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ortho-Induced transition-metal-free *C*-arylation cyclization reaction for the synthesis of polysubstituted isocoumarins

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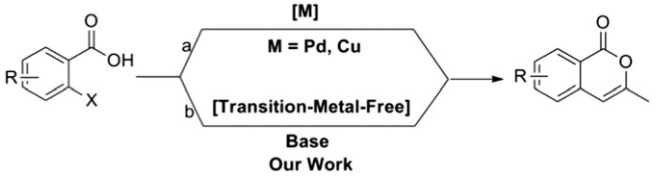
ABSTRACT

A new protocol for the synthesis of polysubstituted isocoumarins from 2-iodobenzoic acid and β-diketone compounds has been developed. The occurrence of *C*-arylation cyclization reaction in transition-metal-free systems and *ortho*-induced substrates has been exploited. Reactions using these inexpensive conditions have displayed high functional group tolerance and excellent yields.

1. Introduction

Isocoumarins and isoquinolinones are naturally occurring lactones that have a wide range of biological activities.[1,2] Consequently, many strategies have been developed for the synthesis of these compounds.[3] Recently, multicomponent tandem-cyclization reaction as a simple and effective methodology received much concern.[4] Our group also have developed some direct and efficient methods for synthesizing a diverse range of valuable five- or six-membered carbo- and heterocyclic compounds over the past few years.[5] In current study, we extended the use of these methods to the synthesis of polysubstituted isocoumarins, and accidentally discovered an intermolecular[6] Ullmann-type tandem reaction.[7] Transition-metal catalyzed intermolecular cyclization of the corresponding 2-iodobenzoic acid and β-diketone or terminal alkynes as a simple and efficient protocol has attracted much attention in recent years (Scheme 1, a).[8] However, the direct *C*-arylation Cyclization of 2-iodobenzoic acid and β-diketone compounds under metal-free conditions for the synthesis of polysubstituted isocoumarins has not previously been reported (Scheme 1, b). Compared with other ways, we report a new method, featuring environmentally friendly metal-free conditions. Our discovery was displayed a pattern by transition-metal-free[9] for the *C*-arylation cyclization reaction.



Scheme 1. Transition-metal catalyzed or base-promoted cyclization reaction of corresponding 2-iodobenzoic acid.

2. Results and discussion

In an initial study, the tandem-cyclization between 2-iodobenzoic acid **1a** and β-diketone compounds **2a** was performed in the presence of CuI (10 mol %) and Cs_2CO_3 (2.0 equiv) as the base in DMF at 100 °C. This set of conditions afforded isocoumarins **3a** in 70% yield after 24 h (Table 1, entry 1). Then analyses showed that *C*-arylation cyclization occurred, and the products **3a** were obtained. Encouraged by this result, the reaction conditions were further optimized. To our excited that the contrast tests showed that only the base can prompt this reaction proceeding very well and copper salts is not needed at all. The product of isocoumarins **3a** was obtained in 68% yield (Table 1, entry 2). Consequently, different loading of Cs_2CO_3 was investigated and 1 equiv of Cs_2CO_3 was found to afford product **3a** in 80% yield (Table 1, entries 3–5). The screening of different solvents (Table 1, entries 6–11) revealed that CH_3CN gave the best result with 88% yield of isolated product **3a**. In addition, different bases were also screened

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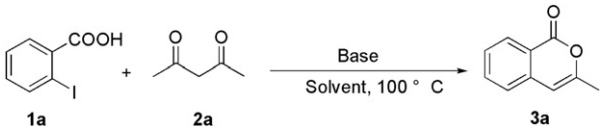
Table 1
Optimization of the intermolecular reactions of 2-iodobenzoic acid (**1a**) with 1,3-diketones (**2a**)[a]



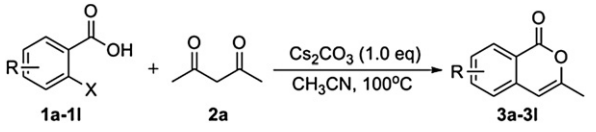
Entry	Base	Solvent	Time [h]	Yield [%][b]
1[c]	CuI, Cs_2Co_3, (2 eq)	DMF	24	70
2	Cs_2CO_3, (2 eq)	DMF	2	68
3	Cs_2CO_3, (0.05 eq)	DMF	36	n.r.
4	Cs_2CO_3, (0.5 eq)	DMF	4	63
5	Cs_2CO_3, (1 eq)	DMF	2	80
6	Cs_2CO_3, (1 eq)	THF	24	20
7	Cs_2CO_3, (1 eq)	Dioxane	24	67
8	Cs_2CO_3, (1 eq)	DMA	4	30
9	Cs_2CO_3, (1 eq)	NMP	4	20
10	Cs_2CO_3, (1 eq)	CH_3CN	4	88
11	Cs_2CO_3, (1 eq)	DMSO	2	84
12	Na_2CO_3, (1 eq)	DMSO	6	75
13	K_3PO_4, (1 eq)	DMSO	10	32
14	K_2CO_3, (1 eq)	DMSO	6	76
15	Li_2CO_3, (1 eq)	DMSO	10	69
16	NaH, (1 eq)	DMSO	5	22
17	KH_2PO_4, (1 eq)	DMSO	24	70
18	NaOH, (1 eq)	DMSO	10	60
19	$NaOCH_3$, (1 eq)	DMSO	24	20
20	K_2CO_3, (1 eq)	CH_3CN	12	70

[a] All reactions were carried out in the presence of 0.2 mmol of **1a**, 0.4 mmol of **2a** and base in 2 mL of solvent at 100 °C.
[b] Isolated yield.
[c] 10% mol CuI was used.

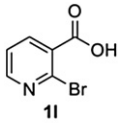
(Table 1, entries 12–20) and the results showed that Cs_2CO_3 was still the best choice.

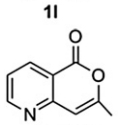
Under the optimized reaction conditions (Table 1, entry 10), various aryl halides were surveyed using β-diketone **2a**. 2-iodobenzoic and 2-bromobenzoic acids with various substituents provided moderate to high yields of desired products (Table 2, **1a**–**1k**). The electronic effect was evident in this transformation. When R was an electron-withdrawing group in the *para* and *ortho*-position, such as chloride and fluoride, the corresponding isocoumarins products were obtained in only 37% and 35% yields, respectively, (Table 2, **3c** and **3j**). While as R was in *meta*-position, the yield was not affected (Table 2, **3i**). Steric hindrance was also observed. The fluoride was placed in the *ortho*-position, and a lower yield was afforded. Notably, bromo-nicotinic acid **1l** also worked very well and provided a product in 60% yield (Table 2, **3l**).

Table 2
Intermolecular reactions with various aryl halides[a,b]



R=H, X=I	**1a**	**3a** (88%)
R=H, X=Br	**1b**	**3b** (60%)
R=4-Cl, X=I	**1c**	**3c** (37%)
R=3-CH_3, X=I	**1d**	**3d** (80%)
R=3-CH_3, X=Br	**1e**	**3e** (50%)
R=5-CH_3, X=I	**1f**	**3f** (70%)
R=3-CH_3, 5-Cl, X=I	**1g**	**3g** (50%)
R=5-Br, X=I	**1h**	**3h** (51%)
R=5-F, X=Br	**1i**	**3i** (60%)
R=6-F, X=Br	**1j**	**3j** (35%)
R=5-CH_3O, X=Br	**1k**	**3k** (57%)

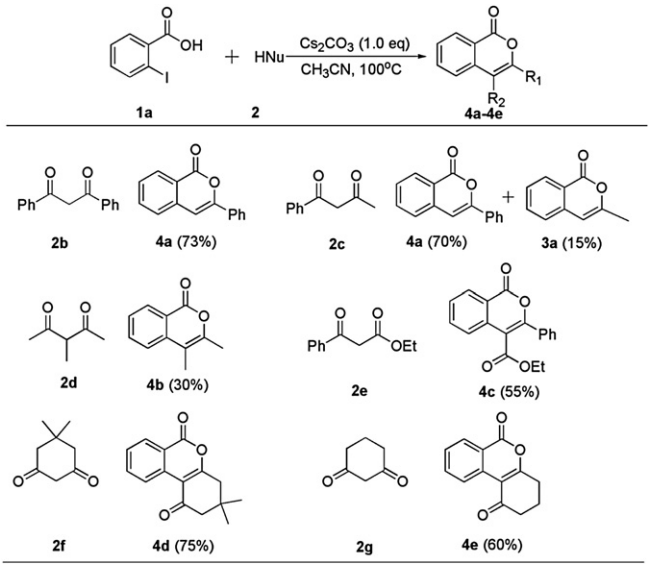




[a] All reactions were carried out in the presence of 0.2 mmol **1a**–**1l**, 0.4 mmol **2a** and 0.2 mmol Cs_2CO_3 in 2 mL of CH_3CN at 100 °C; all reactions were run for 4–10 h.
[b] Isolated yield.

The effects of different nucleophilic compounds were examined next (Table 3). When symmetrical β-diketones, such as alkydiketone, phenydiketone and cyclic diketone were used, the corresponding substituted isocoumarins were obtained in moderate to good yields (Table 3, **2b** and **2d**). However using unsymmetrical phenylmethyl β-diketone, the mixture of phenyl isocoumarins **4a** and methyl isocoumarins **3a** was produced in 70% and 15% yields, respectively, (Table 3, **2c**). Benzoyl acetoacetate also worked well (Table 3, **2e**). The C–C bond cleavage did not occur, and the product **4c** was obtained in 55% yield. Given the annular structural stability of C–C bond, the cleavage did not occur (Table 3, **2f** and **2g**).[10]

Table 3
Intermolecular reactions of acid **1a** with various nucleophilic reagents[a,b]



[a] All reactions were carried out in the presence of 0.2 mmol **1a**, 0.4 mmol **2** and 0.2 mmol Cs_2CO_3 in 2 mL of CH_3CN at 100 °C; all reactions were run for 5 h.
[b] Isolated yield.

Besides lactones, lactams are also common and very useful in organic syntheses. Then, we extended the present methodology to the synthesis of these compounds. *N*-phenylbenzamide was chosen as the substrate to react with β-diketone under the aforementioned reaction conditions. The results showed that the reaction smoothly occurred, and the two products isocoumarins and *N*-phenylacetamide were synchronously produced. Different acetamides were subsequently investigated, and the corresponding products were obtained in high yields. Using the annular β-diketone as the substrate, only the single product lactam was produced in a low yield. This transformation provides a direct and efficient methodology for the synthesis of various lactams and their derivatives (Fig. 1) (Table 4).

During the reaction proceeding, we observed that the precipitate was produced in just beginning and all of the substrates were completely transferred into precipitate after 1 h. Then these solid is starting to redissolved slowly and the product **3a** were formed simultaneously. These results suggest that the intermediate **A** was produced firstly as caesium salts in this transformation and subsequently transformed to **3a** by C–C bond cyclization under the basic conditions. In order to confirmed our deduction and explored the reaction mechanism, the reaction between 2-iodobenzoic acid and β-diketone compounds was performed under the optimized reaction conditions and then was quenched and acidulated with 10% HCl aqueous after an hour. As we expected, the coupling compound

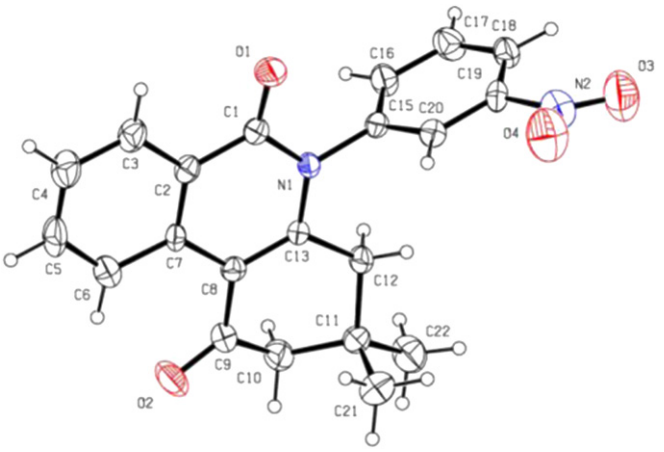
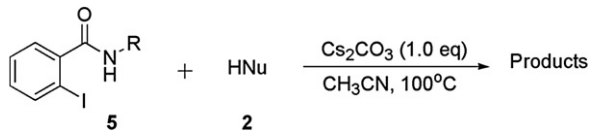
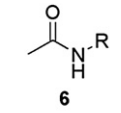


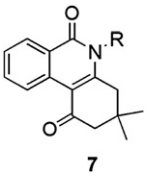
Fig. 1. X-ray crystal of **7c**.

Table 4
Intermolecular reactions with various 2-iodo-*N*-phenyl–benzamide derivatives[a,b]



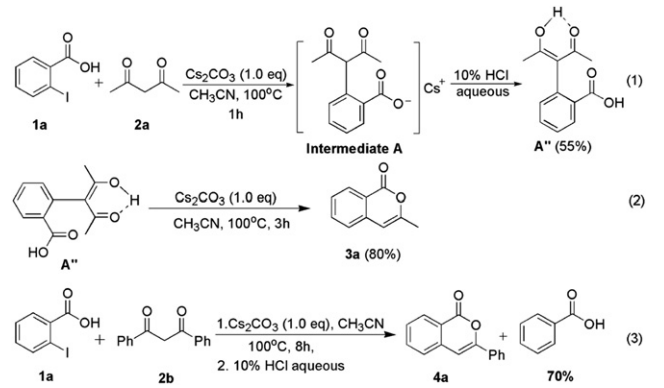
R=Ph	**5a**	**2a**	**3a** (82%)+**6a** (93%)
R=2-CH_3Ph	**5b**	**2a**	**3a** (83%)+**6b** (84%)
R=3-NO_2Ph	**5c**	**2a**	**3a** (88%)+**6c**(91%)
R=2-pyridine	**5d**	**2a**	**3a** (71%)+**6d**(80%)
R=Ph	**5a**	**2f**	**7a** (42%)
R=2-CH_3Ph	**5b**	**2f**	**7b** (35%)
R=3-NO_2Ph	**5c**	**2f**	**7c** (60%)
R=3-OCH_3Ph	**5d**	**2f**	**7d** (33%)
R=Ph	**5a**	**2g**	**7e** (35%)





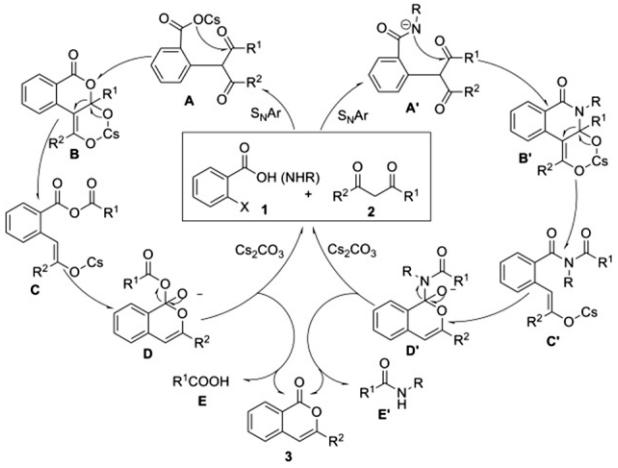
[a] All reactions were carried out in the presence of 0.2 mmol **5**, 0.4 mmol **2** and 0.2 mmol Cs_2CO_3 in 2 mL of CH_3CN at 100 °C; 4 h–10 h for **6a**–**6d**, 24 h for **7a**–**7e**.
[b] Isolated yield.

A″ was obtained in a high yield (Scheme 2, eq. 1). Following, the second reaction of compound **A**″ was carried out in the presence of Cs_2CO_3 (1.0 equiv) in CH_3CN at 100 °C, and the isocoumarin of **3a** was obtained in 80% yield (Scheme 2, eq. 2). The results showed that our suggestion is correct and the formation of precipitate is the intermediate of **A**. Beside the desired product of isocoumarin, the byproduct of acid was also produced in this transformation. In order to obtained the straightforward evidence. We changed the pentane-2,4-dione to 1,3-diphenylpropyldiketone and reacted with 2-iodobenzoic acid under the identical reaction conditions (Scheme 2, eq. 3). After the acidification, the byproduct of benzoic acid really was obtained. In sum, these results provided an important and direct evidence for us to understand the mechanism proposed.



Scheme 2. Verification mechanism.

Based on the experimental results and our understanding of the reaction, a possible mechanism was proposed (Scheme 3). It consists of four key steps: (1) the reaction of substrate **1** with nucleophile **2** produced intermediate **A** or **A**′ via S_NAr[11] substitution in the presence of a base; (2) the cyclic product **B** or **B**′ was formed; (3) intramolecular C–C bond cleavage occurred to form **C** or **C**′ by heating; and (4) the oxygenic anion attacked the carbon of the anhydride to obtain the important compound **D** or **D**′, which released **E** or **E**′ and furnished the final product **3**.



Scheme 3. Proposed mechanism.

3. Conclusion

In summary, a simple, practical, and highly efficient base-promoted method has been developed for the synthesis of substituted isocoumarins and isoquinolinones. The protocol uses readily available substituted 2-iodobenzoic acid and 2-iodo-*N*-phenyl–benzamide as the starting materials. The inexpensive Cs_2CO_3 is used as the base, and CH_3CN as the solvent. The corresponding products were afforded in good to excellent yields. Compared to the expensive transition-metal catalyzed reaction, the process showed considerable synthetic advantages in terms of mild reaction condition, environmentally friendly and low cost.

4. Experimental section

4.1. General remark

Column chromatography was carried out on silica gel. ^1H NMR spectra were recorded on 400 MHz in $CDCl_3$ and ^{13}C NMR spectra were recorded on 100 MHz in $CDCl_3$ using TMS as internal standard. IR spectra were recorded on a FT-IR spectrometer and only major peaks are reported in cm^{-1}. All new compounds were further characterized by HRMS (ESI) Calcd; copies of their ^1H NMR and ^{13}C NMR spectra are provided. Commercially available reagents and solvents were used without further purification.

4.2. Representative procedure

A mixture of 2-iodobenzoic **1a** (0.2 mmol), acetylacetone **2a** (0.4 mmol), and Cs_2CO_3 (65.2 mg, 0.20 mmol) in CH_3CN was stirred at 100 °C. When the reaction was considered complete as determined by TLC analysis, the reaction was allowed to cool to room temperature and quenched by water, and the mixture was

extracted with CH_2Cl_2. The combined organic extracts were washed with water and saturated brine. The organic layers were dried over Na_2SO_4, filtered. Solvents were evaporated under reduced pressure. The residue was purified by chromatography on silica gel to afford isocoumarins derivatives and isoquinolone derivatives.

4.3. Characterization data of compounds

*4.3.1. 3-Methyl-isochromen-1-one (**3a**, **3b**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24–8.22 (d, J=8.0 Hz, 1H), 7.68–7.64 (t, J=7.6 Hz, 1H), 7.45–7.42 (t, J=7.6 Hz, 1H), 7.34–7.32 (d, J=7.6 Hz, 1H), 6.25 (s, 1H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.9, 154.5, 137.6, 134.6, 129.4, 127.5, 124.8, 119.8, 103.5, 19.6 IR (neat, cm^{-1}): 3423, 2920, 2358, 1719, 1437, 1065, 763, 687. HRMS (ESI) Calcd for $C_{10}H_8O$: M+H=161.0597, Found: 161.0600.

*4.3.2. 6-Chloro-3-methyl-isochromen-1-one (**3c**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18–8.16 (d, J=8.4 Hz, 1H), 7.41–7.38 (dd, J=2.0 Hz, 8.4 Hz, 1H), 7.32 (d, J=1.6 Hz, 1H), 6.20 (s, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1, 156.1, 141.4, 138.9, 131.2, 128.0, 124.4, 118.2, 102.6, 19.7 IR (neat, cm^{-1}): 3402, 2921, 2361, 1744, 1331, 1052, 772, 678. HRMS (ESI) Calcd for $C_{10}H_7ClO_2$: M+H=195.0207, Found: 195.0212.

*4.3.3. 3,5-Dimethyl-isochromen-1-one (**3d**, **3e**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11–8.09 (d, J=8.0 Hz, 1H), 7.50–7.48 (d, J=7.6 Hz, 1H), 7.34–7.30 (t, J=7.6 Hz, 1H), 6.36 (s, 1H), 2.43 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2, 154.0, 136.2, 135.5, 132.4, 127.2, 126.9, 119.8, 100.3, 19.8, 19.6 IR (neat, cm^{-1}): 3418, 2943, 2330, 1717, 1426, 1035, 767, 594. HRMS (ESI) Calcd for $C_{11}H_{10}O_2$: M+H=175.0754, Found: 175.0759.

*4.3.4. 7-Chloro-3,5-dimethyl-isochromen-1-one (**3g**).* [1] H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, J=2.0 Hz, 1H), 7.46 (m, 1H), 6.32 (s, 1H), 2.42 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1, 154.5, 135.6, 134.8, 134.6, 132.5, 126.6, 121.1, 99.8, 19.9, 18.5 IR (neat, cm^{-1}): 3399, 2924, 1730, 1655, 1381, 1066, 913, 744. HRMS (ESI) Calcd for $C_{11}H_9ClO_2$: M+H=209.0364, Found: 209.0359.

*4.3.5. 7-Fluoro-3-methyl-isochromen-1-one (**3i**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91–7.88 (dd, J=2.4 Hz, 8.8 Hz, 1H), 7.40–7.33 (m, 2H), 6.25 (s, 1H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.6–160.2 (d, J_{C-F}=247.0 Hz), 162.0 (d, J_{C-F}=3.0 Hz), 153.9 (d, J_{C-F}=2.0 Hz), 134.0 (d, J_{C-F}=3.0 Hz), 127.0 (d, J_{C-F}=8.0 Hz), 123.2–122.9 (d, J_{C-F}=23.0 Hz), 121.4 (d, J_{C-F}=8.0 Hz), 115.0–114.8 (d, J_{C-F}=23.0 Hz), 102.7, 19.4 IR (neat, cm^{-1}): 3421, 2922, 1727, 1495, 912, 744. HRMS (ESI) Calcd for $C_{10}H_7FO_2$: M+H=175.0503, Found: 175.0746.

*4.3.6. 7-Methoxy-3-methyl-isochromen-1-one (**3k**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (s, 1H), 7.26 (d, J=1.2 Hz, 2H), 6.21 (s, 1H), 3.88 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1, 158.9, 152.3, 131.3, 126.3, 124.4, 120.8, 109.7, 103.1, 55.6, 19.3 IR (neat, cm^{-1}): 3420, 2957, 2920, 1721, 1501, 1025, 824, 775, 587. HRMS (ESI) Calcd for $C_{11}H_{10}O_3$: M+H=191.0703, Found: 191.0706.

*4.3.7. 7-Methyl-pyrano[4,3-b]pyridin-5-one (**3l**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.89–8.87 (dd, J=2.0 Hz, 4.8 Hz, 1H), 8.50–8.48 (dd, J=1.2 Hz, 8.0 Hz, 1H), 7.40–7.37 (dd, J=4.8 Hz, 8.0 Hz, 1H), 6.54 (s, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.6, 158.8, 156.1, 154.9, 137.5, 122.5, 116.2, 105.8, 19.9 IR (neat, cm^{-1}): 3399, 1737, 1655, 1217, 1068, 913, 772, 745. HRMS (ESI) Calcd for $C_9H_7NO_2$: M+H=162.0550, Found: 162.0554.

*4.3.8. 3-Phenyl-isochromen-1-one (**4a**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29–8.27 (d, J=8.0 Hz, 1H), 7.87–7.85 (dd, J=1.6 Hz, 8.0 Hz, 2H), 7.71–7.67 (m, 1H), 7.48–7.42 (m, 5H), 6.93 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.2, 153.5, 137.4, 134.7, 131.8, 129.8, 129.5, 128.7, 128.0, 125.9, 125.1, 120.4, 101.7 IR (neat, cm^{-1}): 3447, 3062, 1728, 1234, 1067, 766, 689, 527. HRMS (ESI) Calcd for $C_{15}H_{10}O_2$: M+H=223.0752, Found: 223.0755.

*4.3.9. 3,4-Dimethyl-isochromen-1-one (**4b**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31–8.29 (dd, J=0.8 Hz, 8.0 Hz, 1H), 7.76–7.72 (m, 1H), 7.51–7.45 (m, 2H), 2.32 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.8, 150.1, 138.6, 134.6, 129.6, 127.1, 122.3, 120.4, 107.6, 17.3, 12.2IR (neat, cm^{-1}): 3403, 2923, 1719, 1650, 1085, 745, 692. HRMS (ESI) Calcd for $C_{11}H_{10}O_2$: M+H=175.0754, Found: 175.0759.

*4.3.10. 1-Oxo-3-phenyl-1H-isochromene-4-carboxylic acid ethyl ester (**4c**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37–8.35 (d, J=7.6 Hz, 1H), 7.81–7.77 (m, 2H), 7.75–7.73 (d, J=7.6 Hz, 2H), 7.65–7.63 (m, 1H), 7.59–7.45 (m, 3H), 4.23–4.17 (dd, J=7.2 Hz, 14.0 Hz, 2H), 1.06–1.02 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2, 161.0, 155.3, 135.2, 134.6, 132.5, 130.5, 129.8, 128.7, 128.4, 128.1, 124.1, 119.7, 110.9, 61.8, 13.5 IR (neat, cm^{-1}): 3400, 2984, 2361, 1723, 1241, 1091, 1019, 768, 693. HRMS (ESI) Calcd for $C_{18}H_{14}O_4$: M+H=295.0965, Found: 295.0970.

*4.3.11. 3,3-Dimethyl-3,4-dihydro-2H-benzo[c]chromene-1,6-dione (**4d**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.05–9.03 (d, J=8.4 Hz, 1H), 8.29–8.27 (dd, J=0.8 Hz, 8.0 Hz, 1H), 7.81–7.77 (m, 1H), 7.55–7.51 (t, J=7.6 Hz, 1H), 2.80 (s, 2H), 2.52 (s, 2H), 1.18 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.8, 167.9, 160.6, 135.5, 133.8, 129.5, 128.3, 125.7, 119.7, 110.5, 52.8, 42.5, 31.9, 28.1 IR (neat, cm^{-1}): 3399, 2958, 2361, 1743, 1672, 1370, 1028, 768, 689. HRMS (ESI) Calcd for $C_{15}H_{14}O_3$: M+H=243.1016, Found: 243.1010.

*4.3.12. N-Phenylacetamide (**6a**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (s, 1H), 7.51–7.49 (d, J=7.2 Hz, 2H), 7.30–7.27 (t, J=6.8 Hz, 2H), 7.10–7.07 (t, J=6.8 Hz, 1H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7, 137.9, 128.8, 124.2, 119.9, 24.4 IR (neat, cm^{-1}): 3552, 2930, 1550, 1321, 758, 535.

*4.3.13. N-Pyridin-2-yl-acetamide (**6d**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (s, 1H), 8.26–8.25 (d, J=4.0 Hz, 1H), 8.22–8.19 (d, J=4.4 Hz, 1H), 7.73–7.68 (m, 1H), 7.05–7.02 (m, 1H), 2.20 (s, 3H)^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 151.4, 147.6, 138.4, 119.7, 114.0, 24.7 IR (neat, cm^{-1}): 3388, 2923, 1685, 1434, 1303, 744.

*4.3.14. 3,3-Dimethyl-5-phenyl-3,4-dihydro-2H,5H-phenanthridine-1,6-dione (**7a**).* \$^1$H NMR (400 MHz, $CDCl_3$): δ 9.34–9.31 (d, J=8.8 Hz, 1H), 8.42–8.39 (dd, J=1.2 Hz, 8.0 Hz, 1H), 7.79–7.75 (m, 1H), 7.60–7.51 (m, 4H), 7.23–7.21 (m, 2H), 2.49 (s, 2H), 2.38 (s, 2H), 1.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.0, 163.0, 152.4, 138.2, 134.0, 133.8, 130.0, 129.1, 128.2, 127.8, 127.1, 126.1, 124.5, 110.4, 52.5, 43.8, 32.1, 28.0 IR (neat, cm^{-1}): 3397, 2361, 1736, 1654, 913, 744, 662. HRMS (ESI) Calcd for $C_{21}H_{19}NO_2$: M+H=318.1489, Found: 318.1482.

*4.3.15. 3,3-Dimethyl-5-(3-nitro-phenyl)-3,4-dihydro-2H,5H-phenanthridine-1,6-dione (**7c**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.32–9.30 (d, J=8.0 Hz, 1H), 8.42–8.36 (m, 2H), 8.16–8.15 (t, J=2.0 Hz, 1H), 7.81–7.77 (m, 2H), 7.63–7.60 (m, 1H), 7.55–7.51 (m, 1H), 2.55–2.46 (dd, J=16.0 Hz, 19.6 Hz, 2H), 2.42–2.28 (dd, J=17.6 Hz, 39.6 Hz, 2H), 1.07 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.6, 162.8, 150.8, 149.2, 139.2, 134.9, 134.2, 133.9, 130.9, 127.8, 127.5, 126.3, 124.2, 124.2, 124.0, 111.0, 52.4, 44.0, 32.3, 28.2, 27.8 IR (neat, cm^{-1}): 3400, 1655, 1532, 1381, 913, 745. HRMS (ESI) Calcd for $C_{21}H_{18}N_2O_4$: M+H=363.1339, Found: 363.1329.

*4.3.16. 2-(1-Acetyl-2-hydroxy-propenyl)–benzoic acid (**A″**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11–8.09 (d, J=7.6 Hz, 1H), 7.62–7.58 (t,

J=7.6 Hz, 1H), 7.49–7.45 (t, J=7.6 Hz, 1H), 7.28–7.26 (d, J=7.2 Hz, 1H), 1.81 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.5, 171.9, 138.2, 133.2, 133.2, 131.6, 130.5, 128.2, 23.9; IR (neat, cm-1): 3422, 3007, 2689, 1687, 1602, 1407, 1301, 1267, 919, 767. ESI-MS: m/z=220 $[M+H]^+$

4.4. X-ray crystallographic data

CCDC 828822 and CCDC 828823 contain the supplementary crystallographic data for compound **3a** and **7c** of this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.04.111.

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