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Molecular iodine-catalyzed C3-alkylation of 4-hydroxycoumarins with secondary benzyl alcohols

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ABSTRACT

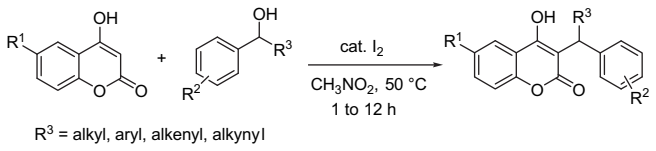
A highly efficient method for the C–C bond formation via molecular iodine-catalyzed C3-alkylation reaction of 4-hydroxycoumarins with benzylic, benzhydrylic, allylic, and propargyl alcohols at 50 °C in $MeNO_2$ is described. The 3-alkylated-4-hydroxycoumarins were obtained in good yields (up to 97%). By applying this reaction as the key step, a multi-substituted pyranocoumarin can easily be synthesized in a one-pot procedure. The advantages of this method are broad scope, mild conditions, and easy handling since water is the only side product.

1. Introduction

Coumarin is a privileged oxygen heterocycle widely distributed throughout the plant kingdom[1] and has received considerable attention since they exhibit a wide range of biological activities such as anti-HIV, antimalarial, antibacterial, and cytotoxic.[2] Among the various substituted coumarins, 3-(benzyl)-substituted 4-hydroxycoumarins represent a significant class of compounds because of the frequent existence of such structures in clinical pharmaceuticals,[3] such as Warfarin, Coumatetralyl, Bromadialone, and Difenacoum, and their role as valuable synthetic intermediates, which can be highly diversified in several ways to synthesize 3,4-substituted compounds.[4] Thus, the development of new methods for the efficient and selective preparation of 3-substituted 4-hydroxycoumarins is of great interest in organic chemistry.

Although there are several reports in the literatures about the C3-alkylation of 4-hydroxycoumarins, most of them need organic halides or boronic acid as substrates by Pd-catalyzed C–C bond formation or base mediated alkylation reactions.[5] From the synthetic point of view, alcohols are an attractive source compared to the corresponding halides or boronic acid. So far as we know, there is a limited number of examples known for the alkylation of 4-hydroxycoumarins with alcohols in the presence of strong acids,[6] and recently $Yb(OTf)_3$[7] and Amberlite IR-120.[8] Hence, the development of new, efficient, catalytic method for direct C3-alkylation of 4-hydroxycoumarins using alcohols is of great importance and highly desirable.

Recently, molecular iodine has received considerable attention as an inexpensive and readily available catalyst for various organic transformations due to its moderate Lewis acidity and water tolerance.[9] Previously, we reported several molecular iodine-catalyzed organic reactions.[10] As a part of our ongoing research into the discovery and development of new synthetic methods of important organic products,[11] herein we describe a highly efficient method for the C–C bond formation via molecular iodine-catalyzed C3-alkylation reaction of 4-hydroxycoumarins with benzylic, benzhydrylic, allylic, and propargyl alcohols (Scheme 1).



Scheme 1.

2. Results and discussion

The selected model reaction was carried out with 4-hydroxycoumarin (**1a**) and 1-phenylethanol (**2a**) in the presence of molecular iodine and the results are summarized in Table 1. We examined several organic solvents, which are commercially available and used

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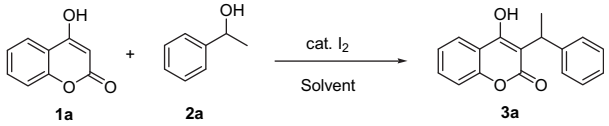
without further purification or drying. We found that a remarkable solvent effect existed in 10 mol % iodine-catalyzed reaction. Only the highly polar solvent such as nitromethane is good solvent for good yield under reflux for 0.3 h and the corresponding 3-alkylated-4-hydroxycoumarin (**3a**) was obtained (Table 1, entry 5), while the other solvents such as THF, MeCN, DCE, and DCM gave no product (Table 1, entries 1–4). When the model reaction was carried out at 50 °C, the desired product (**3a**) was obtained with improved yield although the reaction time was prolonged to 12 h (Table 1, entry 6). Furthermore, the reaction was accelerated when the amount of catalyst was increased to 20 mol %, but the yield didn't change (Table 1, entry 7). When the reaction was catalyzed by 5 mol % iodine, the reaction time was prolonged to 60 h and the desired product (**3a**) was obtained with only 27% (Table 1, entry 8). Thus, the most suitable reaction conditions for the formation of **3a** were established (Table 1, entry 6).

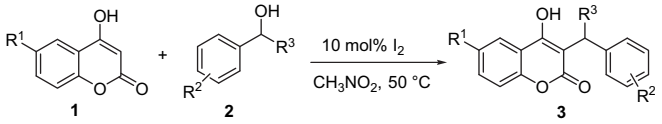
Table 1
Screening for the reaction conditions[a]



Entry	Cat. (mol %)	Solvent	Temp	Time (h)	Yield[b] (%)
1	10	THF	Reflux	1	0
2	10	MeCN	Reflux	1	0
3	10	DCE	Reflux	1	0
4	10	DCM	Reflux	1	0
5	10	$MeNO_2$	Reflux	0.3	72
6	10	$MeNO_2$	50 °C	12	74
7	20	$MeNO_2$	50 °C	3	74
8	5	$MeNO_2$	50 °C	60	27

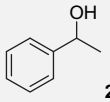
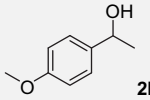
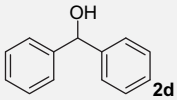
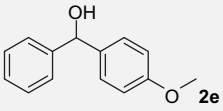
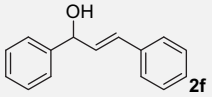
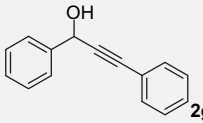
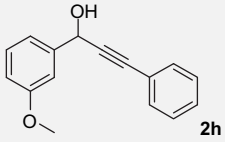
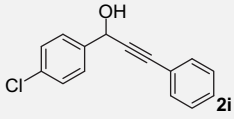
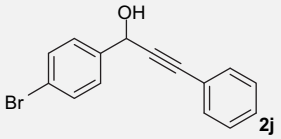
[a] 1.0 mmol **1a**, 1.2 mmol **2a**, cat. I_2 in 10 mL solvent.
[b] Isolated yield.

To reveal the generality of this method, the scope of the reaction was investigated with a variety of reactants under optimized reaction conditions (Scheme 2), and the results are presented in Table 2. From the results of Table 2, the protocol has proven to be useful for benzylation of 4-hydroxycoumarins **1a**–**1c** with variety of secondary benzyl alcohols **2a**–**2j** (Table 2). First, we examined a number of secondary benzylic alcohols **2a**–**2c** as well as 4-hydroxycoumarin **1a**. We obtained the corresponding C3-alkylated products **3a**–**3c** in 74–84% yields for 12 h (Table 2, entries 1–3). The reaction could give higher yields when benzylic alcohols were bearing electron-donating groups such as methoxy (Table 2, entry 2,). Then, we have tested the efficiency of benzhydrylic alcohols **2d** and **2e** in the alkylation of 4-hydroxycoumarins **1a** and **1b**, and found that the reaction proceeded smoothly to give the corresponding C3-benzylated products **3d**, **3e**, and **3i** in good yields for 4 h (Table 2, entries 4, 5, and 9). Furthermore, we performed this reaction with allylic alcohol **2f** and 4-hydroxycoumarin **1a**–**1c** using the established procedure, getting the corresponding C3-benzylated products **3f**, **3h**, and **3k**, and the reaction time was reduced to 1 h. Finally, using the optimized reaction conditions, we investigated 4-hydroxycoumarin **1a**–**1b** and propargyl alcohols **2g**–**2j** underwent the mild nucleophilic substitution process to generate **3g**, **3l**–**3n** in moderate to good yields (65–80%), and the reaction time was only 1 h.



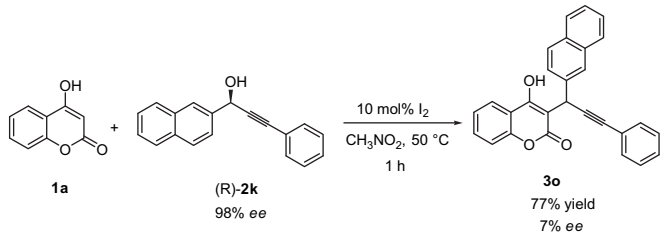
Scheme 2.

Table 2
C3-alkylation of 4-hydroxycomarins[a]

Entry	R^1	Alcohol	Product	Time (h)	Yield[b] (%)
1	H (**1a**)	 **2a**	**3a**	12	74
2	**1a**	 **2b**	**3b**	12	84
3	**1a**	 **2c**	**3c**	12	76
4	**1a**	 **2d**	**3d**	4	82
5	**1a**	 **2e**	**3e**	4	97
6	**1a**	 **2f**	**3f**	4	92
7	**1a**	 **2g**	**3g**	1	80
8	EtO (**1b**)	**2f**	**3h**	1	79
9	**1b**	**2d**	**3i**	4	67
10	**1b**	**2g**	**3j**	1	68
11	Cl (**1c**)	**2f**	**3k**	1	77
12	**1a**	 **2h**	**3l**	1	65
13	**1a**	 **2i**	**3m**	1	74
14	**1a**	 **2j**	**3n**	1	79

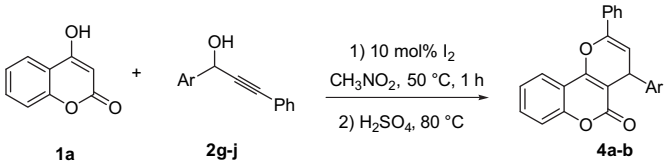
[a] 1.0 mmol **1**, 1.2 mmol **2**, 0.1 mmol I_2 in 10 mL $MeNO_2$ at 50 °C.
[b] Isolated yield.

To probe the reaction mechanism of this I_2-catalyzed alkylation reaction, (*R*)-1-(naphthalen-2-yl)-3-phenylprop-2-yn-1-ol [(*R*)-**2k**, 98% ee] was treated with 4-hydroxycoumarin **1a** under the typical reaction conditions (Scheme 3). After 1 h, product **3o** was isolable in 77% yield with 7% ee. It was obvious that the reaction provided poor enantiomeric excess. Even though the exact reaction mechanism is not quite clear at the moment, the alkylation of the investigated secondary benzyl alcohols most likely proceeds via S_N1 pathway, which is well supported by the above experiment.



Scheme 3.

After successful C3-alkylation of 4-hydroxycoumarin with secondary benzyl alcohols, to further diversify the obtained products, we turned our attention to the application of this method to a one-pot synthesis of pyranocoumarin, which is a key structural unit in many biological active compounds.[12] As shown in Scheme 4, treatment of 4-hydroxycoumarin **1a** with propargylic alcohols **2g–2j** in the presence of 10 mol % iodine followed by addition of concd H_2SO_4 allowed the isolation of multi-substituted pyranocoumarin **4** in moderate yields (Table 3, entries 1–4). This method provides a mild and straightforward route to multi-substituted pyranocoumarins.



Scheme 4.

Table 3
One-pot synthesis of pyranocoumarins[a]

Entry	Alcohol	Product	Yield[b] (%)
1	**2g**	**4a**	65
2	**2h**	**4b**	53
3	**2i**	**4c**	60
4	**2j**	**4d**	61

[a] 1.0 mmol **1**, 1.2 mmol **2**, 0.1 mmol I_2 in 10 mL $MeNO_2$ at 50 °C for 1 h, then 0.05 mL concd sulfuric acid was added and the mixture was stirred at 80 °C overnight.
[b] Isolated yield.

3. Conclusion

In summary, we have successfully employed molecular iodine as an efficient catalyst to promote C3-benzylation of 4-hydroxycoumarin reactions of 4-hydroxycoumarin using secondary benzyl alcohols such as benzylic, benzhydrylic, allylic, and propargyl alcohols, affording the 3-(benzyl)-substituted 4-hydroxycoumarin derivatives in yields of up to 97%. The advantages of this protocol are broad scope, mild conditions, use of inexpensive catalyst, and simplicity of operation since water is the only side product. Furthermore, by applying this reaction as the key step, the multi-substituted pyranocoumarins can easily be synthesized from 4-hydroxycoumarin and propargylic alcohols in a one-pot procedure. This method provides a mild and straightforward route to multi-substituted pyranocoumarins.

4. Experimental

4.1. General

Melting points were obtained on a microscopical instrument and uncorrected. NMR spectra were recorded at 400 MHz spectrometer and TMS as internal standard. IR spectra were recorded on an FT-IR spectrometer. Low-resolution MS was obtained using ESI ionization. Elemental analyses were carried out on EA1112 instrument. All reagents and solvents used were commercially available. Column chromatography was carried out on silica gel (300–400 mesh) with mixed solvents (hexane/ethyl acetate).

4.2. General experimental procedure for the C3-alkylation of 4-hydroxycoumarins

To a mixture of 4-hydroxycoumarin (1.0 mmol) and secondary benzyl alcohol (1.2 mmol) in a $MeNO_2$ (10 mL), I_2 (0.1 mmol) was added and the reaction mixture was stirred for the given time (see Table 2) at 50 °C. After completion of the reaction (monitored by TLC), to the reaction mixture was added saturated solution of Na_2SO_3 and extracted with ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by silica gel column with hexane/ethyl acetate (1:2) as eluent to afford the corresponding C3-alkylated 4-hydroxycoumarin **3**.

4.3. General experimental procedure for one-pot synthesis of pyranocoumarin

To a mixture of 4-hydroxycoumarin (1.0 mmol) and propargyl alcohol (1.2 mmol) in a $MeNO_2$ (10 mL), I_2 (0.1 mmol) was added and the reaction mixture was stirred for 1 h at 50 °C. Then, 0.05 mL concd sulfuric acid was added and the mixture was stirred at 80 °C overnight. After completion of the reaction, to the reaction mixture was added saturated solution of $Na_2S_2O_3$ and extracted with ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by silica gel column with hexane/ethyl acetate (1:4) as eluent to afford the corresponding pyranocoumarin **4**.

4.4. Characterization data

*4.4.1. 4-Hydroxy-3-(1-phenylethyl)-2H-chromen-2-one (**3a**)*[8]. White solid; mp: 204–205 °C. IR (KBr): 3256, 1672, 1626, 1496, 1395, 1215, 1167, 752 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.7 (d, J=8.4 Hz, 1H), 7.52–7.49 (m, 3H), 7.43 (m, 2H), 7.34–7.21 (m, 3H), 6.42 (br s, 1H), 4.74 (q, J=6.4 Hz, 1H), 1.68 (d, J=6.4 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 159.8, 152.4, 141.6, 131.8, 129.6, 127.7, 127.3, 123.8, 122.9, 116.3, 116.0, 110.0, 34.5, 16.5 ppm. MS (ESI): m/z 265 ($[M-1]^-$).

*4.4.2. 4-Hydroxy-3-(1-(4-methoxyphenyl)ethyl)-2H-chromen-2-one (**3b**).* White solid; mp: 169–171 °C. IR (KBr): 3398, 2968, 1672, 1626, 1511, 1246 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, J=8.0 Hz, 1H), 7.52–7.48 (m, 1H), 7.40 (d, J=8.4 Hz, 2H), 7.30–7.21 (m, 2H), 7.40 (d, J=8.4 Hz, 2H), 6.47 (br s, 1H), 4.66 (q, J=7.6 Hz, 1H), 3.81 (s, 3H), 1.64 (d, J=7.6 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5, 159.8, 159.0, 152.4, 133.0, 131.7, 128.4, 123.8, 122.8, 116.3, 116.1, 114.9, 110.0, 55.3, 33.7, 16.7 ppm. MS (ESI): m/z 295 ($[M-1]^-$). Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.95; H, 5.41.

*4.4.3. 4-Hydroxy-3-(1-p-tolylethyl)-2H-chromen-2-one (**3c**).* White solid; mp: 165–166 °C. IR (KBr): 3405, 3236, 1673, 1624, 1567, 1497, 1394, 1217, 1164, 755 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.69 (dd, J=6.8, 8.0 Hz, 1H), 7.52–7.48 (m, 1H), 7.38 (d, J=8.4 Hz, 2H), 7.30–7.20 (m, 4H), 6.47 (br s, 1H), 4.69 (q, J=7.2 Hz, 1H), 2.35 (s, 3H), 1.65 (d, J=7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 159.8, 152.4, 138.3, 137.5, 131.7, 130.3, 127.1, 123.8, 122.9, 116.3, 116.1, 110.0, 34.1, 21.0, 16.5 ppm. MS (ESI): m/z 279 ($[M-1]^-$). Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.07; H, 5.75.

*4.4.4. 3-Benzhydryl-4-hydroxy-2H-chromen-2-one (**3d**)*[8]. White solid; mp: 180–181 °C. IR (KBr): 3293, 1671, 1624, 1608, 1567, 1494, 1450, 1388, 1211, 1085, 896, 756, 715 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.74 (dd, J=6.8, 8.0 Hz, 1H), 7.55–7.50 (m, 1H), 7.39–7.23

(m, 12H), 6.37 (br s, 1H), 5.98 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2, 160.1, 152.3, 139.9, 132.1, 129.4, 128.7, 127.7, 123.9, 123.1, 116.4, 115.9, 107.7, 47.2 ppm. MS (ESI): *m*/*z* 327 ([M−1]$^-$).

*4.4.5. 4-Hydroxy-3-((4-methoxyphenyl) (phenyl) methyl)-2H-chromen-2-one (**3e**)*[8]. Yellow solid; mp: 164–166 °C. IR (KBr): 3398, 1666, 1609, 1509, 1250, 1178, 1036, 756 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (dd, *J*=6.0, 7.6 Hz, 1H), 7.54 (m, 1H), 7.38–7.26 (m, 7H), 7.18 (d, *J*=8.4 Hz, 2H), 6.91 (d, *J*=8.8 Hz, 2H), 6.34 (s, 1H), 5.91 (s, 1H), 3.81 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2, 160.1, 159.0, 152.6, 140.2, 132.0, 131.6, 129.8, 129.3, 128.6, 127.6, 123.9, 123.1, 116.4, 115.9, 114.8, 107.8, 55.3, 46.5 ppm. MS (ESI): *m*/*z* 357 ([M−1]$^-$). Anal. Calcd for $C_{23}H_{18}O_4$: C, 77.08; H, 5.06. Found: C, 77.12; H, 5.02.

*4.4.6. (E)-3-(1,3-Diphenylallyl)-4-hydroxy-2H-chromen-2-one (**3f**)*[8]. White solid; mp: 155–157 °C. IR (KBr): 3327, 1671, 1624, 1610, 1494, 1392, 1201, 754 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (dd, *J*=6.8, 8.0 Hz, 1H), 7.54–7.50 (m, 1H), 7.42–7.24 (m, 13H), 6.79 (dd, *J*=6.0, 16.0 Hz, 1H), 6.52 (d, *J*=16.0 Hz, 1H), 5.47 (d, *J*=6.0 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2, 160.9, 152.6, 139.6, 136.1, 133.8, 132.1, 129.2, 128.6, 128.1, 128.0, 127.6, 126.5, 124.0, 123.1, 116.5, 115.8, 106.4, 43.9 ppm. MS (ESI): *m*/*z* 353 ([M−1]$^-$).

*4.4.7. 3-(1,3-Diphenylprop-2-ynyl)-4-hydroxy-2H-chromen-2-one (**3g**)*[8]. White solid; mp: 157–158 °C. IR (KBr): 3337, 3058, 1668, 1613, 1567, 1492, 1209, 756, 717, 693 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (br s, 1H), 7.86 (dd, *J*=6.8, 8.4 Hz, 1H), 7.61 (d, *J*=7.6 Hz, 2H), 7.56–7.50 (m, 3H), 7.38–7.25 (m, 8H), 5.79 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.6, 161.1, 152.6, 138.5, 132.3, 131.8, 129.1, 129.0, 128.5, 127.7, 127.1, 124.0, 123.4, 121.3, 116.4, 115.9, 104.9, 87.8, 86.4, 33.3 ppm. MS (ESI): *m*/*z* 351 ([M−1]$^-$).

*4.4.8. (E)-3-(1,3-Diphenylallyl)-6-ethoxy-4-hydroxy-2H-chromen-2-one (**3h**).* White solid; mp: 154–155 °C. IR (KBr): 3401, 1668, 1572, 1497, 1448, 1213, 1184, 746, 696 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43–7.24 (m, 11H), 7.19 (d, *J*=2.8 Hz, 1H), 7.12 (dd, *J*=6.0, 9.2 Hz, 1H), 6.99 (s, 1H), 6.75 (dd, *J*=6.0, 16.0 Hz, 1H), 6.52 (d, *J*=16.0 Hz, 1H), 5.48 (d, *J*=6.0 Hz, 1H), 4.03 (q, *J*=6.8 Hz, 2H), 1.14 (t, *J*=6.8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4, 160.8, 155.2, 147.1, 139.6, 136.1, 133.8, 129.2, 128.6, 128.2, 128.0, 128.0, 127.6, 126.5, 120.9, 117.6, 116.1, 106.5, 105.4, 64.1, 44.0, 14.7 ppm. MS (ESI): *m*/*z* 397 ([M−1]$^-$). Anal. Calcd for $C_{26}H_{22}O_4$: C, 78.37; H, 5.57. Found: C, 78.31; H, 5.52.

*4.4.9. 3-Benzhydryl-6-ethoxy-4-hydroxy-2H-chromen-2-one (**3i**).* White solid; mp: 222–223 °C. IR (KBr): 3384, 1697, 1628, 1585, 1495, 1443, 1396, 1272, 1251, 1228, 1180, 1043, 703 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.23 (m, 11H), 7.14–7.09 (m, 2H), 6.25 (s, 1H), 5.99 (s, 1H), 4.01 (q, *J*=6.8 Hz, 2H), 1.41 (t, *J*=6.8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4, 160.5, 155.2, 147.1, 140.0, 129.4, 128.7, 127.7, 120.9, 117.5, 116.1, 107.8, 105.4, 64.0, 47.3, 14.7 ppm. MS (ESI): *m*/*z* 371 ([M−1]$^-$). Anal. Calcd for $C_{24}H_{20}O_4$: C, 77.40; H, 5.41. Found: C, 77.31; H, 5.40.

*4.4.10. 3-(1,3-Diphenylprop-2-ynyl)-6-ethoxy-4-hydroxy-2H-chromen-2-one (**3j**).* White solid; mp: 165–167 °C. IR (KBr): 3333, 3601, 2979, 1673, 1624, 4575, 1493, 1275, 1187, 1047, 756, 692 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (s, 1H), 7.61 (d, *J*=7.6 Hz, 2H), 7.52–7.50 (m, 2H), 7.38–7.21 (m, 8H), 7.10 (dd, *J*=6.0, 8.8 Hz, 1H), 5.79 (s, 1H), 4.04 (q, *J*=7.2 Hz, 2H), 1.42 (t, *J*=7.23 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.7, 160.9, 155.2, 147.0, 138.5, 131.8, 129.1, 128.9, 128.5, 127.7, 127.0, 121.3, 121.1, 117.6, 116.1, 105.5, 105.0, 87.8, 86.5, 64.1, 33.3, 14.7 ppm. MS (ESI): *m*/*z* 395 ([M−1]$^-$). Anal. Calcd for $C_{26}H_{20}O_4$: C, 78.77; H, 5.09. Found: C, 78.77; H, 5.06.

*4.4.11. (E)-6-Chloro-3-(1,3-diphenylallyl)-4-hydroxy-2H-chromen-2-one (**3k**).* White solid; mp:159–161 °C. IR (KBr): 3326, 3026, 1673, 1621, 1566, 1488, 1379, 1269, 1199, 1156, 1116, 965, 745, 696 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J*=6.8 Hz, 1H), 7.48 (dd, *J*=6.4, 8.8 Hz, 1H), 7.41–7.25 (m, 11H), 7.08 (br s, 1H), 6.73 (dd, *J*=6.4, 16.4 Hz, 1H), 6.51 (d, *J*=16.4 Hz, 1H), 5.44 (d, 6.4 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.7, 159.8, 151.0, 139.2, 135.9, 134.1, 132.1, 129.5, 129.4, 128.7, 128.1, 128.0, 127.8, 127.7, 126.5, 122.8, 117.9, 117.0, 107.3, 44.0 ppm. MS (ESI): *m*/*z* 388 ([M−1]$^-$). Anal. Calcd for $C_{24}H_{17}ClO_3$: C, 74.13; H, 4.41. Found: C, 74.43; H, 4.30.

*4.4.12. 6-Chloro-4-hydroxy-3-(1-(3-methoxyphenyl)-3-phenylprop-2-ynyl)-2H-chromen-2-one (**3l**).* Brown solid; mp: 126–128 °C. IR (KBr): 3333, 1683, 1627, 1609, 1571, 1491, 1394, 1260, 1199, 1050, 759, 691 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (br s, 1H), 7.86 (d, *J*=8.4 Hz, 1H), 7.57–7.50 (m, 3H), 7.39–7.26 (m, 6H), 7.22–7.17 (m, 2H), 6.84 (d, *J*=8.4 Hz, 1H), 5.77 (s, 1H), 3.81 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.6, 161.2, 160.0, 152.6, 140.0, 132.4, 131.8, 130.0, 129.1, 128.5, 124.0, 123.4, 121.4, 119.3, 116.5, 115.9, 113.1, 112.9, 104.8, 87.8, 86.2, 55.3, 33.3 ppm. MS (ESI): *m*/*z* 381 ([M−1]$^-$). Anal. Calcd for $C_{25}H_{18}O_4$: C, 78.52; H, 4.74. Found: C, 78.50; H, 4.75.

*4.4.13. 6-Chloro-3-(1-(4-chlorophenyl)-3-phenylprop-2-ynyl)-4-hydroxy-2H-chromen-2-one (**3m**).* Yellow solid; mp: 174–175 °C. IR (KBr): 3311, 1679, 1614, 1570, 1210, 1164, 1109, 1071, 759, 692 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (s, 1H), 7.87 (dd, *J*=6.4, 8.0 Hz, 1H), 7.58–7.50 (m, 5H), 7.40–7.30 (m, 7H), 5.73 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.5, 161.3, 152.6, 137.1, 133.5, 132.5, 131.8, 129.4, 129.0, 128.6, 128.5, 124.2, 123.4, 121.0, 116.5, 115.8, 104.4, 88.2, 85.9, 32.9 ppm. MS (ESI): *m*/*z* 386 ([M−1]$^-$). Anal. Calcd for $C_{24}H_{15}ClO_3$: C, 74.52; H, 3.91. Found: C, 74.45; H, 3.86.

*4.4.14. 3-(1-(4-Bromophenyl)-3-phenylprop-2-ynyl)-6-chloro-4-hydroxy-2H-chromen-2-one (**3n**).* Yellow solid; mp: 179–180 °C. IR (KBr): 3422, 1677, 1625, 1611, 1570, 1490, 1202, 757 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (s, 1H), 7.87 (dd, *J*=6.8, 8.0 Hz, 1H), 7.55–7.47 (m, 7H), 7.38–7.30 (m, 5H), 5.71 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.5, 161.3, 152.6, 137.7, 132.5, 132.0, 131.8, 129.4, 128.9, 128.6, 124.1, 123.4, 121.7, 121.0, 116.5, 115.8, 104.3, 88.3, 85.9, 33.0 ppm. MS (ESI): *m*/*z* 431 ([M−1]$^-$). Anal. Calcd for $C_{24}H_{15}BrO_3$: C, 66.84; H, 3.51. Found: C, 66.74; H, 3.48.

*4.4.15. 4-Hydroxy-3-(1-(naphthalen-2-yl)-3-phenylprop-2-ynyl)-2H-chromen-2-one (**3o**).* Yellow solid; mp: 188–190 °C. 7% ee, determined by HPLC analysis (Chiralcel AD-H column, IPA/hexane=30:70, 254 nm); retention time: t_1=10.703 (53%) and t_2=12.895 (46%) min. IR (KBr): 3385, 1679, 1614, 1570, 1491, 1198, 758 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (br s, 1H), 8.08 (s, 1H), 7.87–7.80 (m, 4H), 7.68–7.66 (m, 1H), 7.56–7.46 (m, 5H), 7.40–7.25 (m, 5H), 5.95 (s, 1H) ppm. ^{13}C NMR (100 MHz, DMSO): δ 161.6, 161.4, 152.8, 137.4, 133.3, 133.0, 132.5, 132.1, 129.2, 128.8, 128.3, 127.9, 126.7, 126.2, 126.0, 124.5, 124.3, 123.5, 116.9, 116.6, 105.9, 89.3, 83.0, 33.0 ppm. MS (ESI): *m*/*z* 401 ([M−1]$^-$). Anal. Calcd for $C_{28}H_{18}ClO_3$: C, 83.57; H, 4.51. Found: C, 83.60; H, 4.51.

*4.4.16. 2,4-Diphenylpyrano[3,2-c]chromen-5(4H)-one (**4a**)*[12a]. White solid; mp: 173–175 °C. IR (KBr): 1716, 1631, 1610, 1493, 1454, 1387, 1271, 1205, 1169, 1112, 1013, 765, 698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (dd, *J*=6.4, 8.0 Hz, 1H), 7.75–7.72 (m, 2H), 7.59–7.55 (m, 1H), 7.48–7.38 (m, 6H), 7.36–7.30 (m, 3H), 7.25–7.21 (m, 1H), 5.85 (d, *J*=4.8 Hz, 1H), 4.72 (d, *J*=4.8 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.4, 155.6, 152.7, 146.8, 143.5, 132.5, 131.9, 129.2, 128.6, 128.6, 128.4, 127.2, 124.6, 124.1, 122.6, 116.7, 114.5, 103.7, 103.6, 36.5 ppm. MS (ESI): *m*/*z* 375 ([M+Na]$^+$).

*4.4.17. 4-(3-Methoxyphenyl)-2-phenylpyrano[3,2-c]chromen-5(4H)-one (**4b**)*[12b]. White solid; mp: 144–146 °C. IR (KBr): 1718, 1628, 1609, 1491, 1389, 1262, 1019, 766 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$):

δ 8.00 (d, J=8.0 Hz, 1H), 7.73–7.71 (m, 2H), 7.58–7.54 (m, 1H), 7.46–7.32 (m, 1H), 7.24–7.22 (m, 1H), 7.02–6.96 (m, 2H), 6.77 (dd, J=6.0, 8.4 Hz, 1H), 5.83 (d, J=4.2 Hz, 1H), 4.68 (d, J=4.2 Hz, 1H), 3.77 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.4, 159.8, 155.8, 152.7, 146.8, 145.1, 132.5, 132.0, 129.6, 129.2, 128.6, 124.6, 124.1, 122.6, 120.7, 116.7, 114.5, 112.2, 103.6, 103.4, 55.2, 36.5 ppm. MS (ESI): m/z 405 ($[M+Na]^+$).

*4.4.18. 4-(4-Chlorophenyl)-2-phenylpyrano[3,2-c]chromen-5(4H)-one (**4c**)*[12b]. Yellow solid; mp: 196–197 °C. IR (KBr): 1724, 1629, 1611, 1493, 1388, 1113, 1015, 760 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02–8.00 (m, 1H), 7.74–7.72 (m, 2H), 7.59–7.55 (m, 1H), 7.48–7.32 (m, 7H), 7.28–7.25 (m, 2H), 5.79 (d, J=5.6 Hz, 1H), 4.68 (d, J=5.6 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.4, 155.8, 152.7, 147.1, 142.0, 133.0, 132.4, 132.1, 129.8, 129.4, 128.7, 124.6, 124.2, 122.7, 116.8, 114.3, 103.2, 103.1, 36.0 ppm. MS (ESI): m/z 409 ($[M+Na]^+$).

*4.4.19. 4-(4-Bromophenyl)-2-phenylpyrano[3,2-c]chromen-5(4H)-one (**4d**)*[12b]. White solid; mp: 210–211 °C. IR (KBr): 1709, 1676, 1629, 1611, 1495, 1392, 1274, 1207, 1113, 1011, 763 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (dd, J=6.4, 8.0 Hz, 1H), 7.73–7.11 (m, 2H), 7.59–7.55 (m, 1H), 7.48–7.25 (m, 9H), 5.79 (d, J=4.8 Hz, 1H), 4.67 (d, J=4.8 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.4, 155.8, 152.7, 147.1, 142.5, 132.4, 132.2, 131.7, 130.2, 129.4, 128.7, 124.6, 124.2, 122.7, 121.1, 116.8, 114.3, 103.1, 103.0, 36.1 ppm. MS (ESI): m/z 453 ($[M+Na]^+$).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.09.007.

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