有机化学 DOI: 10.6023/cjoc202205039 研究论文
Chinese Journal of Organic Chemistry ARTICLE

铑催化的邻苯二甲酸酐与环状 2-重氮-1,3-二酮和甲醇的串联 C—H 活化/跨环偶联/环化反应合成酯基官能化的并环异香豆素类化合物的研究

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摘要 报道了一种铑(III)催化的基于邻苯二价酸酐与环状 2-重氮-1,3-二酮和甲醇的串联反应构建酯基官能化环己烯酮并异香豆素衍生物的方法. 该反应经由 C—H 键活化、跨环偶联及随后的环化反应实现一个 C—C 键和两个 C—O 键的构筑. 该反应体系中无需加入任何添加剂或碱, 并能在空气氛围下很好地进行, 且具有良好的官能团容忍性和底物普适性.

关键词 环化反应; C—H 键活化; 重氮化合物; 异香豆素; 邻苯二甲酸酐

Synthesis of Esterified/Fused Isocoumarins via Rh-Catalyzed C—H Activation/Transannulative Coupling/Annulation of Phthalic Anhydrides with Cyclic 2-Diazo-1,3-diketones and Methanol

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Abstract A rhodium(III)-catalyzed cascade reaction of phthalic anhydrides with cyclic 2-diazo-1,3-diketones and methanol for modular access to esterified cyclohexenone-fused isocoumarins has been developed. This strategy involves the process of one C—C and two C—O bonds formation through C—H activation, transannulative coupling and subsequent annulation process. Furthermore, no additive and base are needed in this transformation, and interestingly, the reaction could proceed well under air atmosphere with broad substrate and good functional groups tolerance.

Keywords annulation; C—H activation; diazo compound; isocoumarin; phthalic anhydride

1 Introduction

Isocoumarins, known as a privileged class of lactones, are usually found in numerous biologically active molecules including natural products with a broad range of bioactivities such as anti-human immunodeficiency virus (HIV), antibacterial, antitumor, antiinflammatory and antidiabetic uses.[1-2] Among them, ring-fused isocoumarins are also commonly encountered as a core in natural products and pharmaceuticals and are widely used as key intermediates for the synthesis of bioimportant molecules.[3] Due to their significance, numerous synthetic approaches have been established.[4] A copper-catalyzed α-arylation of 1,3-cyclohexanedione with 2-bromobenzoic acids followed by intramolecular esterification for the synthesis of fused isocoumarins was firstly reported by McKillop group.[5] Subsequently, this methodology was further studied by the groups of Bryson,[6] Wang,[7] and Fan.[8] Recently, an impressive transition metal-free α-arylation/ring annulation and Rh-catalyzed direct C—H activation of ylides with diazo compounds have been developed for efficient access to fused isocoumarins.[9-13] Despite these approaches being efficient and reliable, developing more streamlined and

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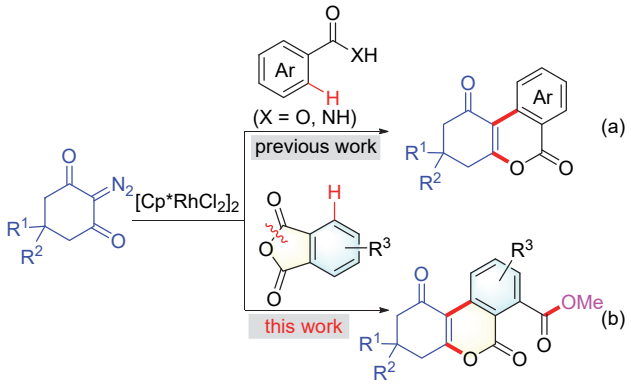
Received May 22, 2022; revised July 3, 2022; published online July 13, 2022.
Project supported by the National Natural Science Foundation of China (Nos. 21772001, 22071100) and the National Undergraduate Training Program for Innovation and Entrepreneurship (No. 202110370035).
国家自然科学基金(Nos. 21772001, 22071100)和大学生创新创业训练计划(No. 202110370035)资助项目.

practical methods from the available reagents for the synthesis of diversified isocoumarins is highly desirable.

In the past several years, transition-metal-catalyzed directing group-assisted C—H functionalization has emerged as a powerful tool in organic synthesis because this elegant strategy has advantages, such as enhanced reaction effectiveness, excellent atom economy, and significant versatility and applicability.[14] Diazo compounds have been widely used as a powerful substrate for the rapid assembly of fused heterocycles through transition-metal-catalyzed cascade aryl C—H bond activation and subsequent annulation.[15] In this regard, we recently disclosed a cascade reaction for access to fused isocoumarins using benzoic acids and benzamides as starting materials (Scheme 1, a).[16] In continuation of our efforts to enrich transition-metal catalyzed cascade C—H activation/intramolecular cyclization for heterocycle synthesis,[17-20] we herein reported a simple and efficient strategy for the synthesis of cyclohexanone-fused/esterified isocoumarins through the Rh(III)-catalyzed cascade C—H bond activation and sequential intramolecular annulation of phthalic anhydrides with cyclic 2-diazo-1,3-diketones and methanol (Scheme 1, b).

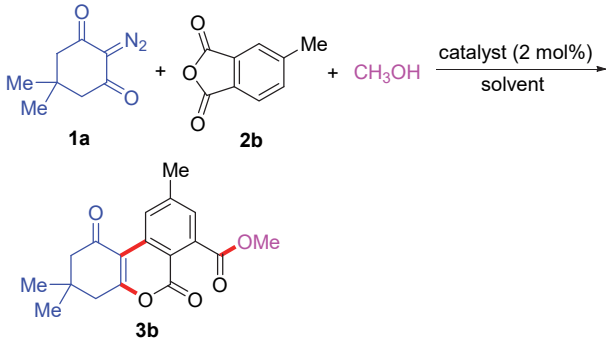


Scheme 1 Rh-catalyzed cascade C—H bond activation/annulation for construction of cyclohexanone-fused isocoumarins

2 Results and discussion

Our investigation was first devised using cyclic 2-diazo-1,3-diketone (**1a**) and 5-methylisobenzofuran-1,3-dione (**2b**) in methanol as the model substrate to optimize the reaction conditions (Table 1). Our initial studies using Rh and Ru catalysts for the three-component reaction under air atmosphere revealed that $[Cp^*RhCl_2]_2$ was the best catalyst to give the product **3b** in 83% yield (Table 1, Entry 5), whereas $[(p\text{-cymene})RuCl_2]_2$ afforded the product albeit in low yield (Table 1, Entry 4). Various Ni catalysts, including $Ni(COD)_2$, $Ni(PPh_3)_2Cl_2$ and $Ni(OTf)_2$, were then investigated, and the reaction hardly took place (Table, Entries 6～8). Decreasing or increasing the amount of $[Cp^*RhCl_2]_2$ could not give a better result (Table 1, Entries 10～13). Subsequent investigations on the solvent effect showed that methanol, which was used both as solvent and as one of the reactants, led to the best result (Table 1, Entries 14～19). Furthermore, there was no extra benefit of product yield by decreasing the reaction temperature or reaction time as well as increasing the reaction time to 20 h (Table 1, Entries 20～25). Thus, the reaction could be best performed in methanol at reflux for 15 h in the presence of $[Cp^*RhCl_2]_2$ (2 mol%) under air atmosphere (Table 1, Entry 5).

Table 1 Optimization of the reaction conditions[a]



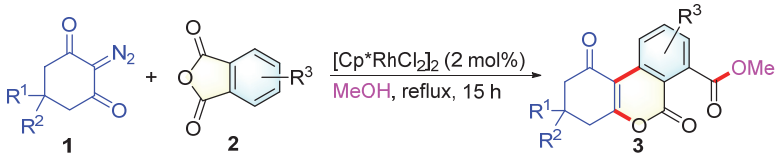
Entry	Catalyst	Solvent	Temp./℃	Time/h	Yield[b]/%
1	$Rh_2(OAc)_4$	MeOH	Reflux	15	Trace
2	$Rh_2(oct)_4$	MeOH	Reflux	15	Trace
3	$(PPh_3)_3RuCl_2$	MeOH	Reflux	15	Trace
4	$[(p\text{-cymene})RuCl_2]_2$	MeOH	Reflux	15	51
5	$[Cp^*RhCl_2]_2$	MeOH	Reflux	15	83
6	$Ni(COD)_2$	MeOH	Reflux	15	nr
7	$Ni(PPh_3)_2Cl_2$	MeOH	Reflux	15	nr
8	$Ni(OTf)_2$	MeOH	Reflux	15	nr
9[c]	$[Cp^*RhCl_2]_2$	MeOH	Reflux	15	60
10[d]	$[Cp^*RhCl_2]_2$	MeOH	Reflux	15	62
11[e]	$[Cp^*RhCl_2]_2$	MeOH	Reflux	15	71
12[f]	$[Cp^*RhCl_2]_2$	MeOH	Reflux	15	83
13	—	MeOH	Reflux	15	nr
14	$[Cp^*RhCl_2]_2$	DMF	Reflux	15	Trace
15	$[Cp^*RhCl_2]_2$	DCM	Reflux	15	35
16	$[Cp^*RhCl_2]_2$	MeCN	Reflux	15	Trace
17	$[Cp^*RhCl_2]_2$	THF	Reflux	15	54
18	$[Cp^*RhCl_2]_2$	Toluene	Reflux	15	Trace
19	$[Cp^*RhCl_2]_2$	1,4-Dioxane	Reflux	15	Trace
20	$[Cp^*RhCl_2]_2$	MeOH	25	15	20
21	$[Cp^*RhCl_2]_2$	MeOH	50	15	45
22	$[Cp^*RhCl_2]_2$	MeOH	Reflux	1	15
23	$[Cp^*RhCl_2]_2$	MeOH	Reflux	5	20
24	$[Cp^*RhCl_2]_2$	MeOH	Reflux	10	76
25	$[Cp^*RhCl_2]_2$	MeOH	Reflux	20	83

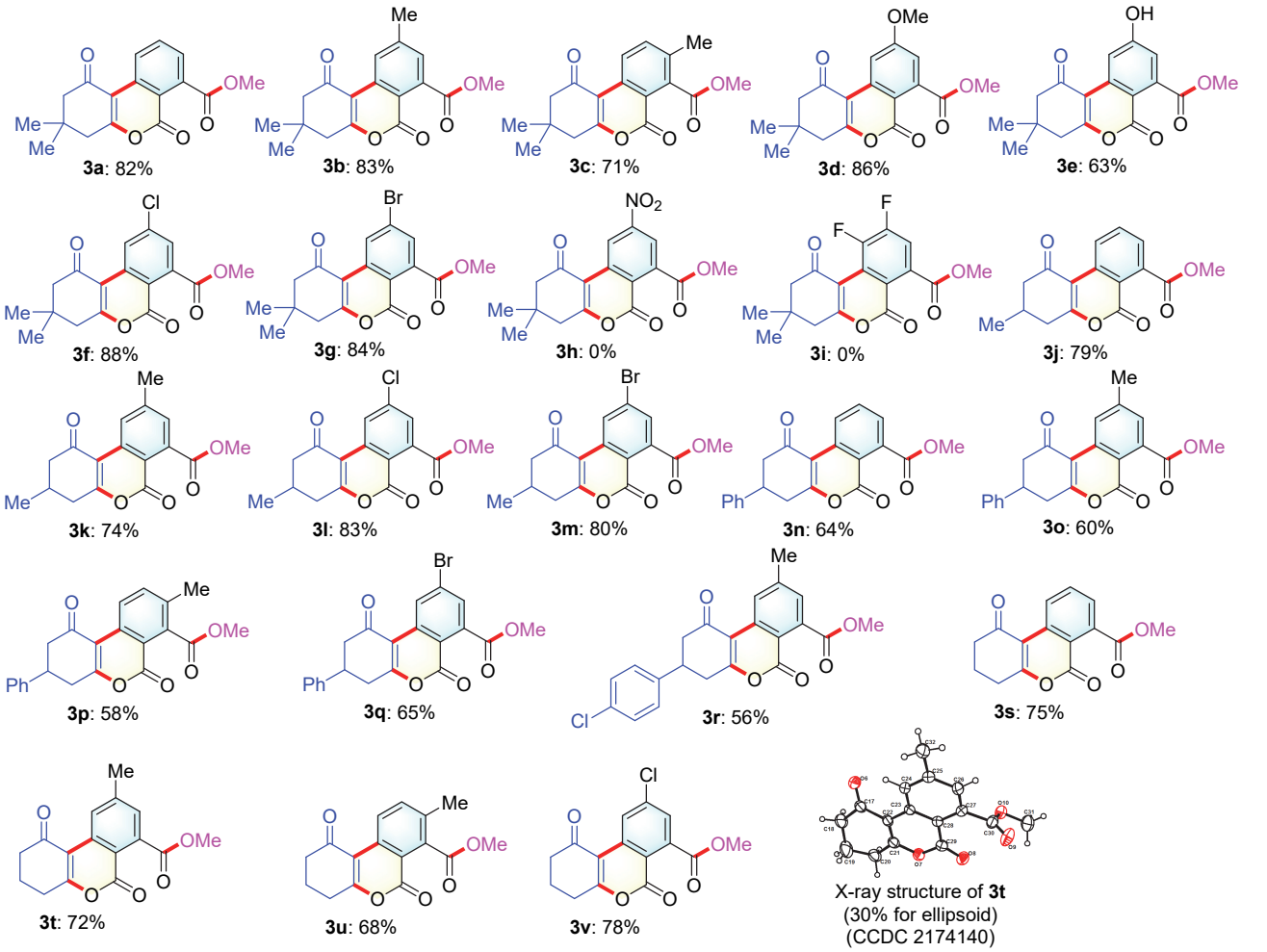
[a] Reaction conditions: 2-diazo-5,5-dimethylcyclohexane-1,3-dione (**1a**, 0.5 mmol), 5-methylisobenzofuran-1,3-dione (**2b**, 0.5 mmol), methanol (0.5 mmol) and catalyst (2 mol%) were stirred in solvent (2 mL) under air atmosphere. nr=no reaction. [b] Isolated yields. [c] 0.5 mol% catalyst was used. [d] 1.0 mol% catalyst was used. [e] 1.5 mol% catalyst was used. [f] 2.5 mol% catalyst was used.

With the optimized reaction conditions in hand, we next set out to explore the generality of this this transformation with a combination of various cyclic 2-diazo-1,3-diketones **1** with phthalic anhydrides **2** in methanol (Table 2). Generally, phthalic anhydride **2a** reacted with cyclic 2-diazo-1,3-

diketone (**1a**) in methanol under the standard condition generated the corresponding product **3a** in 82% yield. Phthalic anhydrides **2** featuring either an electron-donating (*eg*. Me) or electron-withdrawing group (*eg*. Cl, Br) on the benzene ring worked well under the standard conditions, generating the corresponding products **3b**～**3g** in 71%～88% yields. No significant effect was observed when the position of the methyl group was altered (product **3c** showed 71% yield). It was noted that phthalic anhydrides with strong electron-donating groups were also well compatible, giving the desired products **3d** and **3e** in 86% and 63% yields, respectively. Unfortunately, no desired products (**3h** and **3i**) were obtained when mono-substituted phthalic anhydride with a strong electron-withdrawing group (NO_2) and disubstituted phthalic anhydride (5,6-difluoroisobenzofuran-1,3-dione) were chosen as substrates. Subsequently, various cyclic 2-diazo-1,3-diones bearing substituents such as monomethyl (**1b**), phenyl (**1c**), 4-chloro-phenyl (**1d**) and hydrogen (**1e**) were investigated under the standard conditions, generating the corresponding products **3j**, **3n**, **3r** and **3s** in 79%, 64%, 56% and 75% yields, respectively. Furthermore, a series of ester-functionalized isocoumarins **3k**～**3v** were obtained in satisfactory yields (58%～83%) through the cross reaction of different cyclic 2-diazo-1,3-diketones with phthalic anhydrides. The resultant products were characterized by infrared (IR), ^{1}H NMR and ^{13}C NMR spectroscopies, and high-resolution mass spectrometry (HRMS) analysis. In addition, product **3t** was also unambiguously confirmed by X-ray crystallographic analysis.

Table 2 Substrate scope[a,b]

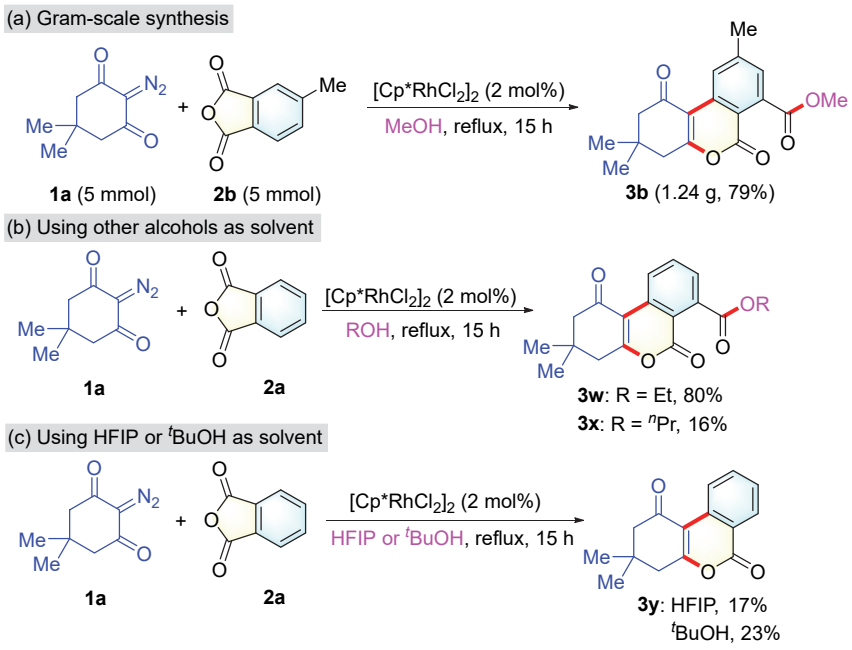




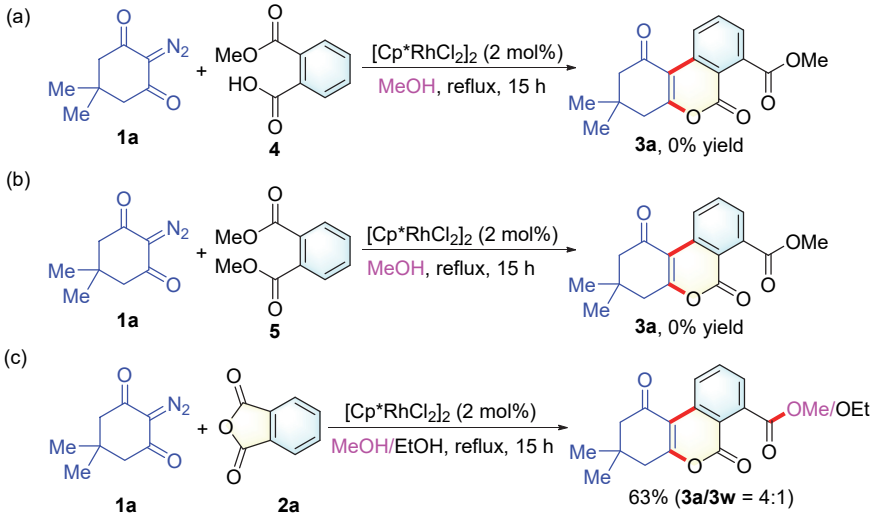
[a] Reaction conditions: cyclic diazo compounds (**1**, 0.5 mmol), phthalic anhydrides (**2**, 0.5 mmol), and $[Cp^*RhCl_2]_2$ (2 mol%) were stirred in methanol (2 mL) at reflux for 15 h under air atmosphere. [b] Islated yields.

In order to investigate the efficiency and utility of this method, a gram-scale reaction of **1a** (5 mmol) and **2b** (5 mmol) was carried out under the standard conditions, and the desired product **3b** was obtained in 79% (1.24 g) yield (Scheme 2, a). The result showed promise for this synthetic method as a useful tool in practical synthetic contexts. Furthermore, in addition to methanol, the applicability of ethanol and *n*-propanol were examined under the standard condition (Scheme 2, b). The desired products **3w** and **3x** were successfully obtained in 80% and 16% yields, respectively. To our delight, when 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) and *tert*-butanol were used as the substrate and solvent, the unexpected decarboxylative product **3y** was isolated in 17% and 23% yields, respectively (Scheme 2, c).

Having established the substrate scope, several control experiments were then performed to explore the preliminary mechanism (Scheme 3). Firstly, *ortho*-substituted methyl benzoates, such as 2-(methoxycarbonyl)benzoic acid (**4**) and dimethyl phthalate (**5**), were employed to this transformation, no desired product **3aa** was obtained (Scheme 3, a, b). Additionally, when the mixture of methanol/ethanol (V∶V=1∶1) was used as solvent under the standard condition (Scheme 3, c), the mixture products of **3a** and **3w** were isolated in 63% yield (the ration of **3a**/**3w** is 4∶1). These results indicated that the reaction proceeded through initial C—H activation with carboxylic group as directing group, followed by transesterification of the phthanlic acid by methanol.



Scheme 2 Further studies



Scheme 3 Control experiments

On the basis of the above experiment results and literature reports,[21] a plausible mechanism is proposed for the formation of product **3a** (Scheme 3). Initially, under the direction and assistance of the oxygen atom of the carbonyl group, the Rh-catalyst **A** activates the α-C(sp^2)—H bond of phthalic anhydride (**2a**) to generate the five-membered rhodacycle intermediate **B** by deprotonation. Subsequently, the cyclic 2-diazo-1,3-diketone (**1a**) coordinates with intermediate **B** to form the intermediate **C** by releasing N_2. Then, migratory insertion of carbene into Rh—C bond completes the C—C coupling and affords the six-membered intermediate **D**. Protonolysis of intermediate **D** leads to intermediate **E**, and releases the Rh(III)-catalyst, which starts a new catalytic cycle. In the next stage of this cascade process, intermolecular transesterification and subsequent nucleophilic addition with the *in situ* generated intermediate **F** by using methanol as a nucleophile. Finally, the desired product **3a** was formed with release of water through β-elimination.

3 Conclusions

In conclusion, an efficient and simple procedure has been developed to allow the modular assembly of esterified cyclohexenone-fused isocoumarins from available cyclic 2-diazo-1,3-diketones, phthalic anhydrides, and methanol. The transformation likely proceeds through Rh(III)-catalyzed cascade C—H activation, transannulative coupling, and subsequent annulation process. Moreover, the use of methanol as solvent and reactant enables the formation of one C—C and two C—O bonds under air atmosphere, without any additive as well as base.

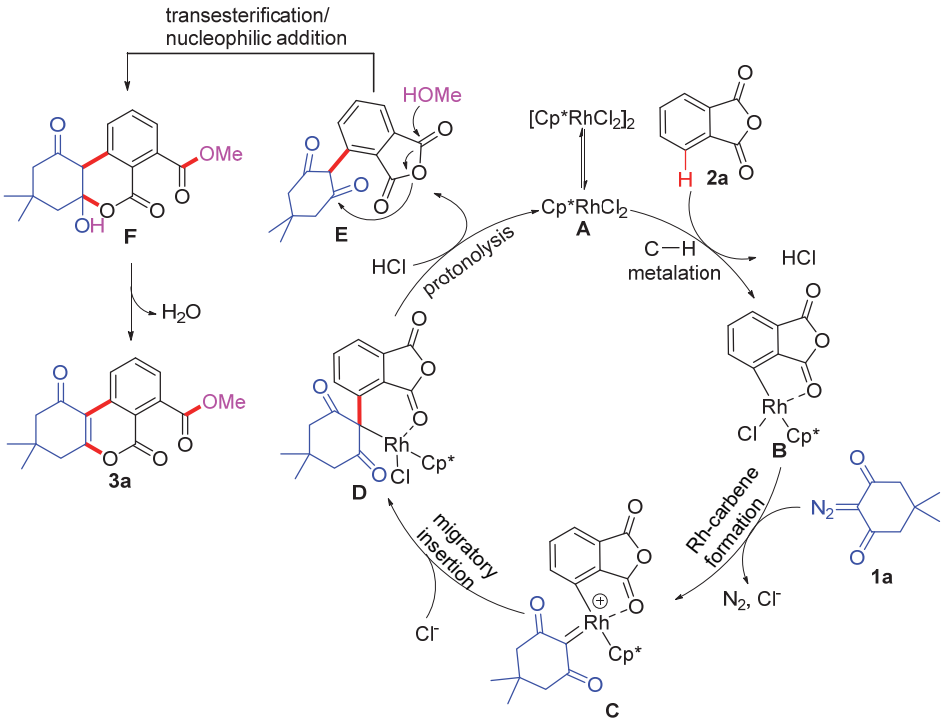
4 Experimental section

4.1 General comments

Reactions were monitored by using thin-layer chromatography (TLC) on commercial silica gel plates (GF 254). Visualization of the developed plates was performed under UV lights (GF 254 nm). Flash column chromatography was performed on silica gel (200～300 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on 300 MHz and 500 MHz spectrometers. HRMS analysis with a quadrupole time-of-flight mass spectrometer yielded ion mass/charge (m/z) ratios in atomic mass units (Agilent 6220). IR spectra were measured as dry films (KBr) (IRPrestige-21), and the peaks are reported in terms of wave number (cm^{-1}). The melting points were measured using SGWX-4 melting point apparatus.

4.2 General procedure for the synthesis of ester-functionalized fused isocoumarins 3

A mixture of cyclic 2-diazo-1,3-diketones (**1**, 0.5 mmol), phthalic anhydrides (**2**, 0.5 mmol), and [Cp*RhCl$_2$]$_2$ (0.01 mmol) in methanol (2 mL) was stirred at reflux in an oil bath preheated to 80 ℃ for 15 h under air atmosphere. After the reaction completed (as determined using TLC), the reaction mixture was cooled to room temperature, extracted with dichloromethane (10 mL × 3), and then washed with brine. The organic layers were combined, dried over Na_2SO_4, filtered, and then evaporated under vacuum. The residue was purified using flash column chromatography with a silica gel (200～300 mesh), using ethyl acetate and petroleum ether (V∶V=1∶6～1∶8) as the elution solvent to give the desired products **3**.



Scheme 3 Proposed mechanism

Methyl 3,3-dimethyl-1,6-dioxo-2,3,4,6-tetrahydro-1*H*-benzo[*c*]chroene-7-carboxylate (**3a**): White solid (123 mg, 82% yield). m.p. 111～112 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.16 (d, J=8.4 Hz, 1H), 7.79 (t, J=7.8 Hz, 1H), 7.49 (d, J=7.2 Hz, 1H), 3.97 (s, 3H), 2.80 (s, 2H), 2.53 (s, 2H), 1.17 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 197.0, 169.6, 168.9, 159.0, 136.6, 135.5, 135.5, 135.0, 127.6, 127.4, 116.9, 110.5, 53.6, 53.5, 53.3, 42.9, 32.3, 28.5; IR (KBr) v: 2914, 1755, 1667, 1610, 1438, 1365, 1288, 1139, 825, 530 cm^{-1}; HRMS (APCI) calcd for $C_{17}H_{17}O_5$ [M+H]$^+$ 301.1071, found 301.1074.

Methyl 3,3,9-trimethyl-1,6-dioxo-2,3,4,6-tetrahydro-1*H*-benzo[*c*]chromene-7-carboxlate (**3b**): White solid (130 mg, 83% yield). m.p. 112～113 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.98 (s, 1H), 7.31 (s, 1H), 3.97 (s, 3H), 2.79 (s, 2H), 2.52 (s, 5H), 1.17 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 197.3, 169.9, 169.1, 159.1, 147.2, 136.6, 135.0, 128.5, 127.6, 114.4, 110.5, 53.6, 53.3, 42.9, 32.3, 28.5, 22.7; IR (KBr) v: 2968, 1741, 1672, 1614, 1460, 1379, 1209, 1026, 864, 540 cm^{-1}; HRMS (APCI) calcd for $C_{18}H_{19}O_5$ [M+H]$^+$ 315.1230, found 315.1233.

Methyl 3,3,8-trimethyl-1,6-dioxo-2,3,4,6-tetrahydro-1*H*-benzo[*c*]chromene-7-carboxylate (**3c**): White solid (111 mg, 71% yield). m.p. 137～138 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.02 (d, J=8.4 Hz, 1H), 7.63 (d, J=8.4 Hz, 1H), 3.99 (s, 3H), 2.78 (s, 2H), 2.51 (s, 2H), 2.39 (s, 3H), 1.16 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 197.2, 169.5, 168.2, 159.6, 137.9, 136.0, 135.7, 132.5, 126.9, 116.8, 110.6, 53.3, 53.2, 42.8, 32.4, 28.5, 19.2; IR (KBr) v: 2968, 1728, 1666, 1618, 1481,1438, 1355, 1143, 1095, 831, 543 cm^{-1}; HRMS (APCI) calcd for $C_{18}H_{19}O_5$ [M+H]$^+$ 315.1230, found 315.1232.

Methyl 9-methoxy-3,3-dimethyl-1,6-dioxo-2,3,4,6-tetrahydro-1*H*-benzo[*c*]chromene-7-carboxylate (**3d**): White solid (142 mg, 86% yield). m.p. 74～75 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.71 (d, J=2.5 Hz, 1H), 7.02 (d, J=2.5 Hz, 1H), 3.97 (s, 3H), 3.96 (s, 3H), 2.79 (s, 2H), 2.52 (s, 2H), 1.17 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 197.4, 169.8, 169.3, 165.2, 158.8, 138.7, 137.5, 110.3, 109.6, 56.4, 53.6, 53.3, 43.0, 32.3, 28.5; IR (KBr) v: 2958, 1748, 1681, 1616, 1572, 1444, 1386, 1251, 881, 768, 545 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{19}O_6$ [M+H]$^+$ 331.1176, found 331.1174.

Methyl 9-hydroxy-3,3-dimethyl-1,6-dioxo-2,3,4,6-tetrahydro-1*H*-benzo[*c*]chromene-7-carboxylate (**3e**): White solid (99 mg, 63% yield). m.p. 74～75 ℃; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.46 (d, J=2.5 Hz, 1H), 6.91 (d, J=2.5 Hz, 1H), 3.79 (s, 3H), 2.79 (s, 2H), 2.47 (s, 2H), 1.06 (s, 6H); ^{13}C NMR (126 MHz, DMSO-d_6) δ: 197.8, 170.7, 169.1, 164.7, 158.8, 139.3, 137.6, 116.2, 112.0, 109.8, 107.7, 53.5, 53.0, 42.3, 40.9, 40.7, 40.5, 40.4, 40.2, 40.0, 39.9, 32.3, 28.3; IR (KBr) v: 3417, 2960, 1740, 1636, 1614, 1584, 1396, 1248, 996, 768, 553 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{17}O_6$ [M+H]$^+$ 317.1020, found 317.1018.

Methyl 9-chloro-3,3-dimethyl-1,6-dioxo-2,3,4,6-tetrahydro-1*H*-benzo[*c*]chromene-7-carboxylate (**3f**): White solid (147 mg, 88% yield). m.p. 108～109 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.23 (s, 1H), 7.46 (s, 1H), 3.98 (s, 3H), 2.80 (s, 2H), 2.53 (s, 2H), 1.17 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 196.6, 170.0, 168.2, 158.4, 142.7, 138.1, 136.3, 127.9, 127.3, 115.2, 109.7, 53.8, 53.1, 42.9, 32.3, 28.5; IR (KBr) v: 2981, 1745, 1730, 1681, 1606, 1458, 1388, 1193, 910, 842 cm^{-1}; HRMS (APCI) calcd for $C_{17}H_{16}ClO_5$ [M+H]$^+$ 335.0684, found 335.0684.

Methyl 9-bromo-3,3-dimethyl-1,6-dioxo-2,3,4,6-tetrahydro-1*H*-benzo[*c*]chromene-7-carboxylate (**3g**): White solid (158 mg, 84% yield). m.p. 100～101 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.38 (s, 1H), 7.60 (s, 1H), 3.96 (s, 3H), 2.80 (s, 2H), 2.52 (s, 2H), 1.17 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 196.6, 170.0, 168.1, 158.5, 137.8, 136.2, 131.4, 130.6, 130.4, 115.6, 109.6, 53.8, 53.1, 42.9, 32.3, 28.5; IR (KBr) v: 2991, 1748, 1739, 1661, 1622, 1586, 1398, 11433, 928, 856 cm^{-1}; HRMS (APCI) calcd for $C_{17}H_{16}BrO_5$ [M+H]$^+$ 379.0182, found 379.0180.

Methyl 3-methyl-1,6-dioxo-2,3,4,6-tetrahydro-1*H*-benzo-[*c*]chromene-7-carboxylate (**3j**): White solid (113 mg, 79% yield). m.p. 137～138 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.18 (d, J=8.1 Hz, 1H), 7.81 (t, J=7.8 Hz, 1H), 7.49 (d, J=7.2 Hz, 1H), 3.98 (s, 3H), 3.01～2.90 (m, 1H), 2.77～2.62 (m, 2H), 2.47～2.30 (m, 2H), 1.19 (d, J=6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 197.0, 169.9, 169.7, 158.9, 136.6, 135.5, 135.1, 127.7, 127.4, 116.9, 111.1, 53.6, 47.5, 37.2, 28.0, 21.1; IR (KBr) v: 2954, 1747, 1737, 1660, 1608, 1450, 1340, 1193, 816, 696 cm^{-1}; HRMS (APCI) calcd for $C_{16}H_{15}O_5$ [M+H]$^+$ 287.0916, found 287.0912.

Methyl 3,9-dimethyl-1,6-dioxo-2,3,4,6-tetrahydro-1*H*-benzo[*c*]chromene-7-carboxylate (**3k**): White solid (111 mg, 74% yield). m.p. 114～115 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.97 (s, 1H), 7.30 (s, 1H), 3.96 (s, 3H), 2.97～2.89 (m, 1H), 2.73～2.60 (m, 2H), 2.50 (s, 3H), 2.42～2.30 (m, 2H), 1.17 (d, J=5.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 197.2, 170.0, 169.8, 158.9, 147.1, 136.5, 135.1, 128.5, 127.6, 114.5, 111.0, 53.5, 47.6, 37.2, 28.0, 22.7, 21.1; IR (KBr) v: 2947, 1757, 1672, 1598, 1379, 1203, 1134, 1033, 866, 533 cm^{-1}; HRMS (APCI) calcd for $C_{17}H_{17}O_5$ [M+H]$^+$ 301.1071, found 301.1075.

Methyl 9-chloro-3-methyl-1,6-dioxo-2,3,4,6-tetrahydro-1*H*-benzo[*c*]chromene-7-carboxylate (**3l**): White solid (132 mg, 83% yield). m.p. 154～155 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.24 (s, 1H), 7.46 (s, 1H), 3.98 (s, 3H), 2.92～3.00 (m, 1H), 2.62～2.76 (m, 2H), 2.33～2.41 (m, 2H), 1.19 (d, J=6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 196.7, 170.8, 168.1, 158.1, 142.5, 136.2, 127.9, 127.4, 115.2, 110.3, 53.8, 47.4, 37.2, 27.9, 21.1; IR (KBr) v: 2968, 2375, 1759, 1666, 1571, 1435, 1274, 1143, 1033, 808 cm^{-1}; HRMS (APCI) calcd for $C_{16}H_{14}ClO_5$ [M+H]$^+$ 321.0527, found 321.0524.

Methyl 9-bromo-3-methyl-1,6-dioxo-2,3,4,6-tetrahydro-1*H*-benzo[*c*]chromene-7-carboxylate (**3m**): White solid (145 mg, 80% yield). m.p. 142～143 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.41 (s, 1H), 7.62 (s, 1H), 3.97 (s, 3H), 2.92～2.98 (m, 1H), 2.62～2.75 (m, 2H), 2.32～2.41 (m, 2H), 1.19 (d, J=6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$)

δ: 196.6, 170.8, 168.1, 158.5, 137.9, 136.3, 131.4, 130.7, 130.5, 115.6, 110.2, 53.8, 47.4, 37.2, 27.9, 21.1; IR (KBr) ν: 2945, 1748, 1643, 1526, 1358, 1212, 1178, 1057, 829, 541 cm^{-1}; HRMS (APCI) calcd for $C_{16}H_{14}BrO_5$ $[M+H]^+$ 365.0021, found 365.0027.

Methyl 1,6-dioxo-3-phenyl-2,3,4,6-tetrahydro-1*H*-benzo[*c*]chromene-7-carboxylate (**3n**): White solid (111 mg, 64% yield). m.p. 142～143 ℃; ^1H NMR (300 MHz, $CDCl_3$) δ: 9.21 (d, J=8.4 Hz, 1H), 7.83 (t, J=7.8 Hz, 1H), 7.51 (d, J=7.2 Hz, 1H), 7.28～7.40 (m, 5H), 3.98 (s, 3H), 3.55～3.63 (m, 1H), 3.16～3.19 (m, 2H), 2.91～2.95 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 196.2, 170.0, 169.6, 158.8, 141.6, 136.6, 135.7, 135.0, 129.5, 128.0, 127.8, 127.6, 127.0, 116.9, 111.3, 53.6, 46.3, 38.2, 36.7; IR (KBr) ν: 2960, 1741, 1689, 1620, 1445, 1342, 1280, 1134, 813, 556 cm^{-1}; HRMS (APCI) calcd for $C_{21}H_{17}O_5$ $[M+H]^+$ 349.1072, found 349.1074.

Methyl 9-methyl-1,6-dioxo-3-phenyl-2,3,4,6-tetrahydro-1*H*-benzo[*c*]chromene-7-carboxylate (**3o**): White solid (109 mg, 60% yield). m.p. 153～154 ℃; ^1H NMR (300 MHz, $CDCl_3$) δ: 9.00 (s, 1H), 7.39～7.28 (m, 6H), 3.96 (s, 3H), 3.58～3.50 (m, 1H), 3.16～3.14 (m, 2H), 2.97～2.89 (m, 2H), 2.51 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 196.3, 170.0, 158.8, 147.3, 141.7, 136.6, 134.9, 129.5, 128.7, 128.0, 127.7, 127.0, 114.4, 111.2, 53.6, 46.3, 38.2, 36.7, 22.8; IR (KBr) ν: 2955, 2375, 1745, 1674, 1456, 1373, 1209, 1020, 859, 696 cm^{-1}; HRMS (APCI) calcd for $C_{22}H_{19}O_5$ $[M+H]^+$ 363.1230, found 363.1233.

Methyl 8-methyl-1,6-dioxo-3-phenyl-2,3,4,6-tetrahydro-1*H*-benzo[*c*]chromene-7-carboxylate (**3p**): White solid (105 mg, 58% yield). m.p. 148～149 ℃; ^1H NMR (300 MHz, $CDCl_3$) δ: 9.07 (d, J=8.4 Hz, 1H), 7.66 (d, J=8.4 Hz, 1H), 7.46～7.26 (m, 5H), 4.00 (s, 3H), 3.51～3.62 (m, 1H), 3.14～3.16 (m, 2H), 2.99～2.84 (m, 2H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 196.3, 169.5, 168.7, 159.3, 141.7, 138.0, 136.3, 135.8, 132.5, 129.5, 128.0, 127.0, 127.0, 116.9, 111.4, 58.9, 53.4, 46.3, 38.3, 36.6, 19.3, 18.8; IR (KBr) ν: 2935, 1732, 1674, 1608, 1490, 1342, 1280, 1033, 837, 565 cm^{-1}; HRMS (APCI) calcd for $C_{22}H_{19}O_5$ $[M+H]^+$ 363.1230, found 363.1232.

Methyl 9-bromo-1,6-dioxo-3-phenyl-2,3,4,6-tetrahydro-1*H*-benzo[*c*]chromene-7-caroxylate (**3q**): White solid (138 mg, 65% yield). m.p. 96～97 ℃; ^1H NMR (300 MHz, $CDCl_3$) δ: 9.44 (s, 1H), 7.64 (s, 1H), 7.41～7.29 (m, 5H), 3.98 (s, 3H), 3.54～3.62 (m, 1H), 3.17～3.19 (m, 2H), 2.85～3.00 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 195.9, 170.5, 168.1, 158.3, 141.3, 137.8, 136.1, 131.6, 130.9, 130.5, 129.5, 128.1, 126.9, 115.7, 110.4, 53.9, 46.1, 38.1, 36.7; IR (KBr) ν: 2902, 1735, 1643, 1562, 1434, 1311, 1232, 1043, 704, 511 cm^{-1}; HRMS (APCI) calcd for $C_{21}H_{16}BrO_5$ $[M+H]^+$ 427.0179 found 427.0176.

Methyl 3-(4-chlorophenyl)-9-methyl-1,6-dioxo-2,3,4,6-tetrahydro-1*H*-benzo[*c*]chromene-7-carboxylate (**3r**): White solid (110 mg, 56% yield). m.p. 157～158 ℃; ^1H NMR (300 MHz, $CDCl_3$) δ: 9.00 (s, 1H), 7.35 (d, J=8.4 Hz, 3H), 7.22 (d, J=8.4 Hz, 2H), 3.97 (s, 3H), 3.67～3.42 (m, 1H), 3.13 (d, J=7.8 Hz, 2H), 2.99～2.77 (m, 2H), 2.53 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 195.9, 169.7, 169.3, 158.7, 147.4, 140.0, 136.6, 134.8, 133.8, 129.6, 128.8, 128.4, 127.7, 114.5, 111.3, 53.6, 46.2, 37.7, 36.6, 22.8; IR (KBr) ν: 2954, 1745, 1674, 1604, 1492, 1375, 1203, 1016, 875, 563 cm^{-1}; HRMS (APCI) calcd for $C_{22}H_{18}ClO_5$ $[M+H]^+$ 397.0841, found 397.0846.

Methyl 1,6-dioxo-2,3,4,6-tetrahydro-1*H*-benzo[*c*]chromene-7-carboxylate (**3s**): White solid (102 mg, 75% yield). m.p. 94～95 ℃; ^1H NMR (300 MHz, $CDCl_3$) δ: 9.15 (d, J=8.4 Hz, 1H), 7.80 (t, J=7.8 Hz, 1H), 7.48 (d, J=7.3 Hz, 1H), 3.97 (s, 3H), 2.94 (t, J=6.3 Hz, 2H), 2.66 (t, J=6.6 Hz, 2H), 2.20～2.13 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 197.0, 170.4, 169.7, 158.8, 136.6, 135.5, 135.2, 127.8, 127.4, 117.0, 111.5, 53.6, 39.3, 29.3, 20.2; IR (KBr) ν: 2914, 1732, 1683, 1585, 1450, 1359, 1284, 1186, 1078, 800 cm^{-1}; HRMS (APCI) calcd for $C_{15}H_{13}O_5$ $[M+H]^+$ 273.0761, found 273.0760.

Methyl 9-methyl-1,6-dioxo-2,3,4,6-tetrahydro-1*H*-benzo[*c*]chromene-7-carboxylate (**3t**): White solid (103 mg, 72% yield). m.p. 152～153 ℃; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.97 (s, 1H), 7.31 (s, 1H), 3.96 (s, 3H), 2.93 (t, J=6.3 Hz, 2H), 2.66 (t, J=6.6 Hz, 2H), 2.51 (s, 3H), 2.20～2.13 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 197.2, 170.5, 169.8, 158.9, 147.2, 136.5, 135.2, 128.5, 127.8, 114.5, 111.5, 53.6, 39.4, 29.4, 22.7, 20.5; IR (KBr) ν: 2947, 1737, 1670, 1608, 1483, 1284, 1138, 1091, 1039, 846 cm^{-1}; HRMS (APCI) calcd for $C_{16}H_{15}O_5$ $[M+H]^+$ 287.0916, found 287.0915.

Methyl 8-methyl-1,6-dioxo-2,3,4,6-tetrahydro-1*H*-benzo[*c*]chromene-7-carboxylate (**3u**): White solid (97 mg, 68% yield). m.p. 99～100 ℃; ^1H NMR (300 MHz, $CDCl_3$) δ: 9.04 (d, J=8.4 Hz, 1H), 7.64 (d, J=8.4 Hz, 1H), 4.00 (s, 3H), 2.92 (t, J=6.3 Hz, 2H), 2.66 (t, J=6.6 Hz, 2H), 2.40 (s, 3H), 2.25～2.06 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 197.2, 169.6, 169.6, 159.4, 137.9, 136.0, 135.7, 132.7, 127.1, 116.9, 111.6, 53.4, 39.3, 29.2, 20.3, 19.2; IR (KBr) ν: 2947, 1735, 1604, 1438, 1274, 1195, 1124, 1072, 777, 671 cm^{-1}; HRMS (APCI) calcd for $C_{16}H_{15}O_5$ $[M+H]^+$ 287.0916, found 287.0914.

Methyl 9-chloro-1,6-dioxo-2,3,4,6-tetrahydro-1*H*-benzo[*c*]chromene-7-carboxylate (**3v**): White solid (119 mg, 78% yield). m.p. 147～148 ℃; ^1H NMR (300 MHz, $CDCl_3$) δ: 9.23 (s, 1H), 7.45 (s, 1H), 3.97 (s, 3H), 2.95 (t, J=6.3 Hz, 2H), 2.67 (t, J=6.6 Hz, 2H), 2.22～2.14 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 196.6, 171.4, 168.2, 158.1, 142.7, 138.0, 136.4, 127.9, 127.5, 115.3, 110.7, 53.8, 39.2, 29.4, 20.1; IR (KBr) ν: 2972, 1768, 1645, 1609, 1475, 1311, 1239, 1128, 873, 536 cm^{-1}; HRMS (APCI) calcd for $C_{15}H_{12}ClO_5$ $[M+H]^+$ 307.0371, found 307.0373.

Ethyl 3,3-dimethyl-1,6-dioxo-2,3,4,6-tetrahydro-1*H*-benzo[*c*]chromene-7-carboxylate (**3w**): White solid (125 mg, 80% yield). m.p. 101～102 ℃; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.98 (s, 1H), 7.31 (s, 1H), 3.97 (s, 3H), 2.79 (s, 2H), 2.52 (s, 5H), 1.17 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 197.3, 169.9, 169.1, 159.1, 147.2, 136.6, 135.0, 128.5, 127.6, 114.4, 110.5, 53.6, 53.3, 42.9, 32.3, 28.5,

22.7; IR (KBr) *v*: 2968, 1741, 1672, 1614, 1460, 1379, 1209, 1026, 864, 540 cm^{-1}; HRMS (APCI) calcd for $C_{18}H_{19}O_5$ $[M+H]^+$ 315.1230, found 315.1233.

Propyl 3,3-dimethyl-1,6-dioxo-2,3,4,6-tetrahydro-1*H*-benzo[*c*]chromene-7-carboxylate (**3x**): Colorless oil (26 mg, 16% yield). ^1H NMR (500 MHz, $CDCl_3$) δ: 9.16 (dd, J=8.4, 1.1 Hz, 1H), 7.81 (dd, J=8.4, 7.5 Hz, 1H), 7.49 (dd, J=7.4, 1.1 Hz, 1H), 4.36 (t, J=6.5 Hz, 2H), 2.80 (s, 2H), 2.53 (s, 2H), 1.82～1.75 (m, 2H), 1.17 (s, 6H), 0.99 (t, J=7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 197.1, 169.4, 168.9, 159.0, 137.1, 135.6, 135.5, 135.0, 127.5, 127.4, 116.8, 110.5, 68.3, 53.3, 42.9, 32.3, 28.5, 22.2, 10.8; IR (KBr) *v*: 2964, 1746, 1677, 1618, 1588, 1456, 1364, 1241, 823, 767, 541 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{21}O_5$ $[M+H]^+$ 329.1384, found 329.1391.

3,3-Dimethyl-3,4-dihydro-1*H*-benzo[*c*]chromene-1,6-(2*H*)-dione (**3y**): Yellow solid (20 mg, 17% yield from HFIP and 28 mg, 23% yield from *t*-BuOH). m.p. 125～126 ℃; ^1H NMR (500 MHz, $CDCl_3$) δ: 9.05 (d, J=8.3 Hz, 1H), 8.29 (d, J=7.6 Hz, 1H), 7.83～7.77 (m, 1H), 7.53 (t, J=7.5 Hz, 1H), 2.80 (s, 2H), 2.52 (s, 2H), 1.18 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 197.4, 168.4, 161.2, 136.1, 134.3, 130.0, 128.8, 126.2, 120.2, 111.0, 53.3, 43.0, 32.4, 28.5; IR (KBr) *v*: 2960, 1738, 1688, 1615, 1417, 1370, 1319, 1246, 1031, 776, 533 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{15}O_3$ $[M+H]^+$243.1016, found 243.1024.

Supporting Information Copies of NMR spectra of products and X-ray structure data of compound **3t**. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn.

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