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One-pot synthesis of 2-aryl-3-alkoxycarbonyl chromones through a cascade Lewis acid-catalyzed aldehyde olefination/oxa-Michael addition/oxidation



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Ningning Wang, Shuying Cai, Chao Zhou, Ping Lu*, Yanguang Wang*

Department of Chemistry, Zhejiang University, Hangzhou 310027, PR China

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1. Introduction

The olefination of aldehydes with alkynes was initially approached by photo irradiation.¹ Later on, this reaction was successfully catalyzed by various Lewis acid, such as TiCl₄, ² BF₃·Et₂O,^{3,4} SbF₅,⁵ MgBr₂·Et₂O,⁶ In(OTf)₃,⁷ Yb(OTf)₃,⁸ AgSbF₆,⁹ and AuCl₃/AgSbF₆.¹⁰ The reaction undergoes a [2+2] cycloaddition to form oxetene intermediates, followed by a ring-opening. Some stable oxetenes have been indicated by isolation.¹¹ The reaction stereoselectivity depends upon the ringopening, which could be regulated by torquoselectivity.^{12–14} In some cases, stereoselectivity was effectively controlled by existing heteroatoms.^{15,16} Alkynes used in aldehyde olefination possessed electronrich triple bonds, such as alkyl aryl alkyne, ynol ethers, ynamines,^{17–19} siloxyalkynes,²⁰ and lithium ynolate.^{13,21,22} To the best of our knowledge, the electron-withdrawing group substituted alkynes were seldom reported for aldehyde olefinations.

4*H*-Chromen-4-one and its derivatives exist in nature and exhibit various bioactivities, such as inhibitory effect on hepatitis B virus (HBV) in vitro without apparent cytotoxicity,²³ radical-scavenging activity,²⁴ and strong affinity to heavy metal ions.²⁵ Chromones were also designed and synthesized as selective adenosine receptor ligands (AR ligands) for cancer therapy,²⁶ as potent cathepsin V inhibitor for the treatment of atherosclerosis.²⁷ Due to the importance

ABSTRACT

2-Aryl-3-alkoxycarbonyl chromones were effectively constructed from aryl aldehydes and 3-(2-(methoxymethoxy)phenyl)propiolates via a cascade Lewis acid catalyzed phenol ether deprotection/aldehyde olefination/intramolecular oxa-Michael addition reaction, and a sequential oxidation. This four-step reaction could be conducted in one-pot with high atom efficiency.

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of 4H-chromen-4-ones, lots of works had been focused on their preparations. By disconnecting the pyran ring, several disconnections were possible (Scheme 1). Synthesis of 4H-chromen-4-ones based on these disconnections had been approached. For instance, Lewis acid induced oxa-Michael addition on alkynones/alkenones provided chromone skeleton with high efficiency and broad diversity (Scheme 1, route a).^{27–30} An alternative method to make C–O bond would be transition-metal-catalyzed O-olefination, which was demonstrated by the Ni-catalyzed cycloaddition of salicylic acid ketals to alkynes (Scheme 1, route a+d).³¹ Cu-catalyzed Ullmann-type intermolecular O-arylations could also effectively construct chromone skeleton (Scheme 1, route b).³² As a significant improvement, this strategy was approached in absence of transition-metal.³³ Although Wittig reaction made the route c in Scheme 1 possible, it was seldom used.³⁴ Finally, a three-component Pd-catalyzed carbonylative annulation afforded chromones with a rapid increment in molecular complexity (Scheme 1, route d+e).^{35–37} Besides of these novel approaches, reaction between 2,3-allenoic acids and benzynes also produced chromone derivatives with a broad substrate diversity due to the substituent-loading in 2,3-allenoic acids (Scheme 1, route b+e).³⁸

Recently, we discovered an iodine mediated reaction between 3-(2-hydroxy-phenyl)propiolates and *N*,*N*-dimethylformamide (DMF), which furnished chromone skeleton with an elimination of dimethylamine.³⁹ Encouraged by these results, we were interested in the reaction between 3-(2-hydroxy-phenyl)propiolates with aldehydes, leading to the formation of 2-aryl-3-alkoxycarbonyl chromones. Herein, we would like to report the results of this effort.



^{*} Corresponding authors. Tel./fax: +86 571 87951512; e-mail addresses: pinglu@ zju.edu.cn (P. Lu), orgwyg@zju.edu.cn (Y. Wang).

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Scheme 1. Synthetic strategies leading to 4H-chromen-4-ones.

2. Results and discussion

We firstly tested the reaction between methyl 3-(2-hydroxyphenyl)propiolate (**1a**) and 4-methylbenzaldehyde (**2a**) in the presence of BF₃·OEt₂ (Table 1). Fortunately, methyl 4-hydroxy-2-*p*-tolyl-2*H*-chromene-3-carboxylate (**3a**) was obtained and its structure was established by the single crystal analysis (Fig. 1).⁴⁰

Table 1

Screening the reaction conditions for the formation of **3a**^a



Entry	Catalyst	Solvent	Temp (°C)	Yield (%) ^b
1	BF ₃ ·Et ₂ O	DCE	50	74
2	I ₂	DCE	50	N.R.
3	AgOTf	DCE	50	N.D.
4	In(OTf) ₃	DCE	50	17
5	$BF_3 \cdot Et_2O$	DCM	50	53
6	$BF_3 \cdot Et_2O$	MeCN	50	Trace
7	$BF_3 \cdot Et_2O$	THF	50	N.R.
8	$BF_3 \cdot Et_2O$	Toluene	50	N.D.
9	$BF_3 \cdot Et_2O$	DCE	rt	64
10	$BF_3 \cdot Et_2O$	DCE	80	55

^a The reaction was conducted with **1a** (1 mmol), **2a** (1 mmol), and Lewis acid (1 mmol) in 10 mL of solvent for 12 h.

^b Isolated yield.

Delighted by this result, we optimized reaction conditions for this transformation. The results are listed in Table 1. Among all the catalysts tested in the solvent of DCE at 50 °C for 12 h (Table 1, entries 1–4), BF₃·OEt₂ performed the best, with a respective yield of **3a** in 74%. When I₂ was utilized as catalyst, there was no significant change in the amount of starting materials, **1a** and **2a**. In the case of AgOTf, we observed a decreased amount of **1a** and **2a**, while **3a** was not detected. When using BF₃·OEt₂ as the catalyst at 50 °C, DCE turned out to be the most suitable solvent as compared to DCM, MeCN, THF, and toluene (Table 1, entries 5–8). In THF environment, no reaction was detected between **1a** and **2a**. When toluene was adapted, the amount of **1a** and **2a** decreased with untraceable **3a** present. We also carried out the reaction at room



Fig. 1. Single crystal structure of 3a.

temperature (Table 1, entry 9) and 80 °C (Table 1, entry 10) and obtained lower yields. Extending reaction time to 15 h or shortening to 9 h also led to a decreased yield. Thus, we determined the optimized reaction conditions to be utilizing $BF_3 \cdot OEt_2$ as catalyst, in solvent of DCE and at 50 °C for 12 h (Table 1, entry 1).

With the optimal reaction conditions in hand, we examined the substrate diversity for this transformation. The results are summarized in Table 2. Electronic effect of substituents on the phenyl ring of aryl aldehyde was observed. The strong electron-donating group (Table 2, entries 3 and 4) or strong electron-withdrawing group substituted substrates (Table 2, entry 8) gave relatively lower yields of the corresponding products than those with moderate electron-donating (Table 2, entry 1) and moderate electron-withdrawing groups (Table 2, entry 5–7). Compounds **1b** (Table 2, entry 9) and **1c** (Table 2, entry 10), modified with methyl or chloro group on the aromatic ring of 3-(2-hydroxyphenyl)propiolates, afforded the corresponding **3i** and **3j** in 58% and 52% yields, respectively. It should be indicated that the products were isolated as a mixture of enols **3** and its tautomers **3'** in most cases. The tautomerism made the NMR spectra of **3** more complicated.



Preparation of **3** from 3-(2-hydroxyphenyl)propiolates **1**^a



 a The reaction was conducted with 1 (1 mmol), 2 (1 mmol), and $BF_3\cdot Et_2O$ (1 mmol) in 10 mL of DCE at 50 °C for 12 h.

' Isolated yield.

Methyl 3-(2-hydroxyphenyl)propiolates **1** were prepared from methyl 3-(2-(methoxymethoxy)phenyl)propiolates **4** in the presence of acid as we previously reported.³⁹ We, therefore, integrated the Lewis acid-catalyzed conversion from **4** into **1**, the Lewis acid-catalyzed aldehyde olefination, the intramolecular oxa-Michael addition, and the DDQ oxidation into one-pot to get chromones **5** (Scheme 2). Under the optimized reaction conditions, **4a**, **2a**, and



BF₃·Et₂O were mixed in DCE and reacted at 50 °C for 16 h to afford 3a in 70% isolated yield. Without purification, the resulting 3a could be converted into 5a via a one-pot oxidation with DDQ in 1,4dioxane (Table 3, entry 1). In this way, chromones 5a-m were synthesized in 25-52% vields. In some cases, although the oxidations from **3** to **5** were carried out for 48 h. we still observed unreacted **3** by TLC tracking. The unsubstituted benzaldehyde **2b** furnished 5b in 52% yield (Table 3, entry 2). With electron withdrawing-group on the phenyl ring of aldehyde, compounds **2e**–**h** afforded the corresponding products **5c**–**f** in yields ranging from 31 to 38% (Table 3, entries 3-6). However, the strong electrondonating group substituted 2c just afforded 3c in 48% yield although the oxidation step had been applied in refluxing 1,4dioxane for 48 h. For the cases of 2d and 2n, both of them possessing electron-rich aromatic system, the dearomatized product 5n was isolated in 22% and 20%, respectively (Scheme 3). A retro Friedel-Crafts alkylation might occur during the oxidation process because the electron-rich aromatic ring was able to be protonated. Furthermore, when picolinaldehyde (20) was used, methyl benzofuran-2-carboxylate (6) was obtained in 30% yield (Scheme 4). Picolinaldehyde did not participate in the reaction and methyl benzofuran-2-carboxylate came from the Lewis acid catalyzed selfcyclization of 4a.

Table 3

One-pot synthesis of 5 from methyl 3-(2-(methoxymethoxy) phenyl)-propiolates 4ª

Entry	4 (R ¹)	2 (R ²)	Yield of 5 (%) ^b
1 ^c	4a (H)	2a (4-MeC ₆ H ₄)	5a /32
2 ^c	4a	2b (C ₆ H ₅)	5b /52
3	4a	2e (4-FC ₆ H ₄)	5c /38
4	4a	2f $(4-ClC_6H_4)$	5d /35
5	4a	2g $(4-ClC_6H_4)$	5e /31
6	4a	2h $(4-NO_2C_6H_4)$	5f /33
7	4a	2i (2-ClC ₆ H ₄)	5g /32
8	4a	2j (3-ClC ₆ H ₄)	5h /30
9	4a	2k $(4-IC_6H_4)$	5i /25
10	4a	21 (2-CF ₃ C ₆ H ₄)	5j /31
11 ^c	4a	2m (2-naphthlenyl)	5k /30
12 ^c	4b (Me)	2b	51 /37
13 ^c	4c (Cl)	2b	5m /41

^a Reactions were conducted with **4** (1 mmol), **2** (1 mmol), and BF₃·Et₂O (1 mmol) in 10 mL of DCE at 50 °C for 16 h. After removal of DCE, DDQ (1.3 mmol) in 1,4-dioxane (10 mL) was added and refluxed for 48 h.

^b Isolated yield based on **4**.

^c **4** and **2** reacted for 12 h, oxidation of **3** lasted for 36 h.

Based on above observations, we proposed a possible mechanism for this cascade process as indicated in Scheme 5. Firstly, phenol ether **4a** undergoes the Lewis acid catalyzed deprotection to yield phenol **1a**. Secondly, the Lewis acid catalyzed formal [2+2] cycloaddition of **2** with either **4a** or **1a** generates the oxetene intermediate **A** or **B**, which undergoes a ring-opening to form α , β -unsaturated ketone **C** or **D**, respectively. Subsequent intramolecular oxa-Michael addition of **C** or **D** leads to the formation of **3**. Finally, **3** is oxidized by



Scheme 3. Formation of 5n from 2d or 2n.



Scheme 4. Formation of benzofuran 6.



Scheme 5. Possible mechanism for the cascade formation of 5.

DDQ into **5**. When the aryl group in **3** is electron-rich, a retro Friedel–Crafts alkylation occurs to give **5n** as the final product.

3. Conclusions

In conclusion, we developed a one-pot cascade method for the construction of 2-aryl-3-alkoxycarbonyl chromones. The process

involves a Lewis acid catalyzed deprotection of phenol ether, a Lewis acid catalyzed olefination of aldehyde with alkyne, an intramolecular oxa-Michael addition, and a DDQ oxidation. The present four-step reaction could be conducted in one-pot with high atom efficiency.

4. Experimental section

4.1. General

Infrared spectra were obtained on a FTIR spectrometer. Flash column chromatography was performed employing 200–300 mesh silica gel. NMR spectra were recorded on 400 MHz or 500 MHz for ¹H NMR and at 100 MHz or 125 MHz for ¹³C NMR in CDCl₃. Chemical shifts were reported in parts per million with either TMS or residual solvent as an internal standard. The following abbreviations are used to describe peak patterns where appropriate: b=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. Coupling constants are reported in Hertz (Hz). High-resolution mass spectra (HRMS) were recorded by EI ionization. Melting points were measured with micro melting point apparatus.

4.2. Typical procedure for the synthesis of 3a

To a solution of **1a** (0.22 g, 1 mmol) and **2a** (0.12 g, 1 mmol) in DCE (10 mL) was added dropwise a solution of boron trifluoride etherate (1 mmol) in DCE (10 mL) at 0 °C under N₂ atmosphere. The reaction mixture was stirred at 50 °C for 12 h. Then, the reaction was quenched with water (1 mL) and the mixture was washed with brine solution (10 mL), dried over anhydrous MgSO₄, and then concentrated under vacuum. The crude product was purified by silica gel column (hexane/ethyl acetate as eluent).

4.2.1. Methyl 4-hydroxy-2-(p-tolyl)-2H-chromene-3-carboxylate (**3a**) and its ketone form **3a**'. Compound **3a**'/**3a**=1/0.55 in CDCl₃; white solid, mp 111–112 °C; yield 74% (0.22 g); IR (cm⁻¹) ν_{max} 2920, 2853, 1738, 1691, 1459, 1145, 811, 761; ¹H NMR (500 MHz, CDCl₃) δ 12.26 (s, 0.55H), 7.95 (d, *J*=7.9 Hz, 1H), 7.68 (d, *J*=7.7 Hz, 0.55H), 7.53 (dd, *J*=11.3, 4.3 Hz, 1H), 7.37 (d, *J*=7.9 Hz, 2H), 7.26 (s, 1H), 7.24–7.20 (m, 2.75H), 7.07 (dd, *J*=7.4, 4.5 Hz, 2H), 7.03 (d, *J*=8.4 Hz, 1H), 6.94 (t, *J*=7.5 Hz, 0.55H), 6.78 (d, *J*=8.2 Hz, 0.55H), 6.21 (s, 0.55H), 5.66 (d, *J*=12.2 Hz, 1H), 4.10 (d, *J*=12.2 Hz, 1H), 3.75 (s, 1.65H), 3.64 (s, 3H), 2.37 (s, 3H), 2.28 (s, 1.65H); ¹³C NMR (125 MHz, CDCl₃) δ 188.2, 167.9, 161.5, 156.1, 139.7, 138.6, 137.5, 137.0, 134.0, 133.7, 129.9, 129.7, 129.4, 127.8, 127.5, 125.8, 124.8, 122.3, 121.5, 120.2, 118.5, 118.2, 117.6, 94.6, 81.4, 74.9, 60.0, 52.7, 52.2, 21.6, 21.5; HRMS (EI): calcd for C₁₈H₁₆O₄ (M⁺): 296.1049, found 296.1055.

4.2.2. Methyl 4-hydroxy-2-phenyl-2H-chromene-3-carboxylate (**3b**) and its ketone form **3b**'. Compound **3b**'/**3b**=1/0.8 in CDCl₃; pink solid, mp 107–109 °C; yield 56% (0.16 g); IR (cm⁻¹) ν_{max} 2920, 1730, 1682, 1645, 1442, 1304, 1030, 762; ¹H NMR (500 MHz, CDCl₃) δ 12.28 (s, 0.8H), 7.95 (dd, *J*=7.9, 1.4 Hz, 1H), 7.68 (dd, *J*=7.7, 1.3 Hz, 0.8H), 7.55–7.51 (m, 1H), 7.49 (dd, *J*=7.6, 1.5 Hz, 2H), 7.40 (t, *J*=6.2 Hz, 3.2H), 7.36 (dd, *J*=7.7, 1.2 Hz, 1.6H), 7.30–7.23 (m, 3H), 7.08 (t, *J*=7.5 Hz, 1H), 7.03 (d, *J*=8.3 Hz, 1H), 6.94 (t, *J*=7.5 Hz, 0.8H), 6.25 (s, 0.8H), 5.70 (d, *J*=12.2 Hz, 1H), 4.10 (d, *J*=12.2 Hz, 1H), 3.75 (s, 2.4H), 3.63 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 188.0, 167.8, 161.4, 156.1, 140.4, 137.1, 136.9, 133.7, 129.8, 129.2, 129.0, 128.7, 128.7, 127.8, 127.5, 125.8, 124.8, 122.4, 121.6, 120.2, 118.5, 118.1, 117.5, 94.5, 81.5, 60.1, 52.7, 52.2; HRMS (EI): calcd for C₁₇H₁₄O₄ (M⁺): 282.0892, found 282.0887.

4.2.3. Methyl 4-hydroxy-2-(4-methoxyphenyl)-2H-chromene-3carboxylate (**3c**) and its ketone form **3c**'. Compound **3c**'/**3c**=1/0.5 in CDCl₃; white solid, mp 108–109 °C; yield 50% (0.16 g); IR (cm⁻¹) $ν_{max}$ 2954, 1745, 1691, 1609, 1465, 1255, 1031, 830; ¹H NMR (500 MHz, CDCl₃) δ 12.27 (s, 0.5H), 7.95 (dd, *J*=7.9, 1.7 Hz, 1H), 7.68 (dd, *J*=7.7, 1.7 Hz, 0.5H), 7.53 (ddd, *J*=8.8, 7.2, 1.7 Hz, 1H), 7.44–7.40 (m, 2H), 7.30–7.23 (m, 1.5H), 7.11–7.05 (m, 1H), 7.02 (dd, *J*=8.4, 1.0 Hz, 1H), 6.94 (m, 2.5H), 6.81–6.75 (m, 1.5H), 6.20 (s, 0.5H), 5.64 (d, *J*=12.4 Hz, 1H), 4.10 (d, *J*=12.4 Hz, 1H), 3.83 (s, 3H), 3.75 (s, 3H), 3.65 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 188.0, 167.7, 161.3, 160.5, 159.8, 155.8, 136.8, 133.5, 132.3, 128.8, 128.8, 128.7, 127.6, 127.1, 124.5, 122.1, 121.3, 120.0, 118.3, 117.9, 117.4, 114.3, 113.8, 94.5, 81.0, 74.5, 59.8, 55.5, 55.3, 52.6, 52.0; HRMS (EI): calcd for C₁₈H₁₆O₅ (M⁺): 312.0998, found 312.0999.

4.2.4. Methyl 2-(4-(dimethylamino)phenyl)-4-hydroxy-2H-chromene-3-carboxylate (3d) and its ketone form 3d'. Compound 3d' **3d**=1/0.15 in CDCl₃; yellow solid, mp 136–137 °C; yield 46% (0.15 g); IR (cm⁻¹) *v*_{max} 2904, 1738, 1686, 1605, 1145, 989, 816, 777; ¹H NMR (500 MHz, CDCl₃) δ 12.27 (s, 0.15H), 7.94 (dd, *J*=7.9, 1.6 Hz, 1H), 7.68 (dd, J=7.8, 1.5 Hz, 0.15H), 7.51 (ddd, J=8.6, 7.3, 1.7 Hz, 1H), 7.36-7.31 (m, 2H), 7.24-7.20 (m, 0.45H), 7.08-7.03 (m, 1H), 7.01 (d, J=8.3 Hz, 1H), 6.95–6.90 (m, 0.15H), 6.75 (d, J=7.7 Hz, 0.15H), 6.71 (t, J=5.8 Hz, 2H), 6.60 (d, J=8.8 Hz, 0.30H), 6.17 (s, 0.15H), 5.58 (d, J=12.4 Hz, 1H), 4.14 (d, J=12.4 Hz, 1H), 3.73 (s, 0.45H), 3.64 (s, 3H), 2.97 (s, 6H), 2.90 (s, 0.90H); ¹³C NMR (125 MHz, CDCl₃) δ 188.7, 168.0, 161.7, 156.1, 151.5, 150.8, 136.9, 133.5, 128.7, 127.8, 126.7, 124.6, 123.9, 122.0, 121.3, 120.3, 120.1, 118.5, 118.3, 117.6, 112.5, 112.2, 94.8, 81.6, 75.0, 59.8, 52.7, 52.1, 40.7; HRMS (EI): calcd for C19H19O4N (M⁺): 325.1314, found 325.1318.

4.2.5. Methyl 2-(4-fluorophenyl)-4-hydroxy-2H-chromene-3carboxylate (3e) and its ketone form 3e'. Compound 3e'/3e=1/1 in CDCl₃; white solid, mp 94–95 °C; yield 61% (0.18 g); IR (cm⁻¹) ν_{max} 2956, 1682, 1605, 1223, 1151, 1000, 833, 766; ¹H NMR (500 MHz, CDCl₃) δ 12.27 (s, 1H), 7.95 (dd, *J*=7.9, 1.4 Hz, 1H), 7.68 (dd, *J*=7.8, 1.3 Hz, 1H), 7.58–7.51 (m, 1H), 7.49 (dd, J=8.6, 5.3 Hz, 2H), 7.33 (dd, J=8.5, 5.4 Hz, 2H), 7.28 (dd, J=7.8, 1.0 Hz, 1H), 7.14–7.07 (m, 3H), 7.03 (d, J=8.4 Hz, 1H), 6.99–6.92 (m, 3H), 6.78 (d, J=8.2 Hz, 1H), 6.21 (s, 1H), 5.68 (d, J=12.3 Hz, 1H), 4.06 (d, J=12.3 Hz, 1H), 3.76 (d, J=4.3 Hz, 3H), 3.65 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 187.8, 170.8, 167.7, 163.5 (d, J=247 Hz), 163.4, 163.0 (d, J=245.5 Hz), 161.3, 155.8, 137.2, 136.2 (J=3 Hz), 133.8, 132.9 (d, J=3 Hz), 129.5 (d, J=8 Hz), 129.3 (d, J=8 Hz), 127.9, 124.8, 122.5, 121.8, 120.2, 118.4, 118.0, 117.6, 116.2 (d, J=22 Hz), 115.6 (d, J=22 Hz), 94.4, 80.8, 74.3, 60.2, 52.8, 52.2; HRMS (EI): calcd for C₁₇H₁₃O₄F (M⁺): 300.0798, found 300.0796.

4.2.6. Methyl 2-(4-chlorophenyl)-4-hydroxy-2H-chromene-3carboxylate (**3f**) and its ketone form **3f**. Compound **3f**'/**3f**=0.40/1 in CDCl₃; white solid, mp 120–121 °C; yield 73% (0.23 g); IR (cm⁻¹) ν_{max} 2953, 1653, 1627, 1439, 1258, 1090, 805, 762; ¹H NMR (500 MHz, CDCl₃) δ 12.26 (s, 1H), 7.95 (dd, *J*=7.9, 1.6 Hz, 0.4H), 7.68 (dd, *J*=7.8, 1.5 Hz, 1H), 7.54 (dd, *J*=11.3, 4.3 Hz, 0.4H), 7.47–7.35 (m, 2H), 7.29 (dd, *J*=7.6, 5.9 Hz, 2.6H), 7.27–7.21 (m, 2H), 7.08 (d, *J*=7.8 Hz, 0.4H), 7.03 (d, *J*=8.3 Hz, 0.4H), 6.95 (dd, *J*=11.0, 4.1 Hz, 1H), 6.78 (d, *J*=8.2 Hz, 1H), 6.20 (s, 1H), 5.68 (d, *J*=12.3 Hz, 0.4H), 4.04 (d, *J*=12.2 Hz, 0.4H), 3.76 (s, 3H), 3.66 (s, 1.2H); ¹³C NMR (125 MHz, CDCl₃) δ 187.6, 170.8, 167.7, 163.5, 161.2, 155.8, 138.9, 137.2, 135.7, 135.5, 134.6, 133.9, 129.4, 129.2, 128.9, 127.9, 127.3, 124.9, 122.6, 121.9, 120.1, 118.4, 118.0, 117.6, 94.2, 80.9, 74.3, 60.0, 52.9, 52.2; HRMS (EI): calcd for C₁₇H₁₃O₄Cl (M⁺): 316.0502, found 316.0499.

4.2.7. Methyl 2-(4-bromophenyl)-4-hydroxy-2H-chromene-3carboxylate (**3g**) and its ketone form **3g**'. Compound **3g**'/**3g**=0/1 in CDCl₃; pink solid, mp 139–141 °C; yield 71% (0.26 g); IR (cm⁻¹) ν_{max} 2951, 1627, 1438, 1261, 1093, 1004, 804, 762; ¹H NMR (500 MHz, CDCl₃) δ 12.26 (s, 1H), 7.68 (dd, *J*=7.7, 1.5 Hz, 1H), 7.44–7.37 (m, 2H), 7.31–7.19 (m, 3H), 6.99–6.93 (m, 1H), 6.79 (d, *J*=8.1 Hz, 1H), 6.19 (s, 1H), 3.76 (s, 3H); 13 C NMR (125 MHz, CDCl₃) δ 170.8, 163.5, 155.8, 139.4, 133.9, 131.9, 129.3, 124.9, 122.8, 121.9, 118.0, 117.6, 94.1, 74.3, 52.3; HRMS (EI): calcd for C₁₇H₁₃O₄Br (M⁺): 359.9997, found 359.9998.

4.2.8. Methyl 4-hydroxy-2-(4-nitrophenyl)-2H-chromene-3carboxylate (**3h**) and its ketone form **3h**'. Compound **3h**'/**3h**=0.38/ 1 in CDCl₃; white solid, mp 43–44 °C; yield 46% (0.15 g); IR (cm⁻¹) ν_{max} 2955, 1744, 1656, 1522, 1346, 1264, 764, 730; ¹H NMR (500 MHz, CDCl₃) δ 12.30 (s, 1H), 8.29 (d, *J*=8.7 Hz, 0.76H), 8.14 (d, *J*=8.7 Hz, 2H), 7.97 (dd, *J*=8.0, 1.7 Hz, 0.38H), 7.70 (td, *J*=5.9, 5.5, 3.1 Hz, 1.76H), 7.58 (ddd, *J*=8.7, 7.3, 1.8 Hz, 0.38H), 7.54 (d, *J*=8.7 Hz, 2H), 7.35–7.28 (m, 1H), 7.14 (t, *J*=7.6 Hz, 0.38H), 7.06 (d, *J*=8.3 Hz, 0.38H), 7.00 (t, *J*=7.5 Hz, 1H), 6.84 (d, *J*=8.2 Hz, 1H), 6.31 (s, 1H), 5.83 (d, *J*=12.2 Hz, 0.38H), 4.04 (d, *J*=12.2 Hz, 0.38H), 3.80 (s, 3H), 3.68 (s, 1.14H); ¹³C NMR (125 MHz, CDCl₃) δ 186.6, 170.3, 167.2, 163.6, 160.6, 155.4, 148.5, 147.9, 147.3, 143.7, 137.2, 134.0, 128.3, 128.1, 127.8, 124.9, 124.2, 123.8, 122.7, 122.1, 119.9, 118.2, 117.6, 117.3, 93.5, 80.1, 73.7, 59.8, 52.9, 52.2; HRMS (EI): calcd for C₁₇H₁₃O₆N (M⁺): 327.0743, found 327.0745.

4.2.9. Methyl 4-hydroxy-6-methyl-2-(p-tolyl)-2H-chromene-3carboxylate (**3i**). White solid, mp 110–112 °C; yield 58% (0.18 g); IR (cm⁻¹) ν_{max} 2910, 1747, 1680, 1515, 1254, 1215, 1000, 828; ¹H NMR (500 MHz, CDCl₃) δ 7.72 (d, *J*=1.6 Hz, 1H), 7.36 (d, *J*=8.1 Hz, 2H), 7.33 (d, *J*=8.5 Hz, 1H), 7.21 (d, *J*=7.9 Hz, 2H), 6.92 (d, *J*=8.4 Hz, 1H), 5.62 (d, *J*=12.2 Hz, 1H), 4.07 (d, *J*=12.2 Hz, 1H), 3.64 (s, 3H), 2.36 (s, 3H), 2.33 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 188.1, 167.8, 159.4, 139.4, 137.9, 133.8, 131.6, 129.6, 127.2, 127.1, 119.6, 118.0, 81.2, 59.8, 52.5, 21.4, 20.6; HRMS (EI): calcd for C₁₉H₁₈O₄ (M⁺): 310.1205, found 310.1201.

4.2.10. Methyl 6-chloro-4-hydroxy-2-(p-tolyl)-2H-chromene-3carboxylate (**3***j*) and its ketone form **3***j*'. Compound **3***j*'/**3***j*=0.85/1 in CDCl₃; yellow solid, mp 97–98 °C; yield 52% (0.17 g); IR (cm⁻¹) ν_{max} 2951, 1655, 1632, 1513, 1260, 1107, 859, 814; ¹H NMR (500 MHz, CDCl₃) δ 12.21 (s, 1H), 7.89 (d, *J*=2.6 Hz, 0.85H), 7.64 (d, *J*=2.6 Hz, 1H), 7.46 (dd, *J*=8.8, 2.7 Hz, 0.85H), 7.35 (d, *J*=8.0 Hz, 1.70H), 7.22 (d, *J*=6.6 Hz, 3.70H), 7.18 (dd, *J*=8.7, 2.6 Hz, 1H), 7.09 (d, *J*=8.1 Hz, 2H), 6.98 (d, *J*=8.8 Hz, 0.85H), 6.71 (d, *J*=8.7 Hz, 1H), 6.21 (s, 1H), 5.65 (d, *J*=12.0 Hz, 0.85H), 4.08 (d, *J*=12.1 Hz, 0.85H), 3.75 (s, 3H), 3.64 (s, 2.55H), 2.37 (s, 2.55H), 2.29 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 186.9, 170.5, 167.3, 161.7, 159.7, 154.3, 139.7, 138.7, 136.7, 136.7, 133.3, 133.1, 129.7, 129.3, 127.7, 127.3, 127.2, 126.8, 126.5, 124.2, 120.8, 120.0, 119.1, 118.8, 95.1, 81.4, 74.9, 59.3, 52.7, 52.1, 21.4, 21.3; HRMS (EI): calcd for C₁₈H₁₅O₄Cl (M⁺): 330.0659, found 330.0659.

4.3. Typical procedure for the synthesis of 5

To a solution of **4a** (0.22 g, 1 mmol) and **2a** (0.12 g, 1 mmol) in DCE (10 mL) was added dropwise a solution of boron trifluoride etherate (10 mmol) in DCE (10 mL) at 0 °C under N₂ atmosphere. The reaction mixture was stirred at 50 °C for 16 h. After quenched with water (1 mL), the reaction mixture was washed with brine solution (10 mL), dried over anhydrous MgSO₄, and concentrated under vacuum. The residue was dissolved in 1,4-dioxane (10 mL). DDQ (0.30 g, 1.3 mmol) was added and the solution was refluxed for 48 h. Water (20 mL) was added and the mixture was washed with EtOAc (20 mL×3). The combined organic layer was washed with water and brine solution, dried over anhydrous MgSO₄, and then concentrated under vacuum. The residue was purified by silica gel column with hexane/ethyl acetate as eluent.

4.3.1. Methyl 4-oxo-2-(p-tolyl)-4H-chromene-3-carboxylate (**5a**). Yellow solid, mp 107–111 °C; yield 32% (95 mg); ¹H NMR (400 MHz, CDCl₃) δ 8.25 (dd, *J*=8.0, 1.5 Hz, 1H), 7.74–7.67 (m, 1H),

7.64 (d, *J*=8.2 Hz, 2H), 7.51 (d, *J*=8.4 Hz, 1H), 7.43 (dd, *J*=11.2, 3.9 Hz, 1H), 7.30 (d, *J*=8.1 Hz, 2H), 3.81 (s, 3H), 2.43 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 175.3, 166.2, 163.5, 156.1, 142.7, 134.6, 129.9, 129.3, 128.2, 126.3, 125.9, 123.3, 118.3, 117.9, 53.1, 21.9; HRMS (EI): calcd for C₁₈H₁₄O₄ (M⁺): 294.0892, found 294.0890.

4.3.2. *Methyl* 4-oxo-2-*phenyl*-4*H*-*chromene*-3-*carboxylate* (**5b**). Yellow solid, mp 76–80 °C; yield 52% (146 mg); ¹H NMR (400 MHz, CDCl₃) δ 8.27 (dd, *J*=7.9, 1.2 Hz, 1H), 7.78–7.69 (m, 3H), 7.53 (ddd, *J*=14.6, 10.0, 4.7 Hz, 4H), 7.46 (t, *J*=7.5 Hz, 1H), 3.79 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 175.3, 165.9, 163.4, 156.1, 134.7, 132.2, 132.0, 129.1, 128.2, 126.3, 126.0, 123.3, 118.4, 118.3, 53.1; HRMS (EI): calcd for C₁₇H₁₂O₄ (M⁺): 280.0736, found 280.0731.

4.3.3. *Methyl* 2-(4-fluorophenyl)-4-oxo-4H-chromene-3-carboxylate (**5c**). Yellow solid, mp 94–96 °C; yield 38% (113 mg); ¹H NMR (400 MHz, CDCl₃) δ 8.22 (d, *J*=7.9 Hz, 1H), 7.75–7.64 (m, 3H), 7.51–7.40 (m, 4H), 3.79 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 175.2, 165.9, 164.9 (d, *J*=254 Hz), 162.3, 156.1, 134.8, 130.7 (d, *J*=9 Hz), 128.38, 128.35, 126.4 (d, *J*=30 Hz), 123.3, 118.3, 116.6, 116.4, 53.2; HRMS (EI): calcd for C₁₇H₁₁FO₄ (M⁺): 298.0641, found 298.0642.

4.3.4. *Methyl* 2-(4-chlorophenyl)-4-oxo-4H-chromene-3-carboxylate (**5d**). Yellow solid, mp 99–103 °C; yield 35% (110 mg); ¹H NMR (400 MHz, CDCl₃) δ 8.26 (d, *J*=7.9 Hz, 1H), 7.81–7.70 (m, 3H), 7.52 (d, *J*=8.4 Hz, 1H), 7.46 (t, *J*=7.5 Hz, 1H), 7.21 (t, *J*=8.6 Hz, 2H), 3.81 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 174.9, 165.5, 161.9, 155.7, 138.1, 134.6, 130.3, 129.4, 129.3, 128.5, 126.1, 125.9, 123.0, 118.1, 53.0; HRMS (EI): calcd for C₁₇H₁₁ClO₄ (M⁺): 314.0346, found 314.0349.

4.3.5. *Methyl* 2-(4-bromophenyl)-4-oxo-4H-chromene-3-carboxylate (**5e**). Yellow solid, mp 121–123 °C; yield 31% (111 mg); ¹H NMR (400 MHz, CDCl₃) δ 8.24 (d, *J*=7.9 Hz, 1H), 7.73 (t, *J*=7.8 Hz, 1H), 7.63 (q, *J*=8.5 Hz, 4H), 7.52 (d, *J*=8.4 Hz, 1H), 7.45 (t, *J*=7.6 Hz, 1H), 3.81 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 175.1, 165.7, 162.2, 156.0, 134.8, 132.5, 131.0, 129.8, 126.8, 126.4, 126.2, 123.3, 118.4, 118.3, 53.2; HRMS (EI): calcd for C₁₇H₁₁BrO₄ (M⁺): 357.9841, found 357.9838.

4.3.6. Methyl 2-(4-nitrophenyl)-4-oxo-4H-chromene-3-carboxylate (**5f**). Yellow solid, mp 150–152 °C; yield 33% (107 mg); ¹H NMR (400 MHz, CDCl₃) δ 8.38 (d, *J*=8.7 Hz, 2H), 8.28 (d, *J*=9.0 Hz, 1H), 7.94 (d, *J*=8.6 Hz, 2H), 7.78 (t, *J*=8.5 Hz, 1H), 7.56 (d, *J*=8.4 Hz, 1H), 7.53–7.47 (m, 1H), 3.82 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 175.1, 165.7, 162.2, 156.0, 134.8, 132.5, 131.0, 129.8, 126.8, 126.4, 126.2, 123.3, 118.4, 118.3, 53.2; HRMS (EI): calcd for C₁₇H₁₁NO₆ (M⁺): 325.0586, found 325.0590.

4.3.7. *Methyl* 2-(2-chlorophenyl)-4-oxo-4H-chromene-3-carboxylate (**5g**). Yellow solid, mp 94–96 °C; yield 32% (100 mg); ¹H NMR (500 MHz, CDCl₃) δ 8.29 (dd, *J*=7.9, 1.1 Hz, 1H), 7.76–7.69 (m, 1H), 7.56–7.45 (m, 5H), 7.39 (td, *J*=7.5, 1.1 Hz, 1H), 3.68 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 174.8, 164.7, 163.6, 156.2, 134.8, 133.5, 132.4, 131.8, 130.7, 130.4, 127.1, 126.6, 126.3, 123.9, 120.0, 118.5, 52.9. HRMS (El): calcd for C₁₇H₁₁ClO₄ (M⁺): 314.0346, found 314.0339.

4.3.8. *Methyl* 2-(3-chlorophenyl)-4-oxo-4H-chromene-3-carboxylate (**5h**). Yellow solid, mp 90–93 °C; yield 30% (95 mg); ¹H NMR (400 MHz, CDCl₃) δ 8.26 (d, *J*=7.9 Hz, 1H), 7.78–7.71 (m, 2H), 7.61 (d, *J*=7.7 Hz, 1H), 7.54 (d, *J*=8.6 Hz, 2H), 7.46 (q, *J*=7.5 Hz, 2H), 3.82 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 175.1, 165.6, 161.7, 156.0, 135.3, 134.9, 133.8, 132.0, 130.5, 128.4, 126.5, 126.5, 126.3, 123.4, 118.8, 118.4, 53.2; HRMS (EI): calcd for C₁₇H₁₁ClO₄ (M⁺): 314.0346, found 314.0351.

4.3.9. Methyl 2-(4-iodophenyl)-4-oxo-4H-chromene-3-carboxylate (**5i**). Yellow solid, mp 139–143 °C; yield 25% (102 mg); ¹H NMR

(400 MHz, CDCl₃) δ 8.26 (d, *J*=7.9 Hz, 1H), 7.87 (d, *J*=8.4 Hz, 2H), 7.74 (t, *I*=7.7 Hz, 1H), 7.52 (d, *I*=8.4 Hz, 1H), 7.47 (m, 3H), 3.82 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 175.2, 165.8, 162.4, 156.1, 138.5, 134.8, 131.7, 129.8, 126.6, 126.2, 123.5, 118.6, 118.4, 99.1, 53.3; HRMS (EI): calcd for C₁₇H₁₁IO₄ (M⁺): 405.9702, found 405.9716.

4.3.10. Methyl 4-oxo-2-(2-(trifluoromethyl)phenyl)-4H-chromene-3carboxylate (5j). Yellow solid; mp 116–118 °C; yield 31% (108 mg); ¹H NMR (400 MHz, CDCl₃) δ 8.29 (dd, *J*=7.9, 1.2 Hz, 1H), 7.89-7.82 (m, 1H), 7.76-7.65 (m, 3H), 7.64-7.58 (m, 1H), 7.52-7.44 (m, 2H), 3.64 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 174.4, 164.3, 163.7, 155.7, 134.6, 131.9, 131.2, 130.6, 130.1 (q, *J*=4 Hz), 129.0 (q, *J*=32 Hz), 127.1 (q, J=5 Hz), 126.2, 126.1, 123.5, 123.4 (q, J=273 Hz), 119.1, 118.2, 52.3; HRMS (EI): calcd for C₁₈H₁₁F₃O₄ (M⁺): 348.0609, found 348.0612.

4.3.11. Methyl 2-(naphthalen-1-yl)-4-oxo-4H-chromene-3carboxylate (5k). Yellow solid, mp 164–167 °C; yield 30% (99 mg); ¹H NMR (400 MHz, CDCl₃) δ 8.35 (dd, *J*=7.9, 1.2 Hz, 1H), 8.08-8.03 (m, 1H), 7.97-7.93 (m, 1H), 7.91-7.84 (m, 1H), 7.79-7.71 (m, 2H), 7.63–7.44 (m, 5H), 3.64–3.43 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) § 175.1, 165.2, 165.1, 156.4, 134.8, 133.8, 131.9, 130.9, 129.9, 128.9, 128.1, 127.8, 127.0, 126.7, 126.3, 125.2, 125.2, 123.9, 120.9, 118.6, 52.8; HRMS (EI): calcd for C₂₁H₁₄O₄ (M⁺): 330.0892, found 330.0894.

4.3.12. Methyl 6-methyl-4-oxo-2-phenyl-4H-chromene-3carboxvlate (51). Yellow solid. mp 81–84 °C: vield 37% (109 mg): ¹H NMR (400 MHz, CDCl₃) δ 8.01 (d, *J*=15.0 Hz, 1H), 7.73 (d, *J*=7.1 Hz, 2H), 7.53 (dd, *J*=13.2, 7.5 Hz, 4H), 7.42 (d, *J*=8.5 Hz, 1H), 3.79 (s, 3H), 2.46 (s. 3H); ¹³C NMR (100 MHz, CDCl₃) δ 175.4, 166.1, 163.3, 154.4, 136.1, 135.9, 132.4, 131.9, 129.1, 128.3, 125.7, 123.1, 118.2, 118.1, 53.1, 21.3; HRMS (EI): calcd for C₁₈H₁₄O₄ (M⁺): 294.0892, found 294.0890.

4.3.13. Methyl 6-chloro-4-oxo-2-phenyl-4H-chromene-3-carboxylate (**5m**). Yellow solid, mp 102–104 °C; yield 41% (129 mg); ¹H NMR (400 MHz, CDCl₃) δ 8.21 (d, *J*=2.5 Hz, 1H), 7.73 (d, *J*=7.6 Hz, 2H), 7.67 (dd, J=8.9, 2.6 Hz, 1H), 7.59-7.47 (m, 4H), 3.79 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 174.2, 165.6, 163.8, 154.5, 134.9, 132.3, 132.1, 131.9, 129.2, 128.3, 125.8, 124.4, 120.2, 118.3, 53.2; HRMS (EI): calcd for C₁₇H₁₁ClO₄ (M⁺): 314.0346, found 314.0340.

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Supplementary data

The Supplementary data contains copies of ¹H and ¹³C NMR spectra along with other experimental details. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/ i.tet.2012.11.008.

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