JOC The Journal of Organic Chemistry

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Regioselective Cross-Couplings of Coumarins and Flavones with Ethers via C(sp^3)−H Functionalization

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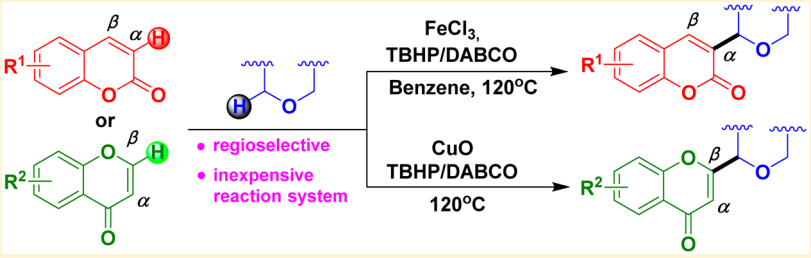
Supporting Information



ABSTRACT: Coumarin and flavone derivatives are highly valuable molecules in drug discovery. Here, two new regioselective cross-dehydrogenation couplings of coumarins and flavones with different ethers via C(sp^3)−H functionalization processes were developed, generating new ether-substituted derivatives not previously reported. These reactions proceeded well via radical mechanisms and provided the corresponding products in good yields.

Transition-metal-catalyzed C−H functionalization has become a powerful strategy for the construction of carbon−carbon and carbon−heteroatom bonds.[1] One such protocol, the cross-dehydrogenation coupling between two different partners, has attracted significant attention in recent years.[2] These reactions can annex two partners directly via oxidation of one C−H bond from each of the two coupling partners, thereby providing an efficient and simple way to generate target molecules in minimum synthetic steps compared with traditional cross-couplings that often require the use of prefunctionalized halides and organometallic reagents as reactants.[3] However, cross-dehydrogenation couplings are still limited by finding suitable reaction partners and challenged by the difficulties associated with controlling product regioselectivities.[4]

Coumarins and flavones are two well-known natural product classes in drug discovery with carbonyl-conjugated olefin functions in their structures.[5] They are suitable partners for cross-dehydrogenation coupling, where adding new substituents could create new biological activity worthy of investigation.[6] Many coumarin and flavone derivatives with substituents on their α and β-positions were achieved via C−H bond functionalization using precious Pd, Rh, and Ru catalysts.[7] However, only a few cross-dehydrogenation couplings were carried out to synthesize these derivatives using radical mechanisms. Recently, Antonchick,[8] Zou,[9] and Han[10] et al. reported cross-dehydrogenation couplings of coumarins and flavones with alkanes or sodium trifluoromethanesulfinate to generate alkyl- and trifluoromethyl-substituted derivatives (Scheme1). However, there are no reports of using ethers as the coupling partners so far.

In this paper, two new cross-dehydrogenation couplings of coumarins and flavones with different ethers via C(sp^3)−H functionalization are reported. Ethers are cheap and readily available building blocks, whose α-H is easily oxidized to generate a radical in the presence of peroxide.[11] Based on prior literature precedent,[12] we first sought suitable reaction conditions for the couplings of coumarins with ethers. Coumarin and 1,4-dioxane were used as the representative reactants, and different catalysts, oxidants, and solvents were screened (Table 1). First, $CuCl_2$ and $Cu(OAc)_2$ were used as catalysts in benzene, and TBHP (*tert*-butyl hydroperoxide, 70 wt % in water) was employed as an oxidant. Neither reaction gave the expected product **3a** (entries 1 and 2). Using $Cu(OAc)_2$ as a catalyst in benzene with a combination of TBHP/DABCO provided a 51% yield of **3a** (entry 3). $CuCl_2$ with TBHP/DBU in benzene only produced a 35% yield of **3a** (entry 4). When $Cu(OAc)_2$ was employed with TBHP/DBU or DTBP (*tert*-butyl peroxide)/DBU, less than 5% of **3a** was observed (entries 5 and 6). The TBHP/DBU combination in the presence of $FeCl_3$ afforded a trace amount of **3a** (entry 7), while the combination of TBHP/DABCO in EtOAc with $FeCl_3$ afforded a 35% yield of **3a** (entry 8). The combination of TBHP/DABCO in a solvent-free environment or in toluene

Received: April 10, 2015
Published: June 8, 2015

DOI: 10.1021/acs.joc.5b00800
J. Org. Chem. 2015, 80, 7251−7257

Scheme 1. Synthesis of Coumarin and Flavone Derivatives via Radical Cross-Dehydrogenation Couplings

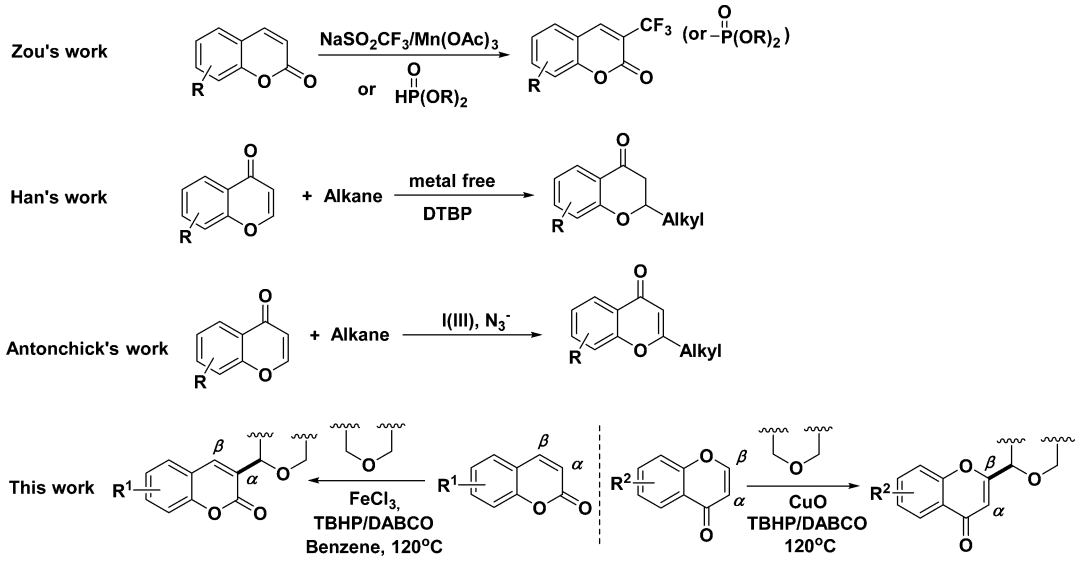
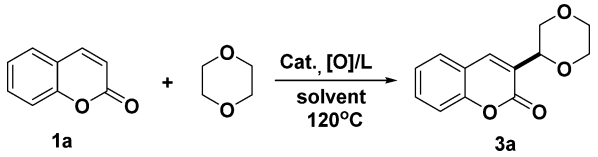


Table 1. Optimization of Reaction Conditions[a]



1a 3a

entry	catalyst	oxidant/ligand	solvent	yield[b] (%)
1	$CuCl_2$	TBHP/---	benzene	trace
2	$Cu(OAc)_2$	TBHP/---	benzene	trace
3	$Cu(OAc)_2$	TBHP/DABCO	benzene	51
4	$CuCl_2$	TBHP/DABCO	benzene	35
5	$Cu(OAc)_2$	TBHP/DBU	benzene	<5
6	$Cu(OAc)_2$	DTBP/DBU	benzene	trace
7	$FeCl_3$	TBHP/DBU		trace
8	$FeCl_3$	TBHP/DABCO	EtOAc	35
9	$FeCl_3$	TBHP/DABCO		50
10	$FeCl_3$	TBHP/DABCO	toluene	45
11	$FeCl_3$	TBHP/DABCO	benzene	65
12	$FeCl_3$	TBHP	benzene	trace
13	$FeCl_3$	DABCO	benzene	trace

[a]Reaction conditions: catalysts (10 mol %), ether (0.5 mL), coumarin (1 equiv), TBHP (70 wt % in water, 3.0 equiv), DTBP (3 equiv), benzene (0.5 mL), DABCO or DBU (1.0 equiv), 120 °C. [b]Isolated yield of product was based on the reactant coumarin. These reactions were run for 36 h.

with $FeCl_3$ afforded **3a** in 50 and 45% yields, respectively (entries 9 and 10). TBHP/DABCO in benzene with $FeCl_3$ as a catalyst gave a 65% yield (entry 11). When TBHP or DABCO was used separately, both reactions gave the trace amount of expected product **3a** (entries 12 and 13). After screening, the suitable conditions selected for the coupling of ether and coumarin are $FeCl_3$ (10.0 mol %), ether (0.5 mL), coumarin (1.0 equiv), TBHP (3.0 equiv), and DABCO (1.0 equiv) in benzene.

After suitable reaction conditions were determined, representative reactions of different ethers with various coumarins were examined and moderate to good yields of ether-substituted coumarin derivatives **3a**–**n** were obtained (Table 2) with high regioselectivities. However, the electron-withdrawing nitro-substituted coumarin did not react with 1,4-dioxane, failing to give **3i**. Interestingly, a different phenomenon was observed with the use of dibenzylether. As the coupling partner, instead of generating ether-substituted derivatives, the benzoyl-substituted product **3j** was produced regioselectively in a 67% yield.

Based on the chemical shifts displayed in the ^1H and ^{13}C NMR spectra of each ether-substituted coumarin derivative, the ether substrate was bonded to the more electron-rich α-position of the coumarin ester.

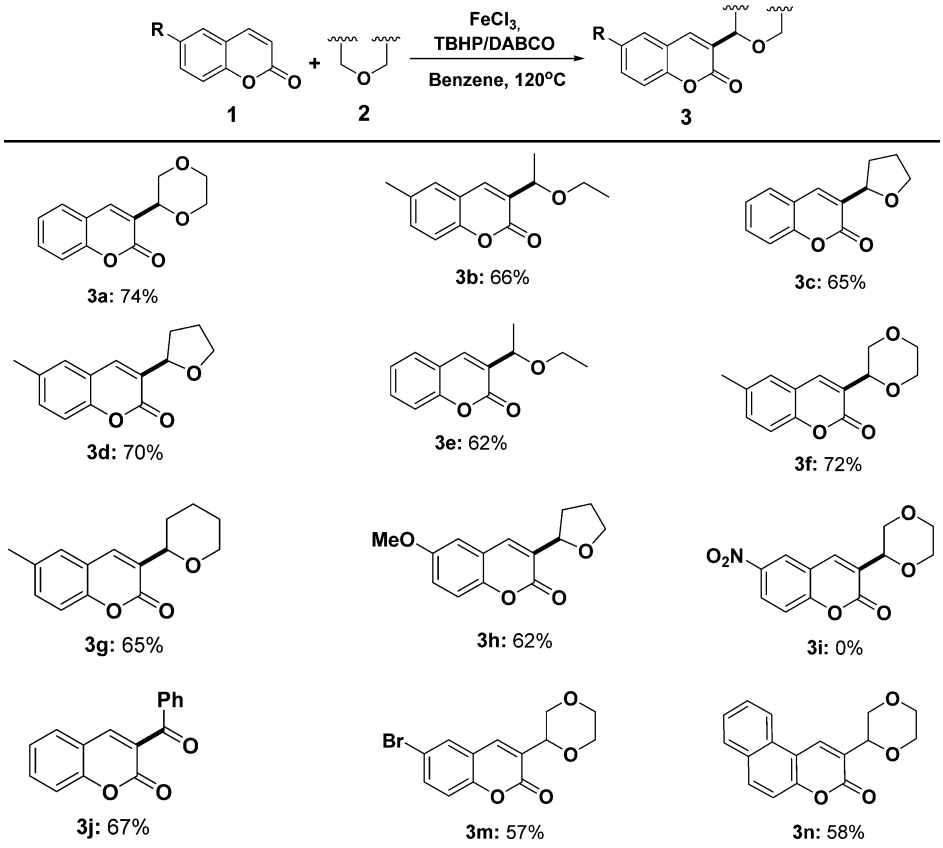
To find suitable conditions for ether/flavone coupling, flavone **4a** and 1,4-dioxane were used as the representative reactants. Different catalysts, oxidants, and solvents were screened. The coupling conditions used for coumarins and ethers also worked well for the coupling of flavone with 1,4-dioxane. This reaction gave a 65% yield of product **5a** (Table 3, entry 1). Switching from DABCO to DBU reduced the yield slightly to 60% (entry 2). $CuBr_2$ and $CuCl_2$ were used with the combination of TBHP/DABCO, but **5a** was not observed in either case (entries 3 and 4). When CuI, $Cu(OAc)_2$, CuBr, or Cu_2O was used with TBHP/DABCO, only 20, 10, 30, or 10% yields of **5a** were produced (entries 5, 6, 7, and 8). Surprisingly, using CuO as the catalyst succeeded, affording a 68% yield of product **5a** (entry 9). In addition, a moderate yield of **5a** was obtained with $FeCl_3$ in EtOAc and DCE (entries 10 and 11). When TBHP or DABCO was used separately, both reactions gave the trace amount of expected product **5a** in the presence of CuO catalyst (entries 12 and 13). Based on these screening results, the conditions chosen for the coupling of ethers with flavones were as follows: CuO (10.0 mol %), flavone (1.0 equiv), ether (1.0 mL), TBHP (70 wt % in water, 3.0 equiv), and DABCO (1.0 equiv) at 120 °C for 36 h.

Using the optimal reaction conditions found above, some representative flavones were reacted with various ethers (Table 4). As expected, these cross-dehydrogenation couplings gave ether-substituted flavone derivatives **5a**–**m** in 55–79% isolated yields. Noticeably, one major product was detected and isolated in each reaction, which was the coupling of ethers to the electron-deficient β-position on the flavones.

To explain these results, understanding the reaction mechanism is necessary. To determine if radicals are involved

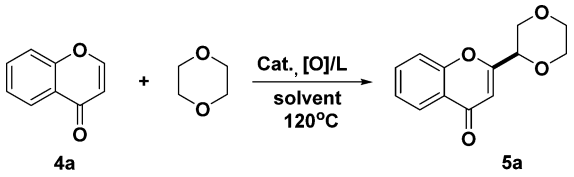
DOI: 10.1021/acs.joc.5b00800
J. Org. Chem. 2015, 80, 7251–7257

Table 2. Syntheses of Ether-Substituted Coumarin Derivatives[a]



[a]Reaction conditions: catalyst (10 mol %), ether (0.5 mL), coumarin (1.0 equiv), TBHP (70 wt % in water, 3.0 equiv), and DBU (1.0 equiv) in benzene (0.5 mL) at 120 °C for 36 h. Isolated yields of **3a**–**n** were based on the reactant coumarin.

Table 3. Screening for Suitable Reaction Conditions[a]



entry	catalyst	oxidant/ligand	solvent	yield[b] (%)
1	$FeCl_3$	TBHP, DABCO		65
2	$FeCl_3$	TBHP, DBU		60
3	$CuBr_2$	TBHP, DABCO		trace
4	$CuCl_2$	TBHP, DABCO		trace
5	CuI	TBHP, DABCO		20
6	$Cu(OAc)_2$	TBHP, DABCO		10
7	CuBr	TBHP, DABCO		30
8	Cu_2O	TBHP, DABCO		10
9	CuO	TBHP, DABCO		68
10	$FeCl_3$	TBHP, DABCO	EtOAc	45
11	$FeCl_3$	TBHP, DABCO	DCE	43
12	CuO	DABCO		trace
13	CuO	TBHP		trace

[a]Reaction conditions: catalysts (10 mol %), ether (1.0 mL), flavone (1.0 equiv), TBHP (70 wt % in water, 3.0 equiv), DABCO, or DBU (1.0 equiv), 120 °C. [b]Isolated yield of product was based on the reactant flavone. These reactions were run for 36 h.

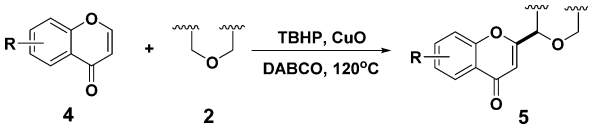
in these two couplings, TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl) was used as a radical scavenger in these reactions. In the presence of TEMPO, no coupling products were observed, indicating that radicals are involved in both of these couplings. Based on these results, a plausible mechanism is proposed (Scheme 2). Heat splits TBHP into two radicals that extract a hydrogen atom from the α-position of ether. The nucleophilic ether radical can attack either the α- or β-position of coumarin's olefin substrate, generating radical intermediate **A** or **B**. The benzylic radical **A** is more stable than the radical species **B**, and thus, radical **A** is more easily formed than radical **B**. Therefore, only α-ether-substituted coumarin derivatives **3** were regiospecifically obtained with coumarins.

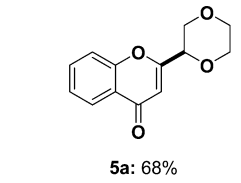
The ether radical also has two choices to add to the α- or β-position of the flavone's unsaturated ketone function. The ether radical is a relatively electron-rich radical with some nucleophilicity. Thus, it is more prone to react at the electron-deficient β-position of the vinylogous ester instead of the relatively electron-rich α-position. The α-position is also more electron-rich due to resonance from the ring's oxygen atom. Also, the ring oxygen's electronegativity further reduces electron density at the β-carbon. After the ether radical has added to the β-position, radical **C** is formed, which is then oxidized to give **5**.

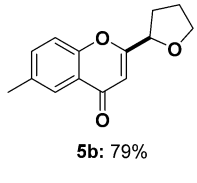
To provide some insight into the reaction mechanism, couplings of α- or β-methyl-substituted coumarins (**1k** and **1l**) or flavones (**4j** and **4k**) with 1,4-dioxane were also carried out (Scheme 3). For **1k** and **4j**, in which the preferred reaction sites were blocked by the methyl group, either no or trace amount of desired product was observed. For coumarin **1l** and flavone **4k**, in which the preferred reaction sites are available, the desired products **3l** and **5k** were obtained in 75 and 50% yield, respectively. These results support the proposed mechanistic

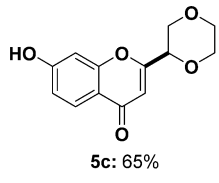
DOI: 10.1021/acs.joc.5b00800
J. Org. Chem. 2015, 80, 7251−7257

Table 4. Syntheses of Ether-Substituted Flavone Derivatives[a]

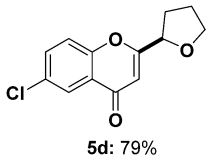



5a: 68%

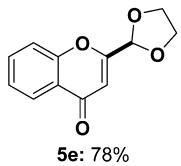

5b: 79%

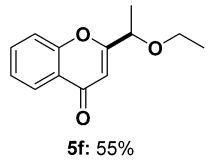


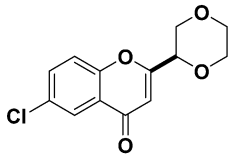
5c: 65%



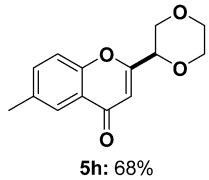
5d: 79%

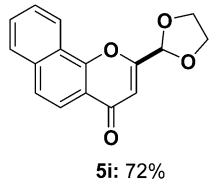

5e: 78%

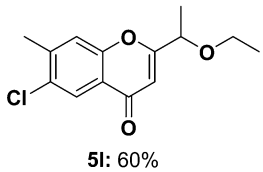

5f: 55%



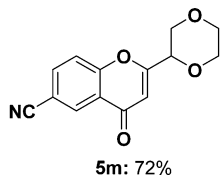
5g: 70%


5h: 68%


5i: 72%



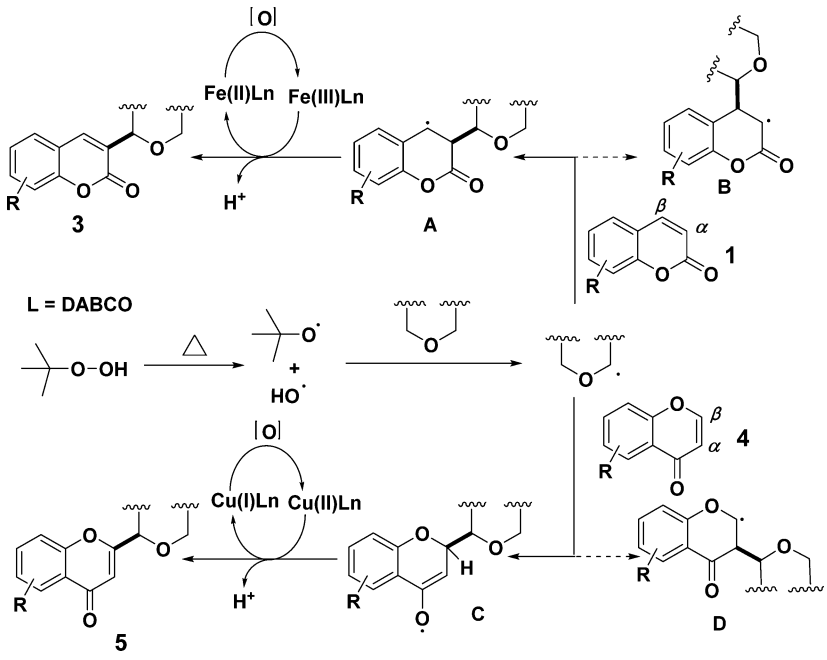
5l: 60%



5m: 72%

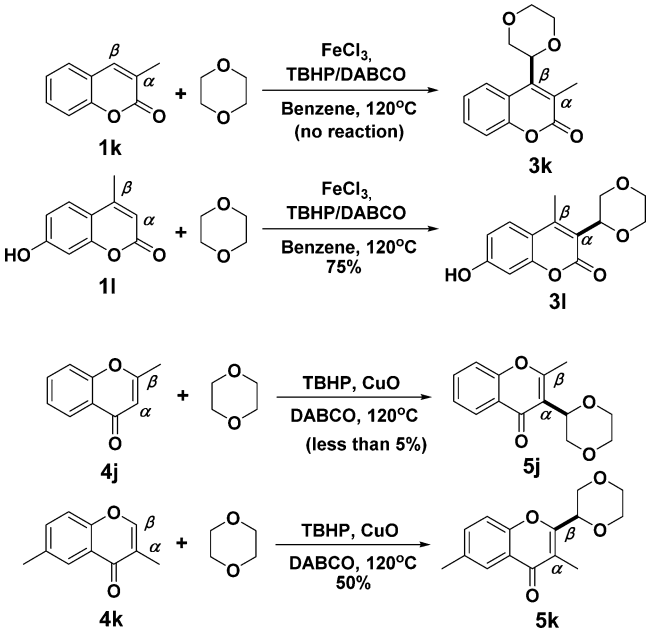
[a]Reaction conditions: CuO (10 mol %), flavone (1.0 equiv), ether (1.0 mL), TBHP (70 wt % in water, 3.0 equiv), and DABCO (1.0 equiv) at 120 °C for 36 h. Isolated yield of product was based on the reactant flavones **4**.

Scheme 2. Proposed Mechanism for Cross-Dehydrogenation Coupling of Coumarins and Flavones with Ethers



DOI: 10.1021/acs.joc.5b00800
J. Org. Chem. 2015, 80, 7251−7257

Scheme 3. Couplings of Coumarin and Flavone with 1,4-Dioxane



explanation in Scheme 2. It should be mentioned that the relatively low yield for **4j** is presumably due to the steric effect from the neighboring methyl group.

CONCLUSIONS

In summary, we have developed two regioselective and atom economical cross-dehydrogenation couplings of ethers with coumarins and flavones via C(sp^3)−H functionalization. These processes gave two new types of ether-substituted derivatives with the ether substituent on α-positions of coumarins and β-positions of flavones, respectively, in good yields and high regioselectivities. Both reactions proceeded via radical addition mechanisms. Despite the above advantages, the method is still limited in scope; the major drawback is that excess ether is used. Investigation of the biological activities of these products is currently underway.

EXPERIMENTAL SECTION

General Procedure for the Synthesis of Compounds 3a−j and 3l−3n. To a dry thick-walled glass pressure tube were added coumarin (1.0 mmol, 1.0 equiv), DABCO (1.0 mmol, 1.0 equiv), ether (0.5 mL), and benzene (anhydrous, 0.5 mL). Then, $FeCl_3$ (0.1 mmol, 10 mol %) and TBHP (3.0 mmol, 3 equiv, 70 wt % in water) were added into the tube. The mixture was stirred at 120 °C for 36 h. After that, the reaction mixture was quenched with brine and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried (anhydrous Na_2SO_4), and concentrated under vacuum. The residue was purified by flash chromatography (EtOAc/petroleum ether = 1:30) on silica gel to provide the desired product **3a** as a colorless oil in a 74% yield; the same procedure was applied for producing other compounds **3b−h**, **3j**, and **3l−3n**.

General Procedure for the Synthesis of Compounds 5a−i and 5k−5m. Flavone (1.0 mmol, 1.0 equiv), ether (1.0 mL), and DABCO (1.0 mmol, 1.0 equiv) were added to a thick-walled pressure tube, and then CuO (0.1 mmol, 10 mol %) and TBHP (3.0 mmol, 3.0 equiv, 70 wt % in water) were also added. The mixture was stirred at 120 °C for 36 h. Then reaction was quenched with water and extracted with ethyl acetate. The organic layers were then combined, washed with brine, dried (anhydrous Na_2SO_4), and concentrated under vacuum. The residue was purified by flash chromatography (EtOAc/petroleum ether = 1:30) on silica gel to give the desired product **5a** as a colorless oil in a 68% yield. The same procedure was applied for producing other compounds **5b−i** and **5k−5m**.

*3-(1,4-Dioxan-2-yl)-2H-chromen-2-one (**3a**):* Following the general procedure, isolated yield (171.7 mg, 74%) as colorless oil; IR 2961, 1721, 1635, 1457, 1288, 1058, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.87 (s, 1H), 7.87 (s, 1H), 7.50 (s, 2H), 7.29 (s, 2H), 4.76 (m, 1H), 4.26 (m, 1H),3.96 (m, 2H), 3.83 (m, 1H), 3.68 (m, 1H), 3.25 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.9, 153.2, 139.2, 131.5, 128.0, 126.1, 124.6, 119.0, 116.5, 72.7, 71.0, 67.3, 66.4; HRMS (ESI-TOF) m/z calcd for $C_{13}H_{12}NaO_4$ 255.0633 $(M + Na)^+$, found 255.0624.

*3-(1-Ethoxyethyl)-6-methyl-2H-chromen-2-one (**3b**):* Following the general procedure, isolated yield (153.2 mg, 66%) as colorless oil; IR 3148, 2927, 1716, 1399, 1279, 994 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.76 (s, 1H), 7.32−7.22 (m, 3H), 4.62 (dd, J = 12.8, 6.4 Hz, 1H), 3.56−3.51 (m, 2H), 2.42 (s, 3H), 1.45 (d, J = 6.4 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.1, 151.3, 137.1, 134.1, 132.1, 131.5, 127.7, 119.1, 116.2, 72.2, 64.7, 21.6, 20.8, 15.5; HRMS (ESI-TOF) m/z calcd for $C_{14}H_{16}NaO_3$ 255.0997 $(M + Na)^+$, found 255.0984.

*3-(Tetrahydrofuran-2-yl)-2H-chromen-2-one (**3c**):* Following the general procedure, isolated yield (140.5 mg, 65%) as colorless oil; IR 2972, 1718, 1608, 1457, 1283, 1021, 757 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.81 (s, 1H), 7.51−7.25 (m, 4H), 4.98−4.95 (m, 1H), 4.14−4.09 (m, 1H), 3.96 (dd, J = 15.2, 7.2 Hz), 2.57−2.48 (m, 1H), 2.05−1.91 (m, 2H), 1.79−1.72 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.5, 153.1, 136.4, 131.1, 130.9, 127.8, 124.4, 119.3, 116.4, 75.9, 68.9, 32.2, 25.7; HRMS (ESI-TOF) m/z calcd for $C_{13}H_{12}NaO_3$ 239.0684 $(M + Na)^+$, found 239.0679.

*6-Methyl-3-(tetrahydrofuran-2-yl)-2H-chromen-2-one (**3d**):* Following the general procedure, isolated yield (161.1 mg, 70%) as colorless oil; IR 2926, 1716, 1635, 1457, 1281, 1024, 817 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.73 (d, J = 0.4 Hz, 1H), 7.28−7.19 (m, 3H), 4.94 (dd, J = 12.8, 6.4 Hz, 1H), 4.13−4.07 (m, 1H), 3.95 (dd, J = 14.8, 7.2 Hz, 1H), 2.55−2.46 (m, 1H), 2.39 (s, 3H), 2.04−1.91 (m, 2H), 1.80−1.73 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.7, 151.2, 136.4, 134.0, 131.9, 127.6, 119.0, 116.1, 76.0, 68.9, 32.2, 25.6, 20.8; HRMS (ESI-TOF) m/z calcd for $C_{14}H_{15}O_3$ 231.1021 $(M + H)^+$, found 231.1014.

*3-(1-Ethoxyethyl)-2H-chromen-2-one (**3e**):* Following the general procedure, isolated yield (135.2 mg, 62%) as colorless oil; IR 2975, 2927, 1724, 1635, 1489, 1174, 1072, 782 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.79 (s, 1H), 7.55−7.50 (m, 2H), 7.37−7.30 (m, 2H), 4.66−4.61 (m, 1H), 3.58−3.52 (m, 2H), 1.44 (d, J = 6.4 Hz, 3H), 1.29 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.8, 153.1, 137.1, 131.6, 131.1, 127.9, 124.4, 119.3, 116.4, 72.2, 64.7, 21.5, 15.5; HRMS (ESI-TOF) m/z calcd for $C_{13}H_{15}O_3$ 219.1021 $(M + H)^+$, found 219.1021.

*3-(1,4-Dioxan-2-yl)-6-methyl-2H-chromen-2-one (**3f**):* Following the general procedure, isolated yield (177.2 mg, 72%) as colorless oil; IR 2918, 1717, 1636, 1436, 1291, 1035, 818 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.80 (s, 1H), 7.31−7.27 (m, 2H), 7.19 (d, J = 8.4 Hz, 1H), 4.77−4.74 (m, 1H), 4.25 (dd, J = 11.2, 2.4 Hz, 1H), 3.99−3.89 (m, 2H), 3.82 (t, J = 2.4 Hz, 1H), 3.71−3.64 (m, 1H), 3.22 (t, J = 1.6 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.1, 151.3, 139.2, 134.3, 132.5, 127.8, 125.9, 118.7, 116.2, 72.7, 71.0. 67.3, 66.4; HRMS (ESI-TOF) m/z calcd for $C_{14}H_{15}O_4$ 247.0970 $(M + H)^+$, found 247.0969.

*6-Methyl-3-(tetrahydro-2H-pyran-2-yl)-2H-chromen-2-one (**3g**):* Following the general procedure, isolated yield (158.7 mg, 65%) as colorless oil; IR 2955, 1733, 1616, 1493, 1283, 1054, 813 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.76 (s, 1H), 7.29−7.19 (m, 3H), 4.46 (d, J = 10.8 Hz, 1H), 4.19−4.15 (m, 1H), 3.68−3.61 (m, 1H), 2.39 (s, 3H), 2.22−2.19 (m, 1H), 1.93−1.90 (m, 1H), 1.74−1.60 (m, 3H), 1.29−1.20 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.5, 151.2, 137.4, 134.0, 132.0, 130.7, 127.7, 119.1, 116.1, 74.6, 69.1, 32.2, 26.0, 23.6, 20.8; HRMS (ESI-TOF) m/z calcd for $C_{15}H_{16}NaO_3$ 267.0997 $(M + Na)^+$, found 267.0988.

DOI: 10.1021/acs.joc.5b00800
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*6-Methoxy-3-(tetrahydrofuran-2-yl)-2H-chromen-2-one (**3h**):* Following the general procedure, isolated yield (152.6 mg, 62%) as colorless oil; IR 2924, 1716, 1579, 1431, 1262, 1021, 817 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.77 (s, 1H), 7.76−7.27 (m, 1H), 7.08−7.05 (m, 1H), 6.94 (d, J = 2.8 Hz, 1H), 4.98−4.95 (m, 1H), 4.14−4.09 (m, 1H), 3.93 (dd, J = 14.8, 6.8 Hz, 1H), 3.85 (s, 3H), 2.57−2.49 (m, 1H), 2.06 (dd, J = 12.4, 5.2 Hz, 1H), 1.99−1.91 (m, 1H), 1.89−1.78 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.7, 156.1, 147.5, 136.2, 131.4, 119.6, 118.6, 117.4, 109.9, 76.0, 68.9, 55.8, 32.3, 25.7; HRMS (ESI-TOF) m/z calcd for $C_{14}H_{15}O_4$ 247.0970 $(M + H)^+$, found 247.0969.

*3-Benzoyl-2H-chromen-2-one (**3j**):* Following the general procedure, isolated yield (167.5 mg, 67%) as colorless oil; IR 3063, 1717, 1607, 1493, 1243, 1055, 813 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.11 (s, 1H), 7.90 (d, J = 7.2 Hz, 2H), 7.70−7.62 (m, 3H), 7.51 (d, J = 7.6 Hz, 2H), 7.49−7.36 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.5, 151.2, 137.4, 134.0, 132.0, 130.7, 127.7, 119.1, 116.1, 74.6, 69.1, 32.2, 26.0, 23.6, 20.8; HRMS (ESI-TOF) m/z calcd for $C_{16}H_{10}NaO_3$ 273.0528 $(M + Na)^+$, found 273.0519.

*3-(1,4-Dioxan-2-yl)-7-hydroxy-4-methyl-2H-chromen-2-one (**3l**):* Following the general procedure, isolated yield (196.5 mg, 75%) as colorless oil; IR 3261, 2963, 1699, 1617, 1570, 1263, 1110, 923 cm^{-1}; ^1H NMR (MeOD, 400 MHz) δ 7.65 (d, J = 8.0 Hz, 1H), 6.82 (dd, J = 8.0, 4.0 Hz, 1H), 6.65 (s, 1H), 5.10 (dd, J = 8.0, 4.0 Hz, 1H), 3.95−3.87 (m, 2H), 3.85−3.81 (m, 2H), 3.79−3.70 (m, 2H), 2.66 (s, 3H); ^{13}C NMR (MeOD, 100 MHz) δ 161.6, 161.4, 154.0, 152.6, 126.4, 116.8, 113.1, 113.0, 101.6, 74.0, 68.0, 67.5, 65.9, 14.5; HRMS (ESI-TOF) m/z calcd for $C_{14}H_{14}NaO_5$ 285.0739 $(M + Na)^+$, found 285.0740.

*6-Bromo-3-(1,4-dioxan-2-yl)-2H-chromen-2-one (**3m**):* Following the general procedure, isolated yield (176.6 mg, 57%) as colorless oil; IR 3072, 2932, 2361, 1745, 1659, 1456, 1244, 1110, 694 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.81 (s, 1H), 7.65 (d, J = 2.0 Hz, 1H), 7.61 (dd, J = 8.8, 2.4 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H), 5.10 (d, J = 8.8 Hz, 1H), 4.28 (dd, J = 11.2, 2.4 Hz, 1H), 3.99−3.96 (m, 2H), 3.84 (dd, J = 11.7, 2.5 Hz, 1H), 3.73−3.67 (m, 1H), 3.23 (dd, J = 10.8, 10.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.2, 152.0, 137.9, 134.2, 130.3, 127.5, 120.6, 118.3, 117.1, 72.7, 70.9, 67.3, 66.4; HRMS (ESI-TOF) m/z calcd for $C_{13}H_{11}BrNaO_4$ 332.9738 $(M + Na)^+$, found 332.9736.

*2-(1,4-Dioxan-2-yl)-3H-benzo[f]chromen-3-one (**3n**):* Following the general procedure, isolated yield (163.6 mg, 58%) as colorless oil; IR 3161, 2973, 1665, 1587, 1470, 1253, 1150, 823 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.67 (s, 1H), 8.36 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 8.8 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.71 (dd, J = 8.0, 0.8 Hz, 1H), 7.59 (t, J = 8.0 Hz, 1H), 7.47 (d, J = 8.8 Hz, 1H), 4.87 (dd, J = 9.6, 1.2 Hz, 1H), 4.36 (dd, J = 11.6, 2.8 Hz, 1H), 4.09−3.98 (m, 2H), 3.89 (t, J = 2.4 Hz, 1H), 3.79−3.73 (m, 1H), 3.32 (dd, J = 11.2, 10.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.0, 152.8, 134.9, 132.8, 130.4, 129.1, 129.0, 128.2, 126.1, 125.1, 121.8, 116.7, 113.3, 73.0, 71.1, 67.4, 66.5; HRMS (ESI-TOF) m/z calcd for $C_{17}H_{14}NaO_4$ 305.0790 $(M + Na)^+$, found 305.0789.

*2-(1,4-Dioxan-2-yl)-4H-chromen-4-one (**5a**):* Following the general procedure, isolated yield (157.8 mg, 68%) as colorless oil; IR 2962, 1654, 1493, 1398, 1115, 911 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.17 (dd, J = 7.6, 1.2 Hz, 1H), 7.68−7.64 (m, 1H), 7.45−7.38 (m, 2H), 6.48 (d, J = 0.8 Hz, 1H), 4.58−4.55 (m, 1H), 4.16 (dd, J = 11.6, 3.2 Hz, 1H), 3.99−3.96 (m, 1H), 3.91−3.81 (m, 2H), 3.76−3.72 (m, 1H), 3.70−3.60 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.0, 164.6, 156.1, 133.8, 125.8, 125.3, 124.0, 118.0, 109.1, 73.8, 69.3, 66.6, 66.4; HRMS (ESI-TOF) m/z calcd for $C_{13}H_{12}NaO_4$ 255.0633 $(M + Na)^+$, found 255.0624.

*6-Methyl-2-(tetrahydrofuran-2-yl)-4H-chromen-4-one (**5b**):* Following the general procedure, isolated yield (181.8 mg, 79%) as colorless oil; IR 2926, 1655, 1485, 1319, 1090, 818 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.97 (d, J = 0.8 Hz, 1H), 7.47 (dd, J = 28.8, 8.4 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 6.41 (d, J = 0.8 Hz, 1H), 4.83 (dd, J = 8.0, 5.2 Hz, 1H), 4.11−4.06 (m, 1H), 4.00−3.94 (m, 1H), 2.41 (s, 3H), 2.40−2.33 (m, 1H), 2.14−2.11 (m, 1H), 2.10−1.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.5, 169.3, 154.6, 135.0, 134.8, 125.1, 123.7, 117.7, 107.5, 76.9, 69.4, 31.1, 25.4, 20.9; HRMS (ESI-TOF) m/z calcd for $C_{14}H_{15}O_3$ 231.1021 $(M + H)^+$, found 231.1014.

*2-(1,4-Dioxan-2-yl)-7-hydroxy-4H-chromen-4-one (**5c**):* Following the general procedure, isolated yield (161.2 mg, 65%) as colorless oil; IR 3448, 2969, 1649, 1457, 1055, 1008, 823 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.85 (s, 1H), 7.85 (d, J = 8.8 Hz, 1H), 6.92 (dd, J = 8.8, 2.0 Hz, 1H), 6.84 (d, J = 2.0 Hz, 1H), 6.21 (s, 1H), 4.58 (dd, J = 9.6, 2.8 Hz, 1H), 4.04 (dd, J = 11.2, 2.8 Hz, 1H), 3.90 (d, J = 12.8, Hz, 1H), 3.79−3.73 (m, 1H), 3.63−3.37 (m, 2H), 2.51−2.50 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 176.3, 164.3, 163.3, 157.9, 127.1, 116.6, 115.6, 108.7, 102.8, 73.6, 68.7, 66.3, 66.2; HRMS (ESI-TOF) m/z calcd for $C_{13}H_{12}NaO_5$ 271.0582 $(M + Na)^+$, found 271.0583.

*6-Chloro-2-(tetrahydrofuran-2-yl)-4H-chromen-4-one (**5d**):* Following the general procedure, isolated yield (197.5 mg, 79%) as colorless oil; IR 2956, 1655, 1437, 1317, 1061, 822 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.14−8.12 (m, 1H), 7.60 (dd, J = 9.2, 2.8 Hz, 1H), 7.41 (d, J = 9.2 Hz, 1H), 6.44 (d, J = 0.8 Hz, 1H), 4.83 (dd, J = 8.0, 4.8 Hz, 1H), 4.11−4.05 (m, 1H), 4.00−3.95 (m, 1H), 2.44−2.35 (m, 1H), 2.15−2.09 (m, 1H), 2.09−2.00 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.0, 169.9, 154.6, 133.8, 131.0, 125.2, 125.0, 119.7, 107.6, 76.7, 69.5, 31.2, 25.4; HRMS (ESI-TOF) m/z calcd for $C_{13}H_{11}ClNaO_3$ 273.0294$(M + Na)^+$, found 273.0305.

*2-(1,3-Dioxolan-2-yl)-4H-chromen-4-one (**5e**):* Following the general procedure, isolated yield (170.1 mg, 78%) as colorless oil; IR 2956, 1655, 1437, 1317, 1101, 762 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.18 (dd, J = 8.0, 1.6 Hz, 1H), 7.69−7.65 (m, 1H), 7.49 (dd, J = 8.4, 0.4 Hz, 1H), 7.41−7.37 (m, 1H), 6.49 (s, 1H), 5.79 (s, 1H), 4.15−4.07 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.3, 163.2, 156.3, 134.0, 125.7, 125.3, 124.1, 118.3, 109.0, 99.6, 65.6; HRMS (ESI-TOF) m/z calcd for $C_{12}H_{10}NaO_4$ 241.0477 $(M + Na)^+$, found 241.0469.

*2-(1-Ethoxyethyl)-4H-chromen-4-one (**5f**):* Following the general procedure, isolated yield (120.0 mg, 55%) as colorless oil; IR 2926, 1660, 1465, 1323, 1120, 759 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.22 (dd, J = 8.0, 1.6 Hz, 1H), 7.69−7.65 (m, 1H), 7.47 (d, J = 8.0 Hz,1H), 7.43−7.39 (m, 1H), 6.43 (s, 1H), 4.29 (dd, J = 13.2, 6.8 Hz, 1H), 3.65−3.50 (m, 2H), 1.56 (d, J = 6.4 Hz, 3H), 1.28 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.4, 169.5, 156.4, 133.7, 125.8, 125.2, 124.1, 118.1, 108.2, 74.8, 65.4, 20.3, 15.3; HRMS (ESI-TOF) m/z calcd for $C_{13}H_{14}NaO_3$ 241.0841 $(M + Na)^+$, found 241.0832.

*6-Chloro-2-(1,4-dioxan-2-yl)-4H-chromen-4-one (**5g**):* Following the general procedure, isolated yield (186.2 mg, 70%) as colorless oil; IR 2923, 1655, 1472, 1374, 1117, 913 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.15 (d, J = 2.4 Hz, 1H), 7.60 (q, J = 8.8, 2.4 Hz, 1H), 7.40 (d, J = 8.8 Hz, 1H), 6.49 (s, 1H), 4.58 (dd, J = 9.6, 2.8 Hz, 1H), 4.17 (dd, J = 11.2, 2.8 Hz, 1H), 4.00 (d, J = 10.8 Hz, 1H), 3.92−3.82 (m, 2H), 3.77−3.70 (m, 1H), 3.66−3.61 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.7, 164.8, 154.4, 134.0, 131.3, 125.3, 125.0, 119.7, 109.1, 73.7, 69.3, 66.6, 66.4; HRMS (ESI-TOF) m/z calcd for $C_{13}H_{11}ClNaO_4$ 289.0244 $(M + Na)^+$, found 289.0252.

*2-(1,4-Dioxan-2-yl)-6-methyl-4H-chromen-4-one (**5h**):* Following the general procedure, isolated yield (167.3 mg, 68%) as colorless oil; IR 2965, 1655, 1485, 1327, 1116, 913 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.95 (d, J = 1.2 Hz, 1H), 7.46 (dd, J = 8.4, 2.0 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 6.44 (d, J = 0.8 Hz, 1H), 4.55 (dd, J = 9.6, 2.8 Hz, 1H), 4.14 (dd, J = 11.6, 2.8 Hz, 1H), 3.90 (d, J = 2.8 Hz, 1H), 3.89−3.83 (m, 2H), 3.79−3.71 (m, 1H), 3.69−3.59 (m, 1H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.0, 164.3, 154.3, 135.3, 135.0, 125.3, 125.1, 123.7, 117.7, 108.9, 73.8, 69.3, 66.6, 66.4, 20.9; HRMS (ESI-TOF) m/z calcd for $C_{14}H_{15}O_4$ 247.0970 $(M + H)^+$, found 247.0969.

*2-(1,3-Dioxolan-2-yl)-4H-benzo[h]chromen-4-one (**5i**):* Following the general procedure, isolated yield (193.0 mg, 72%) as colorless oil; IR 3066, 2894, 1655, 1466, 1322, 1125, 941 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.52 (dd, J = 8.0, 0.8 Hz, 1H), 8.16 (d, J = 8.8 Hz, 1H), 7.93 (t, J = 1.6 Hz, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.75−7.67 (m, 2H), 6.67 (s, 1H), 5.98 (s, 1H), 4.25−4.16 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.1, 162.6, 153.8, 136.0, 129.5, 128.1, 127.2, 125.5,

DOI: 10.1021/acs.joc.5b00800
J. Org. Chem. 2015, 80, 7251−7257

123.9, 122.4, 120.6, 120.5, 110.4, 99.7, 65.7; HRMS (ESI-TOF) m/z calcd for $C_{16}H_{12}NaO_4$ 291.0633 $(M + Na)^+$, found 291.0627.

*2-(1,4-Dioxan-2-yl)-3,6-dimethyl-4H-chromen-4-one (**5k**):* Following the general procedure, isolated yield (130.0 mg, 50%) as colorless oil; IR 2922, 1647, 1619, 1490, 1263, 1112, 932 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.98 (s, 1H), 7.48 (dd, J = 8.0, 0.4 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 4.88−4.85 (m, 1H), 4.00−3.95 (m, 2H), 3.94−3.90 (m, 2H), 3.85−3.83 (m, 2H), 2.46 (s, 3H) 2.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.3, 157.9, 154.1, 134.9, 134.8, 125.1, 122.1, 118.8, 117.7, 73.8, 67.8, 67.1, 66.3, 20.9, 9.4; HRMS (ESI-TOF) m/z calcd for $C_{15}H_{16}NaO_4$ 283.0946 $(M + Na)^+$, found 283.0949.

*6-Chloro-2-(1-ethoxyethyl)-7-methyl-4H-chromen-4-one (**5l**):* Following the general procedure, isolated yield (159.6 mg, 60%) as colorless oil; IR 2932, 2361, 2334, 1659, 1463, 1112, 952 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.16 (s, 1H), 7.38 (s, 1H), 6.40 (s, 1H), 4.29−4.24 (m, 1H), 3.62−3.52 (m, 2H), 2.51 (s, 3H), 1.53 (d, J = 6.4 Hz, 3H), 1.26 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.2, 169.5, 154.6, 142.9, 131.8, 125.4, 123.1, 119.9, 108.0, 74.8, 65.4, 20.8, 20.2, 15.3; HRMS (ESI-TOF) m/z calcd for $C_{14}H_{15}ClNaO_3$ 289.0607 $(M + Na)^+$, found 289.0607.

*2-(1,4-Dioxan-2-yl)-4-oxo-4H-chromene-6-carbonitrile (**5m**):* Following the general procedure, isolated yield (185.0 mg, 72%) as colorless oil; IR 3022, 1747, 1619, 1560, 1233, 1212, 862 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.94 (d, J = 8.8 Hz, 1H), 7.80 (d, J = 6.0 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 6.38 (d, J = 6.0 Hz, 1H), 6.32 (dd, J = 10.0, 3.2 Hz, 1H), 4.14 (dd, J = 11.2, 2.8 Hz, 1H), 4.01 (d, J = 8.0 Hz, 1H), 3.99 (dd, J = 18.8, 10.4 Hz, 2H), 3.83 (d, J = 8.0 Hz, 1H), 3.73 (dd, J = 11.2, 10.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.5, 158.7, 153.7, 145.9, 138.7, 122.7, 119.3, 117.8, 114.9, 109.4, 73.1, 69.4, 66.7, 65.9; HRMS (ESI-TOF) m/z calcd for $C_{14}H_{11}NNaO_4$ 280.0586 $(M + Na)^+$, found 280.0586.

■ ASSOCIATED CONTENT

Supporting Information

Spectral characterization for all compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00800.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

A.Z. gratefully acknowledges Jiangsu University for financial support (1281290006).

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DOI: 10.1021/acs.joc.5b00800
J. Org. Chem. 2015, 80, 7251−7257