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Synthesis of 3-Substituted Isocoumarins via a Cascade Intramolecular Ullmann-Type Coupling−Rearrangement Process

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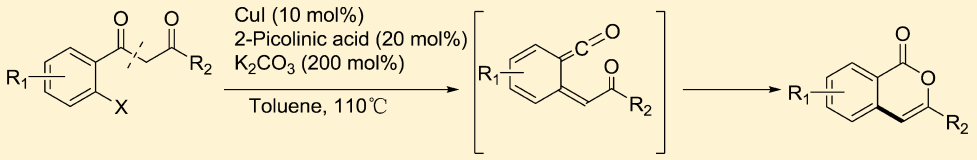
Supporting Information



ABSTRACT: A simple and highly efficient strategy for the synthesis of 3-substituted isocoumarins through a copper(I)-catalyzed reaction of 1-(2-halophenyl)-1,3-diones has been developed. The procedure is based on a cascade copper-catalyzed intramolecular Ullmann-type C-arylation and rearrangement process. This methodology is tolerant of a wide range of substrates and applicable to library synthesis.

INTRODUCTION

Recently, transition-metal-catalyzed coupling reactions, as a powerful tool for the formation of C−C and C−X (X = N, O, S) bonds, have gained much interest due to their high regiospecificity and broad compatibility regarding functional groups.[1] In 2011, our group successfully synthesized isoflavones from β-ketonaldehydes via CuI-catalyzed intramolecular cyclization.[2] We hypothesized that the same strategy might be applicable to prepare flavones via the copper-catalyzed tandem reaction of 1-(2-halophenyl)-3-phenylpropane-1,3-dione. Simultaneously, a catalyst-free methodology for the synthesis of flavones was reported (path a in Scheme 1).[3] Unexpectedly, isocoumarin was obtained instead of flavone in our ongoing experiments. Isocoumarins[4] are an important class of naturally occurring lactones that exhibit a broad range of biological activities such as antimicrobial and antiallergic,[5] antifungal,[6] anticancer,[7] and anti-HIV[8] properties and are also used as important intermediates for the synthesis of some natural products.[9] As a result, we transferred our research objective to the synthesis of isocoumarin (path b in Scheme 1).

The wide range of biological activities has led to continued interest in the synthesis of isocoumarin derivatives, especially isocoumarins substituted in the 3-position. Various methods for constructing these molecules have been reported,[10] including cyclization of 2-alkenyl or 2-allylbenzoic acid derivatives,[11] condensation of benzoic acid derivatives with alkynes or alkenes,[12] palladium-catalyzed carbonylation of *o*-iodobenzyl alkyl ketones or α-(*o*-haloaryl)-substituted ketones,[13] microwave-assisted reaction of homophthalic acid with acid chlorides or esters,[14] NHC-catalyzed oxidative cyclization of 2-alkynyl benzaldehydes,[15] and thermal cyclization reaction of δ-ketoamides.[16] These methods were presented as efficient protocols for both carbon and heterocycle assembly. However, the synthetic strategies for the construction of these molecules involved multistep reaction sequences, harsh conditions, or expensive catalysts. Recently, several copper-catalyzed intermolecular domino reactions from 2-halobenzoic acids or 2-halobenzoic acid derivatives with 1,3-diketones have been recognized as substantial methods for the synthesis of 3-substituted isocoumarins (Scheme 2a).[17] A similar method was previously used in the synthesis of isoquinolinones.[18] As part of our continuing effort at the construction of heterocycles via copper-catalyzed reactions,[2,19] herein, we would like to report a serendipitous finding, an atom-economical tandem process for the construction of various 3-substituted isocoumarins by a copper-catalyzed reaction of 1-(2-halophenyl)-3-phenylpropane-1,3-diones (Scheme 2b).

RESULTS AND DISCUSSION

Using 1-(2-iodophenyl)-3-phenylpropane-1,3-dione **1a** as the model substrate, optimization of the reaction conditions was investigated through systematic screening. As shown in Table 1, several solvents were examined in the presence of CuI, 2-picolinic acid, and K_2CO_3 (Table 1, entries 1−5), and the expected product **2a** was formed in 81% yield when toluene was employed (Table 1, entry 5). To further improve the yield, we surveyed a series of reaction conditions and found that 2-picolinic acid, in comparison with other ligands or a ligand-free condition, produced **2a** in the best yield (Table 1, entries 6−8), and only a small amount of **2a** (less than a 5% yield) was obtained in the absence of a catalyst and a ligand (Table 1, entry 9). Our investigation of bases showed that K_2CO_3 was optimal (Table 1, entries 5, 10, and 11). Then, the activity of the catalyst was also investigated, and a comparison of catalysts indicated that CuI was superior to the others (Table 1, entries

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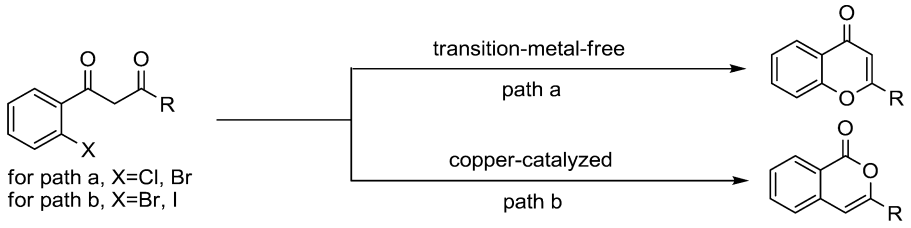
Scheme 1. Cyclization of 1-(2-Halophenyl)-3-phenylpropane-1,3-diones



Scheme 2. Copper-Catalyzed Intermolecular and Intramolecular Reactions Leading to 3-Substituted Isocoumarins from 1,3-Diketones

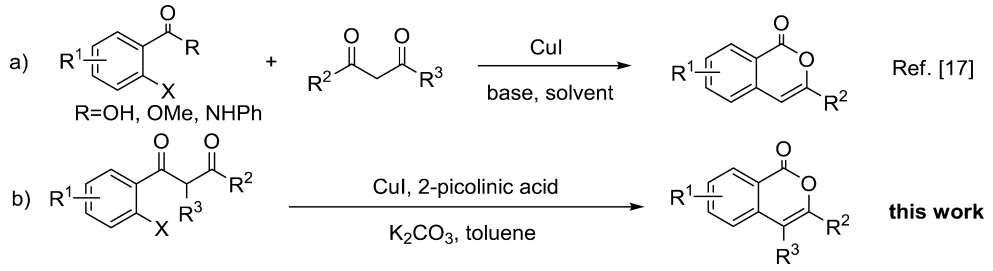
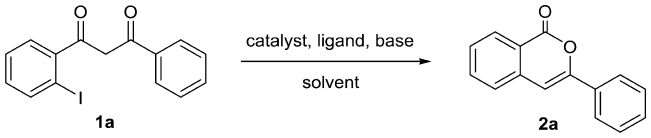


Table 1. Condition Optimizations for Isocoumarin Synthesis[a]



entry	catalyst	ligand[b]	base	solvent[c]	yield (%)[d]
1	CuI	L1	K_2CO_3	1,4-dioxane	50
2	CuI	L1	K_2CO_3	DMSO	8
3	CuI	L1	K_2CO_3	DMF	<5
4	CuI	L1	K_2CO_3	THF	32
5	CuI	L1	K_2CO_3	toluene	81
6	CuI	L2	K_2CO_3	toluene	68
7	CuI	L3	K_2CO_3	toluene	70
8	CuI	–	K_2CO_3	toluene	65
9	–	–	K_2CO_3	toluene	<5
10	CuI	L1	Cs_2CO_3	toluene	44
11	CuI	L1	K_3PO_4	toluene	38
12	$Cu(OAc)_2$	–	K_2CO_3	toluene	58
13	$Cu(OAc)_2$	L1	K_2CO_3	toluene	65
14	$Pd(OAc)_2$	–	K_2CO_3	toluene	<5
15	$Pd(OAc)_2$	L4	K_2CO_3	toluene	32

[a]All reactions were run with **1a** (0.5 mmol), catalyst (0.05 mmol), ligand (0.1 mmol), base (1.0 mmol), and solvent (2 mL) under nitrogen in a sealed tube for 6 h. [b]L1, 2-picolinic acid; L2, (±)-*trans*-1,2-diaminocyclohexane; L3, 1,10-phenanthroline; L4, triphenylphosphine (PPh_3). [c]The reaction temperature for 1,4-dioxane and toluene was 110 °C; DMSO and DMF were at 120 °C, and THF was at 70 °C. [d]Isolated yield.

12−15). Therefore, the optimal reaction conditions were run in the presence of CuI (10 mol %), 2-picolinic acid (20 mol %), and K_2CO_3 (200 mol %) in anhydrous toluene (2 mL) within a sealed tube under nitrogen at 110 °C.

With these results in hand, we sought to examine the scope and generality of the method. As shown in Tables 2 and 3, the catalyst system was tolerant of a wide range of substrates. Various substituents, including aryl (Table 2, entries 1−11), heteroaryl (Table 2, entries 12−16), and alkyl (Table 2, entries 17 and 18), which were present in compound **1**, were well tolerated during the course of the reaction. R^2 affected the reaction significantly, with electron rich aromatics giving higher yields than electron poor counterparts (Table 2, entries 2−11). It is interesting that good yields were also obtained when R^2 was a heteroaryl or aliphatic group (Table 2, entries 12−18). Steric hindrance caused a considerable decrease in the yields (Table 2, entries 8, 9, and 15). In addition, when the substrate was changed from iodoarene to bromoarene, a slightly lower yield was observed (Table 2, entry 19).

As illustrated in Table 3, this process was compatible with a variety of electron-withdrawing and electron-donating groups (Table 3, entries 1−4). It was noted that when R^1 was an electron-withdrawing group, higher yields were obtained (Table 3, entries 1, 3, and 4). Interestingly, the corresponding products **2a′** and **2b′** were produced in high yields when 1-(1-bromonaphthalen-2-yl) was the substituent on substrates **1a′** and **1b′** (Table 3, entries 9 and 10) probably owing to the weak aromaticity of the naphthalene ring. Besides, as an anticipated 4-substituted isocoumarin, the R^3 substituent on **1** was also tolerated, and the target product 4-methyl-3-phenyl-1*H*-isochromen-1-one (**2c′**) was generated in moderate yield (Table 3, entry 11).

To elucidate the reaction mechanism for the synthesis of the 3-substituted isocoumarin derivatives, the following three control experiments were carried out (Scheme 3). Two equivalents of the radical scavenger 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO) did not have an observable effect on the outcome of the reaction, suggesting that the reaction does not proceed via a radical intermediate (Scheme 3a). The product **2a** was obtained in good yield when 1,3-diphenylpropane-1,3-dione was added to the reaction system (Scheme 3b), which implies the reaction is on an intramolecular mechanism basis. Under the same reaction conditions, when N-benzoyl-2-bromobenzamide was employed as starting material, 2-phenyl-4*H*-3,1-benzoxazin-4-one was obtained in 42% yield (Scheme 3c), which supports the fact that the reaction mechanism may involve an intramolecular Ullmann-type coupling process.

Based on the above experimental results, together with related reports,[17c,20] a plausible mechanism for the copper-

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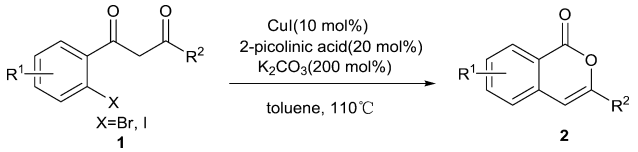
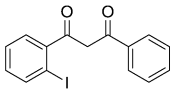
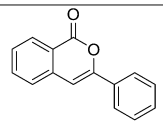
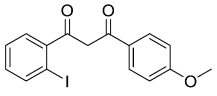
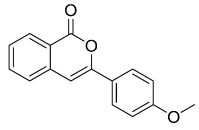
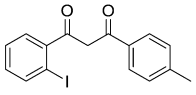
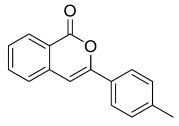
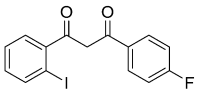
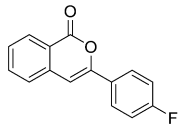
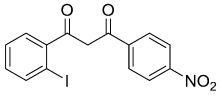
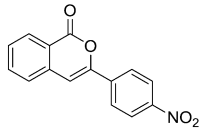
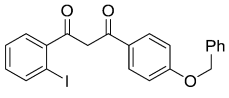
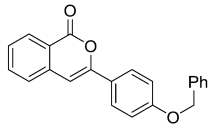
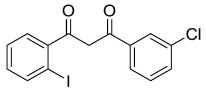
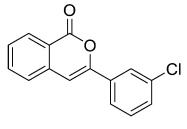
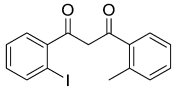
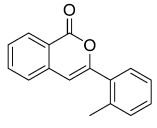
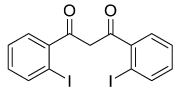
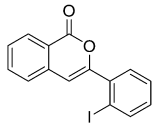
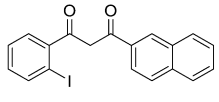
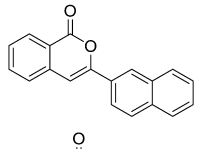
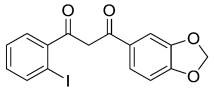
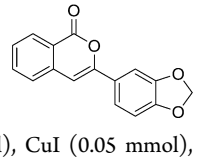
Table 2. Synthesis of 3-Substituted Isocoumarins[a]



Entry	Substrate		Product		Time	Yield [%] [b]
1		**1a**		**2a**	6h	81
2		**1b**		**2b**	6h	87
3		**1c**		**2c**	6h	84
4		**1d**		**2d**	6h	79
5		**1e**		**2e**	12h	62
6		**1f**		**2f**	6h	86
7		**1g**		**2g**	6h	80
8		**1h**		**2h**	8h	74
9		**1i**		**2i**	10h	61
10		**1j**		**2j**	6h	81
11		**1k**		**2k**	6h	81

[a]The reactions were performed in a sealed tube with **1** (0.5 mmol), CuI (0.05 mmol), 2-picolinic acid (0.1 mmol), and K_2CO_3 (1.0 mmol) in toluene (2 mL) at 110 °C under nitrogen. [b]Isolated yield.

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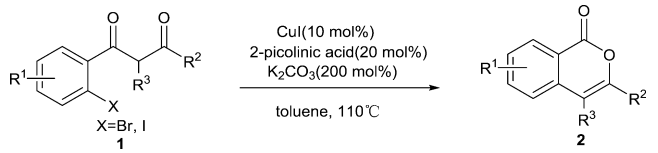
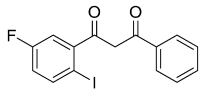
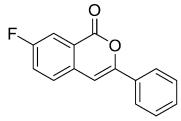
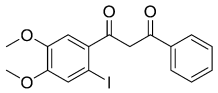
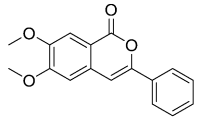
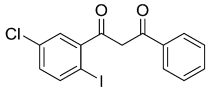
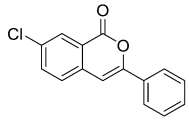
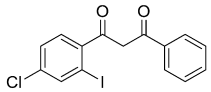
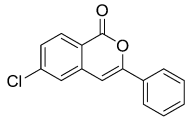
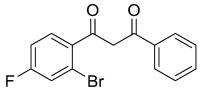
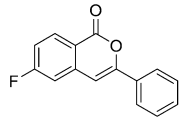
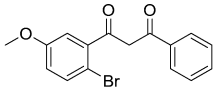
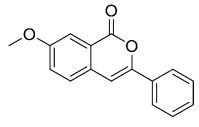
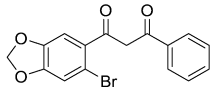
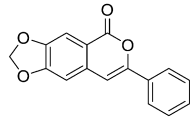
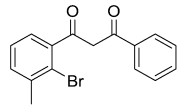
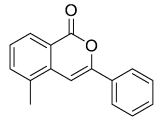
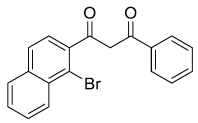
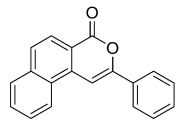
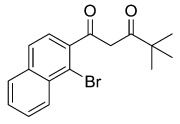
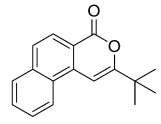
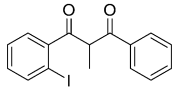
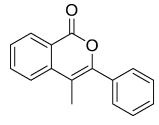
Table 3. Synthesis of Functionalized 3-Substituted Isocoumarins[a]



Entry	Substrate		Product		Time	Yield [%][b]
1		**1s**		**2s**	5h	89
2		**1t**		**2t**	8h	76
3		**1u**		**2u**	6h	96
4		**1v**		**2v**	6h	93
5		**1w**		**2w**	6h	64
6		**1x**		**2x**	12h	47
7		**1y**		**2y**	12h	62
8		**1z**		**2z**	5h	72
9		**1a'**		**2a'**	5h	98
10		**1b'**		**2b'**	5h	91
11		**1c'**		**2c'**	8h	78

[a]The reactions were performed in a sealed tube with **1** (0.5 mmol), CuI (0.05 mmol), 2-picolinic acid (0.1 mmol), and K_2CO_3 (1.0 mmol) in toluene (2 mL) at 110 °C under nitrogen. [b]Isolated yield.

catalyzed tandem reaction of the 1,3-dione compound **1a** is proposed as shown in Scheme 4. Initially, copper iodide would activate the 1,3-dione (**1a**) to generate a copper(I) complex, **A**, which would then give rise to the four-membered ring intermediate, **B**, via the intramolecular Ullmann-type coupling process of the C−C bond. Then, release of ring strain from **B** led rapidly to the ketene compound, **C**. Finally, ring closure would lead to the desired six-membered annulation product, **2a**.

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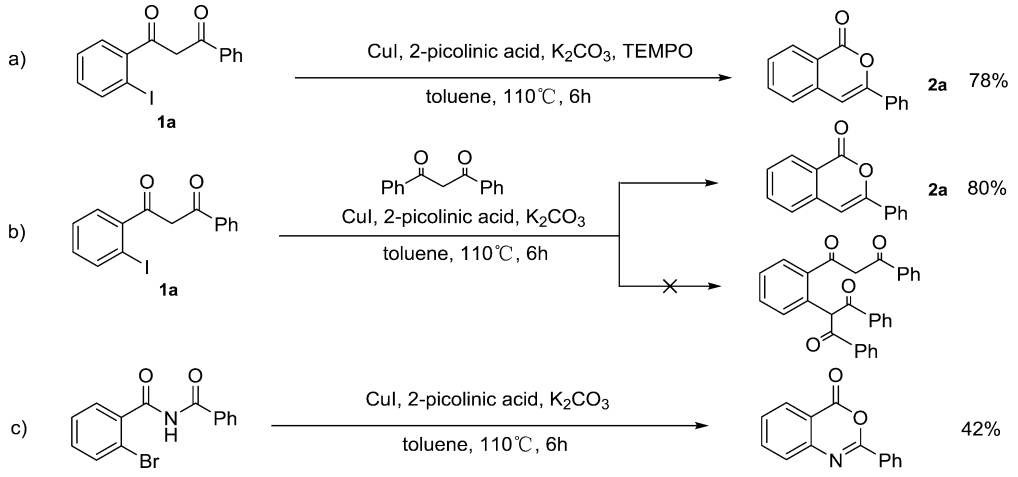
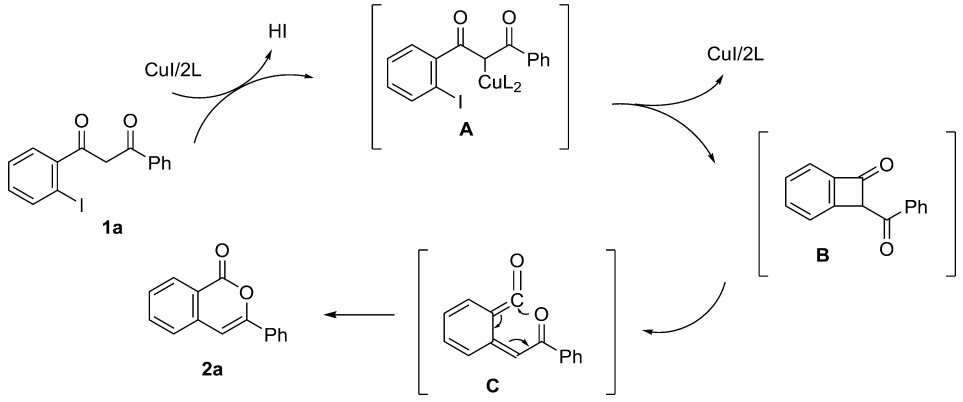
Scheme 3. Investigation of the Reaction Mechanism for the Synthesis of the 3-Substituted Isocoumarin Derivatives



Scheme 4. A Plausible Reaction Mechanism



During the conversion of **1a** to **2a**, the four-membered ring transition state was produced, in which the copper(I) catalyst would play a significant role.

CONCLUSION

In summary, we have developed a new method for the synthesis of 3-substituted isocoumarins. The protocol uses readily available 1-(2-halophenyl)-1,3-diones (obtained from 2-haloarylcarboxylic acid chloride with ketones)[21] as starting materials and CuI/2-picolinic acid as the catalyst system. The procedure involves an intramolecular-sequential copper-catalyzed C−C coupling reaction and a rearrangement process. Characterized by mild reaction conditions, good to excellent yields, and a wide functional-group tolerance, this protocol should be very attractive in synthetic organic and medicinal chemistry.

EXPERIMENTAL SECTION

General Remarks. Chemicals and reagents were purchased from commercial suppliers and used without special instructions. All anhydrous solvents used in the reactions were dried and freshly distilled. Thin-layer chromatography (TLC) was performed using silica HSGF254 plates. Melting points were determined without correction on a digital melting-point apparatus. ^{1}H and ^{13}C NMR spectra were obtained from a solution in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard using a 400:101 MHz (^{1}H/^{13}C) or 300:75 MHz (^{1}H/^{13}C) spectrometer, δ in parts per million, and J in hertz. Infrared (IR) spectra were obtained using KBr tablets and wavenumbers in cm^{-1}. High-resolution mass spectra (HRMS) analyses were carried out using time-of-flight mass spectrometry (TOF-MS) or electrospray ionization (ESI) mass spectrometry.

General Procedure for the Synthesis of Compounds 2a−2c′. A sealed tube was charged with a magnetic stir bar, 1,3-dione, **1** (0.5 mmol), CuI (0.05 mmol, 10 mg), 2-picolinic acid (0.1 mmol, 12 mg), K_2CO_3 (1.0 mmol, 138 mg), and anhydrous toluene (2 mL). The tube was purged with nitrogen gas, and its contents were stirred at 110 °C for the indicated time. After reaction completion, the mixture was filtered through a short plug of Celite and washed with EtOAc (3 mL, two times). The combined filtrates were concentrated on a rotary evaporator and purified on a silica gel column using petroleum ether/EtOAc as the eluent to give the pure target product.

Characterization Data of the Isolated Compounds. *3-Phenyl-1H-isochromen-1-one (**2a**).* Eluent: petroleum ether/EtOAc (100:1). Yield: for substrate **1a**, 81% (90 mg); for substrate **1aa**, 68% (76 mg). White solid. Mp: 81−82 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, J = 8.1 Hz, 1H), 7.87 (d, J = 7.8 Hz, 2H), 7.71 (t, J = 7.6 Hz, 1H), 7.53−7.39 (m, 5H), 6.94 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.3, 153.5, 137.4, 134.8, 131.9, 129.9, 129.6, 128.8, 128.1, 125.9, 125.2, 120.5, 101.8. IR (KBr): ν = 3071, 1719, 1635, 1481, 1230, 1071, 1028, 1011, 765, 744, 684 cm^{-1}. HRMS (EI): calcd for $C_{15}H_{10}O_2$ $[M]^+$, 222.0681; found, 222.0683.

*3-(4-Methoxyphenyl)-1H-isochromen-1-one (**2b**).* Eluent: petroleum ether/EtOAc (50:1). Yield: 87% (110 mg). White solid. Mp: 115−116 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.7 Hz, 2H), 7.66 (t, J = 7.5 Hz, 1H), 7.50−7.36 (m, 2H), 6.93 (d, J = 8.7 Hz, 2H), 6.78 (s, 1H), 3.83 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.4, 161.0, 153.6, 137.8, 134.8, 129.5, 127.6, 126.7, 125.6, 124.4, 120.0, 114.1, 100.2, 55.3. IR (KBr): ν = 2999, 2845, 1739, 1633, 1603, 1512, 1262, 1065, 1023, 839, 817, 751, 685

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cm^{-1}. HRMS (EI): calcd for $C_{16}H_{12}O_3$ [M]$^+$, 252.0786; found, 252.0785.

*3-p-Tolyl-1H-isochromen-1-one (**2c**).* Eluent: petroleum ether/EtOAc (200:1). Yield: 84% (99 mg). White solid. Mp: 113−115 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.2 Hz, 2H), 7.70 (t, J = 7.6 Hz, 1H), 7.53−7.40 (m, 2H), 7.27 (d, J = 5.7 Hz, 2H), 6.91 (s, 1H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.4, 153.8, 140.2, 137.6, 134.8, 129.5, 129.5, 129.1, 127.8, 125.8, 125.1, 120.3, 101.0, 21.3. IR (KBr): ν = 3068, 2919, 1737, 1626, 1509, 1482, 1237, 1070, 815, 751, 684 cm^{-1}. HRMS (ESI): calcd for $C_{16}H_{13}O_2$ [M + H]$^+$, 237.0910; found, 237.0910.

*3-(4-Fluorophenyl)-1H-isochromen-1-one (**2d**).* Eluent: petroleum ether/EtOAc (200:1). Yield: 79% (95 mg). White solid. Mp: 132−133 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, J = 7.8 Hz, 1H), 7.92−7.79 (m, 2H), 7.72 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.3 Hz, 2H), 7.14 (t, J = 8.2 Hz, 2H), 6.88 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.9, 162.4, 162.1, 152.6, 137.3, 134.9, 129.6, 128.2, 127.2, 127.2, 125.9, 120.3, 116.0, 115.8, 101.5. IR (KBr): ν = 3098, 1722, 1641, 1599, 1508, 1234, 1069, 826, 745, 681 cm^{-1}. HRMS (EI): calcd for $C_{15}H_9FO_2$ [M]$^+$, 240.0587; found, 240.0587.

*3-(4-Nitrophenyl)-1H-isochromen-1-one (**2e**).* Eluent: petroleum ether/EtOAc (20:1). Yield: 62% (83 mg). Yellow solid. Mp: 227−229 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (t, J = 8.7 Hz, 3H), 8.05 (d, J = 8.8 Hz, 2H), 7.79 (t, J = 7.6 Hz, 1H), 7.59 (t, J = 8.7 Hz, 2H), 7.13 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.4, 150.9, 148.2, 137.6, 136.4, 135.2, 129.8, 129.4, 126.6, 125.8, 124.1, 120.9, 104.8. IR (KBr): ν = 3094, 1738, 1594, 1516, 1345, 1057, 860, 839, 762, 685 cm^{-1}. HRMS (EI): calcd for $C_{15}H_9NO_4$ [M]$^+$, 267.0532; found, 267.0534.

*3-(4-(Benzyloxy)phenyl)-1H-isochromen-1-one (**2f**).* Eluent: petroleum ether/EtOAc (50:1). Yield: 86% (141 mg). White solid. Mp: 135−137 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, J = 8.1 Hz, 1H), 7.84 (d, J = 8.9 Hz, 2H), 7.71 (t, J = 7.5 Hz, 1H), 7.52−7.32 (m, 7H), 7.06 (d, J = 8.8 Hz, 2H), 6.85 (s, 1H), 5.13 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.4, 160.2, 153.6, 137.8, 136.4, 134.8, 129.6, 128.6, 128.1, 127.7, 127.5, 126.8, 125.7, 124.7, 120.1, 115.05, 100.3, 70.0. IR (KBr): ν = 3067, 2934, 1736, 1675, 1601, 1510, 1257, 1072, 827, 785, 749, 669 cm^{-1}. HRMS (EI): calcd for $C_{22}H_{16}O_3$ [M]$^+$, 328.1099; found, 328.1099.

*3-(3-Chlorophenyl)-1H-isochromen-1-one (**2g**).* Eluent: petroleum ether/EtOAc (200:1). Yield: 80% (103 mg). White solid. Mp: 165−167 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, J = 7.8 Hz, 1H), 7.81 (s, 1H), 7.70 (d, J = 6.1 Hz, 2H), 7.48 (t, J = 7.4 Hz, 2H), 7.35 (d, J = 4.0 Hz, 2H), 6.91 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.8, 151.8, 136.9, 135.5, 134.9, 133.5, 130.0, 129.8, 129.6, 128.5, 126.1, 125.1, 123.1, 120.5, 102.6. IR (KBr): ν = 3109, 1726, 1634, 1604, 1486, 1235, 1064, 780, 750, 688 cm^{-1}. HRMS (ESI): calcd for $C_{15}H_{10}ClO_2$ [M + H]$^+$, 257.0364; found, 257.0362.

*3-o-Tolyl-1H-isochromen-1-one (**2h**).* Eluent: petroleum ether/EtOAc (100:1). Yield: 74% (87 mg). White solid. Mp: 55−57 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, J = 7.9 Hz, 1H), 7.73 (t, J = 7.6 Hz, 1H), 7.58−7.44 (m, 3H), 7.35 (t, J = 7.4 Hz, 1H), 7.28 (d, J = 7.6 Hz, 2H), 6.61 (s, 1H), 2.51 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.6, 155.5, 137.4, 136.7, 134.8, 132.7, 131.0, 129.8, 129.5, 129.1, 128.2, 125.9, 125.8, 120.2, 105.9, 20.7. IR (KBr): ν = 3068, 2959, 1731, 1643, 1484, 1341, 1231, 1062, 844, 766, 688 cm^{-1}. HRMS (EI): calcd for $C_{16}H_{12}O_2$ [M]$^+$, 236.0837; found, 236.0838.

*3-(2-Iodophenyl)-1H-isochromen-1-one (**2i**).* Eluent: petroleum ether/EtOAc (200:1). Yield: 61% (106 mg). White solid. Mp: 124−126 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (d, J = 7.9 Hz, 1H), 7.97 (d, J = 7.9 Hz, 1H), 7.75 (t, J = 7.5 Hz, 1H), 7.62−7.47 (m, 3H), 7.43 (t, J = 7.5 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 6.73 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.2, 155.4, 140.2, 137.8, 136.8, 134.9, 131.0, 130.5, 129.7, 128.6, 128.2, 126.1, 120.6, 107.0, 96.4. IR (KBr): ν = 3071, 1717, 1653, 1482, 1338, 1299, 1070, 1010, 757, 743, 688 cm^{-1}. HRMS (ESI): calcd for $C_{15}H_{10}IO_2$ [M + H]$^+$, 348.9720; found, 348.9720.

*3-(Naphthalen-2-yl)-1H-isochromen-1-one (**2j**).* Eluent: petroleum ether/EtOAc (200:1). Yield: 81% (110 mg). White solid. Mp: 160−162 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.44 (s, 1H), 8.32 (d, J = 7.9 Hz, 1H), 7.97−7.79 (m, 4H), δ 7.72 (t, J = 7.6 Hz, 1H), 7.58−7.45 (m, 4H), 7.06 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.4, 153.4, 137.5, 134.9, 133.8, 133.1, 129.6, 128.8, 128.8, 128.6, 128.2, 127.6, 127.2, 126.8, 126.0, 125.2, 121.9, 120.5, 102.2. IR (KBr): ν = 3053, 1719, 1635, 1484, 1372, 1191, 1073, 852, 819, 748, 680 cm^{-1}. HRMS (EI): calcd for $C_{19}H_{12}O_2$ [M]$^+$, 272.0837; found, 272.0834.

*3-(Benzo[d][1,3]dioxol-5-yl)-1H-isochromen-1-one (**2k**).* Eluent: petroleum ether/EtOAc (50:1). Yield: 81% (108 mg). White solid. Mp: 160−162 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, J = 7.9 Hz, 1H), 7.68 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 7.5 Hz, 2H), 7.40 (dd, J = 8.2, 1.7 Hz, 1H), 7.29 (d, J = 1.5 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 6.77 (s, 1H), 6.01 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.6, 155.5, 137.4, 136.7, 134.8, 132.7, 131.0, 129.7, 129.5, 129.1, 128.2, 125.9, 125.8, 120.2, 105.9, 20.7. IR (KBr): ν = 3056, 1732, 1618, 1498, 1261, 1113, 1034, 927, 807, 759, 687 cm^{-1}. HRMS (EI): calcd for $C_{16}H_{10}O_4$ [M]$^+$, 266.0579; found, 266.0578.

*3-(Pyridin-3-yl)-1H-isochromen-1-one (**2l**).* Eluent: petroleum ether/EtOAc (10:1). Yield: 69% (77 mg). Yellow solid. Mp: 162−164 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.12 (s, 1H), 8.67 (d, J = 3.2 Hz, 1H), 8.33 (d, J = 7.8 Hz, 1H), 8.20 (d, J = 7.7 Hz, 1H), 7.77 (t, J = 7.3 Hz, 1H), 7.56 (t, J = 7.2 Hz, 2H), 7.42 (dd, J = 7.2, 5.1 Hz, 1H), 7.04 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.8, 151.0, 150.6, 146.5, 136.8, 135.1, 132.6, 129.8, 128.8, 128.1, 126.2, 123.6, 120.7, 103.0. IR (KBr): ν = 3038, 1730, 1641, 1486, 1244, 1069, 1022, 847, 803, 752 cm^{-1}. HRMS (ESI): calcd for $C_{14}H_{10}NO_2$ [M + H]$^+$, 224.0706; found, 224.0711.

*3-(Furan-2-yl)-1H-isochromen-1-one (**2m**).* Eluent: petroleum ether/EtOAc (150:1). Yield: 59% (63 mg). Red solid. Mp: 119−121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, J = 8.0 Hz, 1H), 7.69 (t, J = 7.5 Hz, 1H), 7.50 (s, 1H), 7.48−7.40 (m, 2H), 6.94 (d, J = 2.8 Hz, 1H), 6.85 (s, 1H), 6.53 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.5, 146.8, 146.0, 144.0, 137.2, 134.9, 129.7, 127.9, 125.9, 120.4, 112.1, 110.1, 100.0. IR (KBr): ν = 3151, 1736, 1647, 1479, 1089, 1005, 886, 816, 749, 686 cm^{-1}. HRMS (ESI): calcd for $C_{13}H_9O_3$ [M + H]$^+$, 213.0546; found, 213.0555.

*3-(Thiophen-2-yl)-1H-isochromen-1-one (**2n**).* Eluent: petroleum ether/EtOAc (100:1). Yield: 85% (97 mg). Yellow solid. Mp: 109−111 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, J = 7.9 Hz, 1H), 7.70 (t, J = 7.6 Hz, 1H), 7.61 (d, J = 3.7 Hz, 1H), 7.51−7.43 (m, 2H), 7.40 (d, J = 5.0 Hz, 1H), 7.12 (t, J = 4.3 Hz, 1H), 6.79 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.7, 149.4, 137.4, 135.6, 134.9, 129.8, 128.1, 127.9, 127.4, 126.1, 125.7, 120.3, 100.8. IR (KBr): ν = 3102, 1734, 1631, 1559, 1484, 1072, 1026, 840, 819, 755, 707 cm^{-1}. HRMS (ESI): calcd for $C_{13}H_9O_2S$ [M + H]$^+$, 229.0318; found, 229.0330.

*3-(1-Methyl-1H-indol-2-yl)-1H-isochromen-1-one (**2o**).* Eluent: petroleum ether/EtOAc (200:1). Yield: 53% (73 mg). Yellow solid. Mp: 159−161 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (d, J = 7.9 Hz, 1H), 7.77 (t, J = 7.4 Hz, 1H), 7.67 (d, J = 7.9 Hz, 1H), 7.57 (t, J = 7.5 Hz, 2H), 7.45−7.32 (m, 3H), 7.22 (d, J = 6.7 Hz, 1H), 7.06 (s, 1H), 3.93 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.7, 145.0, 137.0, 136.9, 135.0, 129.8, 128.9, 127.3, 126.3, 125.3, 124.7, 120.9, 120.8, 119.2, 109.9, 109.6, 107.1, 32.3. IR (KBr): ν = 3062, 2942, 1732, 1637, 1347, 1215, 1058, 870, 841, 733, 683 cm^{-1}. HRMS (ESI): calcd for $C_{18}H_{14}NO_2$ [M + H]$^+$, 276.1019; found, 276.1024.

*3-(1-Methyl-1H-indol-3-yl)-1H-isochromen-1-one (**2p**).* Eluent: petroleum ether/EtOAc (200:1). Yield: 93% (128 mg). Yellow solid. Mp: 173−174 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, J = 7.8 Hz, 1H), 8.18 (d, J = 7.6 Hz, 1H), 7.68 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.3 Hz, 2H), 7.34−7.18 (m, 4H), 6.97 (s, 1H), 3.78 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.5, 150.4, 138.2, 135.5, 134.6, 129.5, 127.3, 125.5, 125.4, 124.5, 123.0, 121.7, 120.9, 119.8, 109.3, 105.2, 102.8, 30.1. IR (KBr): ν = 3099, 2927, 1701, 1627, 1557, 1083, 832, 756, 746, 689 cm^{-1}. HRMS (ESI): calcd for $C_{18}H_{14}NO_2$ [M + H]$^+$, 276.1019; found, 276.1023.

*3-tert-Butyl-1H-isochromen-1-one (**2q**).* Eluent: petroleum ether/EtOAc (100:1). Yield: 84% (85 mg). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, J = 7.9 Hz, 1H), 7.67 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.39 (d, J = 7.8 Hz, 1H), 6.31 (s, 1H), 1.33 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.1, 163.0, 137.6, 134.6, 129.3, 127.5, 125.4, 120.0, 99.6, 35.6, 27.9. IR (KBr): ν = 2967, 2926, 1729, 1645, 1481, 1338, 1085, 1051, 1014, 952, 826, 767, 690 cm^{-1}.

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HRMS (ESI): calcd for $C_{13}H_{15}O_2$ $[M + H]^+$, 203.1067; found, 203.1061.

*3-Cyclohexyl-1H-isochromen-1-one (**2r**).* Eluent: petroleum ether/EtOAc (200:1). Yield: 79% (90 mg). White solid. Mp: 91−92 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, J = 7.8 Hz, 1H), 7.66 (t, J = 7.3 Hz, 1H), 7.43 (t, J = 7.4 Hz, 1H), 7.36 (d, J = 7.7 Hz, 1H), 6.23 (s, 1H), 2.44 (t, J = 11.1 Hz, 1H), 2.03 (d, J = 11.6 Hz, 2H), 1.85 (d, J = 11.9 Hz, 2H), 1.74 (d, J = 13.4 Hz, 1H), 1.54−1.17 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.1, 162.3, 137.7, 134.6, 129.4, 127.4, 125.2, 120.2, 100.8, 41.8, 30.5, 25.9, 25.8. IR (KBr): ν = 2927, 2851, 1722, 1649, 1482, 1160, 1061, 958, 897, 830, 760 cm^{-1}. HRMS (ESI): calcd for $C_{15}H_{17}O_2$ $[M + H]^+$, 229.1223; found, 229.1228.

*7-Fluoro-3-phenyl-1H-isochromen-1-one (**2s**).* Eluent: petroleum ether/EtOAc (200:1). Yield: 89% (107 mg). White solid. Mp: 154−156 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, J = 8.2 Hz, 1H), 7.86 (d, J = 6.3 Hz, 2H), 7.55−7.39 (m, 5H), 6.94 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4, 161.4, 160.1, 153.1, 134.0, 131.6, 130.0, 128.8, 128.2, 128.1, 125.1, 123.5, 123.2, 122.1, 122.0, 115.3, 115.0, 101.0. IR (KBr): ν = 3086, 1714, 1618, 1501, 1334, 1256, 1067, 864, 816, 758, 679 cm^{-1}. HRMS (ESI): calcd for $C_{15}H_{10}FO_2$ $[M + H]^+$, 241.0659; found, 241.0659.

*6,7-Dimethoxy-3-phenyl-1H-isochromen-1-one (**2t**).* Eluent: petroleum ether/EtOAc (10:1). Yield: 76% (107 mg). Yellow solid. Mp: 169−171 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, J = 5.9 Hz, 2H), 7.64 (s, 1H), 7.42 (d, J = 8.1 Hz, 3H), 6.86 (d, J = 4.1 Hz, 2H), 4.00 (s, 3H), 3.98 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.2, 155.1, 152.6, 149.7, 133.1, 132.0, 129.6, 128.7, 124.9, 113.6, 109.4, 106.4, 101.5, 56.2. IR (KBr): ν = 3071, 3007, 2941, 1712, 1610, 1514, 1387, 1238, 1060, 891, 835, 781, 703 cm^{-1}. HRMS (ESI): calcd for $C_{17}H_{15}O_4$ $[M + H]^+$, 283.0965; found, 283.0965.

*7-Chloro-3-phenyl-1H-isochromen-1-one (**2u**).* Eluent: petroleum ether/EtOAc (150:1). Yield: 96% (123 mg). White solid. Mp: 182−183 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (s, 1H), 7.87 (d, J = 6.6 Hz, 2H), 7.67 (d, J = 8.3 Hz, 1H), 7.53−7.35 (m, 4H), 6.94 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.1, 153.8, 135.8, 135.2, 133.7, 131.4, 130.2, 129.0, 128.8, 127.4, 125.2, 121.5, 100.9. IR (KBr): ν = 3104, 1718, 1637, 1474, 1324, 1226, 1075, 868, 764, 687 cm^{-1}. HRMS (ESI): calcd for $C_{15}H_{10}ClO_2$ $[M + H]^+$, 257.0364; found, 257.0364.

*6-Chloro-3-phenyl-1H-isochromen-1-one (**2v**).* Eluent: petroleum ether/EtOAc (100:1). Yield: 93% (119 mg). White solid. Mp: 220−221 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, J = 8.3 Hz, 1H), 7.87 (d, J = 5.8 Hz, 2H), 7.54−7.38 (m, 5H), 6.88 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.5, 154.9, 141.5, 138.9, 131.5, 131.3, 130.4, 128.9, 128.5, 125.4, 118.7, 100.7. IR (KBr): ν = 3108, 1713, 1640, 1447, 1326, 1242, 1063, 893, 769, 756, 681 cm^{-1}. HRMS (ESI): calcd for $C_{15}H_{10}ClO_2$ $[M + H]^+$, 257.0364; found, 257.0364.

*6-Fluoro-3-phenyl-1H-isochromen-1-one (**2w**).* Eluent: petroleum ether/EtOAc (500:1). Yield: 64% (77 mg). White solid. Mp: 169−170 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37−8.25 (m, 1H), 7.87 (d, J = 5.8 Hz, 2H), 7.46 (d, J = 5.7 Hz, 2H), 7.17 (dd, J = 17.9, 8.8 Hz, 3H), 6.90 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.4, 165.0, 161.3, 154.8, 140.2, 140.1, 133.0, 132.9, 131.5, 130.3, 128.8, 127.5, 127.4, 125.4, 116.9, 116.6, 116.2, 115.9, 111.6, 111.3, 101.2, 100.9. IR (KBr): ν = 3106, 1716, 1622, 1347, 1258, 1068, 885, 827, 757, 679 cm^{-1}. HRMS (ESI): calcd for $C_{15}H_{10}FO_2$ $[M + H]^+$, 241.0659; found, 241.0661.

*7-Methoxy-3-phenyl-1H-isochromen-1-one (**2x**).* Eluent: petroleum ether/EtOAc (30:1). Yield: 47% (59 mg). White solid. Mp: 165−167 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, J = 7.2 Hz, 2H), 7.71 (d, J = 2.6 Hz, 1H), 7.47−7.34 (m, 4H), 7.28 (dd, J = 8.6, 2.7 Hz, 1H), 6.88 (s, 1H), 3.89 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.3, 159.7, 151.8, 132.2, 131.2, 129.5, 128.8, 127.5, 125.0, 124.6, 121.8, 110.2, 101.5, 55.7. IR (KBr): ν = 3099, 2925, 1713, 1634, 1499, 1356, 1263, 1073, 1027, 859, 779, 759 cm^{-1}. HRMS (ESI): calcd for $C_{16}H_{13}O_3$ $[M + H]^+$, 253.0859; found, 253.0864.

*7-Phenyl-5H-[1,3]dioxolo[4,5-g]isochromen-5-one (**2y**).* Eluent: petroleum ether/EtOAc (10:1). Yield: 62% (83 mg). Yellow solid. Mp: 189−191 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J = 6.5 Hz, 2H), 7.64 (s, 1H), 7.44 (d, J = 7.7 Hz, 3H), 6.85 (s, 2H), 6.11 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.9, 153.7, 152.7, 148.3, 135.1, 131.9, 129.7, 128.8, 125.0, 115.2, 107.5, 104.3, 102.2, 101.8. IR (KBr): ν = 3105, 2926, 1704, 1598, 1484, 1262, 1053, 939, 877, 752, 680 cm^{-1}. HRMS (ESI): calcd for $C_{16}H_{11}O_4$ $[M + H]^+$, 267.0652; found, 267.0658.

*5-Methyl-3-phenyl-1H-isochromen-1-one (**2z**).* Eluent: petroleum ether/EtOAc (500:1). Yield: 72% (85 mg). White solid. Mp: 100−102 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, J = 7.9 Hz, 1H), 7.87 (d, J = 7.1 Hz, 2H), 7.52 (d, J = 7.3 Hz, 1H), 7.48−7.38 (m, 3H), 7.35 (t, J = 7.6 Hz, 1H), 7.02 (s, 1H), 2.53 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.6, 153.0, 136.1, 135.7, 133.5, 132.1, 129.8, 128.7, 127.6, 127.4, 125.2, 120.5, 98.5, 18.8. IR (KBr): ν = 3039, 2963, 1719, 1632, 1381, 1231, 1077, 1032, 948, 759, 702, 685 cm^{-1}. HRMS (ESI): calcd for $C_{16}H_{13}O_2$ $[M + H]^+$, 237.0910; found, 237.0917.

*2-Phenyl-4H-benzo[f]isochromen-4-one (**2a′**).* Eluent: petroleum ether/EtOAc (100:1). Yield: 98% (133 mg). Yellow solid. Mp: 186−189 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (d, J = 6.7 Hz, 1H), 8.18 (d, J = 8.5 Hz, 1H), 7.95 (d, J = 6.8 Hz, 2H), 7.87 (d, J = 6.4 Hz, 1H), 7.80 (d, J = 8.5 Hz, 1H), 7.66 (d, J = 2.4 Hz, 2H), 7.61 (s, 1H), 7.53−7.41 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.5, 154.8, 136.6, 135.9, 132.0, 130.2, 129.3, 128.8, 128.3, 127.7, 127.23, 125.4, 124.1, 123.9, 117.4, 97.4. IR (KBr): ν = 3052, 1716, 1631, 1564, 1345, 1098, 1062, 855, 827, 757, 688 cm^{-1}. HRMS (ESI): calcd for $C_{19}H_{13}O_2$ $[M + H]^+$, 273.0910; found, 273.0929.

*2-tert-Butyl-4H-benzo[f]isochromen-4-one (**2b′**).* Eluent: petroleum ether/EtOAc (30:1). Yield: 91% (115 mg). White solid. Mp: 127−129 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, J = 7.7 Hz, 1H), 8.18 (d, J = 8.6 Hz, 1H), 7.89 (d, J = 7.4 Hz, 1H), 7.80 (d, J = 8.6 Hz, 1H), 7.73−7.61 (m, 2H), 7.07 (s, 1H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.7, 163.2, 136.8, 136.0, 129.1, 128.9, 127.8, 127.8, 127.0, 124.1, 124.0, 117.0, 95.2, 36.1, 28.1. IR (KBr): ν = 2965, 1870, 1715, 1638, 1565, 1331, 1091, 1048, 870, 818, 751 cm^{-1}. HRMS (ESI): calcd for $C_{17}H_{17}O_2$ $[M + H]^+$, 253.1223; found, 253.1226.

*4-Methyl-3-phenyl-1H-isochromen-1-one (**2c′**).* Eluent: petroleum ether/EtOAc (200:1). Yield: 78% (92 mg). White solid. Mp: 68−70 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (dd, J = 8.0, 1.2 Hz, 1H), 7.68−7.61 (m, 3H), 7.55−7.49 (m, 3H), 7.45 (d, J = 8.4 Hz, 1H), 7.39 (t, J = 7.5 Hz, 1H), 2.17 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 178.8, 160.9, 156.0, 133.4, 133.3, 130.1, 128.9, 128.4, 125.8, 124.6, 122.4, 117.8, 117.5, 11.7. IR (KBr): ν = 3052, 2929, 1636, 1615, 1574, 1470, 1396, 1368, 1138, 1015, 755, 701cm^{-1}. HRMS (ESI): calcd for $C_{16}H_{13}O_2$ $[M + H]^+$, 237.0910; found, 237.0915.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra. 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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