JOC The Journal of Organic Chemistry

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Pd-Catalyzed C−S Activation for [3 + 3] Annulation of 2-(Methylthio)benzofuran-3-carboxylates and 2-Hydroxyphenylboronic Acids: Synthesis of Coumestan Derivatives

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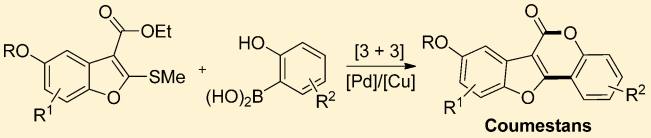
Supporting Information

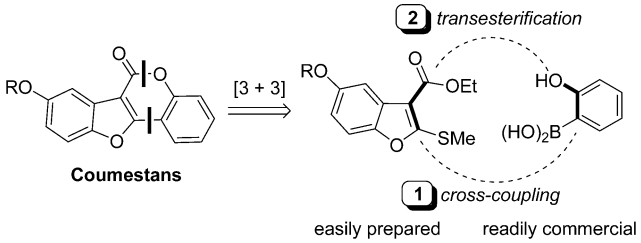
ABSTRACT: Pd-catalytic C−S activation was successfully applied to initiate the cross-coupling of (2-methylthio-3-ester)benzofurans with 2-hydroxyphenylboronic acids and sequential intramolecular transesterification process under Liebeskind-Srogl conditions. Thus, a novel [3 + 3] annulation strategy for efficient synthesis of coumestan derivatives has been developed from readily available starting materials.



Coumestans, a class of polycyclic lactones, form the central core of a variety of natural compounds. Because they possess diverse pharmacological and biological properties,[1] especially the potential of estrogenic activity for human health,[1h] many different methods have been developed that allow the preparation of coumestan analogues.[2] For example, $FeCl_3$-mediated oxidative ring closure of 4-hydroxy coumarins for coumestan construction effectively presents a classical synthetic strategy based on the assembly of the furan nucleus on the chromenone scaffold.[2a,b] On the other hand, the tandem construction of furan and pyranone nucleus starting from 1,2-bis(2-alkoxyphenyl)ethynes or bis-*ortho*-methoxy cis-stilbene also provides an efficient route to coumestans and their related analogues.[2c−f] Additionally, the base-catalyzed condensation of phenylacetic acid methyl ester with benzoylchloride, followed by intramolecular cyclization, was reported to successfully synthesize a naturally occurring coumestan, psoralidin, in a highly convergent and regioselective manner.[2g,h] Snieckus provided a combined DreM−carbamoyl migration−transition-metal-catalyzed cross-coupling strategy for the preparation of series of coumestan.[2i] Recently, Detsi reported that the crude enzyme preparation effectively promotes the reaction between catechol and 4-hydroxycoumarin to afford the corresponding coumestans in satisfactory yields.[2j] Although each of the approaches represents an important advance toward the objective of an access to coumestans, novel and efficient methods are still desired.

Pd-Catalyzed C−S activation has been paid much attention from the standpoints of synthetic and bioinorganic chemistry.[3] Liebeskind and Srogl developed a novel C−C cross-coupling protocol, involving the Pd(0)-catalyzed, Cu(I)-mediated coupling of thioether-type species with boronic acids under neutral conditions.[3e] Recently, we focused on the development of desulfitative C−C coupling[4] of boronic acids and α-oxo ketene dithioacetals, which are important intermediates easily prepared and widely used in organic synthesis.[5] Just a little later, the Pd(0)-catalyzed C−S bond activation based on ketene dithioacetals[6] was also reported to allow this desulfitative cross-coupling process.[6b] Encouraged by this work along with a set of new 2-methylthio-3-EWG-benzofurans (EWG: electron withdrawing group) in hand,[7] we envisaged that the coumestan molecular skeleton might be constructed by a formal [3 + 3] annulation of 2-methylthio-3-alkoxycarbonyl-benzofurans and 2-(hydroxyphenyl)boronic acids *via* a tandem cross-coupling and intramolecular transesterification[8] under the catalysis of Pd (Scheme 1). Herein, we report this new route to coumestan derivatives based on the desulfitative cross-coupling.

Scheme 1. Retrosynthesis of Coumestan Skeleton

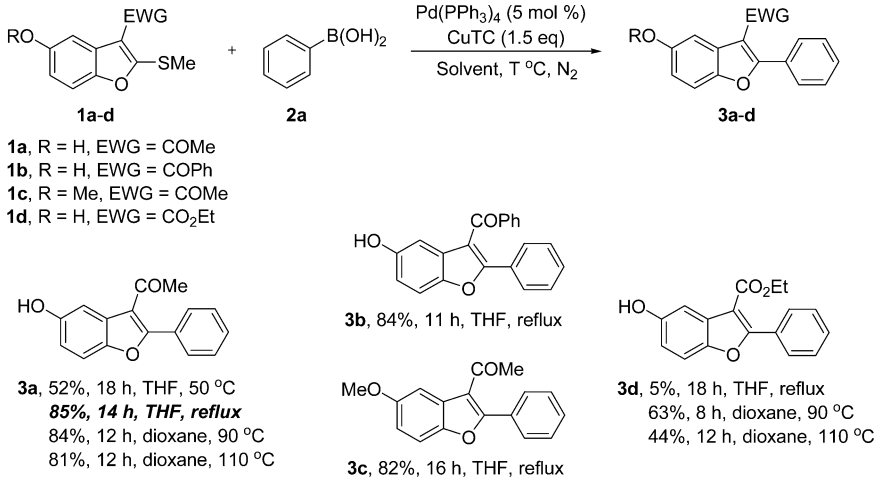


In the present work, we initially examined the possibility of the coupling between 2-(methylthio) benzofurans **1a−d** and phenylboronic acid **2a**. Upon treatment of **1a** and **2a** with 5 mol % of various Pd catalysts in the presence of at least 1.5 equiv of Cu salt, the coupling product **3a** could be isolated in up to 85% yield (Scheme 2). Among the tested catalytic systems, including $Pd(PPh_3)_4$/CuTC (copper(I) thiophene-2-carboxylate), $Pd(PPh_3)_4$/CuMeSal, $Pd(PPh_3)_4/Cu(OAc)_2$, $Pd(PPh_3)_4/CuBr_2$, and $Pd(OAc)_2$/CuTC, the best results were obtained with the $Pd(PPh_3)_4$/CuTC in THF at reflux condition. Dioxane also seemed to be a good solvent for this process and coupling product **3a** was obtained in 84% yield

Received: May 5, 2013
Published: June 17, 2013

dx.doi.org/10.1021/jo400984h | J. Org. Chem. 2013, 78, 7293−7297

Scheme 2. Pd-Catalyzed Cross-Coupling of 2-Methylthio Benzofurans and Phenylboronic Acid



when reaction was performed at 90 °C for 12 h. High reaction temperature seems to make reaction mixtures more complex. As shown in Scheme 2, other 2-(methylthio)benzofurans **1b−d** could also give the desired **3b−d** in high yields under identical reaction conditions. In the case of substrate **1d** with ester functionality, the reaction in dioxane gave the improved yield (63%) at 90 °C. Indeed, the results represent an efficient method for the synthesis of 2-arylbenzofurans[9] and appear to provide an alternative entry to coumestans, which has never been associated with in this synthetic field.

Toward this end, we selected various 2-(hydroxyphenyl)-boronic acids as the coupling partner to investigate the possibility of the [3 + 3] annulation strategy. It was found that, under the reaction conditions for the cross-coupling reaction of **1a** and phenylboronic acid **2a**, the [3 + 3] annulation of **1d** and 2-(hydroxyphenyl)boronic acid **2b** occurred but with low yield in THF. When using dioxane as the solvent at reflux and with the 1:2 ratio of **1d** to **2b**, the desired product **4a** was formed in 70% yield. No significant improvement was observed for the reaction yield by further elevating reaction temperature.

Then, under the optimized conditions described above, the scope and generality of the reaction were explored. Various ethyl 2-(methylthio)benzofuran-3-carboxylates **1d−j** were prepared to react with 2-(hydroxyphenyl)boronic acid **2b**. As shown in Table 1, all the tested benzofurans **1d−j** bearing electron-donating groups at the phenyl ring could give the desired products **4a−g** in fair to good yields. The position of substituents on phenyl ring of benzofurans was proven to affect the reaction yield slightly. On the other hand, boronic acids **2** with various functional groups, including methoxyl (**2c**), methyl (**2d**), fluoro (**2e**), chloro (**2f**), and bromo (**2g**) also proved to be well tolerated under the optimized conditions and the annulations afforded the desired coumestan products (**4h−p**) in fair to good yields. Thus, we developed a practical method to rapidly synthesize diverse coumestans.

The possible mechanism of the annulation is likely to undergo a cross-coupling between benzofurans and boronic acids based on Pd-catalyzed C−S bond activation and a sequential intramolecular transesterification process (Scheme 1). To get more information about this two step reaction mechanism, a control experiment was set up under the identical conditions mentioned previously. It was found that no reaction was observed under the TLC when benzofuran **1e** was reacted with phenol **5** (Scheme 3). This result indicated intermolecular transesterification and a sequential Pd-catalyzed C−S bond activation is not a likely reaction pathway.

In conclusion, we have demonstrated a novel [3 + 3] annulation strategy for the construction of coumestan derivatives based on C−S activation. Under the catalysis of $Pd(PPh_3)_4$ and mediated by CuTC (Liebeskind-Srogl couplings), the reaction of 2-(methylthio)benzofuran-3-carboxylates and 2-hydroxyphenylboronic acids in dioxane at reflux proceeds smoothly *via* a tandem cross-coupling and intramolecular transesterification to afford substituted coumestans in fair to good yield. The readily available thiol organic compounds and boronic acids, fair to good yields, and broad generality of the reactions make this method an attractive route to make natural products.

EXPERIMENTAL SECTION

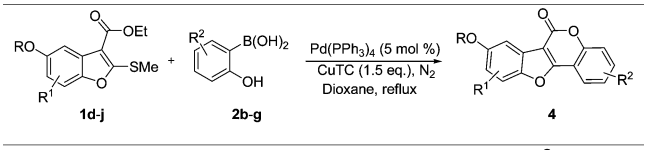
General Procedure for the Preparation of 3 (3a for Example). To a 50 mL three-necked round-bottomed flask equipped with a magnetic stir bar were added **1a** (111 mg, 0.5 mmol), **2a** (122 mg, 1.0 mmol), $Pd(PPh_3)_4$ (29 mg, 0.025 mmol), and CuTC (143 mg, 0.75 mmol) under an atmosphere of N_2. Then, 1,4-dioxane (5 mL) was added to the mixture by using a syringe, and the resultant mixture was stirred at 90 °C for 12 h to consume the starting materials as indicated by TLC. The resulting mixture was filtered through Buchner funnel. The filtrate was poured into saturated aqueous NaCl (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with water (3 × 10 mL), dried over $MgSO_4$, and concentrated in vacuum. The residue was purified by flash silica gel chromatography (petroleum ether/ethyl acetate = 40/1, v/v) to give **3a** (102 mg, 84%) as a white solid.

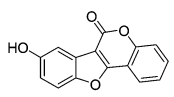
1-(5-Hydroxy-2-phenylbenzofuran-3-yl)-ethanone (3a). Yield: 84% (102 mg, 0.41 mmol); White solid; mp 207−209 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.27 (s, 3H), 6.83−6.85 (m, 1H), 7.43−7.44 (m, 1H), 7.47−7.48 (m, 1H), 7.55−7.59 (m, 3H), 7.78−7.80 (m, 2H), 9.46 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 30.7, 107.0, 112.1, 114.7, 118.2, 127.6, 129.1 (2C), 130.1 (2C), 130.3, 131.1, 148.0, 155.0, 161.1, 195.0; HRMS (ESI-TOF): calcd for $C_{16}H_{13}O_3$ 253.0859 ($M+H^+$), found 253.0868.

(5-Hydroxy-2-phenylbenzofuran-3-yl)-phenyl-methanone (3b). Yield: 84% (132 mg, 0.42 mmol); White solid; mp 260−262 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.85 (t, J = 9.0 Hz, 2H), 7.33−7.40 (m, 5H), 7.56 (d, J = 7.5 Hz, 4H), 7.75 (d, J = 7.5 Hz, 2H), 9.43 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 105.6, 112.4, 115.0, 116.1, 128.5 (2C), 129.0 (2C), 129.0, 129.1 (2C), 129.5 (2C), 129.8, 130.3, 133.8, 137.8, 148.0, 154.8, 158.3, 192.2; HRMS (ESI-TOF): calcd for $C_{21}H_{15}O_3$ 315.1021 ($M+H^+$), found 315.1019.

dx.doi.org/10.1021/jo400984h | J. Org. Chem. 2013, 78, 7293−7297

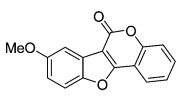
Table 1. [3 + 3] Annulation of 1 and 2 for the Synthesis of Coumestans 4[a]





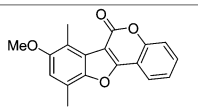
4a: from **1d** and **2b**

70 %, 14 h



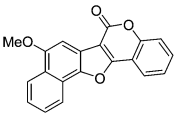
4b: from **1e** and **2b**

66 %, 14 h



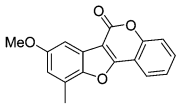
4c: from **1f** and **2b**

52 %, 15 h



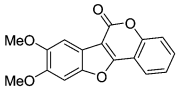
4d: from **1g** and **2b**

44 %, 16 h



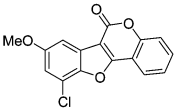
4e: from **1h** and **2b**

62 %, 15 h



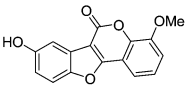
4f: from **1i** and **2b**

57 %, 10 h



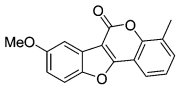
4g: from **1j** and **2b**

74 %, 18 h



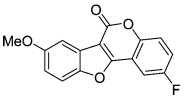
4h: from **1d** and **2c**

66 %, 15 h



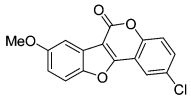
4i: from **1e** and **2d**

72 %, 16 h



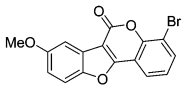
4j: from **1e** and **2e**

61 %, 16 h



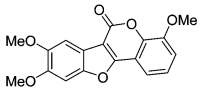
4k: from **1e** and **2f**

68 %, 16 h



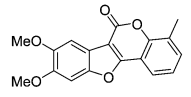
4l: from **1e** and **2g**

48 %, 18 h



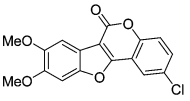
4m: from **1i** and **2c**

52 %, 18 h



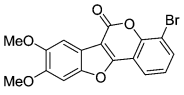
4n: from **1i** and **2d**

59 %, 18 h



4o: from **1i** and **2f**

65 %, 16 h

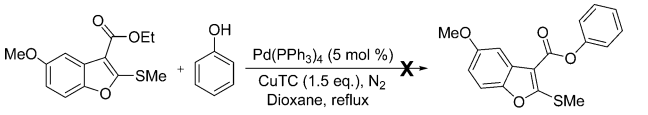


4p: from **1i** and **2g**

55 %, 16 h

[a]Reaction conditions: **1** (0.5 mmol), **2** (1 mmol), $Pd(PPh_3)_4$ (0.05 equiv), CuTC (1.5 equiv), dioxane (5 mL), reflux, N_2, isolated yield.

Scheme 3. Control Reaction between 1e and Phenol 5



1-(5-Methoxy-2-phenylbenzofuran-3-yl)-ethanone (3c). Yield: 82% (109 mg, 0.41 mmol); White solid; mp 139−141 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.33 (s, 3H), 3.89 (s, 3H), 6.96 (dd, J = 2.0, 8.5 Hz, 1H), 7.39 (d, J = 9.0 Hz, 1H), 7.52 (d, J = 3.5 Hz, 3H), 7.62 (d, J = 2.5 Hz, 1H), 7.70 (t, J = 4.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.3, 55.9, 104.2, 111.5, 114.6, 118.5, 127.4, 128.6 (2C), 129.6 (2C), 130.2, 130.5, 148.8, 157.0, 161.3, 195.5; HRMS (ESI-TOF): calcd for $C_{17}H_{15}O_3$ 267.1016 ($M+H^+$), found 267.1023.

5-Hydroxy-2-phenylbenzofuran-3-carboxylic Acid Ethyl Ester (3d). Yield: 63% (89 mg, 0.31 mmol); White solid; mp 178−180 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.31 (t, J = 7.0 Hz, 3H), 4.31 (q, J = 7.0 Hz, 2H), 6.85 (dd, J = 2.5, 8.5 Hz, 1H), 7.37 (d, J = 2.5 Hz, 1H), 7.49−7.54 (m, 4H), 7.92−7.94 (m, 2H), 9.48 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 14.5, 60.9, 107.0, 108.8, 112.3, 114.9, 127.8, 128.7 (2C), 129.7 (2C), 129.7, 130.9, 147.9, 154.9, 160.8, 163.6; HRMS (ESI-TOF): calcd for $C_{17}H_{15}O_4$ 283.0965 ($M+H^+$), found 283.0963.

General Procedure for the Preparation of Coumestan Derivatives 4 (4a for Example). To a 50 mL three-necked round-bottomed flask equipped with a magnetic stir bar were added **1d** (126 mg, 0.5 mmol), **2b** (138 mg, 1.0 mmol), $Pd(PPh_3)_4$ (29 mg, 0.025 mmol), and CuTC (143 mg, 0.75 mmol) under an atmosphere of N_2. Then, 1,4-dioxane (5 mL) was added to the mixture by using a syringe, and the resultant mixture was stirred in reflux condition for 16 h to consume the starting materials as indicated by TLC. The resulting mixture was filtered through Buchner funnel. The filtrate was poured into saturated aqueous NaCl (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with water (3 × 10 mL), dried over $MgSO_4$, and concentrated in vacuum. The residue was purified by flash silica gel chromatography (petroleum ether/ethyl acetate = 50/1, v/v) to give **4a** (88 mg, 70%) as a white solid.

8-Hydroxy-benzo[4,5]furo[3,2-*c*]chromen-6-one (4a). Yield: 70% (88 mg, 0.35 mmol); White solid; mp 257−258 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.97 (dd, J = 3.0, 9.0 Hz, 1H), 7.32 (d, J = 2.0 Hz, 1H), 7.51 (s, 1H), 7.62 (d, J = 8.5 Hz, 1H), 7.70−7.73 (m, 2H), 8.08 (dd, J = 1.5, 8.0 Hz, 1H), 9.78 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 105.7, 106.0, 112.8, 113.5, 116.1, 117.9, 122.5, 124.4, 125.8, 133.1, 149.6, 153.7, 156.0, 158.1, 160.7; HRMS (ESI-TOF): calcd for $C_{15}H_9O_4$ 253.0495 ($M+H^+$), found 253.0491.

8-Methoxy-benzo[4,5]furo[3,2-*c*]chromen-6-one (4b). Yield: 66% (88 mg, 0.33 mmol); White solid; mp 229−230 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.86 (s, 3H), 7.12 (dd, J = 2.5, 9.0 Hz, 1H), 7.39 (d, J = 3.0 Hz, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.71−7.75 (m, 1H), 7.80 (d, J = 9.0 Hz, 1H), 8.06 (dd, J = 1.0, 8.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 56.3, 103.5, 105.7, 112.6, 113.5, 115.9, 117.8, 122.3, 124.2, 125.6, 133.0, 150.1, 153.6, 157.7, 157.8, 160.6; HRMS (ESI-TOF): calcd for $C_{16}H_{11}O_4$ 267.0652 ($M+H^+$), found 267.0653.

8-Methoxy-7,10-dimethyl-benzo[4,5]furo[3,2-*c*]chromen-6-one (4c). Yield: 52% (76 mg, 0.26 mmol); White solid; mp 253−254 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.59 (s, 3H), 2.85 (s, 3H), 3.88 (s, 3H), 6.83 (s, 1H), 7.38 (t, J = 7.5 Hz, 1H), 7.47 (d, J = 8.5 Hz, 1H), 7.58 (t, J = 8.0 Hz, 1H), 8.04 (d, J = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.3, 15.1, 56.8, 106.9, 112.3, 112.6, 117.0, 118.8, 119.1, 121.9, 123.7, 124.3, 131.7, 149.2, 153.5, 155.1, 158.0, 160.6; HRMS (ESI-TOF): calcd for $C_{18}H_{15}O_4$ 295.0965 ($M+H^+$), found 295.0966.

8-Methoxy-5,13-dioxa-dibenzo[*a,i*]fluoren-6-one (4d). Yield: 44% (70 mg, 0.22 mmol); White solid; mp 245−246 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.10 (s, 3H), 7.40 (s, 1H), 7.43 (d, J = 7.5 Hz, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.57 (dd, J = 9.0, 16.5 Hz, 2H), 7.68 (t, J = 7.0 Hz, 1H), 8.08 (d, J = 7.5 Hz, 1H), 8.31 (d, J = 8.5 Hz, 1H), 8.34 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.1, 95.8, 107.1, 113.0, 117.4, 119.3, 119.7 (2C), 121.1, 121.4, 123.4, 124.6, 124.9, 125.8, 127.6, 131.2, 146.2, 153.0, 153.8, 158.6; HRMS (ESI-TOF): calcd for $C_{20}H_{12}NaO_4$ 339.0628 ($M+H^+$), found 339.0618.

8-Methoxy-10-methyl-benzo[4,5]furo[3,2-*c*]chromen-6-one (4e). Yield: 62% (87 mg, 0.31 mmol); White solid; mp 295−296 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.91 (s, 3H), 6.88 (s, 1H), 7.43 (d, J = 9.0 Hz, 2H), 7.51 (d, J = 8.5 Hz, 1H), 7.61 (t, J = 7.5 Hz, 1H), 8.06 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.1, 55.9, 100.6, 106.2, 112.8, 117.0, 117.4, 121.7, 123.0, 123.5, 124.5, 131.6, 149.5, 153.4, 157.5, 158.4, 160.0; HRMS (ESI-TOF): calcd for $C_{17}H_{13}O_4$ 281.0808 ($M+H^+$), found 281.0805.

dx.doi.org/10.1021/jo400984h | J. Org. Chem. 2013, 78, 7293−7297

8,9-Dimethoxy-benzo[4,5]furo[3,2-*c*]chromen-6-one (4f). Yield: 57% (84 mg, 0.29 mmol); White solid; mp 260−261 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.00 (s, 3H), 4.02 (s, 3H), 7.22 (s, 1H), 7.41 (d, J = 7.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.54 (s, 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.97 (d, J = 7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.4, 56.5, 95.4, 102.2, 106.3, 112.9, 115.3, 117.4, 121.2, 124.6, 131.1, 148.0, 149.5, 150.3, 152.9, 158.5, 158.9; HRMS (ESI-TOF): calcd for $C_{17}H_{13}O_5$ 297.0757 ($M+H^+$), found 297.0759.

10-Chloro-8-methoxy-benzo[4,5]furo[3,2-*c*]chromen-6-one (4g). Yield: 74% (111 mg, 0.37 mmol); White solid; mp 247−248 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.90 (s, 3H), 7.06 (d, J = 2.0 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 7.46 (d, J = 2.5 Hz, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.61−7.65 (m, 1H), 8.08 (d, J = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.2, 102.3, 106.2, 112.3, 115.9, 117.5 (2C), 122.0, 124.8, 125.3, 132.3, 146.1, 153.6, 157.8, 158.0, 160.6; HRMS (ESI-TOF): calcd for $C_{16}H_{10}ClO_4$ 301.0262 ($M+H^+$), found 301.0268.

8-Hydroxy-4-methoxy-benzo[4,5]furo[3,2-*c*]chromen-6-one (4h). Yield: 66% (93 mg, 0.33 mmol); White solid; mp 299−300 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.97 (s, 3H), 6.97 (dd, J = 2.5, 8.5 Hz, 1H), 7.32 (d, J = 2.5 Hz, 1H), 7.41−7.44 (m, 2H), 7.60 (t, J = 6.0 Hz, 1H), 7.71 (d, J = 8.5 Hz, 1H), 9.78 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 56.7, 105.6, 105.9, 113.3 (2C), 115.0, 115.9 (2C), 124.2, 125.7, 143.0, 147.7, 149.4, 155.9, 157.5, 160.6; HRMS (ESI-TOF): calcd for $C_{16}H_{11}O_5$ 283.0601 ($M+H^+$), found 283.0606.

8-Methoxy-4-methyl-benzo[4,5]furo[3,2-*c*]chromen-6-one (4i). Yield: 72% (101 mg, 0.36 mmol); White solid; mp 216−217 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.56 (s, 3H), 3.93 (s, 3H), 7.05 (d, J = 7.0 Hz, 1H), 7.30 (t, J = 7.5 Hz, 1H), 7.45 (d, J = 7.0 Hz, 1H), 7.54 (d, J = 9.5 Hz, 1H), 7.59 (s, 1H), 7.85 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.1, 55.9, 103.3, 105.6, 112.2, 112.3, 115.7, 119.3, 124.1, 124.1, 126.9, 133.0, 150.1, 151.8, 157.4, 158.2, 160.8; HRMS (ESI-TOF): calcd for $C_{17}H_{13}O_4$ 281.0808 ($M+H^+$), found 281.0807.

2-Fluoro-8-methoxy-benzo[4,5]furo[3,2-*c*]chromen-6-one (4j). Yield: 61% (87 mg, 0.31 mmol); White solid; mp 243−245 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.93 (s, 3H), 7.08 (dd, J = 2.5, 9.0 Hz, 1H), 7.27−7.34 (m, 1H), 7.49 (dd, J = 4.0, 9.0 Hz, 1H), 7.57 (t, J = 2.5 Hz, 2H), 7.68 (dd, J = 2.5, 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.0, 103.3, 106.6, 107.6, 112.5, 113.4, 116.6, 119.2, 119.4, 123.9, 149.6, 150.3, 157.7, 157.9, 159.4, 159.9; HRMS (ESI-TOF): calcd for $C_{16}H_{10}FO_4$ 285.0558 ($M+H^+$), found 285.0564.

2-Chloro-8-methoxy-benzo[4,5]furo[3,2-*c*]chromen-6-one (4k). Yield: 68% (102 mg, 0.34 mmol); White solid; mp 259−260 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.88 (s, 3H), 7.17 (dd, J = 2.5, 9.0 Hz, 1H), 7.42 (d, J = 2.5 Hz, 1H), 7.66 (d, J = 9.0 Hz, 1H), 7.77 (dd, J = 2.5, 9.0 Hz, 1H), 7.83 (d, J = 9.0 Hz, 1H), 8.12 (d, J = 2.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 56.4, 103.5, 106.6, 113.8, 114.1, 116.5, 119.9, 121.7, 124.1, 129.7, 132.6, 150.4, 152.2, 157.5, 158.0, 159.5; HRMS (ESI-TOF): calcd for $C_{16}H_{10}ClO_4$ 301.0262 ($M+H^+$), found 301.0262.

4-Bromo-8-methoxy-benzo[4,5]furo[3,2-*c*]chromen-6-one (4l). Yield: 48% (83 mg, 0.24 mmol); White solid; mp 251−253 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.93 (s, 3H), 7.07 (dd, J = 2.5, 9.0 Hz, 1H), 7.29 (d, J = 7.5 Hz, 1H), 7.54−7.56 (m, 2H), 7.82 (d, J = 7.5 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.1, 103.4, 106.4, 111.1, 112.5, 114.1, 116.5, 120.9, 123.9, 125.3, 135.3, 150.2, 150.5, 156.9, 157.8, 159.6; HRMS (ESI-TOF): calcd for $C_{16}H_{10}BrO_4$ 344.9757 ($M+H^+$), found 344.9757.

4,8,9-Trimethoxy-benzo[4,5]furo[3,2-*c*]chromen-6-one (4m). Yield: 52% (85 mg, 0.26 mmol); White solid; mp 323−324 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.99 (s, 3H), 4.00 (s, 3H), 4.02 (s, 3H), 7.11 (d, J = 8.5 Hz, 1H), 7.20 (s, 1H), 7.33 (t, J = 8.5 Hz, 1H), 7.54 (d, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.2, 56.3, 56.5, 95.3, 102.2, 106.3, 112.6, 112.7, 113.6, 115.3, 124.6, 142.5, 147.6, 147.9, 149.4, 150.3, 157.8, 158.9; HRMS (ESI-TOF): calcd for $C_{18}H_{15}O_6$ 327.0863 ($M+H^+$), found 327.0871.

8,9-Dimethoxy-4-methyl-benzo[4,5]furo[3,2-*c*]chromen-6-one (4n). Yield: 59% (91 mg, 0.30 mmol); White solid; mp 267−268 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.48 (s, 3H), 3.91 (s, 3H), 3.94 (s, 3H), 7.11 (s, 1H), 7.20 (d, J = 5.0 Hz, 1H), 7.33 (d, J = 7.5 Hz, 1H), 7.45 (s, 1H), 7.72 (d, J = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.2, 56.3, 56.5, 95.4, 102.3, 106.0, 112.6, 115.4, 118.9, 124.1, 126.9, 132.4, 148.0, 149.4, 150.3, 151.4, 158.4, 159.3; HRMS (ESI-TOF): calcd for $C_{18}H_{15}O_5$ 311.0914 ($M+H^+$), found 311.0924.

2-Chloro-8,9-dimethoxy-benzo[4,5]furo[3,2-*c*]chromen-6-one (4o). Yield: 65% (107 mg, 0.33 mmol); White solid; mp 285−286 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.01 (s, 3H), 4.02 (s, 3H), 7.21 (s, 1H), 7.44 (d, J = 8.5 Hz, 1H), 7.51 (dd, J = 2.5, 9.0 Hz, 1H), 7.54 (s, 1H), 7.94 (d, J = 2.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.4, 56.5, 95.4, 102.2, 107.1, 114.0, 115.1, 118.9, 120.7, 130.2, 131.0, 148.3, 150.0, 150.6, 151.2, 157.5, 157.9; HRMS (ESI-TOF): calcd for $C_{17}H_{11}ClNaO_5$ 353.0187 ($M+Na^+$), found 353.0197.

4-Bromo-8,9-dimethoxy-benzo[4,5]furo[3,2-*c*]chromen-6-one (4p). Yield: 55% (103 mg, 0.28 mmol); White solid; mp 285−286 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.00 (s, 3H), 4.02 (s, 3H), 7.20 (s, 1H), 7.52 (s, 2H), 7.78 (d, J = 7.5 Hz, 2H), 7.91 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.4, 56.6, 95.4, 102.2, 106.8, 111.0, 114.3, 115.1, 120.4, 125.2, 134.5, 148.3, 149.6, 149.9, 150.7, 157.1, 158.1; HRMS (ESI-TOF): calcd for $C_{17}H_{12}BrO_5$ 374.9863 ($M+H^+$), found 374.9872.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **3** and **4** (PDF). 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.

■ ACKNOWLEDGMENTS

We acknowledge NNSFC-21172031/21202017 and New Century Excellent Talents in Chinese University (NCET-11-0613) for funding support of this research.

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