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Reactions of 2-(trifluoromethyl)-2-hydroxy-2*H*-chromenes with silyl enol ethers promoted by $AlCl_3$

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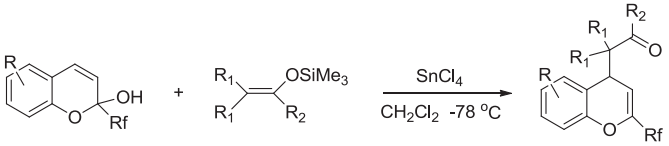
ABSTRACT

An efficient and straightforward nucleophilic substitution reaction between 2-(trifluoromethyl)-2-hydroxy-2*H*-chromenes and various silyl enol ethers promoted by Lewis acid has been studied. A series of novel 4-functionalized-2-trifluoromethyl-3-ethoxycarbonyl-4*H*-chromenes were prepared in good yields under mild conditions.

1. Introduction

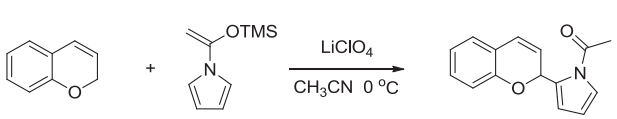
Chromenes are considered to be one of the most imperative heterocycle in nature because of their usefulness as biologically active agents.[1] In the last few years, much attention has been focused on the synthesis of chromene ring system,[2] for their potential application as antioxidant,[3] antitubercular,[4] anti-HIV,[5] antitumor,[6] cytotoxic agent,[7] and antileishmanial.[8] On the other hand, trifluoromethylated compounds have been recognized as one of the most potentially important and efficient probes in finding new biologically compounds[9] because of the unique role of the CF_3 group in enhancing the bioactivity of organic molecules.[10] Owing to this, 2-(trifluoromethyl)-2-hydroxy-2*H*-chromenes have attracted our attention to develop a new general and efficient method for the preparation of a variety of 2*H*-chromene heterocycles with CF_3 group.

Laurent has reported the synthesis of substituted 2-perfluoroalkyl-4*H*-chromenes with good yields in the presence of $SnCl_4$ (Scheme 1).[11] Hiemstra synthesized 2-substituted chromenes via ring-closing metathesis and stable 1-benzopyrylium ions.[12] More recently, many substituted 2*H*-chromenes and isochromenes have been synthesized through oxidative carbon–hydrogen cleavage by Floreancig group (Scheme 2).[13]



R=H, p-OMe, m-OMe, o-OMe, o-Cl, p-Cl, p-NO_2
R_1=H, Me; R_2=H, Me, OMe; Rf=CF_3, C_3F_7, C_5F_{11}

Scheme 1.



Scheme 2.

Our group has recently reported reactions of 2-(trifluoromethyl)-2-hydroxy-2*H*-chromenes with indoles and thiophenols promoted by Lewis acid (Scheme 3-1).[14,15] When indoles were used as the nucleophile, only 2-substituted or 4-substituted

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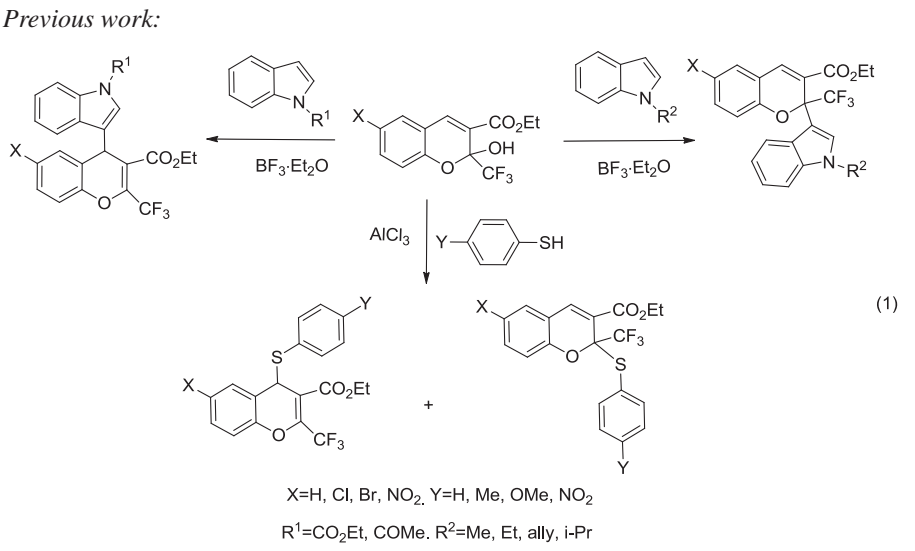
products were obtained, while both 2-substituted and 4-substituted products were isolated when the nucleophile was thiophenols. Herein, we report the reaction of 2-(trifluoromethyl)-2-hydroxy-2*H*-chromenes **1** with silyl enol ethers **2** affording a series of substituted 2-trifluoromethyl-4*H*-chromenes (Scheme 3-2).

According to Table 2, it was indicated that all these reactions occurred exclusively at 4-position of the 2*H*-chromenes. It seems that the C2 trifluoromethyl group due to its steric effect on the chromenol ring hinders the nucleophile to attack silyl enol ethers **2**. The reaction occurred between **1d** and **2a**, which both contained



Scheme 3.

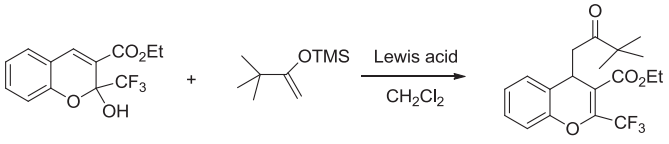
2. Results and discussion

In the previous studies, we have reported reactions of 2-(trifluoromethyl)-2-hydroxy-2*H*-chromenes **1** with indoles and thiophenols, and found the nucleophilic substitution took place at 2-position or 4-position of **1**. In this regard, a model reaction between **1a** (1 equiv) and silyl enol ether **2a** (1.5 equiv) was examined to optimize the reaction conditions (Table 1).

It was found that no reaction took place without Lewis acids (Table 1, entries 1 and 2). When the reaction was promoted by $SnCl_4$, only little product was detected by ^{19}F NMR (Table 1, entries 3 and 4). After different Lewis acids were examined, $AlCl_3$ was found to act as a good promoter to give the product **3aa** in 87% yield (Table 1, entry 7). When the dosage of $AlCl_3$ was changed, the yields decreased (Table 1, entries 6 and 8). However, when the amount of **2a** was decreased, a little lower yield of **3aa** was found under the same conditions (Table 1, entry 12). Other aprotic solvents, such as CH_3CN and THF were also examined (Table 1, entries 10 and 11). Thus, the optimal reaction conditions for this reaction were established: 1.5 equiv of **2a**, 1.0 equiv of $AlCl_3$, and performing the reaction at room temperature in CH_2Cl_2.

To our surprise, the nucleophilic substitution only take place at 4-position of **1a**. With the optimized reaction conditions on hand, reactions of 2-(trifluoromethyl)-2-hydroxy-2*H*-chromenes with other silyl enol ethers were further studied. The results were summarized in Table 2.

Table 1
Screening of the reaction conditions

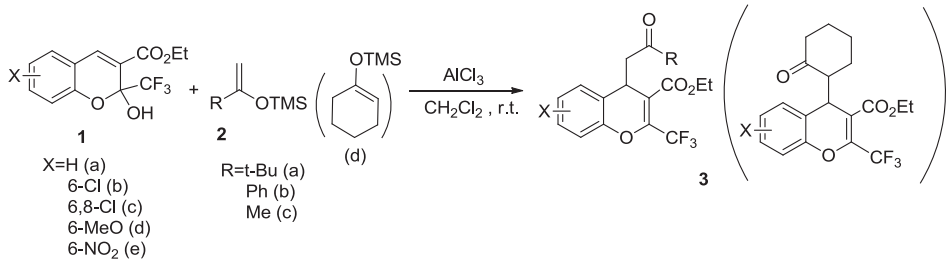


1a **2a** **3aa**

Entry	Lewis acid (equiv)	Solvent	Time (h)	Temp	Product yield[a]
1	—	CH_2Cl_2	48	rt	—
2	—	CH_3CN	48	rt	—
3	$SnCl_4$ (0.5)	CH_2Cl_2	10	−78 °C to rt	Trace
4	$SnCl_4$ (1.0)	CH_2Cl_2	30	−78 °C to rt	10
5	$BF_3{\cdot}OEt_2$ (1.0)	CH_2Cl_2	5	0 °C to rt	Trace
6	$AlCl_3$ (0.5)	CH_2Cl_2	10	rt	47
7	$AlCl_3$ (1.0)	CH_2Cl_2	3	rt	87
8	$AlCl_3$ (1.5)	CH_2Cl_2	3	rt	80
9	$ZnCl_2$ (1.0)	CH_2Cl_2	5	rt	23
10	$AlCl_3$ (1.0)	CH_3CN	18	rt	54
11	$AlCl_3$ (1.0)	THF	18	rt	7
12[b]	$AlCl_3$ (1.0)	CH_2Cl_2	3	rt	78

[a] Isolated yields.
[b] The mole ratio of **1a** to **2a** was 1:1.

Table 2
Reactions of **1** with **2** promoted by $AlCl_3$ in CH_2Cl_2 at room temperature



Entry	1	2	Time (h)	Product	Yield[a] (%)
1	**1a**	**2a**	3	**3aa**	87
2	**1a**	**2b**	3	**3ab**	85
3	**1a**	**2c**	5	**3ac**	63
4	**1a**	**2d**	3	**3ad**	83
5	**1b**	**2a**	3	**3ba**	83
6	**1b**	**2b**	3	**3bb**	57
7	**1b**	**2c**	5	**3bc**	34
8	**1b**	**2d**	3	**3bd**	62
9	**1c**	**2a**	3	**3ca**	38
10	**1c**	**2b**	3	**3cb**	29
11	**1c**	**2d**	3	**3cd**	33
12	**1d**	**2a**	3	**3da**	89
13	**1d**	**2b**	3	**3db**	82
14	**1d**	**2c**	5	**3dc**	77
15	**1d**	**2d**	3	**3dd**	81
16	**1e**	**2a**	10	**3ea**	n.r.
17	**1e**	**2b**	10	**3eb**	n.r.

n.r.=no reaction.
[a] Isolated yields.

electron-donating functional groups (X=OCH_3, R=*t*-Bu), corresponding 4-substituted chromene was obtained in a good yield (Table 2, entry 12). However, when the electron-donating ability of the group X was decreased, yield of the affording product was reduced accordingly (Table 2, entries 3, 7, and 14). What is more, once a nitro group was introduced into the 2*H*-chromene, the reaction could not proceed to produce the desired products (Table 2, entries 16 and 17). This is probably due to the strong electron-withdrawing effect of the nitro group.

All new compounds were characterized by ^1H, ^{13}C, ^{19}F NMR spectroscopy and mass spectrometry. All of the data in the spectra were in good accordance with the structures. The structure of compound **3ca** was also confirmed by X-ray crystallography (Fig. 1).

According to the related literature[11] and previous research in our group, the possible reaction mechanism is proposed in Scheme 4. Initially, the hydroxy group of **1** is activated by $AlCl_3$ to form the intermediate **A**. Subsequently, an elimination of $AlCl_2O^-$ produces the oxonium intermediate **B**, which is attacked by silyl enol ethers to form product **3**. Because of the electron delocalization of oxonium intermediate, the intermediate **C** is formed and followed by the attack of **2** to produce substituted 4*H*-chromenes **3**. It is noted that the attack prefer to take place at 4-position rather than at 2-position probably due to the combined action of the steric hindrance of CF_3 group and the effect of ester carbonyl group in 2*H*-chromenes, which can explain why 4*H*-chromenes **3** are the exclusive products.

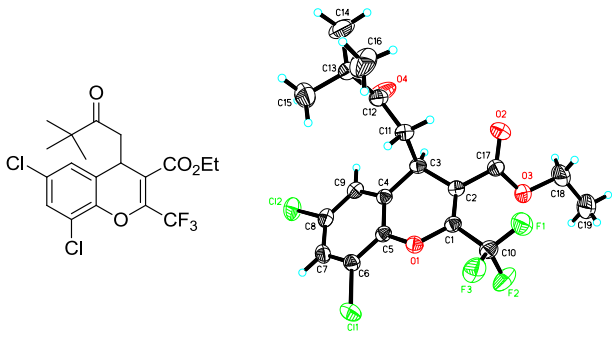


Fig. 1. The structure of compound **3ca**.

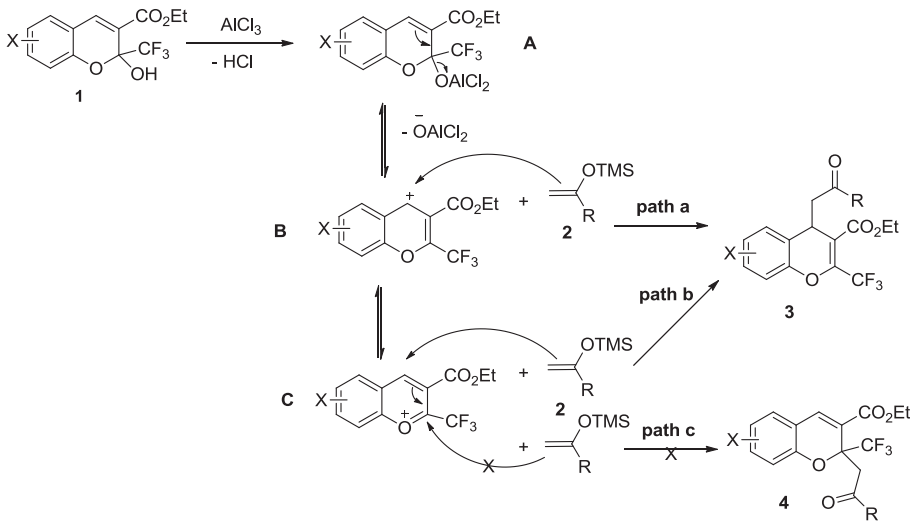
3. Conclusion

In conclusion, we have developed an efficient and new nucleophiles substitution reaction of 2-(trifluoromethyl)-2-hydroxy-2*H*-chromenes **1** and the silyl enol ether **2** in heterocyclic systems under mild conditions. It was found that the regioselective nucleophilic attack occurred at 4-position of the 2*H*-chromenes promoted by $AlCl_3$. The possible mechanism of the reaction was also discussed.

4. Experimental

4.1. General information

Commercial reagents were used without further purification. All solvents used were dried and purified by distillation. Chromenes **1a**–**d** and silyl enol ethers **2a**–**d** were prepared according to the literature of 2e and 16, accordingly. Melting points were measured on a Temp-Melt apparatus and uncorrected. ^1H NMR and ^{19}F NMR spectra were recorded on an Agilent AM-400 instrument with Me_4Si and $CFCl_3$ as the internal standard, respectively. ^{13}C NMR spectra were recorded on an Agilent AM-400 instrument with Me_4Si and as the internal standard. FT-IR spectra were obtained with a Nicolet AV-360 spectrophotometer. Mass spectra were obtained on a Finnigan GC–MS 4021 or a Finnigan MAT8430 instrument. Single crystal X-ray structure analysis was performed on a Bruker P4 instrument. All reactions were monitored by TLC or ^{19}F NMR.



Scheme 4. The possible mechanism for the formation of 4-substituted products **3**.

4.2. Typical procedure for the reaction of ethyl 2-hydroxy-2-(trifluoromethyl)-2*H*-chromene-3-carboxylate (1a) with silyl enol ether (2a) in the presence of $AlCl_3$ in CH_2Cl_2

To a stirred solution of chromene (**1a**, 288 mg, 1 mmol) and anhydrous aluminum chloride (133 mg, 1 mmol) in anhydrous dichloromethane (12 mL) under nitrogen was added silyl enol ether (**2a**, 258 mg, 1.5 mmol) at room temperature. At the end of the reaction as judged by ^{19}F NMR spectroscopy or TLC, the mixture was diluted with water (10 mL), quenched carefully with a solution of sodium bicarbonate (15 mL), and then extracted with dichloromethane (3×20 mL). The organic layers were washed with brine (2×20 mL). Then the organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. The crude products were chromatographed over silica gel using an eluent of ethyl acetate/petroleum ether (1:20) to afford the desired chromene.

*4.2.1. 2-(Trifluoromethyl)-3-ethoxycarbonyl-4-(3,3-dimethyl-2-oxobutyl)-4H-chromene (**3aa**).* Yield 87%, yellow oil. IR (KBr): 2973, 1734, 1710, 1489, 1479, 1460, 1377, 1300, 1232, 1197, 1150, 1111, 1087, 1034, 759 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.99 (s, 9H), 1.29 (t, J=7.2 Hz, 3H), 2.85–3.00 (m, 2H), 4.23 (q, J=7.2 Hz, 2H), 4.36–4.39 (m, 1H), 7.05–7.10 (m, 2H), 7.17–7.26 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 25.8, 32.2, 44.2, 45.2, 61.9, 114.0, 115.0 (q, $^1J_{C-F}$=271 Hz, CF_3), 116.4, 123.4, 125.3, 128.2, 128.5, 142.0 (q, $^2J_{C-F}$=37 Hz, CF_3), 150.0, 165.2, 212.4. ^{19}F NMR (376 MHz, $CDCl_3$): δ −67.3 (s, 3F, CF_3). MS (ESI): m/z=393.2 $(M+Na)^+$. HRMS (ESI): m/z calcd for $(C_{19}H_{21}F_3O_4+Na)^+$: 393.1290; found: 393.1284.

*4.2.2. 2-(Trifluoromethyl)-3-ethoxycarbonyl-4-(2-oxo-2-phenylethyl)-4H-chromene (**3ab**).* Yield 85%, yellow oil. IR (KBr): 1732, 1686, 1586, 1489, 1449, 1377, 1292, 1226, 1197, 1163, 1111, 1085, 1002, 757, 689 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.27 (t, J=7.2 Hz, 3H), 3.30–3.39 (m, 1H), 3.54–3.61 (m, 1H), 4.22 (q, J=7.2 Hz, 2H), 4.58–4.61 (m, 1H), 7.06–7.11 (m, 2H), 7.20–7.30 (m, 2H), 7.44 (t, J=10.0 Hz, 2H), 7.53 (t, J=10.0 Hz, 1H), 7.91 (d, J=10.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 32.4, 47.2, 62.0, 113.8, 116.5, 119.1 (q, $^1J_{C-F}$=271 Hz, CF_3), 123.2, 125.5, 128.1, 128.4, 128.6, 128.7, 133.4, 136.6, 142.8 (q, $^2J_{C-F}$=37 Hz, CF_3), 150.0, 165.3, 196.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ −67.6 (s, 3F, CF_3). MS (ESI): m/z=413.1 $(M+Na)^+$. HRMS (ESI): m/z calcd for $(C_{21}H_{17}F_3O_4+Na)^+$: 413.0977; found: 413.0971.

*4.2.3. 2-(Trifluoromethyl)-3-ethoxycarbonyl-4-(2-oxopropyl)-4H-chromene (**3ac**).* Yield 63%, yellow oil. IR (KBr): 2983, 2926, 1725, 1587, 1490, 1459, 1377, 1299, 1227, 1198, 1161, 1112, 1088, 1039, 759 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.29 (t, J=7.2 Hz, 3H), 2.08 (s, 3H), 2.75 (q, J=7.6 Hz, 1H), 2.80 (q, J=4.4 Hz, 1H), 4.23 (q, J=7.2 Hz, 2H), 4.35–4.36 (m, 1H), 7.04–7.12 (m, 2H), 7.22 (d, J=6.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 30.4, 31.9, 51.6, 61.9, 113.4, 114.9 (q, $^1J_{C-F}$=273 Hz, CF_3), 116.5, 123.0, 125.5, 128.4, 128.5, 141.8 (q, $^2J_{C-F}$=37 Hz, CF_3), 149.8, 165.2, 205.2. ^{19}F NMR (376 MHz, $CDCl_3$): δ −67.4 (s, 3F, CF_3). MS (ESI): m/z=351.1 $(M+Na)^+$. HRMS (ESI): m/z calcd for $(C_{16}H_{15}F_3O_4+Na)^+$: 351.0820; found: 351.0814.

*4.2.4. 2-(Trifluoromethyl)-3-ethoxycarbonyl-4-(2-oxocyclohexyl)-4H-chromene (**3ad**).* Yield 83%, yellow oil. IR (KBr): 2938, 2866, 1731, 1712, 1585, 1487, 1459, 1379, 1299, 1235, 1197, 1149, 1112, 1085, 994, 760 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.31 (t, J=7.2 Hz, 3H), 1.33–1.45 (m, 2H), 1.62–1.84 (m, 2H), 1.95–2.02 (m, 2H), 2.23–2.35 (m, 1H), 2.41–2.47 (m, 1H), 2.82–2.88 (m, 1H), 4.21 (q, J=7.2 Hz, 2H), 4.72 (s, 1H), 6.34 (d, J=10.8 Hz, 1H), 7.26 (q, J=10.4 Hz, 1H), 7.23 (t, J=10.0 Hz, 1H), 7.41 (d, J=11.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 24.7, 26.3, 26.9, 34.9, 41.8, 56.0, 61.9, 113.1, 116.0, 119.1 (q, $^1J_{C-F}$=273 Hz, CF_3), 120.8, 125.4, 128.3, 130.1, 143.5 (q, $^2J_{C-F}$=37 Hz, CF_3), 151.3, 165.4, 209.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ −67.5 (s, 3F, CF_3). MS (ESI): m/z=391.0 $(M+Na)^+$. HRMS (ESI): m/z calcd for $(C_{19}H_{19}F_3O_4+Na)^+$: 391.1133; found: 391.1128.

*4.2.5. 2-(Trifluoromethyl)-3-ethoxycarbonyl-4-(3,3-dimethyl-2-oxobutyl)-6-chloro-4H-chromene (**3ba**).* Yield 83%, yellow oil. IR (KBr): 2971, 1735, 1710, 1480, 1373, 1307, 1236, 1198, 1152, 1119, 1080, 998, 819 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.23 (s, 9H), 1.29 (t, J=7.2 Hz, 3H), 2.85–3.02 (m, 2H), 4.23 (q, J=7.2 Hz, 2H), 4.32–4.25 (m, 1H), 6.99–7.02 (m, 1H), 7.17–7.19 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 25.9, 32.0, 44.1, 45.0, 62.0, 113.6, 114.8 (q, $^1J_{C-F}$=271 Hz, CF_3), 117.8, 125.0, 128.2, 128.4, 130.3, 141.8 (q, $^2J_{C-F}$=37 Hz, CF_3), 148.4, 164.9, 212.2. ^{19}F NMR (376 MHz, $CDCl_3$): δ −67.3 (s, 3F, CF_3). MS (ESI): m/z=427.2 $(M+Na)^+$. HRMS (ESI): m/z calcd for $(C_{19}H_{20}ClF_3O_4+Na)^+$: 427.0900; found: 427.0894.

*4.2.6. 2-(Trifluoromethyl)-3-ethoxycarbonyl-4-(2-oxo-2-phenylethyl)-6-chloro-4H-chromene (**3bb**).* Yield 57%, yellow solid, mp 108–110 °C. IR (KBr): 1740, 1690, 1487, 1377, 1277, 1244, 1229, 1198, 1141, 1079, 1003, 830, 760 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.25 (t, J=7.2 Hz, 3H), 3.32 (q, J=7.2 Hz, 1H), 3.55 (q, J=4.0 Hz, 1H), 4.22 (q, J=7.2 Hz, 2H), 4.55 (m, 1H), 7.00 (d, J=8.8 Hz, 1H), 7.16 (q, J=2.4 Hz, 1H), 7.30 (d, J=2.4 Hz, 1H), 7.43 (t, J=8.0 Hz, 2H), 7.54 (t, J=7.6 Hz, 1H), 7.90 (d, J=7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 32.0,

46.8, 62.1, 113.4, 114.8 (q, $^1J_{C-F}$=273 Hz, CF_3), 117.9, 124.8, 128.1, 128.5, 128.7, 130.4, 133.5, 136.3, 142.1 (q, $^2J_{C-F}$=37 Hz, CF_3), 148.5, 164.9, 196.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ −67.2 (s, 3F, CF_3). MS (ESI): m/z=447.0 $(M+Na)^+$. HRMS (ESI): m/z calcd for $(C_{21}H_{16}ClF_3O_4+Na)^+$: 447.0587; found: 447.0581.

*4.2.7. 2-(Trifluoromethyl)-3-ethoxycarbonyl-4-(2-oxopropyl)-6-chloro-4H-chromene (**3bc**).* Yield 34%, yellow oil. IR (KBr): 2983, 2920, 1726, 1483, 1374, 1307, 1244, 1199, 1162, 1082, 1032, 814, 732 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (t, J=7.2 Hz, 3H), 2.11 (s, 3H), 2.77 (q, J=7.2 Hz, 1H), 3.03 (q, J=4.0 Hz, 1H), 4.23 (q, J=7.2 Hz, 2H), 4.30–4.32 (m, 1H), 6.99 (d, J=8.4 Hz, 1H), 7.17–7.24 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 30.3, 31.6, 51.3, 62.1, 113.1, 114.8 (q, $^1J_{C-F}$=273 Hz, CF_3), 117.9, 124.7, 128.3, 128.5, 130.4, 142.1 (q, $^2J_{C-F}$=37 Hz, CF_3), 148.4, 164.9, 204.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ −67.4 (s, 3F, CF_3). MS (ESI): m/z=385.2 $(M+Na)^+$. HRMS (ESI): m/z calcd for $(C_{16}H_{13}ClF_3O_4+Na)^+$: 385.0430; found: 385.0425.

*4.2.8. 2-(Trifluoromethyl)-3-ethoxycarbonyl-4-(2-oxocyclohexyl)-6-chloro-4H-chromene (**3bd**).* Yield 62%, yellow oil. IR (KBr): 2938, 2858, 1712, 1480, 1450, 1374, 1351, 1307, 1238, 1199, 1151, 1083, 997, 818, 740 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (m, J=3.6 Hz, 1H), 1.28 (t, J=7.2 Hz, 3H), 1.46–1.53 (m, 1H), 1.60–1.66 (m, 1H), 1.82–1.85 (m, 1H), 1.92–2.00 (m, 2H), 2.24–2.33 (m, 1H), 2.44–2.47 (m, 1H), 2.82 (m, 1H), 4.24 (q, J=7.2 Hz, 2H), 4.67 (s, 1H), 6.96 (d, J=8.8 Hz, 1H), 7.17 (q, J=2.4 Hz, 1H), 7.43 (d, J=2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 24.7, 26.4, 26.8, 34.9, 41.8, 55.8, 62.0, 112.7, 114.8 (q, $^1J_{C-F}$=273 Hz, CF_3), 117.4, 122.5, 128.4, 129.8, 130.4, 142.9 (q, $^2J_{C-F}$=37 Hz, CF_3), 149.8, 165.1, 209.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ −67.2 (s, 3F, CF_3). MS (ESI): m/z=425.1 $(M+Na)^+$. HRMS (ESI): m/z calcd for $(C_{19}H_{18}ClF_3O_4+Na)^+$: 425.0743; found: 425.0738.

*4.2.9. 2-(Trifluoromethyl)-3-ethoxycarbonyl-4-(3,3-dimethyl-2-oxobutyl)-6,8-dichloro-4H-chromene (**3ca**).* Yield 38%, yellow solid, mp 93–94 °C. IR (KBr): 2978, 1723, 1703, 1574, 1458, 1375, 1309, 1244, 1197, 1165, 1090, 1016, 872, 775 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04 (s, 9H), 1.29 (t, J=7.2 Hz, 3H), 2.84–3.03 (m, 2H), 4.24 (q, J=7.2 Hz, 2H), 4.35–4.37 (m, 1H), 7.10 (d, J=3.2 Hz, 1H), 7.28 (d, J=2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 25.9, 32.5, 44.1, 44.9, 62.2, 114.5, 114.5 (q, $^1J_{C-F}$=271 Hz, CF_3), 122.9, 126.4, 126.7, 128.8, 130.2, 141.8 (q, $^2J_{C-F}$=37 Hz, CF_3), 144.8, 164.4, 211.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ −67.1 (s, 3F, CF_3). MS (ESI): m/z=461.1 $(M+Na)^+$. HRMS (ESI): m/z calcd for $(C_{19}H_{19}Cl_2F_3O_4+Na)^+$: 461.0510; found: 461.0505.

*4.2.10. 2-(Trifluoromethyl)-3-ethoxycarbonyl-4-(2-oxo-2-phenylethyl)-6,8-dichloro-4H-chromene (**3cb**).* Yield 29%, yellow solid, mp 74–75 °C. IR (KBr): 1729, 1682, 1598, 1456, 1360, 1307, 1266, 1242, 1202, 1168, 1086, 1011, 978, 862, 780, 756, 692 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, J=7.2 Hz, 3H), 3.32 (q, J=7.2 Hz, 1H), 3.54 (q, J=4.0 Hz, 1H), 4.23 (q, J=7.2 Hz, 2H), 4.57–4.58 (m, 1H), 7.25 (q, J=2.0 Hz, 2H), 7.44 (t, J=6.8 Hz, 2H), 7.56 (t, J=6.8 Hz, 1H), 7.89 (d, J=8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 32.6, 46.6, 62.3, 114.4, 114.7 (q, $^1J_{C-F}$=273 Hz, CF_3), 116.5, 123.0, 125.9, 126.3, 127.0, 128.1, 128.8, 129.0, 130.3, 133.6, 136.3, 142.2 (q, $^2J_{C-F}$=37 Hz, CF_3), 145.0, 164.5, 196.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ −67.0 (s, 3F, CF_3). MS (ESI): m/z=457.0 $(M-H)^-$. HRMS (ESI): m/z calcd for $(C_{21}H_{14}Cl_2F_3O_4+Na)^+$: 457.0221; found: 457.0223.

*4.2.11. 2-(Trifluoromethyl)-3-ethoxycarbonyl-4-(2-oxocyclohexyl)-6,8-dichloro-4H-chromene (**3cd**).* Yield 33%, yellow solid, mp 82–83 °C. IR (KBr): 2932, 1724, 1705, 1575, 1461, 1373, 1309, 1256, 1240, 1198, 1166, 1091, 1004, 870, 787 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (m, J=3.6 Hz, 1H), 1.29 (t, J=7.2 Hz, 3H), 1.47–1.54 (m, 1H), 1.60–1.67 (m, 1H), 1.85–1.88 (m, 1H), 1.93–2.03 (m, 2H), 2.25–2.34 (m, 1H), 2.45–2.48 (m, 1H), 2.82–2.87 (m, 1H), 4.25 (q, J=7.2 Hz, 2H), 4.68 (s, 1H), 7.30 (d, J=2.4 Hz, 1H), 7.37 (d, 2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 24.7, 26.4, 27.0, 35.4, 41.8, 55.7, 62.2, 113.6, 114.7 (q, $^1J_{C-F}$=273 Hz, CF_3), 122.7, 123.9, 128.4, 129.0, 130.3, 142.9 (q, $^2J_{C-F}$=37 Hz, CF_3), 146.0, 164.6, 209.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ −66.9 (s, 3F, CF_3). MS (ESI): m/z=459.1 $(M+Na)^+$. HRMS (ESI): m/z calcd for $(C_{19}H_{17}Cl_2F_3O_4+Na)^+$: 459.0354; found: 459.0348.

*4.2.12. 2-(Trifluoromethyl)-3-ethoxycarbonyl-4-(3,3-dimethyl-2-oxobutyl)-6-methoxy-4H-chromene (**3da**).* Yield 89%, yellow oil. IR (KBr): 2967, 1710, 1499, 1466, 1397, 1375, 1307, 1265, 1213, 1151, 1088, 1036, 738 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00 (s, 9H), 1.28 (t, J=7.2 Hz, 3H), 2.85–2.99 (m, 2H), 3.72 (s, 3H), 4.21 (q, J=7.2 Hz, 2H), 4.34–4.36 (m, 1H), 6.66 (d, J=2.8 Hz, 1H), 6.72 (d, J=2.8 Hz, 1H), 6.96 (d, J=9.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 25.9, 32.5, 44.2, 55.7, 61.8, 112.1, 112.8, 114.5, 114.9 (q, $^1J_{C-F}$=271 Hz, CF_3), 117.3, 124.2, 142.4 (q, $^2J_{C-F}$=37 Hz, CF_3), 143.8, 156.8, 165.3, 212.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ −67.2 (s, 3F, CF_3). MS (ESI): m/z=423.1 $(M+Na)^+$. HRMS (ESI): m/z calcd for $(C_{20}H_{23}F_3O_5+Na)^+$: 423.1395; found: 423.1390.

*4.2.13. 2-(Trifluoromethyl)-3-ethoxycarbonyl-4-(2-oxo-2-phenylethyl)-6-methoxy-4H-chromene (**3db**).* Yield 82%, yellow solid, mp 53–55 °C. IR (KBr): 2932, 1732, 1688, 1500, 1444, 1375, 1308, 1242, 1217, 1151, 1087, 1032, 689 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (t, J=7.2 Hz, 3H), 3.31 (q, J=8.0 Hz, 1H), 3.54 (q, J=4.0 Hz, 1H), 3.72 (s, 3H), 4.22 (q, J=7.2 Hz, 2H), 4.56–4.57 (m, 1H), 6.73 (m, 2H), 6.99 (d, J=8.8 Hz, 1H), 7.42 (t, J=7.2 Hz, 2H), 7.53 (t, J=7.2 Hz, 1H), 7.90 (d, J=7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 32.6, 47.2, 55.6, 61.9, 112.5, 114.5, 115.0 (q, $^1J_{C-F}$=273 Hz, CF_3), 117.4, 123.9, 128.1, 128.6, 133.4, 136.5, 142.7 (q, $^2J_{C-F}$=37 Hz, CF_3), 156.9, 165.4, 196.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ −67.1 (s, 3F, CF_3). MS (ESI): m/z=443.1 $(M+Na)^+$. HRMS (ESI): m/z calcd for $(C_{22}H_{19}F_3O_5+Na)^+$: 443.1082; found: 443.1077.

*4.2.14. 2-(Trifluoromethyl)-3-ethoxycarbonyl-4-(2-oxopropyl)-6-methoxy-4H-chromene (**3dc**).* Yield 77%, yellow oil. IR (KBr): 2937, 1727, 1500, 1467, 1436, 1375, 1308, 1215, 1151, 1088, 1035, 817 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (t, J=7.2 Hz, 3H), 2.09 (s, 3H), 2.76 (q, J=7.6 Hz, 1H), 3.02 (q, J=4.0 Hz, 1H), 3.76 (s, 3H), 4.22 (q, J=7.2 Hz, 2H), 4.33 (m, 1H), 6.75 (d, J=7.6 Hz, 2H), 6.98 (d, J=8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 30.4, 32.2, 51.6, 55.7, 61.9, 112.2, 112.3114.5, 115.0 (q, $^1J_{C-F}$=273 Hz, CF_3), 117.4, 123.9, 142.3 (q, $^2J_{C-F}$=37 Hz, CF_3), 143.7, 157.0, 165.3, 205.4. ^{19}F NMR (376 MHz, $CDCl_3$): δ −67.2 (s, 3F, CF_3). MS (ESI): m/z=381.1 $(M+Na)^+$. HRMS (ESI): m/z calcd for $(C_{17}H_{17}F_3O_5+Na)^+$: 381.0926; found: 381.0920.

*4.2.15. 2-(Trifluoromethyl)-3-ethoxycarbonyl-4-(2-oxocyclohexyl)-6-methoxy-4H-chromene (**3dd**).* Yield 81%, yellow solid, mp 79–81 °C. IR (KBr): 2940, 1719, 1705, 1500, 1317, 1294, 1244, 1212, 1191, 1153, 1136, 1088, 885, 820 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (q, J=10.4 Hz, 1H), 1.28 (t, J=7.2 Hz, 3H), 1.43–1.46 (m, 1H), 1.63–1.67 (m, 2H), 1.79–1.82 (m, 1H), 1.91–1.99 (m, 2H), 2.24–2.32 (m, 1H), 2.41–2.45 (m, 1H), 2.81–2.86 (m, 1H), 3.76 (s, 3H), 4.22 (q, J=7.2 Hz, 2H), 4.68 (s, 1H), 6.74 (d, J=8.8 Hz, 1H), 6.94 (d, J=6.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 24.7, 26.4, 26.7, 35.2, 41.8, 55.7, 56.0, 61.8, 111.7, 113.6, 114.6, 115.0 (q, $^1J_{C-F}$=273 Hz, CF_3), 116.9, 121.5, 143.6 (q, $^2J_{C-F}$=37 Hz, CF_3), 145.3, 156.9, 165.5, 209.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ −67.0 (s, 3F, CF_3). MS (ESI): m/z=421.1 $(M+Na)^+$. HRMS (ESI): m/z calcd for $(C_{20}H_{21}F_3O_5+Na)^+$: 421.1240; found: 421.1233.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.07.004. These data include MOL files and InChiKeys of the most important compounds described in this article.

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