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Domino Reaction to Functionalized 2-Hydroxybenzophenones from Electron-Deficient Chromones and 1,3-Dicarbonyl Compounds

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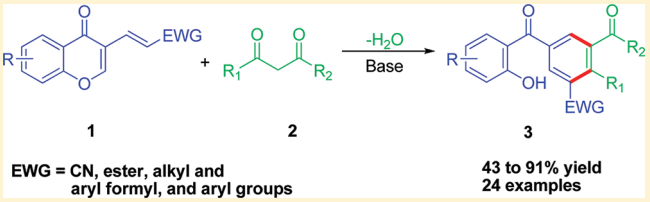
Supporting Information

ABSTRACT: A base-promoted one-pot tandem reaction sequence has been developed to transform electron-deficient chromone-fused dienes **1** and 1,3-dicarbonyl compounds **2** to functionalized 2-hydroxybenzophenones **3** under mild conditions. This domino process, which involves multiple reactions, including Michael addition/cyclization/elimination, serves as an efficient, economic, and eco-friendly method for the construction of diversified 2-hydroxybenzophenone scaffolds without a transition-metal catalyst and inert atmosphere.



The substituted 2-hydroxybenzophone framework is ubiquitous in a wide variety of naturally occurring and synthetic compounds that exhibit important biological activities.[1a−h] Classical approaches for the synthesis of these substances generally involve addition of organometallic reagents, such as aryllithium or -magnesium reagents, to aldehydes followed by oxidation of the resulting alcohols.[2a−c] Recently, metal-catalyzed direct C−H bond arylation reactions of aryl aldehydes with boronic acids or aryl halides have been utilized for the generation of benzophenones.[3a−j] In addition, attention has been paid to the preparation of functionalized 2-hydroxybenzophones starting with the corresponding chromones, especially 3-formylchromone, which serves as a bis-electrophile. In this regard, Langer and his co-workers developed a domino Michael/retro-Michael/aldol process that takes place between 3-formylchromones and 1,3-bis-silyl enol ethers in the presence of catalytic trimethylsilyl triflate to generate functionalized 2-hydroxybenzophenones, in which aroyl and OH groups are present at the 3- and 4-positions of the phenyl ring, respectively.[4a−e] 3-Formylchromones are also known to undergo Michael addition and cyclization reactions with bis-nucleophilic reagents under basic conditions to produce similarly functionalized 2-hydroxybenzophenones[5a−d] and (2-hydroxyphenyl)(heteroaryl)methanones.[6a−d]

In recent efforts, we have conducted investigations aimed at the synthesis of natural productlike scaffolds through cascade reactions that take advantage of the multiple reactivity of substituted chromones.[7a−f] In this study, we observed that tandem reactions of 3-(1-alkynyl)chromones with 1,3-dicarbonyl compounds lead to the formation of functionalized xanthones.[7a] More recently, we observed that treatment of the electron-deficient chromone-linked acrylonitrile derivative **1a** with 1,3-dicarbonyl compound **2a** in the presence of DBU in THF at room temperature leads to generation of a product mixture containing 2-hydroxybenzophenone **3aa**. We envisioned that this transformation occurs by way of a tandem process involving sequential Michael addition/intramolecular cyclization/elimination (Scheme 1). In this pathway, the electron-deficient chromone behaves as an acceptor in Michael addition of the nucleophilic 1,3-dicarbonyl compound to generate intermediate **A**. This process is followed by chromone ring opening to form intermediate **B** and a 5,1-hydrogen shift to give the highly conjugated intermediate **C**. The resulting carbanion derived by deprotonation of **C** then undergoes intramolecular cyclization at the internal carbonyl group followed by elimination to afford the functionalized 2-hydroxybenzophenone **3**.

It is important to note that the participation of electron-deficient chromones, containing multiple reactive centers, in domino reactions has not been fully investigated or applied to the synthesis of heterocycles.[8a−h] Only a few reports exist describing inverse-electron-demand Diels−Alder reactions of these substances, which afford xanthones and 2-hydroxybenzophenones in low to moderate yields.[9a−c] Although many useful methods have been developed, there are some inconveniences: for example, use of a metal catalyst, lack of atom economy, incompatibility with substrate scopes, and inconvenient operation under an inert atmosphere. Herein, we describe the results of a recent investigation aiming at developing a mild, simple, efficient, and catalyst-free method for the synthesis of polyfunctionalized 2-hydroxybenzophenones via cascade reactions of electron-deficient chromones **1** with 1,3-dicarbonyl compounds **2**.

At the beginning of the current study, we examined the reaction of chromone-linked acrylonitrile **1a** with acetylacetone **2a** under a variety of conditions (Table 1). The results show that reaction of these substrates in the presence of 1 equiv of DBU at room temperature in THF leads to the formation of the desired

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Scheme 1. Proposed Mechanism

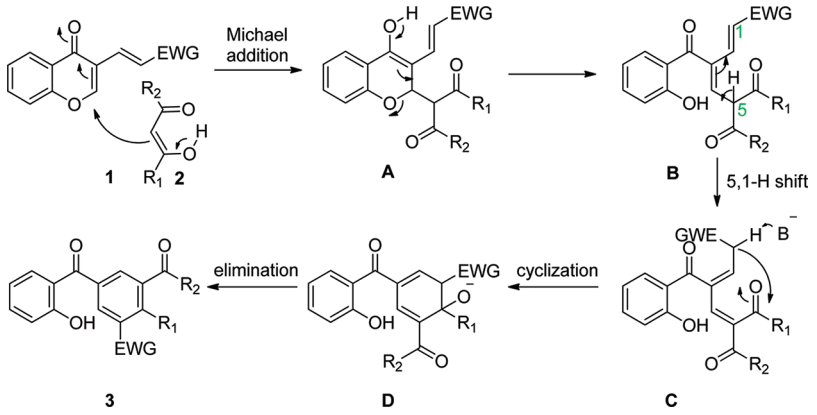
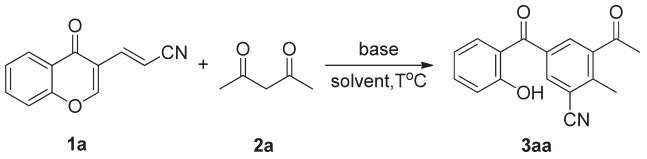


Table 1. Optimization of the Reaction To Form Functionalized Benzophenone 3aa[a]



entry	solvent	vase	temp (°C)	time (h)	yield (%)
1	THF	DBU	room temp	2	<30[c]
2	THF	DBU	room temp	24	60[b]
3	THF	DBU	60	2	63[b]
4	THF	Et_3N	60	2	<30[c]
5	THF	*t*-BuOK	60	2	64[b]
6	THF	K_2CO_3	60	2	60[b]
7	THF	KOH	60	2	<30[c]
8	THF	NaH	60	2	<30[c]
9	CH_3CN	DBU	60	2	57[b]
10	DMF	DBU	60	2	50[b]
11	DMSO	DBU	60	2	39[b]
12	toluene	DBU	60	2	<30[c]
13	EtOH	DBU	60	2	77[b]
14	EtOH	*t*-BuOK	60	2	69[b]
15	EtOH	K_2CO_3	60	2	74[b]

[a] General conditions: substrate **1a** (0.2 mmol), **2a** (0.2 mmol), and base (0.2 mmol, 1 equiv) in solvent (1 mL). [b] Isolated yield. [c] The yield was evaluated by thin-layer chromatography (TLC), which determined the remaining starting material **1**.

hydroxyl benzophenone derivative **3aa** in yields that vary with time (<30% yield in 2 h and 60% yield in 24 h). In contrast, at 60 °C, the process proceeds to completion, giving **3aa** in 63% yield. Among others, DBU, K_2CO_3, and *t*-BuOK perform as optimal bases for promoting this reaction (Table 1, entries 3−8). In addition, ethanol (EtOH) appears to be the best solvent for the reaction (Table 1, entries 13−15). Thus, the optimized conditions, involving reaction of **1a** with **2a** in EtOH at 60 °C in the presence of 1 equiv of DBU, results in the formation of **3aa** in 77% yield.

Reactions of various 1,3-dicarbonyl compounds **2** with **1a** under the optimized conditions were explored to probe the scope of the process (Table 2). The findings show that these reactions lead to production of the corresponding functionalized benzophenones **3** in moderate to excellent yields (Table 2). 1-Phenylbutane-1,3-dione (**2c**) (Table 2, entry 3) gave complicated products, and **3ac** was found to be the major product in 45% yield. This means that the substitution of the carbonyl group at phenyl is more active. Notably, the presence of bulky groups leads to slightly decreased yields and prolonged reaction times as a consequence of steric hindrance in the cyclization step (Table 2, entries 9−12). It is clear that an electron-donating group on the phenyl ring will decrease the reactivity of the carbonyl group (Table 1, entry 11). Interestingly, reactions at 60 °C of β-ketone esters **2m** and **2n** containing α-substituents that activate α-hydrogens are less efficient, perhaps a result of formation and the ensuing reaction of bis-carbanions at high temperature. However, reactions of the keto esters at room temperature for 4 and 6 h yield the desired products **3am** and **3an** in respective yields of 66% and 62%. Diethyl malonate (**2g**) and malononitrile (**2o**) react under the optimized conditions to yield complicated product mixtures. An exploration of this process led to the finding that **3ao** was generated in 54% yield by carrying out the reaction in the presence of *t*-BuOK (2 equiv) in DMF at 120 °C for 30 min under microwave irradiation conditions.

Further studies showed that the tandem reaction can be extended to other electron-deficient chromone-linked substrates, which react with ethyl acetoacetate to form the corresponding functionalized benzophenones **3** in 43−80% yield (Table 3). The electronic effects of substituents on the aryl chromone ring did not affect the reactions (Table 3, entries 1 and 2). Notably, reactions of substrates **1i** and **1j**, which lack electron-withdrawing groups, require prolonged reaction times to afford the desired products, albeit in lower yields. Clearly, only electron-deficient chromones serve as strong Michael acceptors in this process.

In conclusion, the investigation described above has led to the development of an efficient method for the synthesis of functionalized 2-hydroxybenzophenones starting with easily prepared electron-deficient chromone-linked substrates and commercially available 1,3-dicarbonyl compounds. The attractive features of this procedure, which involves a tandem reaction sequence with simplicity of execution, takes place under mild conditions without a transition-metal catalyst and inert atmosphere and tolerates a variety of functional groups to generate complex 2-hydroxybenzophenones. Finally, the functionalized

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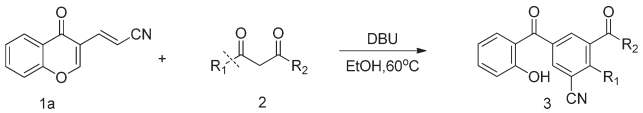
Table 2. Reactions of 1a with Various 1,3-Dicarbonyl Compounds 2[a]



Entry	Substrate	Product	Yield (%)[b]	Entry	Substrate	Product	Yield (%)[b]
1	2a	3aa	77	9	2i	3ai	57
2	2b	3ab	76	10	2j	3aj	67
3	2c	3ac	45	11	2k	3ak	49
4	2d	3ad	85	12	2l	3al	63
5	2e	3ae	91	13[c]	2m	3am	66
6	2f	3af	80	14[c]	2n	3an	62
7	2g	complex		15[d]	2o	3ao	54
8	2h	3ah	82				

[a] Reaction conditions: substrate **1a** (0.2 mmol), **2** (0.2 mmol) and DBU (0.2 mmol) in EtOH (1 mL) at 60 °C. After complete conversion of the starting material **1a** as determined by TLC, the reactions were quenched. [b] Isolated yield. [c] The reaction was carried out at room temperature. [d] The reaction was carried out at 120 °C on microwave for 30 min in the DMF/*t*-BuOK system (2 equiv).

2-hydroxybenzophenones prepared in this effort are currently being subjected to biological evaluation.

EXPERIMENTAL SECTION

General Methods. Melting points were measured on a Kofler hot stage and are uncorrected. ^{1}H NMR spectral data were recorded in $CDCl_3$ or DMSO-d_6 solutions on a 300 or 400 MHz spectrometer, and ^{13}C NMR were recorded in $CDCl_3$ or $(CD_3)_2CO$ on a 100 MHz spectrometer. Chemical shifts (δ) are reported in parts per million (ppm), and the signals are described as br s (broad singlet), d (doublet), dd (doublet of doublet), m (multiple), q (quartet), s (singlet), and t (triplet). Coupling constants (J values) are given in Hz. Low-resolution mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded at an ionizing voltage of 70 eV. Column chromatography was carried out on silica gel (200−300 mesh). All reactions were monitored using TLC on silica gel plates. All of the reagents were used directly as obtained commercially or synthesized according to literature procedures.

General Procedure. *Representative Experimental Procedure for the Synthesis of 3-Acetyl-5-(2-hydroxybenzoyl)-2-methylbenzonitrile (**3aa**).* DBU (1 equiv, 0.2 mmol, 30 mg) was added to a mixture of compound **1a** (1 equiv, 0.2 mmol, 39.4 mg) and compound **2a** (1 equiv, 0.2 mmol, 20 mg) in dry EtOH (1 mL), and the resulting solution was heated to 60 °C for 2 h. After complete conversion of the starting material (TLC), the mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to give the crude product, which was further purified by column chromatography to afford the desired compound **3aa** (77%, 42.9 mg) as a yellow solid: mp 143−145 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.63 (s, 1 H), 8.12 (s, 1 H), 8.01 (s, 1 H), 7.58 (t, J = 7.8 Hz, 1 H), 7.46 (d, J = 8.0 Hz, 1 H), 7.12 (d, J = 8.4 Hz, 1 H), 6.94 (t, J = 7.7 Hz, 1 H), 2.79 (s, 3 H), 2.64 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6, 197.8, 163.3, 145.2, 139.8, 137.4,

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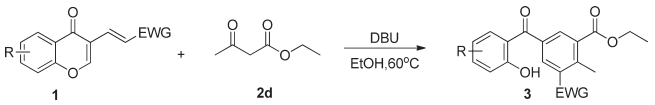
Table 3. Reactions of 2d with Various Dienes 1[a]



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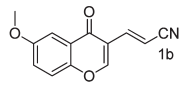
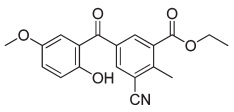
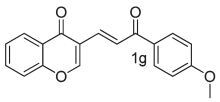
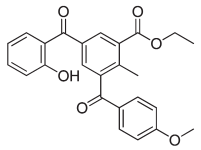
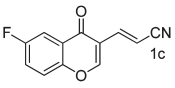
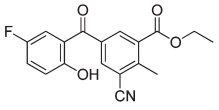
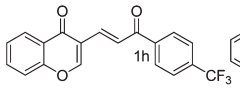
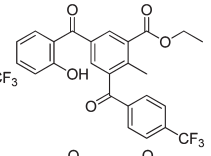
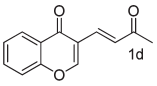
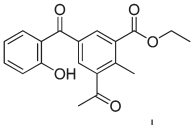
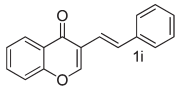
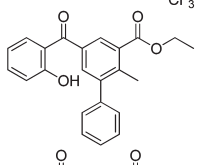
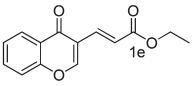
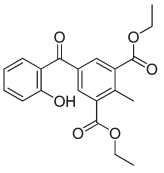
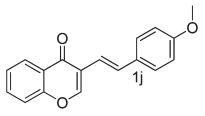
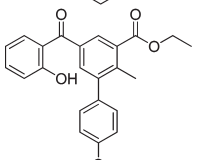
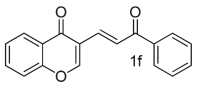
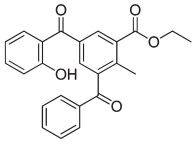
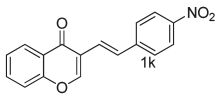
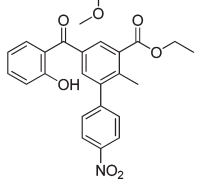
1		 3bd	67	6		 3gd	62
2		 3cd	73	7		 3hd	68
3		 3dd	79	8		 3id	48
4		 3ed	80	9		 3jd	43
5		 3fd	71	10		 3kd	63

[a] Reaction conditions: substrate **1** (0.2 mmol), **2d** (0.2 mmol) and DBU (0.2 mmol) in EtOH (1 mL) at 60 °C. After complete conversion of the starting material **1** as determined by TLC, the reactions were quenched. [b] Isolated yield.

136.1, 135.2, 132.6, 132.5, 119.3, 118.9, 118.2, 116.7, 115.7, 29.9, 19.3; HRMS calcd for $C_{17}H_{13}NO_3$ 279.0895, found 279.0902.

Characterization of 3ab−3af, 3ah−3ao, and 3bd−3kd. *3-Acetyl-5-(2-hydroxybenzoyl)-2-(trifluoromethyl)benzonitrile (**3ab**):* reaction was run for 9 h; yellow solid; mp 155−156 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.47 (s, 1H), 8.13 (s, 1H), 7.80 (s, 1H), 7.61 (t, J = 7.8 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.13 (d, J = 8.5 Hz, 1H), 6.96 (t, J = 7.6 Hz, 1H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 196.6, 163.5, 143.1, 141.8, 138.1, 135.2, 132.4, 130.1, 119.6, 119.2, 117.8, 114.3, 112.0, 30.9; HRMS calcd for $C_{17}H_{10}F_3NO_3$ 333.0613, found 333.0616.

*3-Benzoyl-5-(2-hydroxybenzoyl)-2-methylbenzonitrile (**3ac**):* reaction was run for 6 h; yellow gum; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.65 (s, 1 H), 8.07 (s, 1 H), 7.81−7.78 (m, 3 H), 7.66 (t, J = 7.3 Hz, 1 H), 7.58−7.48(m, 4 H), 7.09 (d, J = 8.5 Hz, 1 H), 6.92 (t, J = 7.6 Hz, 1 H), 2.61 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.92, 195.34, 163.29, 144.02, 140.51, 137.28, 135.90, 134.47, 134.32, 132.68, 131.89, 130.09, 129.02, 119.23, 118.87, 118.28, 116.60, 115.12, 18.67; HRMS calcd for $C_{22}H_{15}NO_3$ 341.1052, found 341.1043.

*Ethyl 3-Cyano-5-(2-hydroxybenzoyl)-2-methylbenzoate (**3ad**):* reaction was run for 2 h; yellow solid; mp 80−81 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.68 (s, 1 H), 8.38 (s, 1 H), 8.05 (s, 1 H), 7.58 (t, J = 8.1 Hz, 1 H), 7.46 (d, J = 8.1 Hz, 1 H), 7.11 (d, J = 8.1 Hz, 1 H), 6.93 (t, J = 8.1 Hz, 1 H), 4.42 (q, J = 7.1 Hz, 2 H), 2.91 (s, 3 H), 1.41 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 165.3, 163.3, 146.9, 137.3, 136.1, 135.8, 134.6, 132.7, 132.2, 119.2, 118.8, 118.3, 116.7, 115.6, 62.0, 19.6, 14.2; HRMS calcd for $C_{18}H_{15}NO_4$ 309.1001, found 309.1006.

*tert-Butyl 3-Cyano-5-(2-hydroxybenzoyl)-2-methylbenzoate (**3ae**):* reaction was run for 2 h; yellow solid; mp 75−76 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.70 (s, 1 H), 8.26 (s, 1 H), 8.01 (s, 1 H), 7.57 (t, J = 7.8 Hz, 1 H), 7.47 (d, J = 7.6 Hz, 1 H), 7.11 (d, J = 7.9 Hz, 1 H), 6.93 (t, J = 7.6 Hz, 1 H), 2.86 (s, 3 H), 1.61 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0, 164.7, 163.3, 146.1, 137.2, 135.9, 135.3, 134.3, 134.0, 132.7, 119.1, 118.8, 118.3, 116.8, 115.3, 83.2, 28.1, 19.6; HRMS calcd for $C_{20}H_{19}NO_4$ 337.1314, found 337.1313.

*Ethyl 3-Cyano-5-(2-hydroxybenzoyl)-2-(trifluoromethyl)benzoate (**3af**):* reaction was run for 3 h; yellow gum; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.49 (s, 1H), 8.17 (s, 1H), 8.06 (s, 1H), 7.62 (t, J = 7.8 Hz, 1H), 7.39 (d, J = 8.1 Hz, 1H), 7.13 (d, J = 8.5 Hz, 1H), 6.97 (t, J = 7.6 Hz, 1H), 4.45 (q, J = 7.1 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 165.2, 163.5, 141.4, 138.0, 135.9, 134.9, 132.7 (d, J = 15.7 Hz), 122.8, 120.1, 119.6, 119.0, 117.8, 114.4, 112.0, 63.3, 13.7; HRMS calcd for $C_{18}H_{12}F_3NO_4$ 363.0718, found 363.0719.

*Ethyl 3-Cyano-5-(2-hydroxybenzoyl)-2-propylbenzoate (**3ah**):* reaction was run for 2 h; yellow gum; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.68 (s, 1 H), 8.34 (d, J = 1.8 Hz, 1 H), 8.04 (d, J = 1.8 Hz, 1 H), 7.57 (t, J = 7.8 Hz, 1 H), 7.48 (d, J = 8.0 Hz, 1 H), 7.11 (d, J = 8.5 Hz, 1 H), 6.94 (t, J = 7.6 Hz, 1 H), 4.42 (q, J = 7.1 Hz, 2 H), 3.35−3.15 (m, 2 H), 1.74 (dd, J = 15.5, 7.6 Hz, 2 H), 1.41 (t, J = 7.7, 6.6 Hz, 3 H), 1.09 (t, J = 7.3 Hz,

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3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 164.8, 162.7, 150.7, 136.6, 135.5, 135.4, 134.3, 132.1, 131.4, 118.6, 118.2, 117.7, 116.2, 114.6, 61.4, 34.0, 24.1, 13.7, 13.6; HRMS calcd for $C_{20}H_{19}NO_4$ 337.1314, found 337.1305.

*Ethyl 3-Cyano-5-(2-hydroxybenzoyl)-2-isopropylbenzoate (**3ai**):* reaction was run for 8 h; yellow gum; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.67 (s, 1 H), 8.03 (s, 2 H), 7.57 (s, 1 H), 7.49 (dd, J = 8.0, 1.7 Hz, 1 H), 7.11 (dd, J = 8.4, 1.1 Hz, 1 H), 6.94 (t, J = 0.9 Hz, 1 H), 4.41 (q, J = 7.1 Hz, 2 H), 3.77−3.65 (m, 1 H), 1.54 (d, J = 7.2 Hz, 6 H), 1.40 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 167.0, 163.3, 154.4, 137.2, 136.9, 136.0, 134.2, 133.4, 132.7, 119.2, 118.8, 118.3, 117.6, 112.7, 62.3, 31.6, 21.1, 14.1; HRMS calcd for $C_{20}H_{19}NO_4$ 337.1314, found 337.1306.

*Ethyl 6-Cyano-4-(2-hydroxybenzoyl)-[1,1′-biphenyl]-2-carboxylate (**3aj**):* reaction was run for 6 h; yellow solid; mp 105−106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.67 (s, 1 H), 8.32 (s, 1 H), 8.15 (s, 1 H), 7.65−7.44 (m, 5 H), 7.38 (d, J = 3.0 Hz, 2 H), 7.13 (d, J = 8.3 Hz, 1 H), 6.97 (t, J = 7.6 Hz, 1 H), 4.07 (q, J = 7.3 Hz, 2 H), 0.96 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.7, 166.0, 163.3, 148.2, 137.4, 137.4, 136.2, 135.5, 133.7, 133.7, 132.8, 129.2, 128.4, 128.3, 119.3, 118.9, 118.2, 116.6, 114.8, 61.9, 13.5; HRMS calcd for $C_{23}H_{17}NO_4$ 371.1158, found 371.1163.

*Ethyl 6-Cyano-4-(2-hydroxybenzoyl)-4′-methoxy-[1,1′-biphenyl]-2-carboxylate (**3ak**):* reaction was run for 6 h; yellow solid; mp 129−130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.68 (s, 1H), 8.27 (s, 1H), 8.13 (s, 1H), 7.68−7.47 (m, 2H), 7.32 (d, J = 8.5 Hz, 2H), 7.13 (d, J = 8.6 Hz, 1H), 7.07−6.90 (m, 3H), 4.12 (q, J = 7.6 Hz, 2H), 3.88 (s, 3H), 1.04 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 166.3, 163.3, 160.4, 148.0, 137.3, 137.1, 135.5, 134.0, 133.6, 132.8, 129.9, 128.2, 119.3, 118.9, 118.3, 116.8, 114.9, 114.0, 61.92, 55.31, 13.67; HRMS calcd for $C_{24}H_{19}NO_5$ 401.1263, found 401.1269.

*Ethyl 6-Cyano-4′-fluoro-4-(2-hydroxybenzoyl)-[1,1′-biphenyl]-2-carboxylate (**3al**):* reaction was run for 5 h; yellow solid; mp 97−99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.66 (s, 1H), 8.33 (d, J = 1.8 Hz, 1H), 8.15 (d, J = 1.8 Hz, 1H), 7.65−7.55 (m, 1H), 7.53 (dd, J = 8.1, 1.5 Hz, 1H), 7.41−7.31 (m, 2H), 7.25− 7.16 (m, 2H), 7.13 (dd, J = 8.5, 0.9 Hz, 1H), 6.96 (ddd, J = 8.2, 7.2, 1.1 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 1.03 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 165.7, 164.5, 163.4, 162.0, 147.2, 137.7, 137.5, 135.5, 133.8 (d, J = 17.6 Hz), 132.7, 132.2, 130.4 (d, J = 8.4 Hz), 119.3, 119.0, 118.2, 116.4, 115.8, 115.6, 115.1, 62.05, 13.62; HRMS calcd for $C_{23}H_{16}FNO_4$ 389.1063, found 389.1062.

*Ethyl 2-(Chloromethyl)-3-cyano-5-(2-hydroxybenzoyl)benzoate (**3am**):* reaction was run for 6 h; yellow solid; mp 83−84 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.60 (s, 1 H), 8.44 (s, 1 H), 8.10 (s, 1 H), 7.59 (t, J = 7.9 Hz, 1 H), 7.44 (d, J = 8.0 Hz, 1 H), 7.12 (d, J = 8.5 Hz, 1 H), 6.95 (t, J = 7.7 Hz, 1 H), 5.27 (s, 2 H), 4.47 (q, J = 7.2 Hz, 2 H), 1.44 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 163.7, 162.8, 143.8, 138.0, 137.0, 135.5, 134.6, 132.0, 131.4, 118.8, 118.4, 117.5, 114.9, 62.1, 39.0, 13.5; HRMS calcd for $C_{18}H_{14}ClNO_4$ 343.0611, found 343.0613.

*Ethyl 2-Benzyl-3-cyano-5-(2-hydroxybenzoyl)benzoate (**3an**):* reaction was run for 6 h; yellow solid; mp 67−68 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.94 (s, 1 H), 7.54 (m, 3 H), 7.49 (s, 1 H), 7.48−7.35 (m, 5 H), 7.09 (d, J = 8.4 Hz, 1 H), 6.88 (t, J = 7.6 Hz, 1 H), 4.62 (q, J = 7.1 Hz, 2 H), 4.05 (s, 2 H), 1.56 (t, J = 7.3 Hz, 3 H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.0, 169.6, 163.0, 161.2, 137.1, 134.9, 134.5, 132.7, 130.4, 130.3, 129.4, 128.7, 127.7, 127.6, 119.0, 118.8, 118.1, 116.9, 112.7, 63.0, 21.0, 13.3; HRMS calcd for $C_{24}H_{19}NO_4$ 385.1314, found 385.1295.

General Procedure for Synthesis of 2-Amino-5-(2-hydroxybenzoyl)isophthalonitrile (3ao). *t*-BuOK (0.8 mmol, 89.6 mg) was added to a mixture of compound **1a** (0.4 mmol, 78.8 mg) and **2o** (0.4 mmol, 26.5 mg) in dry DMF (2 mL), and the resulting solution was reacted at 120 °C for 30 min under microwave irradiation. Then the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to give the crude product, which was further purified by column chromatography (4/1 petroleum ether/ethyl acetate) to afford compound **3ao** (54%, 56.8 mg) as a yellow solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.25 (s, 1 H), 8.02 (s, 2 H), 7.68 (s, 2 H), 7.43 (t, J = 7.8 Hz, 1 H), 7.33 (d, J = 7.7 Hz, 1 H), 7.04− 6.89 (m, 2 H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 196.3, 162.3, 155.0, 140.5, 136.8, 133.3, 127.2, 120.7, 120.1, 118.7, 115.8, 97.8; HRMS calcd for $C_{15}H_9N_3O_2$ 263.0695, found 263.0704.

*Ethyl 3-Cyano-5-(2-hydroxy-5-methoxybenzoyl)-2-methylbenzoate (**3bd**):* reaction was run for 2 h; yellow solid; mp 105−106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.25 (s, 1H), 8.40 (s, 1H), 8.08 (s, 1H), 7.20 (dd, J = 9.1, 3.0 Hz, 1H), 7.05 (d, J = 9.1 Hz, 1H), 6.88 (d, J = 3.0 Hz, 1H), 4.42 (q, J = 7.1 Hz, 2H), 3.72 (s, 3H), 2.90 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 165.3, 157.7, 151.7, 147.0, 136.1, 135.7, 134.6, 132.1, 125.3, 119.8, 117.8, 116.7, 115.7, 114.9, 62.0, 55.9, 19.6, 14.2; HRMS calcd for $C_{19}H_{17}NO_5$ 339.1107, found 339.1105.

*Ethyl 3-Cyano-5-(5-fluoro-2-hydroxybenzoyl)-2-methylbenzoate (**3cd**):* reaction was run for 2 h; yellow solid; mp 149−151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.40 (s, 1H), 8.37 (d, J = 1.6 Hz, 1H), 8.06 (d, J = 1.6 Hz, 1H), 7.33 (ddd, J = 9.2, 7.7, 3.1 Hz, 1H), 7.15 (dd, J = 8.6, 3.0 Hz, 1H), 7.09 (dd, J = 9.2, 4.4 Hz, 1H), 4.43 (q, J = 7.1 Hz, 2H), 2.92 (s, 3H), 1.42 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2, 165.3, 159.7, 156.0, 153.6, 147.5, 135.7 (d, J = 3.9 Hz), 134.6, 132.5, 125.3, 125.0, 120.5 (d, J = 7.2 Hz), 118.0 (d, J = 6.3 Hz), 117.6, 117.3, 116.8, 116.1, 62.3, 19.8, 14.4; HRMS calcd for $C_{18}H_{14}FNO_4$ 327.0907, found; 327.0914.

*Ethyl 3-Acetyl-5-(2-hydroxybenzoyl)-2-methylbenzoate (**3dd**):* reaction was run for 2 h; yellow solid; mp 65−66 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.82 (s, 1 H), 8.15 (s, 1 H), 7.90 (s, 1 H), 7.58−7.52 (m, 2 H), 7.11 (d, J = 8.3 Hz, 1 H), 6.92 (t, J = 7.5 Hz, 1 H), 4.41 (q, J = 7.2 Hz, 2 H), 2.68 (s, 3 H), 2.62 (s, 3 H), 1.40 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 199.4, 166.8, 163.2, 141.8, 141.1, 136.8, 135.1, 133.2, 133.0, 132.3, 130.3, 119.0, 118.7, 61.7, 30.7, 18.1, 14.2; HRMS calcd for $C_{19}H_{18}O_5$ 326.1154, found 326.1151.

*Diethyl 5-(2-Hydroxybenzoyl)-2-methylisophthalate (**3ed**):*[5d] reaction was run for 2 h; yellow solid; mp 55−57 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.84 (s, 1 H), 8.16 (s, 2 H), 7.57−7.52 (m, 2 H), 7.09 (d, J = 9.0 Hz, 1 H), 6.91 (t, J = 7.6 Hz, 1 H), 4.40 (q, J = 7.1 Hz, 4 H), 2.79 (s, 3 H), 1.40 (t, J = 7.1 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7, 166.3, 162.6, 142.7, 136.1, 134.4, 132.7, 132.5, 132.2, 118.3, 118.1, 118.0, 61.0, 17.7, 13.6; HRMS calcd for $C_{20}H_{20}O_6$ 356.1260, found 356.1257.

*Ethyl 3-Benzoyl-5-(2-hydroxybenzoyl)-2-methylbenzoate (**3fd**):* reaction was run for 2 h; yellow solid; mp 69−70 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.82 (s, 1 H), 8.28 (s, 1 H), 7.81 (d, J = 7.2 Hz, 2 H), 7.69 (s, 1 H), 7.65−7.46 (m, 5 H), 7.07 (d, J = 8.3 Hz, 1 H), 6.89 (t, J = 7.6 Hz, 1 H), 4.41 (q, J = 7.1 Hz, 2 H), 2.55 (s, 3 H), 1.41 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 197.1, 166.6, 163.2, 141.3, 141.2, 136.8, 136.4, 135.0, 134.1, 133.1, 132.3, 132.0, 130.6, 130.1, 128.8, 119.0, 118.6, 118.6, 61.6, 18.4, 14.2; HRMS calcd for $C_{24}H_{20}O_5$ 388.1311, found 388.1318.

*Ethyl 5-(2-Hydroxybenzoyl)-3-(4-methoxybenzoyl)-2-methylbenzoate (**3gd**):* reaction was run for 4 h; yellow solid; mp 111−113 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.83 (s, 1 H), 8.26 (s, 1 H), 7.78 (d, J = 8.7 Hz, 2 H), 7.67 (s, 1 H), 7.58−7.49 (m, 2 H), 7.07 (d, J = 8.4 Hz, 1 H), 6.96−6.86 (m, 3 H), 4.41 (q, J = 7.1 Hz, 2 H), 3.88 (s, 3 H), 2.54 (s, 3 H), 1.41 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6, 195.6, 166.6, 164.4, 163.2, 141.8, 141.0, 136.8, 135.0, 133.1, 132.5, 132.1, 131.7, 130.3, 129.4, 119.0, 118.7, 118.6, 114.1, 61.6, 55.6, 18.3, 14.2; HRMS calcd for $C_{25}H_{22}O_6$ 418.1416, found 418.1419.

*Ethyl 5-(2-Hydroxybenzoyl)-2-methyl-3-(4-(trifluoromethyl)benzoyl)-benzoate (**3hd**):* reaction was run for 2 h; yellow solid; mp 85−86 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.78 (s, 1 H), 8.30 (s, 1 H), 7.93 (d, J = 8.1 Hz, 2 H), 7.76 (d, J = 8.0 Hz, 2 H), 7.69 (s, 1 H),

7.56−7.51 (m, 2 H), 7.08 (d, J = 8.8 Hz, 1 H), 6.90 (t, J = 7.4 Hz, 1 H), 4.42 (q, J = 7.2 Hz, 2 H), 2.56 (s, 3 H), 1.42 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2, 195.9, 166.4, 163.2, 141.3, 140.5, 139.2, 136.9, 135.3, 132.9, 132.5, 132.4, 130.6, 130.3, 125.9, 125.9, 119.0, 118.7, 118.6, 61.7, 18.4, 14.2; HRMS calcd for $C_{25}H_{19}F_3O_5$ 456.1185, found 456.1192.

*Ethyl 5-(2-Hydroxybenzoyl)-2-methyl-[1,1′-biphenyl]-3-carboxylate (**3id**):* reaction was run for 10 h; yellow solid; mp 87−89 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.95 (s, 1 H), 8.12 (s, 1 H), 7.68 (s, 1 H), 7.63 (d, J = 8.3 Hz, 1 H), 7.57−7.39 (m, 4 H), 7.32 (d, J = 8.3 Hz, 2 H), 7.08 (d, J = 8.4 Hz, 1 H), 6.90 (t, J = 7.6 Hz, 1 H), 4.41 (q, J = 7.2 Hz, 2 H), 2.51 (s, 3 H), 1.41 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.3, 167.5, 163.2, 144.0, 141.0, 140.3, 136.5, 134.9, 133.3, 133.2, 132.1, 129.7, 129.2, 128.4, 127.6, 119.0, 118.8, 118.5, 61.4, 18.8, 14.3; HRMS calcd for $C_{23}H_{20}O_4$ 360.1362, found 360.1362.

*Ethyl 5-(2-Hydroxybenzoyl)-4′-methoxy-2-methyl-[1,1′-biphenyl]-3-carboxylate (**3jd**):* reaction was run for 10 h; yellow gum; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.95 (s, 1 H), 8.09 (s, 1 H), 7.66−7.61 (m, 2 H), 7.51 (t, J = 8.1 Hz, 1 H), 7.24 (d, J = 9.5 Hz, 2 H), 7.07 (d, J = 8.3 Hz, 1 H), 6.97 (d, J = 8.4 Hz, 2 H), 6.89 (t, J = 7.6 Hz, 1 H), 4.40 (q, J = 7.1 Hz, 2 H), 3.86 (s, 3 H), 2.51 (s, 3 H), 1.40 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.2, 167.4, 162.9, 158.8, 143.5, 140.9, 136.2, 134.7, 133.1, 133.1, 132.4, 131.9, 130.2, 129.2, 118.8, 118.6, 118.3, 113.5, 61.2, 55.1, 18.6, 14.1; HRMS calcd for $C_{24}H_{22}O_5$ 390.1467, found 390.1456.

*Ethyl 5-(2-Hydroxybenzoyl)-2-methyl-4′-nitro-[1,1′-biphenyl]-3-carboxylate (**3kd**):* reaction was run for 8 h; yellow solid; mp 97−98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.85 (s, 1 H), 8.32 (d, J = 8.5 Hz, 2 H), 8.18 (s, 1 H), 7.72−7.46 (m, 5 H), 7.09 (d, J = 8.6 Hz, 1 H), 6.91 (d, J = 7.5 Hz, 1 H),4.43 (q, J = 7.8 Hz, 2 H), 2.50 (s, 3 H), 1.41 (t, J = 7.1 Hz, 3 H).^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 167.0, 163.2, 147.3, 147.0, 141.8, 140.5, 136.7, 135.3, 133.0, 132.6, 132.3, 130.7, 123.7, 118.9, 118.8, 118.6, 61.6, 18.8, 14.2; HRMS calcd for $C_{23}H_{19}NO_6$ 405.1212, found 405.1208.

■ ASSOCIATED CONTENT

Supporting Information. Figures giving ^{1}H NMR, ^{13}C NMR, and HRMS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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