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SYNNTHESIS OF 2,3-DIHYDRO-4*H*-FURO[3,2-*c*]CHROMEN-4-ONE DERIVATIVES BY OXIDATIVE RADICAL CYCLIZATION OF 4-HYDROXY-2*H*-CHROMEN-2-ONE WITH ALKENES

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Abstract – Oxidative radical cyclization of 4-hydroxy-2*H*-chromen-2-one with aryl-substituted alkenes has been developed. 2,3-Dihydro-4*H*-furo[3,2-*c*]chromen-4-ones having substituents at the 2-position were produced when the reactions were carried out in the presence of CAN as an oxidant. Various substituted products were regioselectively synthesized via a successive cyclization.

The carbon–carbon bonds formation using free radicals have been extensively studied due to their versatile reactivities.[1] Among them, oxidative cyclization reactions of 1,3-dicarbonyl alkylradicals to alkenes are known as one of the useful methodology for the synthesis of cyclic compounds.[1-4] For example, we recently reported the total synthesis of brevione B using a diastereoselective oxidative coupling of a tricyclic diene with an α-pyrone (Scheme 1).[3] During the course of our studies on the related oxidative radical cyclization process,[3,4] we focused on the reactivity of 4-hydroxy-2*H*-chromen-2-one. It is expected that a 2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-one, which is included in natural products as the core structure,[5] could be obtained in one step. Herein, we describe an oxidative radical cyclization of aryl-substituted alkenes **1** with 4-hydroxy-2*H*-chromen-2-one (**2**), in which the substituted 2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-ones **3** were produced in a regioselective manner (Scheme 1).

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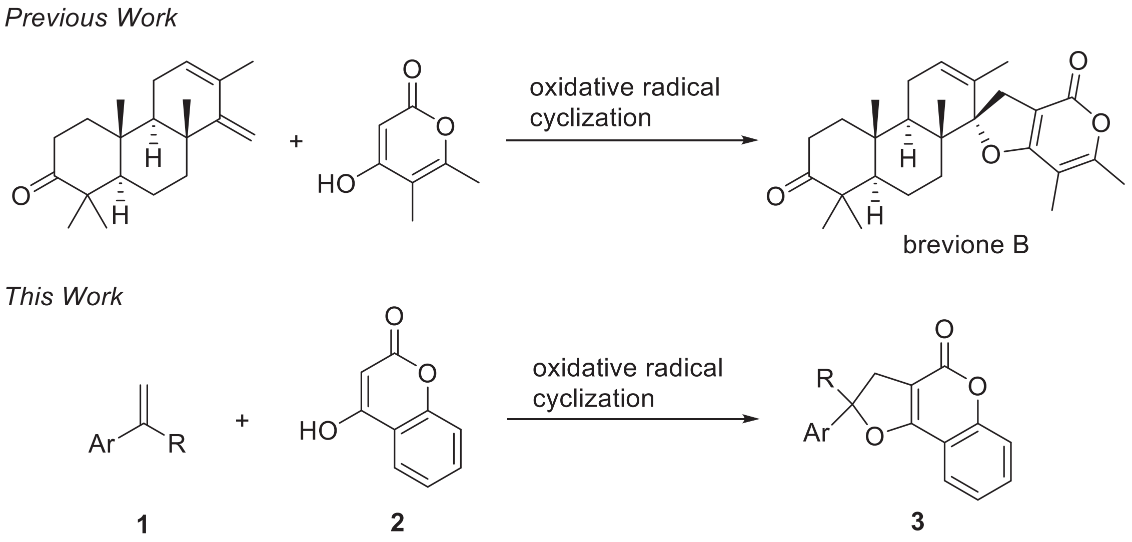
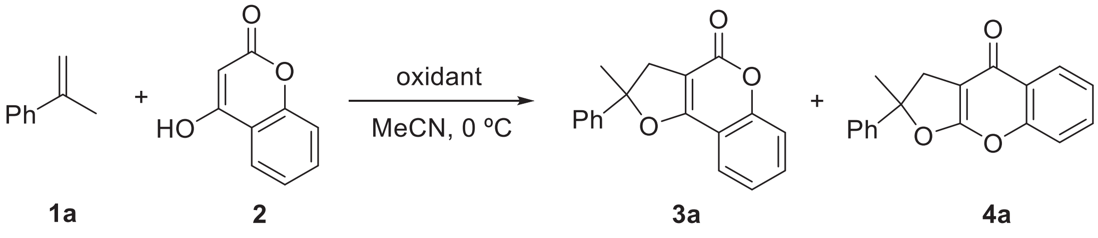
‡ This paper is dedicated to Professor Dr. Lutz F. Tietze on the occasion of his 75th birthday.



Scheme 1

The examinations were started using α-methylstyrene (**1a**) and 4-hydroxy-2*H*-chromen-2-one (**2**) (Table 1). When **1a** and **2** were treated with 2 equiv ceric ammonium nitrate (CAN) and 1 equiv $Cu(OAc)_2$ in MeCN at 0 °C according to our oxidative radical cyclization condition,[3,4,6] the expected 2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-one **3a** was produced. However, the yield of **3a** was 32% and the same amount of 2,3-dihydro-4*H*-furo[2,3-*b*]chromen-4-one **4a**, which is a regioisomer of **3a**, was also obtained (entry 1).[7] After several attempts, **3a** was selectively produced in the absence of $Cu(OAc)_2$ (entry 2). Finally, we found that the reaction in the presence of 3 equiv CAN afforded **3a** in 71% yield as a sole product (entry 3).

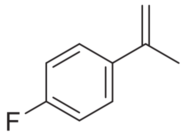
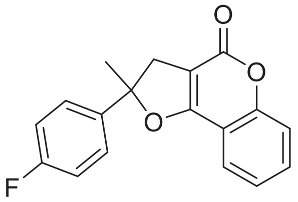
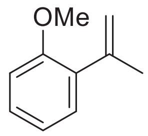
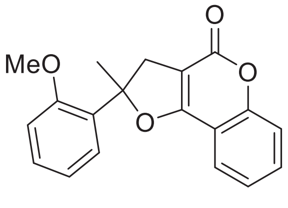
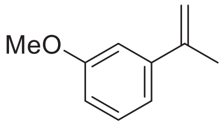
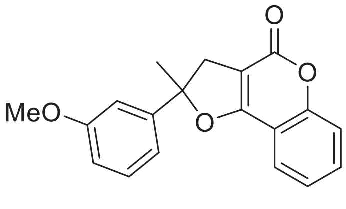
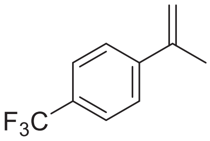
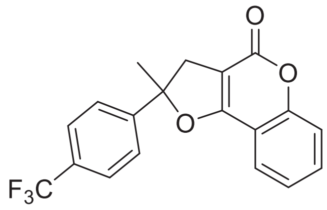
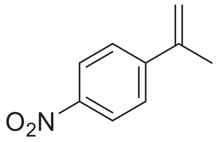
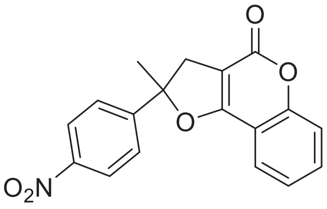
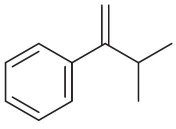
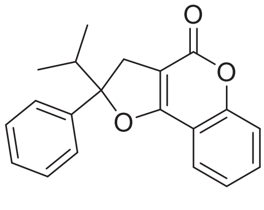
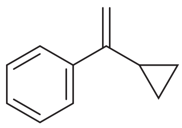
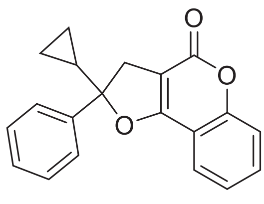
Table 1. Initial attempts using **1a** with **2**



Entry	Oxidant	Yield (%)[a]	
		3a	**4a**
1	CAN (2 equiv), $Cu(OAc)_2$ (1 equiv)	32	32
2	CAN (2 equiv)	56	7
3	CAN (3 equiv)	71	–

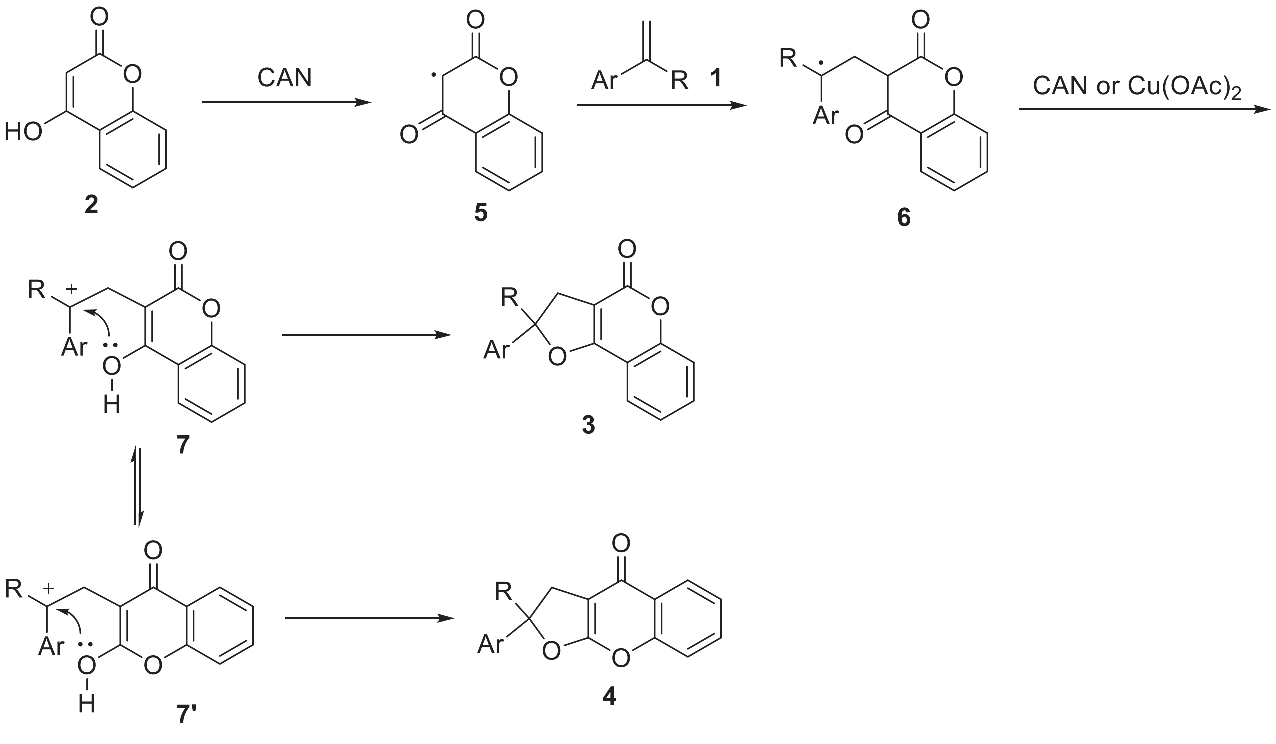
[a] Isolated yields.

Table 2. Reactions using aryl-substituted alkenes **1b–1h** with **2**

Entry	Substrate	Product	Yield (%)[a,b]
1	 **1b**	 **3b**	66
2	 **1c**	 **3c**	57
3	 **1d**	 **3d**	64
4	 **1e**	 **3e**	46
5	 **1f**	 **3f**	55
6	 **1g**	 **3g**	30
7	 **1h**	 **3h**	79

[a] All the reactions were carried out with **2** in the presence of 3 equiv CAN in MeCN at 0 ºC for 1 h. [b] Trace amont of the corresponding regioisomers **4** were observed in each case.

We next attempted the reactions using various aryl-substituted alkenes **1b–1h** (Table 2). When a 4-fluorophenyl-substituted substrate **1b** was subjected to the reaction with **2**, the 2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-one **3b** was produced in 66% yield (Table 2, entry 1). The reactions of 2- and 3-methoxyphenyl-substituted substrates **1c** and **1d** afforded the corresponding products **3c** and **3d** in 57% and 64% yields, respectively (entries 2 and 3). The substrates **1e** and **1f**, having an electron-withdrawing trifluoromethyl and nitro group on the aromatic ring, were transformed to the corresponding cyclized products **3e** and **3f** in moderate yields (entries 4 and 5). When the substrate **1g** containing an isopropyl group at the alkenyl position was subjected to the reaction, the corresponding products **3g** was obtained in low yield, presumably because of the steric hindrance of the isopropyl group (entry 6). On the other hand, the reaction of the substrate **1h** which contains a cyclopropyl moiety successfully afforded the cyclized product **3h** in 79% yield (entry 7).



Scheme 2

A plausible mechanism for the formation of 2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-ones is shown in Scheme 2. The radical species **5**, which results from a 4-hydroxy-2*H*-chromen-2-one (**2**) with CAN, reacts with the alkene **1** to give the benzylic radical intermediate **6**. The intermediate **6** is further oxidized with CAN leading to the cationic intermediate **7**, which causes intramolecular cyclization to afford the cyclized product **3**. There is equilibrium between **7** and the tautomeric intermediate **7'**, and the regioisomer **4** would be obtained when the cyclization occurs from **7'**. Information on the reaction mechanism was gained by the reaction of the resulting product **3** with CAN and Cu(OAc)$_2$. When the isolated **3a** was subjected to the reaction with 2 equiv CAN and 1 equiv Cu(OAc)$_2$ in MeCN at 0 °C, no reaction proceeded and the starting material **3a** was only recovered. This result indicates that conversion of the product **3** to the regioisomer **4** does not occur during the oxidative radical cyclization process. Although the reason for the production of **4** by the use of Cu(OAc)$_2$ as the oxidant is not clear, the equilibrium between **7** and **7'** would be altered depending on the type of oxidant, which controls the formation of **3** or **4**.

In conclusion, the studies described above have resulted in the synthesis of functionalized 2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-ones by the oxidative radical cyclization of alkenes with 4-hydroxy-2*H*-chromen-2-one. The reactions using various aryl-substituted alkenes afforded the corresponding cyclized product in a regioselective manner.

EXPERIMENTAL

All reactions were carried out under a positive atmosphere of argon in dried glassware unless otherwise indicated. Materials were obtained from commercial suppliers and used without further purification except when otherwise noted. Solvents were dried and distilled according to the standard protocols.

Typical Procedure for the Synthesis of 2,3-Dihydro-4*H*-furo[3,2-*c*]chromen-4-one 3.

Synthesis of 3a (entry 3 in Table 1): To a stirred solution of alkene **1a** (44.0 mg, 0.370 mmol) in acetonitrile (2 mL) was added 4-hydroxy-2*H*-chromen-2-one (**2**) (50.0 mg, 0.308 mmol) and CAN (507 mg, 0.925 mmol) at 0 °C. After stirring was continued for 1 h at the same temperature, the reaction was quenched with sat. aq. NH$_4$Cl. The contents were then extracted with AcOEt, and dried over anhydrous MgSO$_4$, filtered and concentrated. The residue was chromatographed on silica gel with hexane-AcOEt (80:20 v/v) as eluent to give the 2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-one **3a** (60.6 mg, 71%) as colorless crystals.

2-Methyl-2-phenyl-2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-one (3a): Yield 71%; colorless crystals; mp 114.9–117.1 ºC (recrystallized from CHCl$_3$/hexane); IR (KBr): 1715, 1648, 1498, 1413, 1281, 1033 cm^{-1}; ^{1}H-NMR (400 MHz, CDCl$_3$) 1.90 (3H, s), 3.35 (1H, d, J = 15.2 Hz), 3.44 (1H, d, J = 15.2 Hz), 7.30–7.35 (2H, m), 7.37–7.42 (3H, m), 7.44–7.47 (2H, m), 7.56–7.61 (1H, m), 7.78–7.80 (1H, m); ^{13}C-NMR (100 MHz, CDCl$_3$) 29.4 (CH$_3$), 41.6 (CH$_2$), 94.7 (Cq), 101.4 (Cq), 112.7 (Cq), 117.0 (CH), 122.7 (CH), 123.9 (CH), 124.2 (CH), 127.9 (CH), 128.6 (CH), 132.3 (CH), 144.7 (Cq), 155.0 (Cq), 160.5 (Cq), 165.2 (Cq); HRMS (ESI) *m/z* calcd for $C_{18}H_{14}O_3Na$ [M+Na]$^+$ 301.0841, found 301.0840.

2-Methyl-2-phenyl-2,3,3a,9a-tetrahydro-4*H*-furo[2,3-*b*]chromen-4-one (4a): Yield 32% (entry 1 in Table 1); colorless oil; IR (KBr): 1644, 1633, 1556, 1505, 1455, 1370 cm^{-1}; ^{1}H-NMR (400 MHz, CDCl$_3$)

1.89 (3H, s), 3.39 (1H, d, J = 15.2 Hz), 3.49 (1H, d, J = 15.2 Hz), 7.41–7.43 (3H, m), 7.45–7.47 (4H, m), 7.61–7.64 (1H, m), 8.23 (1H, d, J = 8.0 Hz); HRMS (ESI) *m/z* calcd for $C_{18}H_{14}O_3Na$ $[M+Na]^+$ 301.0841, found 301.0841.

2-(4-Fluorophenyl)-2-methyl-2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-one (3b): Yield 66%; colorless crystals; mp 119.3–122.0 ºC (recrystallized from $CHCl_3$/hexane); IR (KBr): 1714, 1644, 1498, 1412, 1278, 1224, 1161, 1033 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) 1.89 (3H, s), 3.34 (1H, d, J = 15.2 Hz), 3.40 (1H, d, J = 15.2 Hz), 7.06–7.01 (2H, m), 7.31–7.34 (1H, m), 7.39–7.45 (3H, m), 7.57–7.61 (1H, m), 7.76–7.78 (1H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) 29.4 (CH_3), 41.6 (CH_2), 94.3 (Cq), 101.4 (Cq), 112.6 (Cq), 115.5 (CH, d, J = 21.5 Hz), 117.0 (CH), 122.7 (CH), 124.0 (CH), 126.1 (CH, d, J = 8.2 Hz), 132.4 (CH), 140.5 (Cq, d, J = 4.1 Hz), 155.1 (Cq), 160.5 (Cq), 162.2 (Cq, d J = 245.4 Hz), 165.1 (Cq); HRMS (ESI) *m/z* calcd for $C_{18}H_{14}FO_3$ $[M+H]^+$ 297.0927, found 297.0927.

2-(2-Methoxyphenyl)-2-methyl-2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-one (3c): Yield 57%; colorless crystals; mp 168.6–169.6 ºC (recrystallized from $CHCl_3$/hexane); IR (KBr): 1715, 1650, 1502, 1411, 1248, 1022 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) 1.87 (3H, s), 3.40 (2H, s), 3.86 (3H, s), 6.94–6.99 (2H, m), 7.28–7.40 (3H, m), 7.55–7.59 (2H, m), 7.81–7.84 (1H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) 27.6 (CH_3), 40.7 (CH_2), 55.3 (CH_3), 94.3 (Cq), 102.5 (Cq), 111.3 (CH), 112.9 (Cq), 117.0 (CH), 120.4 (CH), 122.7 (CH), 123.8 (CH), 124.9 (CH), 129.1 (CH), 132.1 (CH), 132.7 (Cq), 155.0 (Cq), 155.3 (Cq), 161.0 (Cq), 164.8 (Cq); HRMS (ESI) *m/z* calcd for $C_{19}H_{17}O_4$ $[M+H]^+$ 309.1127, found 309.1131.

2-(3-Methoxyphenyl)-2-methyl-2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-one (3d): Yield 64%; colorless crystals; mp 136.1–139.9 ºC (recrystallized from $CHCl_3$/hexane); IR (KBr): 1714, 1644, 1311, 1212, 1083, 1034 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) 1.88 (3H, s), 3.33 (1H, d, J = 14.8 Hz), 3.43 (1H, d, J = 14.8 Hz), 3.82 (3H, s), 6.85 (1H, d, J = 8.0 Hz), 7.02 (2H, d, J = 8.0 Hz), 7.30–7.40 (3H, m), 7.56–7.60(1H, m), 7.78 (1H, d, J = 8.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) 29.4 (CH_3), 41.5 (CH_2), 55.3 (CH_3), 94.6 (Cq), 101.4 (Cq), 110.7 (CH), 112.5 (CH), 112.7 (Cq), 116.5 (CH), 117.0 (CH), 122.7 (CH), 123.9 (CH), 129.8 (CH), 132.3 (CH), 146.4 (Cq), 155.0 (Cq), 159.8 (Cq), 160.5 (Cq), 165.2 (Cq); HRMS (ESI) *m/z* calcd for $C_{19}H_{17}O_4$ $[M+H]^+$ 309.1127, found 309.1129.

2-Methyl-2-[4-(trifluoromethyl)phenyl]-2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-one (3e): Yield 46%; colorless crystals; mp 97.0–99.1 ºC (recrystallized from $CHCl_3$/hexane); IR (KBr): 1724, 1650, 1496, 1406, 1327, 1162, 1113, 1032 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) 1.93 (3H, s), 3.40 (2H, s), 7.27–7.42 (2H, m), 7.58–7.68 (5H, m), 7.79–7.81 (1H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) 29.3 (CH_3), 41.4 (CH_2), 94.0 (Cq), 101.2 (Cq), 112.4 (Cq), 116.9 (CH), 122.6 (CH), 123.7 (Cq, d, J = 241.2 Hz), 124.0 (CH), 124.6 (CH), 125.6 (CH, t, J = 3.4 Hz), 130.1 (Cq, d, J = 32.2 Hz), 132.5 (CH), 148.6 (Cq), 155.0 (Cq), 160.2 (Cq), 165.0 (Cq); HRMS (ESI) *m/z* calcd for $C_{19}H_{14}F_3O_3$ $[M+H]^+$ 347.0895, found 347.0896.

2-Methyl-2-(4-nitrophenyl)-2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-one (3f): Yield 55%; yellow crystals; mp 169.0–173.3 ºC (recrystallized from $CHCl_3$/hexane); IR (KBr): 1725, 1643, 1567, 1498, 1351, 1292, 1031 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) 1.93 (3H, s), 3.40 (1H, d, J = 15.2 Hz), 3.44 (1H, d, J = 15.2 Hz), 7.34–7.43 (2H, m), 7.60–7.66 (3H, m), 7.80 (1H, d, J = 7.6 Hz), 8.26–8.28 (2H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) 29.5 (CH_3), 41.6 (CH_2), 93.7 (Cq), 101.3 (Cq), 112.4 (Cq), 117.2 (CH), 122.7 (CH), 124.1 (CH), 124.2 (CH), 125.4 (CH), 132.7 (CH), 147.5 (Cq), 151.7 (Cq), 155.1 (Cq), 160.2 (Cq), 165.0 (Cq); HRMS (ESI) *m/z* calcd for $C_{18}H_{14}NO_5$ $[M+H]^+$ 324.0872, found 324.0875.

2-Isopropyl-2-phenyl-2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-one (3g): Yield 30%; yellow crystals; mp 95.1–98.3 ºC (recrystallized from $CHCl_3$/hexane); IR (KBr): 1731, 1651, 1499, 1412, 1179, 1098, 1028 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) 0.92 (3H, d, J = 6.8 Hz), 0.99 (3H, d, J = 6.8 Hz), 2.34 (1H, septet, J = 6.8 Hz), 3.39 (1H, d, J = 15.6 Hz), 3.52 (1H, d, J = 15.6 Hz) 7.28–7.44 (7H, m), 7.55–7.59 (1H, m), 7.82–7.84 (1H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) 16.5 (CH_3), 17.3 (CH_3), 37.3 (CH_2), 38.8 (CH), 100.1 (Cq), 101.8 (Cq), 112.5 (Cq), 117.0 (CH), 122.6 (CH), 123.9 (CH), 125.1 (CH), 127.6 (CH), 128.2 (CH), 132.2 (CH), 143.2 (Cq), 155.0 (Cq), 160.5 (Cq), 165.5 (Cq); HRMS (ESI) *m/z* calcd for $C_{20}H_{18}O_3Na$ $[M+Na]^+$ 329.1154, found 329.1154.

2-Cyclopropyl-2-phenyl-2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-one (3h): Yield 79%; yellow crystals; mp 110.7–115.1 ºC (recrystallized from $CHCl_3$/hexane); IR (KBr): 1712, 1650, 1605, 1495, 1255, 1036 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) 0.43–0.50 (1H, m), 0.56–0.67 (3H, m), 1.54–1.66 (1H, m), 3.37 (2H, s), 7.29–7.40 (5H, m), 7.49–7.51 (2H, m), 7.54–7.58 (1H, m), 7.76–7.78 (1H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) 1.3 (CH_2), 1.8 (CH_2), 21.2 (CH), 39.0 (CH_2), 96.6 (Cq), 101.7 (Cq), 112.4 (Cq), 116.9 (CH), 122.6 (CH), 123.8 (CH), 124.9 (CH), 127.8 (CH), 128.3 (CH), 132.2 (CH), 143.7 (Cq), 155.0 (Cq), 160.3 (Cq), 165.4 (Cq); HRMS (ESI) *m/z* calcd for $C_{20}H_{17}O_3$ $[M+H]^+$ 305.1178, found 305.1181.

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