Novel and Efficient One-Step Parallel Synthesis of Dibenzopyranones via Suzuki−Miyaura Cross Coupling

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Microwave-promoted novel and efficient one-step parallel synthesis of dibenzopyranones and heterocyclic analogues from bromo arylcarboxylates and *o*-hydroxyarylboronic acids via Suzuki−Miyaura cross coupling reaction is described. Spontaneous lactonization gave dibenzopyranones and heterocyclic analogues bearing electron-donating and -withdrawing groups on both aromatic rings in good to excellent yields.

Introduction

Dibenzopyranone is a privileged scaffold in many natural products,[1] such as alternariol, graphislactones, autumnariol, autumnariniol, and altenuisol, and in biologically active compounds.[2] Such lactones have been used as intermediates in the synthesis of several pharmaceutically interesting compounds including progesterone, androgen, glucocorticoid modulators,[3] and endothelial cell proliferation inhibitors.[4] Furthermore, dibenzopyranones occur naturally in many food sources including citrus fruits, herbs, and vegetables.[5] There are several methods available for the synthesis of dibenzopyranones. The most popular involves Suzuki−Miyaura cross coupling followed by Lewis acid[6] or metal[7] mediated lactonization. More recently the Diels−Alder cycloaddition of 4-cyanocoumarins,[8] *tert*-butyllithium-mediated cyclization of bromobenzylfluorophenyl ethers,[9] and ruthenium-catalyzed cyclotrimerization of aryl diynes[10] have been reported. In 2002, Abbott Laboratories reported a practicable and scalable synthesis of glucocorticoid receptor A-224817.0 through a Negishi cross coupling.[11] However, none of these methods are suitable for the parallel synthesis approach to generating large numbers of analogues for drug discovery research. The disadvantages include low overall yields, long reaction times, low temperature conditions, multistep sequences, and the need to purify intermediates. Although the previous method of coupling of *o*-methoxyphenylboronic acids with bromo arylcarboxylates **1**, followed by borontribromide[6] or hydroiodic acid mediated lactonization,[12] has potential for parallel synthesis, but suffers from the following drawbacks: (a) it is two step procedure requiring minimum the purification of two intermediates, (b) alkoxy and alkoxyester substituents undergo demethylation in the presence of borontribromide,[13] and (c) BBr_3-mediated lactonization[6] requires the reaction to be performed at −78 °C, while HI-mediated lactonization requires to be conducted at 110 °C.[12]

Recently, we reported[13] that dibenzopyranone analogues act as CB2 agonists and that they are being investigated for the treatment of neuropathic pain, inflammation, and Alzheimer's diseases. As part of an ongoing lead optimization project, we required a facile route to prepare a library of dibenzopyranones and heterocyclic analogues **3**. We have, therefore, investigated a straightforward route for dibenzopyranones **3** via tandem Suzuki coupling of bromo arylcarboxylates **1** with *o*-hydroxyarylboronic acids **2**, followed by lactonization (Scheme 1).

In addition, we utilized microwave-assisted organic synthesis, which has attracted increasing attention because of its potential to accelerate drug discovery research.[15] Reaction times of many organic transformations are often dramatically reduced from hours to minutes or seconds. Moreover, there have been several reports of microwave-assisted syntheses of combinatorial libraries.[16] We now report a novel and efficient one step parallel synthesis of a library of dibenzopyaranones and heterocyclic analogues **3** via Suzuki−Miyaura cross coupling of bromo arylcarboxylates **1** with *o*-hydroxylarylboronic acids **2**.

Results and Discussion

To develop an efficient methodology for the synthesis of dibenzopyranones and heterocyclic analogues **3**, using bromo arylcarboxylates **1** and *o*-hydroxylarylboronic acids **2**, various catalysts, ligands, bases, and solvents were first screened for the Suzuki−Miyaura cross coupling reaction (Table 1). At the outset of the studies, commercially available methyl 2-bromo-5-methoxybenzoate **1**{*1*}, methyl 2-bromo-4-fluorobenzoate **1**{*2*}, and *o*-hydroxyphenylboronic acid **2**{*1*} were selected as representative reactants (Table 1). We initially examined the reaction conditions reported for

Scheme 1. Suzuki−Miyaura Cross Coupling of Bromo Arylcarboxylates **1** and *o*-Hydroxyarylboronic Acids **2**

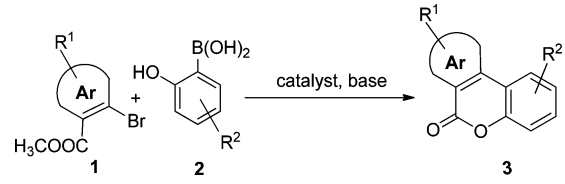

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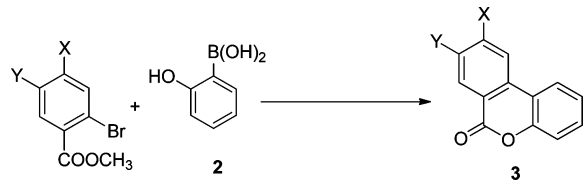
Table 1. Optimization of Suzuki−Miyaura Cross Coupling Reaction Conditions



1{1} X = H, Y = OCH_3
1{2} X = F, Y = H

entry	conditions	yield[a] (%) 3{1}	3{2}
1	chloro(di-2-norbornylphosphino)(2′-dimethylamino-1,1′-biphenyl-2yl)palladium(II) (5 mol %), KF (5 equiv), dioxane, 130 °C, 15 min	54	48
2	$Pd(OAc)_2$ (1 mol %), (*o*-biphenyl)P(t-Bu)$_2$ (2 mol %), KF (3 equiv), THF, rt, 24 h	45	47
3	$PdCl_2(PPh_3)_2$ (10 mol %), Cs_2CO_3 (4 equiv), DME, H_2O, 130 °C, 15 min	38	41
4	1,1′-bis(diphenylphosphino) ferrocene dichloropalladium(II) (10 mol %), NaOAc (5 equiv), DME, H_2O, 150 °C, 15 min	31	29
5	$Pd(PCy_3)_2Cl_2$ (5 mol %), CsF (2 equiv), NMP, 130 °C, 15 min	31	32
6	$Pd(PPh_3)_4$ (10 mol %), Cs_2CO_3 (4 equiv), DME, H_2O, 125 °C, 15 min	98	96

[a] Isolated product after purification by silica gel column chromatography.

chloro(di-2-norbornylphosphino)(2′-dimethylamino-1,1′-biphenyl-2yl)palladium(II), an air-stable catalyst that is highly active for C−C and C−N coupling reactions with aryl chlorides.[17] When a solution of **1**{*1*} or **1**{*2*} (1 equiv), **2**{*1*} (1.2 equiv), potassium fluoride (5 equiv), and 5 mol % of the above catalyst in dioxane was heated in a microwave reactor at 130 °C for 15 min, the desired product, that is, 8-methoxy-6H-benzo[c]chromen-6-one **3**{*1*} or 9-fluoro-6H-benzo[c]chromen-6-one **3**{*2*}, was obtained in 54 and 48% isolated yields, respectively (entry 1, Table 1). Coupling under Buchwald's conditions using highly active palladium catalyst, that is,[18] potassium fluoride, $Pd(OAc)_2$ and (*o*-biphenyl)P(*t*-Bu)$_2$ in THF at room temperature, afforded **3**{*1*} and **3**{*2*} in 45% and 47% yields, respectively (entry 2, Table 1). To improve the yields for the desired products **3**, we screened several catalysts, such as $Pd(PCy_3)_2Cl_2$, $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$, and 1,1′-bis(diphenylphosphino) ferrocene dichloropalladium(II), bases, such as NaOAc, Cs_2CO_3, CsF, and KF, and ligand (*o*-biphenyl)P(*t*-Bu)$_2$) with different equivalents and combinations of reagents and microwave irradiation temperatures in THF, NMP, DME, or dioxane. The results of formation of products **3**{*1*} and **3**{*2*} are shown in Table 1. From the screening results, the best conditions for coupling of **1**{*1*} or **1**{*2*} with **2**{*1*} were found to be the use of $Pd(PPh_3)_4$ as a catalyst in the presence of Cs_2CO_3 in DME at 125 °C under microwave irradiation for 15 min (Table 1, entry 6).

Utilizing the above optimized conditions, Suzuki−Miyaura cross coupling of various bromo arylcarboxylates **1** (Figure 1) with *o*-hydroxyarylboronic acids **2** (Figure 2) was conducted and the results are summarized in Table 2. The coupling of *o*-hydroxyarylboronic acids **2** with bromo arylcarboxylates **1** bearing a range of electron-donating and electron-withdrawing groups gave corresponding benzopyaranones **3** in good to excellent yields (entries 1−19, Table 2). In addition, bromothiophene carboxylates (entry 20, 21), bromopyridine carboxylates (entries 22 and 23), and fused bromoaryl carboxylates (entries 24 and 25) also reacted well to give the corresponding products (entries 20−25, Table 2). Clearly, the tandem coupling followed by lactonization is a facile protocol to generate a library of compounds **3**.

Conclusion

A simple, rapid and versatile one-step synthetic route to dibenzopyranones **3** and their heterocyclic analogues has been developed. The tandem C−C bond formation via Suzuki−Miyaura cross coupling, followed by lactonization affords the desired dibenzopyranones **3** in a manner suitable for parallel synthesis. The protocol is complementary to the existing syntheses for dibenzopyranones in terms of number of synthetic steps, ease of accessibility of starting materials, and suitability for combinatorial format.

Experimental Section

General. Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. All palladium catalysts were purchased from Strem chemicals, Inc., and boronic acids were purchased from Combi-Blocks Inc., unless otherwise mentioned. ^{1}H NMR spectra were recorded on a Varian Inova 500 and 400 MHz spectrometers; the chemical shifts are reported in parts per million (δ), and the coupling constants are reported in hertz. IR spectra were obtained on a Bruker ALPHA ATR spectrometer. The high-resolution mass spectral (HRMS) data (EI) were obtained on a Micromass 70-VSE instrument. The final compounds were purified with WATERS preparative LC/MS autopurification system, unless otherwise mentioned. The microwave reactions were conducted in a Emrys optimizer from Personal Chemistry, and generally, 10 reactions were performed sequentially for parallel library synthesis.

Methyl 2-Bromo-5-(trifluoromethyl)benzoate (1{*7*}). To a solution of 2-bromo-5-(trifluoromethyl) benzoic acid (5.00 g, 18.58 mmol) in methanol (20 mL) was added thionyl chloride (1.0 mL, 13.7 mmol), and the resulting mixture was refluxed for 8 h. After the mixture was cooled to room temperature, the solvent was concentrated to dryness under reduced pressure. The residue was dissolved in dichloromethane (40 mL) and washed with saturated aqueous sodium bicarbonate solution (50 mL) and water (100 mL). The organic layer was dried over anhydrous Na_2SO_4, and the filtrate was concentrated to dryness under reduced pressure to give **1**{*7*} (4.98 g, 95% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07 (s, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.59−7.56 (m, 1H), 3.97 (s, 3H).

General Procedure for the Preparation of 2-Hydroxyarylboronic Acids (1{*27*−*32*}). To a solution of corresponding methoxy boronicacids (1 mmol) in anhydrous dichloromethane (15 mL), was added boron tribromide (1.2 mmol) at −78 °C under nitrogen atmosphere. The resulting solution was stirred for 15 min at −78 °C. The cooling bath was removed, and the reaction mixture was continued to stir for 30 min at room temperature. The reaction was quenched with anhydrous methanol (1 mL) at −78 °C, concentrated in vacuo to dryness. The desired corresponding *o*-hydroxy

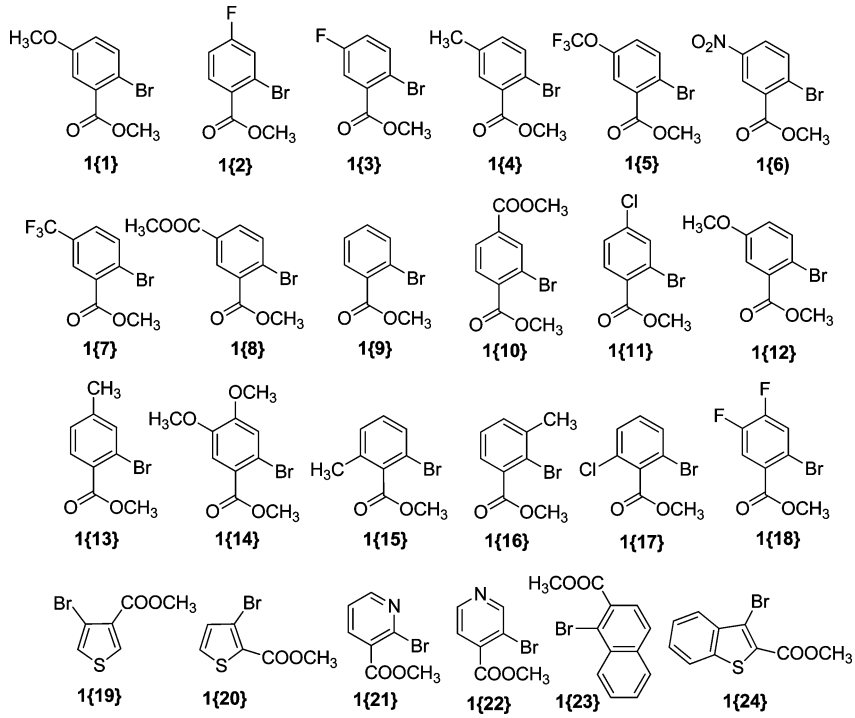


Figure 1. Diversity of bromo arylcarboxylates **1**.

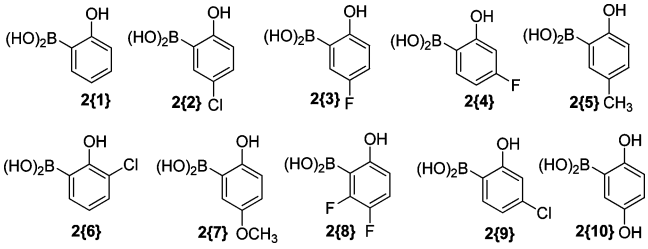


Figure 2. Diversity of *o*-hydroxyarylboronic acids **2**.

boronic acids were confirmed by LC/MS and used without further purification.

Illustrative Example: Preparation of 8-Methoxy-6*H*-benzo[*c*]chromen-6-one (3{*1*}).[19] A solution of methyl 3-methoxybenzoate (**1**{*1*}, 0.5 mmol), 2-hydroxyarylboronic acid (**2**{*1*}, 0.65 mmol, 1.3 equiv), and cesium carbonate (2 mmol, 4 equiv) in a mixture of dimethoxyethane (5 mL) and water (0.75 mL) was degassed with argon for 5 min. Tetrakis(triphenylphosphine)palladium (0) (10 mol %) was added, and the reaction tube was sealed. The reaction mixture was heated in a microwave (Emrys optimizer from Personal Chemistry) at 125 °C (power 300 W) for 15 min. After it was cooled at room temperature, the reaction mixture was diluted with water (30 mL) and extracted with dichloromethane (2 × 15 mL). The combined organic layers were passed through a phase separator and concentrated in vacuo. The residue was purified with WATERS preparative LC/MS autopurification system to afford the title compound in 98% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.05 (d, J = 8.5 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 3.0 Hz, 1H), 7.45−7.31 (m, 4H), 3.95 (s, 3H). IR (cm^{-1}): 1707.9, 1610.1, 1479.8, 1276.1, 1024.4, 824.1, 742.1. LC/MS: 226.98 (M + 1). HRMS (EI): *m*/*z* calcd for $C_{14}H_{10}O_3$ 226.0630, found 226.0635.

9-Fluoro-6*H*-benzo[*c*]chromen-6-one (3{*2*}). Yield: 96%, white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.44−8.41 (m, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.74−7.72 (m, 1H), 7.54−7.50 (m, 1H), 7.38−7.34 (m, 2H), 7.29−7.25 (m, 1H). IR (cm^{-1}): 1731.6, 1611.2, 1420.8, 1300.8, 1187.5, 877.3, 742.1. LC/MS: 215.0 (M + 1). HRMS (EI): *m*/*z* calcd for $C_{13}H_7FO_2$ 214.0430, found 214.0422.

8-Fluoro-6*H*-benzo[*c*]chromen-6-one (3{*3*}). Yield 88%, white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.14−8.12 (m, 1H), 8.06−8.03 (m, 1H), 8.02−7.99 (m, 1H), 7.57−7.53 (m, 1H), 7.50−7.47 (m, 1H), 7.38−7.34 (m, 2H). LC/MS: 214.9 (M + 1). HRMS (EI): *m*/*z* calcd for $C_{13}H_7FO_2$ 214.0430, found 214.0437.

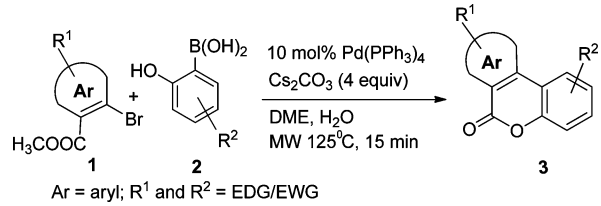
8-Methyl-6*H*-benzo[*c*]chromen-6-one (3{*4*}).[6a] Yield: 88%, white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.18 (s, 1H), 8.02−7.98 (m, 2H), 7.63−7.61 (m, 1H), 7.46−7.43 (m, 1H), 7.35−7.30 (m, 2H), 2.49 (s, 3H). LC/MS: 211.0 (M + 1). HRMS (EI): *m*/*z* calcd for $C_{14}H_{10}O_2$ 210.0681, found 210.0682.

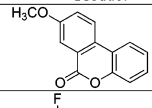
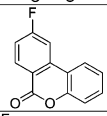
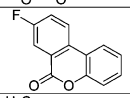
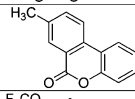
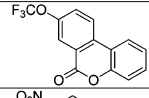
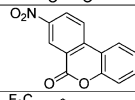
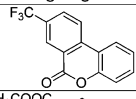
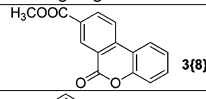
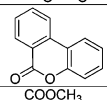
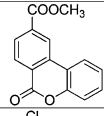
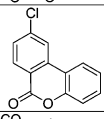
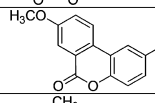
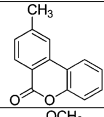
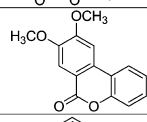
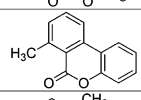
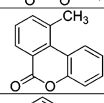
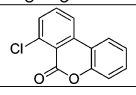
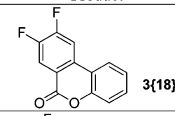
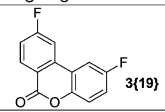
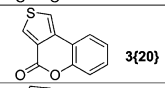
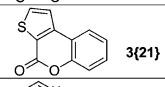
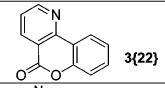
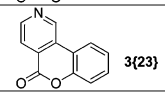
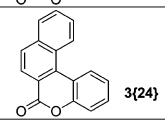
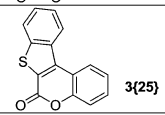
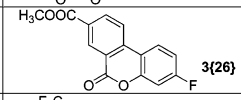
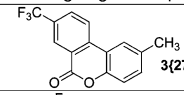
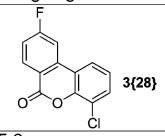
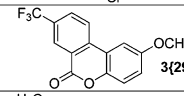
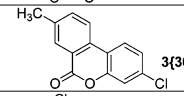
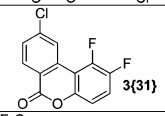
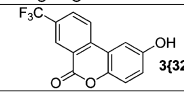
8-(Trifluoromethoxy)-6*H*-benzo[*c*]chromen-6-one (3{*5*}). Yield: 80%, white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.25 (s, 1H), 8.19 (d, J = 8.5 Hz, 1H), 8.04 (d, J = 8.0, 1H), 7.69−7.66 (m, 1H), 7.54−7.51 (m, 1H), 7.41−7.36 (m, 2H). LC/MS: 280.9 (M + 1). HRMS (EI): *m*/*z* calcd for $C_{14}H_7F_3O_2$ 280.0347, found 280.0388.

8-Nitro-6*H*-benzo[*c*]chromen-6-one (3{*6*}).[6a] Yield: 88%, white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.25 (d, J = 2.5 Hz, 1H), 8.09 (d, J = 9.0, 2.5 Hz, 1H), 8.31 (d, J = 8.5 Hz, 1H), 8.14−8.12 (m, 1H), 7.65−7.62 (m, 1H), 7.46−7.42 (m, 2H). LC/MS: 241.9 (M + 1). HRMS (EI): *m*/*z* calcd for $C_{13}H_7NO_4$ 241.0375, found 241.0358.

8-(Trifluoromethyl)-6*H*-benzo[*c*]chromen-6-one (3{*7*}). Yield: 83%, white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.70 (s, 1H), 8.27 (d, J = 8.0 Hz, 1H), 8.11 (dd, J = 8.0, 1.5 Hz, 1H), 8.05 (dd, J = 8.5, 2.0 Hz, 1H), 7.60−7.56 (m, 1H), 7.43−7.39 (m, 2H). LC/MS: 264.9 (M + 1). HRMS (EI): *m*/*z* calcd for $C_{14}H_7F_3O_2$ 264.0398, found 264.0407.

Table 2. Synthesis of a Library of Benzopyranone and Heterocyclic Analogues **3**



Entry	1	2	Product	Yield[a] (%)
1	1{1}	2{1}	 3{1}	98[b,19]
2	1{2}	2{1}	 3{2}	96
3	1{3}	2{1}	 3{3}	88
4	1{4}	2{1}	 3{4}	88[b,6a]
5	1{5}	2{1}	 3{5}	80
6	1{6}	2{1}	 3{6}	88[b,6a]
7	1{7}	2{1}	 3{7}	83
8	1{8}	2{1}	 3{8}	80
9	1{9}	2{1}	 3{9}	85
10	1{10}	2{1}	 3{10}	90
11	1{11}	2{1}	 3{11}	92
12	1{12}	2{2}	 3{12}	89
13	1{13}	2{1}	 3{13}	92[b, 6a]
14	1{14}	2{1}	 3{14}	84
15	1{15}	2{1}	 3{15}	92
16	1{16}	2{1}	 3{16}	86
17	1{17}	2{1}	 3{17}	68
18	1{18}	2{1}	 3{18}	86
19	1{2}	2{3}	 3{19}	94
20	1{19}	2{1}	 3{20}	85
21	1{20}	2{1}	 3{21}	84
22	1{21}	2{1}	 3{22}	95
23	1{22}	2{1}	 3{23}	83
24	1{23}	2{1}	 3{24}	87
25	1{24}	2{1}	 3{25}	94
26	1{8}	2{4}	 3{26}	88
27	1{7}	2{5}	 3{27}	69
28	1{2}	2{6}	 3{28}	71
29	1{7}	2{7}	 3{29}	85
30	1{4}	2{9}	 3{30}	92
31	1{11}	2{8}	 3{31}	70
32	1{7}	2{10}	 3{32}	72

[a] Isolated product after purification by silica gel column chromatography. [b] For known compounds, see refs 6a and 19.

Methyl 6-Oxo-6*H*-benzo[*c*]chromene-8-carboxylate (3{*8*}). Yield: 80%, white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.08 (s, 1H), 8.47 (d, J = 8.5 Hz, 1H), 8.23 (d, J = 8.5 Hz, 1H), 8.13−8.11 (m, 1H), 7.57−7.55 (m, 1H), 7.42−7.39 (m, 2H), 3.99 (s, 3H). LC/MS: 254.9 (M + 1). HRMS (EI): *m*/*z* calcd for $C_{15}H_{10}O_4$ 254.0579, found 254.0570.

6*H*-Benzo[*c*]chromen-6-one (3{*9*}). Yield: 85%, white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.42 (d, J = 8.0 Hz, 1H), 8.14 (d, J = 7.5 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.86−7.83 (m, 1H), 7.61−7.58 (m, 1H), 7.51−7.48 (m, 1H), 7.39−7.33 (m, 2H). IR (cm^{-1}): 1725.5, 1604.9, 1431.6, 1302.1, 1262.2, 1076.2, 743.9. LC/MS: 196.9 (M + 1). HRMS (EI): *m*/*z* calcd for $C_{13}H_8O_2$ 196.0529, found 196.0524.

Methyl 6-Oxo-6*H*-benzo[*c*]chromene-9-carboxylate (3{*10*}). Yield: 90%, white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.79 (s, 1H), 8.47 (d, J = 8.5 Hz, 1H), 8.20−8.15 (m, 2H), 7.53−7.51 (m, 1H), 7.40−7.37 (m, 2H), 4.03 (s, 3H). LC/MS: 254.9 (M + 1). HRMS (EI): *m*/*z* calcd for $C_{15}H_{10}O_4$ 254.0579, found 254.0571.

9-Chloro-6*H*-benzo[*c*]chromen-6-one (3{*11*}). Yield: 92%, white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.35 (d, J = 8.5 Hz, 1H), 8.64 (d, J = 2.0 Hz, 1H), 8.02−8.00 (m, 1H), 7.56−7.51 (m, 2H), 7.40−7.35 (m, 2H). LC/MS: 230.9, 232.9 (M + 1). HRMS (EI): *m*/*z* calcd for $C_{13}H_7ClO_2$ 230.0140, found 230.0134.

2-Chloro-8-methoxy-6*H*-benzo[*c*]chromen-6-one (3{*12*}). Yield: 89%, white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.97 (d, J = 8.5 Hz, 1H), 7.93 (d, J = 2.5 Hz, 1H), 7.80 (d, J = 2.0 Hz, 1H), 7.41 (dd, J = 8.5, 2.5 Hz, 1H), 7.37 (dd, J = 8.5, 2.5 Hz, 1H), 7.30 (d, J = 8.5 Hz, 1H). LC/MS: 260.9, 263.0 (M + 1). HRMS (EI): *m*/*z* calcd for $C_{14}H_9ClO_3$ 260.0240, found 260.0225.

9-Methyl-6*H*-benzo[*c*]chromen-6-one (3{*13*}).[6a] Yield: 92%, white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.27 (d, J = 8.0 Hz, 1H), 8.05 (d, J = 1.0 Hz, 1H), 7.89 (s, 1H), 7.48−7.45 (m, 1H), 7.39−7.31 (m, 2H), 2.56 (s, 3H). LC/MS: 211.0 (M + 1). HRMS (EI): *m*/*z* calcd for $C_{14}H_{10}O_2$ 210.0680, found 210.0674.

8,9-Dimethoxy-6*H*-benzo[*c*]chromen-6-one (3{*14*}). Yield: 84%, white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.96 (d, J = 8.00 Hz, 1H), 7.75 (s, 1H), 7.61−7.28 (m, 2H), 7.37−7.31 (m, 2H). LC/MS: 257.0 (M + 1). HRMS (EI): *m*/*z* calcd for $C_{15}H_{12}O_4$ 256.0735, found 256.0729.

7-Methyl-6*H*-benzo[*c*]chromen-6-one (3{*15*}). Yield: 92%, white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.04−7.98 (m, 2H), 7.67−7.64 (m, 1H), 7.46−7.43 (m, 1H), 7.38−7.37 (m, 1H), 7.33−7.28 (m, 2H), 2.87 (s, 3H). IR (cm^{-1}): 1716.2, 1461.1, 1242.9 1206.4, 1049.0, 785.1, 751.5. LC/MS: 211.0 (M + 1). HRMS (EI): *m*/*z* calcd for $C_{14}H_{10}O_2$ 210.0680, found 210.0675.

10-Methyl-6*H*-benzo[*c*]chromen-6-one (3{*16*}). Yield: 86%, white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.39−8.30 (m, 2H), 7.66−7.64 (m, 1H), 7.49−7.46 (m, 2H), 7.42−7.39 (m, 1H), 7.35−7.32 (m, 1H), 2.91 (s, 3H). LC/MS: 211.0 (M + 1). HRMS (EI): *m*/*z* calcd for $C_{14}H_{10}O_2$ 210.0680, found 210.0682.

7-Chloro-6*H*-benzo[*c*]chromen-6-one (3{*17*}). The residue was purified with Biotage SP1 flash autopurification system to afford the white solid in 68% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.52 (d, J = 3.0 Hz, 1H), 7.82 (dd, J = 8.0, 1.5 Hz, 1H), 7.79−7.78 (m, 1H), 7.43−7.40 (m, 1H), 7.35−7.33 (m, 1H), 7.30−7.26 (m, 1H). LC/MS: 230.9, 232.9 (M + 1). HRMS (EI): *m*/*z* calcd for $C_{13}H_7ClO_2$ 230.0134, found 230.0126.

8,9-Difluoro-6*H*-benzo[*c*]chromen-6-one (3{*18*}). Yield: 86%, white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.21−8.18 (m, 1H), 7.92−7.86 (m, 2H), 7.55−7.51 (m, 1H), 7.40−7.36 (m, 2H). LC/MS: 232.9 (M + 1). HRMS (EI): *m*/*z* calcd for $C_{13}H_6F_2O_2$ 232.0335, found 232.0342.

2,9-Difluoro-6*H*-benzo[*c*]chromen-6-one (3{*19*}). Yield: 94%, white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.47−8.44 (m, 1H), 7.67−7.62 (m, 2H), 7.39−7.31 (m, 2H), 7.27−7.23 (m, 1H). LC/MS: 232.9 (M + 1). HRMS (EI): *m*/*z* calcd for $C_{13}H_6F_2O_2$ 232.0335, found 232.0343.

4*H*-Thieno[3,4-*c*]chromen-4-one (3{*20*}). Yield: 85%, white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.52 (d, J = 3.0 Hz, 1H), 7.82 (dd, J = 8.0, 1.5 Hz, 1H), 7.79−7.78 (m, 1H), 7.43−7.40 (m, 1H), 7.35−7.33 (m, 1H), 7.30−7.26 (m, 1H). LC/MS: 202.9 (M + 1). HRMS (EI): *m*/*z* calcd for $C_{11}H_6O_2S$ 202.0088, found 202.0083.

4*H*-Thieno[2,3-*c*]chromen-4-one (3{*21*}). Yield: 84%, white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.94 (d, J = 5.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 5.0 Hz, 1H), 7.53−7.45 (m, 2H), 7.38−7.34 (m, 1H). LC/MS: 202.9 (M + 1). HRMS (EI): *m*/*z* calcd for $C_{11}H_6O_2S$ 202.0088, found 202.0093.

5*H*-Chromeno[4,3-*b*]pyridin-5-one (3{*22*}). Yield: 95%, white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.03−9.02 (m, 1H), 8.63−8.57 (m, 2H), 7.60−7.57 (m, 1H), 7.54−7.51 (m, 1H), 7.42−7.38 (m, 2H). LC/MS: 197.9 (M + 1). HRMS (EI): *m*/*z* calcd for C12H7NO$_2$ 197.0476, found 197.0482.

5*H*-Chromeno[4,3-*c*]pyridin-5-one (3{*23*}). Yield: 83%, white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.58 (s, 1H), 8.88−8.87 (m, 1H), 8.21−8.16 (m, 2H), 7.58−7.55 (m, 1H), 7.44−7.41 (m, 2H). LC/MS: 198.0 (M + 1). HRMS (EI): *m*/*z* calcd for $C_{12}H_7NO_2$ 197.0476, found 197.0469.

6*H*-Naphtho[2,1-*c*]chromen-6-one (3{*24*}). Yield: 87%, white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.87 (d, J = 7.5 Hz, 1H), 8.52 (d, J = 8.0 Hz, 1H), 8.33 (d, J = 8.5 Hz, 1H), 8.01−7.94 (m, 2H), 7.75−7.68 (m, 2H), 7.56−7.49 (m, 2H), 7.42−7.39 (m, 1H). LC/MS: 246.9 (M + 1). HRMS (EI): *m*/*z* calcd for $C_{17}H_{10}O_2$ 246.0680, found 246.0689.

6*H*-[1]Benzothieno[2,3-*c*]chromen-6-one (3{*25*}). Yield: 94%, white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.65−8.62 (m, 1H), 8.49 (d, J = 8.0 Hz, 1H), 8.03−8.01 (m, 1H), 7.65−7.61 (m, 2H), 7.58−7.52 (m, 2H), 7.47−7.44 (m, 1H). LC/MS: 252.9 (M + 1). HRMS (EI): *m*/*z* calcd for $C_{15}H_8O_2S$ 252.0245, found 252.0241.

Methyl 3-Fluoro-6-oxo-6*H*-benzo[*c*]chromene-8-carboxylate (3{*26*}). Yield: 88%, white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.05 (s, 1H), 8.46 (dd, J = 7.0, 2.0 Hz, 1H), 8.13−8.12 (m, 2H), 7.14−7.12 (m, 2H), 3.99 (s, 3H); LC/MS 273.2 (M + 1). HRMS (EI): *m*/*z* calcd for $C_{15}H_9FO_4$ 272.0430, found 272.0428.

2-Methyl-8-(trifluoromethyl)-6*H*-benzo[*c*]chromen-6-one (3{*27*}). The residue was purified with Biotage SP1 flash autopurification system to afford the white solid in 69% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.67 (s, 1H), 8.24−8.23 (d,

J = 8.0 Hz, 1H), 8.03−8.02 (d, J = 2.0, 1H), 7.87 (s, 1H), 7.35−7.27 (m, 2H), 2.49 (s, 3H). LC/MS: 279.9 (M + 1). HRMS (EI): *m/z* calcd for $C_{15}H_9F_3O_2$ 278.0554, found 278.0545.

4-Chloro-9-fluoro-6*H*-benzo[*c*]chromen-6-one (3{*28*}). Yield: 71%, white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.47−8.44 (m, 1H), 7.88 (dd, J = 7.0, 1.0 Hz, 1H), 7.74 (dd, J = 7.5, 2.5 Hz, 1H), 7.59 (dd, J = 6.0, 1.5 Hz, 1H), 7.34−7.28 (m, 2H). LC/MS: 249.8 (M + 1). HRMS (EI): *m/z* calcd for $C_{13}H_6ClFO_2$ 248.0040, found 248.0029.

2-Methoxy-8-(trifluoromethyl)-6*H*-benzo[*c*]chromen-6-one (3{*29*}). Yield: 85%, white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.69 (s, 1H), 8.19 (d, J = 8.5 Hz, 1H), 8.04 (d, J = 2.0 Hz, 1H), 7.51 (s, 1H), 7.34 (m, 1H), 7.14−7.12 (m, 1H). LC/MS: 295.1 (M + 1). HRMS (EI): *m/z* calcd for $C_{15}H_9F_3O_3$ 294.0503, found 294.0512.

3-Chloro-8-methyl-6*H*-benzo[*c*]chromen-6-one (3{*30*}). Yield: 92%, white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.19 (s, 1H), 7.97−7.94 (m, 2H), 7.65−7.64 (m, 1H), 7.36−7.28 (m, 2H), 2.50 (s, 3H). LC/MS: 245.6, 247.2 (M + 1). HRMS (EI): *m/z* calcd for $C_{14}H_9ClO_2$ 244.0291, found 244.0306.

9-Chloro-1,2-difluoro-6*H*-benzo[*c*]chromen-6-one (3{*31*}). Yield: 70%, white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.51−8.50 (m, 1H), 8.40 (d, J = 8.0 Hz, 1H), 7.64 (dd, 7.0, 2.0 Hz, 1H), 7.37−7.33 (m, 1H), 7.19−7.17 (m, 1H). LC/MS 267.8, 269.9 (M + 1). HRMS (EI): *m/z* calcd for $C_{13}H_5ClF_2O_2$ 266.9946, found 265.9955.

2-Hydroxy-8-(trifluoromethyl)-6*H*-benzo[*c*]chromen-6-one (3{*32*}). The residue was purified with Biotage SP1 flash autopurification system to afford the white solid in 72% yield. ^{1}H NMR (CD_3OD, 500 MHz): δ 9.33−9.30 (m, 1H), 9.24 (s, 1H), 9.05−9.03 (m, 1H), 8.48−8.47 (m, 1H), 8.13−8.11 (m, 1H), 7.90−7.87 (m, 1H). LC/MS: 281.1 (M + 1). HRMS (EI): *m/z* calcd for $C_{14}H_7F_3O_3$ 280.0428, found 280.0431.

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Supporting Information Available. General experimental details, yields, and compound characterization data (^{1}H NMR, IR, and MS analysis) of all final products. This information is available free of charge via the Internet at http://pubs.acs.org.

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