e] which undergoes the C−C bond and the C−O bond disconnection to yield 3-substituted isocoumarin **4**.

CONCLUSION

We have demonstrated a new method based on the CuI-catalyzed domino coupling/addition/deacylation process for the construction of 3-substituted isocoumarins from various 2-halobenzoic acids and 1,3-diketones. The efficiency and functional group tolerance of this procedure have been fully demonstrated by synthesizing a number of 3-alkylisocoumarins and 3-arylisocoumarins. Considering the relatively inexpensive catalytic system and the commercial availability of the starting materials, it should be of great benefit for organic synthesis.

Table 2. Synthesis of 3-Substituted Isocoumarins from 2-Bromobenzoic Acid Derivatives[a]

entry	2-halobenzoic acid	1,3-diketone	temp (°C)	time (h)	product	yield (%)[b]
1	 **1b**	**2a**	100	24	 **4a**	71
2	 **1c**	**2a**	100	24	 **4g**	83
3	 **1d**	**2a**	100	24	 **4h**	70
4	**1c**	**2b**	100	24	 **4i**	79
5	**1c**	**2c**	100	24	 **4j**	85
6	**1d**	**2c**	100	24	 **4k**	75
7	**1d**	**2d**	120	36	 **4l**	48
8[c]	 **1e**	**2a**	120	36	 **4m**	54
9	 **1f**	**2a**	100	48	 **4n**	44
10	**1f**	**2b**	100	48	 **4o**	48
11	**1e**	**2c**	100	36	 **4p**	60
12	**1f**	**2c**	100	24	 **4q**	52
13	 **1g**	**2a**	100	24	 **4r**	82
14	**1g**	**2c**	100	24	 **4s**	88
15	 **1h**	**2a**	120	24	**4a**	64
16	 **1i**	**2a**	120	24	 **4t**	43

[a]Unless otherwise noted, the reactions were performed in a sealed tube with 2-bromobenzoic acid (0.5 mmol), 1,3-diketones (0.5 mmol), and K_3PO_4 (1.0 mmol) in DMF (1 mL). [b]Isolated yields. [c]In this reaction, 27% of 6-(dimethylamino)-3-methyl-1*H*-isochromen-1-one was isolated.

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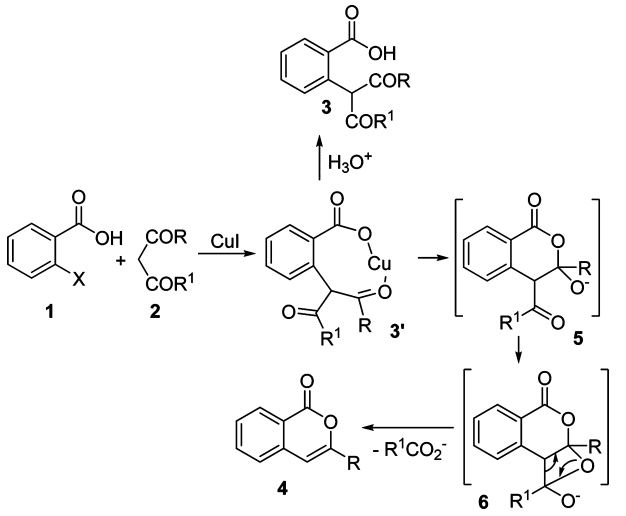
Scheme 4. Proposed Reaction Pathway



EXPERIMENTAL SECTION

General Comments. All the reactions were carried out in a predried screwcapped tube with a Teflon-lined septum under a N_2 atmosphere. Unless otherwise indicated, all materials were obtained from commercial sources and used as received. DMF, toluene, CH_3CN, and DMSO were freshly distilled. Column chromatography was performed on silica gel. ^1H NMR and ^{13}C NMR spectra were recorded on 300 and 600 MHz spectrometers at ambient temperature with $CDCl_3$ or DMSO-d_6 as the solvent. Chemical shifts (δ) were given in parts per million, referenced to the residual proton resonance of $CDCl_3$ (7.26) or DMSO (2.5), and to the carbon resonance of $CDCl_3$ (77.16) or DMSO-d_6 (39.52). Coupling constants (J) were given in hertz (Hz). The terms m, d, and s refer to multiplet, doublet, and singlet. The melting points were measured on an X-4 digital melting point apparatus and were uncorrected. The reaction progress was monitored by ^1H NMR. ^1H NMR yields, using trichloroethene as an internal standard, were obtained in proportion to the integral area of the trichloroethene signal.

General Procedure for the Synthesis of 3-Substituted Isocoumarins 4. A sealed tube was charged with the mixture of *o*-halobenzoic acid **1** (0.5 mmol), 1,3-diketone **2** (0.5 mmol), CuI (0.05 mmol, 10 mg), and K_3PO_4 (1.0 mmol, 212 mg), and the mixture was then stirred in DMF (1 mL) at room temperature under a nitrogen atmosphere. Half an hour later, the tube was sealed and the mixture was allowed to stir at 90−120 °C for an indicated time. After completion, the mixture was cooled to room temperature. H_2O (5 mL) was then added, and the mixture was extracted with EtOAc (5 mL × 3) and dried by anhydrous Na_2SO_4. Evaporation of the solvent, followed by purification on silica gel (petroleum ether/ethyl acetate = 5/1), provided the corresponding product **4**.

*3-Methyl-1H-isochromen-1-one (**4a**):*[22] White solid, 60 mg (76% yield), mp 72−73 °C; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.22 (s, 3H), δ 6.52 (s, 1H), δ 7.48−7.52 (m, 2H), δ 7.74−7.79 (m, 1H), δ 8.07 (d, J_{H-H} = 8.2 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 19.1, 103.2, 119.1, 125.3, 127.8, 128.7, 135.1, 137.4, 154.4, 161.9; ESI-MS $[M + H]^+$ m/z 161.3.

*3-Ethyl-1H-isochromen-1-one (**4b**):*[22] White solid, 65 mg (75% yield), mp 73−74 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.24 (t, J_{H-H} = 7.6 Hz, 3H), δ 2.49−2.57 (m, 2H), δ 6.21 (s, 1H), δ 7.30−7.42 (m, 2H), δ 7.63 (t, J_{H-H} = 7.6 Hz, 1H), δ 8.20 (d, J_{H-H} = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.3, 26.7, 102.0, 120.2, 125.1, 127.6, 129.5, 134.7, 137.7, 159.5, 163.1; ESI-MS $[M + H]^+$ m/z 175.3.

*3-Phenyl-1H-isochromen-1-one (**4c**):*[22] White solid, 75 mg (68% yield), mp 81−82 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.92 (s, 1H), δ 7.37−7.49 (m, 5H), δ 7.66−7.71 (m, 1H), δ 7.84−7.87 (m, 2H), δ 8.28 (d, J_{H-H} = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 101.9, 120.6, 125.3, 126.1, 128.2, 128.9, 129.7, 130.0, 132.0, 134.9, 137.6, 153.7, 162.4; ESI-MS $[M + H]^+$ m/z 223.4.

*3-(4-Methoxyphenyl)-1H-isochromen-1-one (**4d**):*[23] White solid, 81 mg (65% yield), mp 110−112 °C; ^1H NMR ($CDCl_3$, 600 MHz) δ 3.82 (s, 3H), 6.77 (s, 1H), 6.92 (d, J_{H-H} = 8.8 Hz, 2H), 7.41 (dd, J_{H-H} = 7.6, 4.3 Hz, 2H), 7.64 (t, J_{H-H} = 7.4 Hz, 1H), 7.76 (d, J_{H-H} = 8.7 Hz, 2H), 8.23 (d, J_{H-H} = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 55.4, 100.2, 114.2, 120.1, 124.5, 125.8, 126.8, 127.6, 129.6, 134.8, 137.9, 153.7, 161.1, 162.5; ESI-MS $[M + H]^+$ m/z 253.6.

*3,4-Dimethyl-1H-isochromen-1-one (**4f**):*[10b] White solid, 31 mg (36% yield), mp 133−134 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.15 (s, 3H), δ 2.29 (s, 3H), δ 7.41−7.48 (m, 2H), δ 7.71 (t, J_{H-H} = 6.6 Hz, 1H), δ 8.27 (d, J_{H-H} = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.3, 17.4, 107.8, 120.5, 122.5, 127.2, 129.7, 134.7, 138.7, 150.2, 162.9; ESI-MS $[M + H]^+$ m/z 175.3.

*3,6-Dimethyl-1H-isochromen-1-one (**4g**):* White solid, 72 mg (83% yield), mp 61−62 °C; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.20 (s, 3H), δ 2.39 (s, 3H), δ 6.41 (s, 1H), δ 7.27 (t, J_{H-H} = 8.3 Hz, 2H), δ 7.93 (d, J_{H-H} = 8.3 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 19.1, 21.4, 103.1, 116.7, 125.0, 128.6, 128.9, 137.4, 145.8, 154.4, 161.8; ESI-MS $[M + H]^+$ m/z 175.3. HRMS calcd for $C_{11}H_{10}O_2$, 174.0681; found, 174.0685.

*7-Methoxy-3-methyl-1H-isochromen-1-one (**4h**):*[13] White solid, 66 mg (70% yield), mp 101−103 °C; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.19 (d, J_{H-H} = 1.0 Hz, 3H), δ 3.83 (s, 3H), δ 6.43 (s, 1H), δ 7.32−7.36 (m, 1H), δ 7.40−7.45 (m, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 18.8, 55.5, 102.8, 109.6, 120.2, 123.9, 127.0, 131.0, 152.0, 158.5, 161.9; ESI-MS $[M + H]^+$ m/z 191.3. HRMS calcd for $C_{11}H_{10}O_3$, 190.0630; found, 190.0626.

*3-Ethyl-6-methyl-1H-isochromen-1-one (**4i**):* White solid, 74 mg (79% yield), mp 62−63 °C; ^1H NMR ($CDCl_3$, 600 MHz) δ 125 (t, J_{H-H} = 8.4, 3H), 2.44 (s, 3H), 2.54 (q, J_{H-H} = 7.5 Hz, 2H), 6.17 (s, 1H), 7.13 (s, 1H), 7.24 (d, J_{H-H} = 8.1 Hz, 1H), 8.11 (d, J_{H-H} = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.2, 21.9, 26.6, 101.9, 117.6, 125.1, 128.9, 129.3, 137.7, 145.7, 159.5, 163.1; ESI-MS $[M + H]^+$ m/z 189.3. HRMS calcd for $C_{12}H_{12}O_2$, 188.0837; found, 188.0839.

*6-Methyl-3-phenyl-1H-isochromen-1-one (**4j**):*[24] White solid, 100 mg (85% yield), mp 107−108 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.41 (s, 3H), 6.80 (s, 1H), 7.19−7.23 (m, 2H), 7.34−7.43 (m, 3H), 7.80 (dd, J_{H-H} = 7.7, 1.7 Hz, 2H), 8.10 (d, J_{H-H} = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.9, 101.7, 118.1, 125.1, 126.0, 128.8, 129.5, 129.5, 129.8, 132.0, 137.5, 146.0, 153.5, 162.3; ESI-MS $[M + H]^+$ m/z 237.2.

*7-Methoxy-3-phenyl-1H-isochromen-1-one (**4k**):*[24] Yellow solid, 94 mg (75% yield), mp 167−168 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.86 (s, 3H), 6.85 (s, 1H), 7.24 (dd, J_{H-H} = 8.6, 2.6 Hz, 1H), 7.27−7.43 (m, 4H), 7.65 (d, J_{H-H} = 2.4 Hz, 1H), 7.79 (d, J_{H-H} = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.8, 101.6, 110.0, 121.6, 124.7, 124.9, 127.6, 128.8, 129.6, 131.2, 132.1, 151.6, 159.6, 162.5; ESI-MS $[M + H]^+$ m/z 253.7.

*7-Methoxy-3-(4-methoxyphenyl)-1H-isochromen-1-one (**4l**):*[24] Light yellow solid, 67 mg (48% yield), mp 139−141 °C; ^1H NMR ($CDCl_3$, 600 MHz) δ 3.86 (s, 3H), 3.91 (s, 3H), 6.80 (s, 1H), 6.95 (d, J_{H-H} = 8.8 Hz, 2H), 7.29 (dd, J_{H-H} = 8.6, 2.5 Hz, 1H), 7.39 (d, J_{H-H} = 8.7 Hz, 1H), 7.70 (d, J_{H-H} = 2.3 Hz, 1H), 7.79 (d, J_{H-H} = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 55.5, 55.9, 100.2, 110.1, 114.4, 121.3, 124.9, 126.6, 127.4, 131.8, 152.0, 159.4, 160.9, 162.8; ESI-MS $[M + H]^+$ m/z 283.7.

*6-Fluoro-3-methyl-1H-isochromen-1-one (**4m**):* White solid, 48 mg (54% yield), mp 96−97 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.26 (s, 3H), δ 6.20 (s, 1H), δ 6.94−6.98 (m, 1H), δ 7.07−7.14 (m, 1H), δ 8.21−8.26 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.8, 103.2 (d, J_{F-C} = 2.2 Hz), 110.6 (d, J_{F-C} = 22.2 Hz), 115.9 (d, J_{F-C} = 23.7 Hz), 116.5 (d, J_{F-C} = 2.2 Hz), 132.9 (d, J_{F-C} = 10.8 Hz), 140.4 (d, J_{F-C} = 10.8 Hz), 156.1, 162.0, 166.8 (d, J_{F-C} = 255.8 Hz); ESI-MS $[M + H]^+$ m/z 179.3. HRMS calcd for $C_{10}H_7FO_2$, 178.0430; found, 178.0434.

*7-Chloro-3-methyl-1H-isochromen-1-one (**4n**):*[13] White solid, 42 mg (44% yield), mp 165−167 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.26 (s, 3H), δ 6.22 (s, 1H), δ 7.19−7.26 (m, 1H), δ 7.73−7.75

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(m, 1H), δ 8.35 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.8, 103.1, 120.9, 121.5, 126.7, 132.1, 136.5, 137.9, 155.3, 161.7; ESI-MS $[M + H]^+$ *m/z* 194.3. HRMS calcd for $C_{10}H_7ClO_2$, 194.0135; found, 194.0131.

*7-Chloro-3-ethyl-1H-isochromen-1-one (**4o**):* White solid, 50 mg (48% yield), mp 73−75 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.26 (t, J_{H-H} = 7.5 Hz, 3H), 2.55 (q, J_{H-H} = 7.5 Hz, 2H), 6.21 (s, 1H), 7.23 (d, J_{H-H} = 8.4 Hz, 1H), 7.73 (dd, J_{H-H} = 8.4, 1.9 Hz, 1H), 8.35 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 11.2, 26.8, 101.5, 120.9, 121.6, 126.8, 132.1, 136.5, 137.9, 160.2, 161.8; ESI-MS $[M + H]^+$ *m/z* 208.3. HRMS calcd for $C_{11}H_9ClO_2$, 208.0291; found, 208.0292.

*6-Fluoro-3-phenyl-1H-isochromen-1-one (**4p**):* White solid, 72 mg (60% yield), mp 162−163 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.88 (s, 1H), 7.11−7.22 (m, 2H), 7.43−7.49 (m, 3H), 7.84−7.87 (m, 2H), 8.30 (dd, J_{H-H} = 8.7, 5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 101.3 (d, J_{F-C} = 2.6 Hz), 111.6 (d, J_{F-C} = 22.6 Hz), 116.5 (d, J_{F-C} = 23.4 Hz), 117.1, 125.5, 129.0, 130.5, 131.6, 133.1 (d, J_{F-C} = 10.5 Hz), 140.3 (d, J_{F-C} = 10.9 Hz), 155.0, 161.4, 166.8 (d, J_{F-C} = 256.5 Hz); ESI-MS $[M + H]^+$ *m/z* 241.3. HRMS calcd for $C_{15}H_9FO_2$, 240.0587; found, 240.0586.

*7-Chloro-3-phenyl-1H-isochromen-1-one (**4q**):*[24] Yellow solid, 66 mg (52% yield), mp 183−185 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.89 (s, 1H), 7.34−7.44 (m, 4H), 7.76−7.85 (m, 3H), 8.40 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 101.2, 121.6, 121.9, 125.4, 127.7, 129.0, 130.4, 131.7, 132.3, 136.3, 138.1, 154.2, 161.1; ESI-MS $[M + H]^+$ *m/z* 257.1.

*6,7-Dimethoxy-3-methyl-1H-isochromen-1-one (**4r**):*[10a] White solid, 90 mg (82% yield), mp 141−142 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.20 (s, 1H), 3.90 (s, 3H), 3.92 (s, 3H), 6.11 (s, 1H), 6.65 (s, 1H), 7.53 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.6, 56.2, 103.2, 105.6, 109.3, 112.8, 133.4, 149.2, 153.5, 155.1, 162.9; ESI-MS $[M + H]^+$ *m/z* 221.2.

*6,7-Dimethoxy-3-phenyl-1H-isochromen-1-one (**4s**):*[24] White solid, 124 mg (88% yield), mp 168−170 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.98 (s, 3H), 4.00 (s, 3H), 6.87 (d, J_{H-H} = 12.0 Hz, 2H), 7.39−7.43 (m, 3H), 7.65 (s, 1H), 7.84 (d, J_{H-H} = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 56.3, 101.6, 106.6, 109.5, 113.7, 125.0, 128.8, 129.7, 132.1, 133.2, 149.8, 152.7, 155.2, 162.3; ESI-MS $[M + H]^+$ *m/z* 283.9.

*7-Chloro-8-methoxy-3-methyl-1H-isochromen-1-one (**4t**):* White solid, 48 mg (43% yield), mp 115−117 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.24 (s, 3H), 3.98 (s, 3H), 6.17 (s, 1H), 7.01 (d, J_{H-H} = 8.4 Hz, 1H), 7.64 (d, J_{H-H} = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 19.6, 61.8, 103.1, 115.0, 121.5, 127.6, 136.5, 139.1, 155.4, 157.9, 158.7; ESI-MS $[M + H]^+$ *m/z* 225.1. HRMS calcd for $C_{11}H_9ClO_3$, 224.0240; found, 224.0243.

■ ASSOCIATED CONTENT

Supporting Information

Copies of spectra for compounds **4a−4d** and **4f−4t**. 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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