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Brønsted acid promoted one-pot synthesis of 4-aryl-3,4-dihydrocoumarins

Cheng Chen [b], Rui Zhang [a], Long Lin [a], Guang-Fu Yang [a,*], Qiong-You Wu [a,*]

[a] Key Laboratory of Pesticide & Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, Wuhan 430079, PR China

[b] State Key Laboratory of Advanced Technology for Materials Synthesis and Processing, Wuhan University of Technology, Wuhan 430070, PR China

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ABSTRACT

4-Aryl-3,4-dihydrocoumarins are a class of valuable molecules demonstrating attractive pharmaceutical and biological properties. In this paper, we designed a new and facile approach to synthesis of 4-aryl-3,4-dihydrocoumarin derivatives by Brønsted acid catalyzed Friedel–Crafts alkylation and cycloaddition reaction. With this protocol, 15 examples of 4-aryl-3,4-dihydrocoumarins were successfully prepared with yields ranging from 82 to 99%.

1. Introduction

Coumarins have widely existed in a variety of natural products, pharmaceuticals, and agrochemicals, and they are attractive due to their *anti*-inflammatory, *anti*-aging, *anti*-oxidative and *anti*-cancer activities.[1] Besides, dihydrocoumarins have been frequently used as food flavouring[2] and fragrance in cosmetics,[3] and they are also well-known in perfumery industries.[4] Among this class of compounds, 4-aryl-3,4-dihydrocoumarins are particularly interesting since they exhibit promising activities such as *anti*-herpetic,[5] *anti*-bacterial,[6,7] *anti*-viral,[8] *anti*-hypertension,[9] *anti*-inflammatory,[10] antioxidant activities,[1] as well as aldose reductase inhibition[11] and protein kinase inhibition.[12] For instance, the dihydrocoumarin **1** is a synthetic compound showing excellent *in vitro* *anti*-bacterial activity against members of the Tripanosoma family (Fig. 1).[6,7] In addition, compound **2**, a natural dihydrocoumarin, demonstrates outstanding *anti*-inflammatory and antioxidant activities (Fig. 1).[13]

Owing to the diverse advantages of 4-aryl-3,4-dihydrocoumarins, it is of vital importance to develop efficient synthetic approaches for this kind of compounds. Conventional methods for their synthesis include the transition-metal-mediated catalytic hydrogenation,[14,15] treatment of cinnamic acid derivatives (cinnamic acids,[16–24] cinnamoyl chlorides,[25] or cinnamate esters[26,27]) with phenols, annulation reactions of phenols with other reagents,[28–30] the use of oxidants on acids,[31–35] arylacrylate lactonization,[6,7,36] and one-pot synthesis via Fischer carbenes.[37]

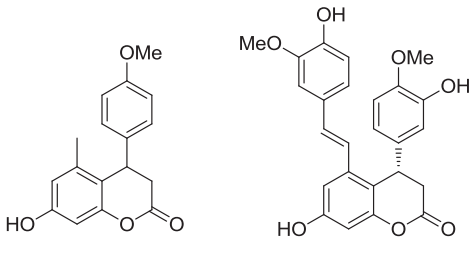

Fig. 1. Representative examples of synthetic and natural 4-aryl-3,4-dihydrocoumarins.

Although various methods have been developed, it is still highly desirable to design a facile and economic route for synthesis of 4-aryl dihydrocoumarins under mild reaction conditions. Through literature survey, we poured our attention to a report by Claude et al. describing an efficient intramolecular cycloaddition reaction from a secondary alcohol group and an ester moiety in the presence

* Corresponding authors. Tel.: +86 27 67867800; fax: +86 27 67867141; e-mail addresses: gfyang@mail.ccnu.edu.cn (G.-F. Yang), qywu@mail.ccnu.edu.cn (Q.-Y. Wu).

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of a Brønsted acid (Fig. 2a).[38] In addition, the Bra group[39] and the Barbero group[40] reported Brønsted-acid-catalyzed alkylation of arenes (or heteroarenes) with benzylic alcohols (Fig. 2b). Notably, both the intramolecular lactone formation and the intermolecular arylation could be promoted by Brønsted acids. Thus, we envisioned that the combination of these two processes into a Brønsted-acid-mediated one-pot fashion should provide a convenient approach to synthesis of 4-aryl dihydrocoumarins (Fig. 2c).

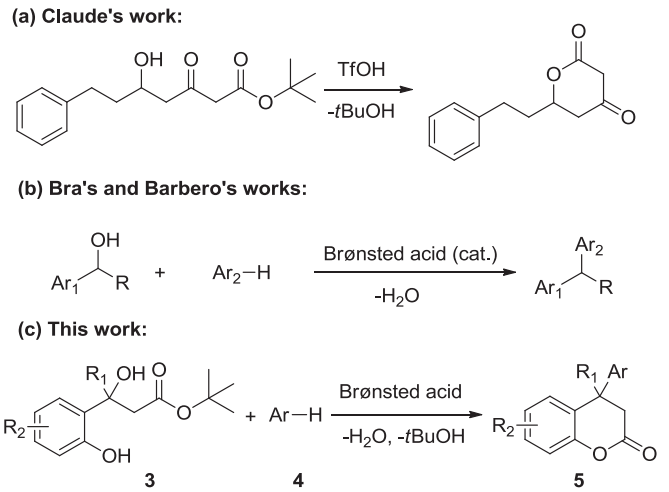


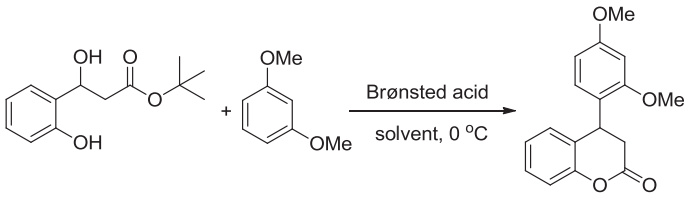
Fig. 2. One-pot synthesis of 4-aryl dihydrocoumarin derivatives through combination of intermolecular arylation and intramolecular cyclization.

2. Results and discussion

In order to examine the feasibility of our methodology, we selected the reaction of **3a** and **4a** as a model reaction for optimization of reaction conditions (Table 1). Initially, screening of different Brønsted acids were performed. Trifluoroacetic acid, active for reactions shown in both Fig. 2a and b, was first attempted for the reaction. To our delight, compound **5a** was obtained in 90% isolated yield after 930 min at 0 °C by using dichloromethane as solvent (entry 1). When the Brønsted acid was changed to concentrated HCl or *p*-toluenesulfonic acid, comparable yields were observed, but quite long reaction time (1440 min for each case, entries 2–3) is necessary. Fortunately, methanesulfonic acid and perchloric acid were found to accelerate the reaction efficiently and yield **5a** in excellent yields, and the reaction time was shortened from 1440 min to no more than 30 min (entries 4–5). Compared with methanesulfonic acid, perchloric acid is a better promoter in terms of a slightly higher yield (88% in entry 4 vs 90% in entry 5) and shorter reaction time (30 min in entry 4 vs 20 min in entry 5). Except the strong acids mentioned above, acetic acid, a weaker acid, was also investigated. However, no reaction was observed even the reaction time was prolonged to 1440 min (entry 6). Therefore, perchloric acid was identified as the optimal Brønsted acid. Secondly, we investigated the effect of the amount of perchloric acid on the product yield. It was found that when the acid amount increased from 2.0 equiv to 3.0 equiv, the reaction could be completed within 10 min and a slightly improved yield of 92% was produced (entry 7). After setting up the acid amount, we next optimized the influence of solvent on the product yield. Among the solvent investigated, acetonitrile was demonstrated to be the best one and provided a yield of 95% within the same reaction time (entries 8–14). Interestingly, when the reaction was performed in a diluted solution by increasing the volume of the acetonitrile from 2 mL to 3 mL, a further improvement of the yield of 99% was achieved (entry 15). Therefore, the optimized reaction conditions, identified as **3** (1.0 mmol), **4** (2.0 mmol), Brønsted acid (3.0 mmol), and solvent (3.0 mL), were used for further study until otherwise noted.

With the optimized reaction conditions in hand, the substrate scope and limitations of this method were investigated. A range of 4-aryl dihydrocoumarins were obtained in excellent yields (Table 2). *tert*-Butyl 3-hydroxy-3-(2-hydroxyphenyl)propanoate

Table 1
Optimization of reaction conditions[a]

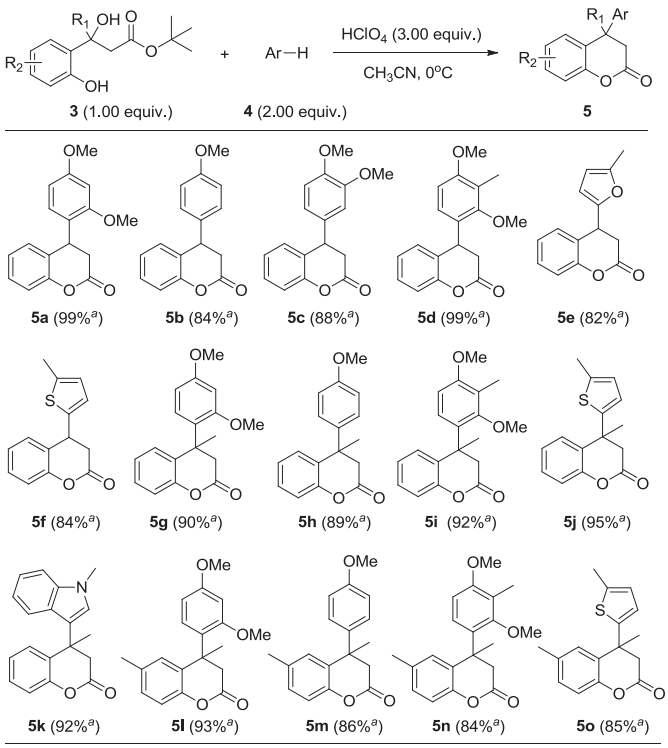


3a 4a 5a

Entry	Brønsted acid	Solvent	**3a**: **4a**: Brønsted acid	Time (min)	Yield[b]
1	TfOH	DCM	1:2:2	930	90%
2	conc. HCl	DCM	1:2:2	1440	85%
3	TsOH	DCM	1:2:2	1440	85%
4	MsOH	DCM	1:2:2	30	88%
5	$HClO_4$	DCM	1:2:2	20	90%
6	AcOH	DCM	1:2:2	1440	–[c]
7	$HClO_4$	DCM	1:2:3	10	92%
8	$HClO_4$	DCE	1:2:3	10	91%
9	$HClO_4$	$CHCl_3$	1:2:3	10	90%
10	$HClO_4$	THF	1:2:3	10	50%
11	$HClO_4$	Acetone	1:2:3	10	65%
12	$HClO_4$	MeOH	1:2:3	10	55%
13	$HClO_4$	Et_2O	1:2:3	10	90%
14	$HClO_4$	MeCN	1:2:3	10	95%
15[d]	$HClO_4$	MeCN	1:2:3	10	99%

[a] **3a** (1.0 mmol), **4a** (2.0 mmol), Brønsted acid (2.0 mmol), and solvent (2.0 mL) were used.
[b] Isolated yields.
[c] No reaction.
[d] 3.0 mL acetonitrile was used.

Table 2
Investigation of the substrate scope



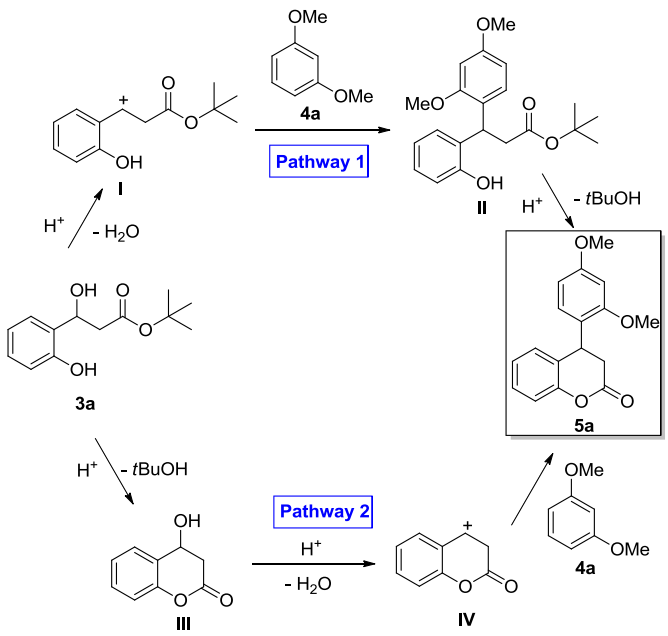
[a] Isolated yields.

(**3a**), with both R_1 and R_2 as H, reacted smoothly with various electron-rich arenes to give compounds **5a**–**5d** with the yields ranging from 84% to 99%. Heteroarenes such as 2-methylfuran and 2-methylthiophene can also tolerate this reaction and produced the respective products **5e** and **5f** in good yields. In addition, *tert*-butyl 3-hydroxy-3-(2-hydroxyphenyl)propanoate (**3b**) where a methyl group was assembled at the R_1 position was further utilized as the starting material. The results indicated that 1,3-dimethoxybenzene (**4a**), anisole (**4b**), 1,3-dimethoxy-2-methylbenzene (**4d**), 2-methylthiophene (**4f**) and 1-methyl-1H-indole (**4g**) could be successfully transformed into the corresponding dihydrocoumarins with a quaternary carbon atom at the benzylic position (**5g**–**5k**). It was worth noting that no noteworthy steric effect was observed in terms of the excellent yields obtained. Moreover, incorporation of a methyl group at the *p*-position of phenolic ring of compound **3** did not have significant influence on the product yields since compound **5l**–**5o** with the yields ranging from 84% to 93% were obtained depending on the aryl substituent introduced.

The plausible mechanism of the reaction was described in Scheme 1. It was assumed that compound **5a** could be obtained via two processes including a process featuring an SN_1-type alcohol nucleophilic substitution via a benzylic carbenium species (also called Friedel–Crafts alkylation)[39,40] and a cycloaddition process,[38] and the major difference of the two pathways lies in the sequence of the two processes. In pathway **1**, treatment of **3a** with perchloric acid initially afforded a benzylic carbocation **I**, which then reacted with **4a** to give intermediate **II**. Afterwards, intermediate **II** could go through an intramolecular cycloaddition under an acidic condition to generate **5a** with elimination of *tert*-butanol. In pathway 2, Brønsted acid-aided intramolecular cycloaddition occurred first to produce intermediated **III**, which could be then transformed to the corresponding carbenium ion **IV** in the presence of perchloric acid. Finally, the final product **5a** could be yielded via reaction of intermediate **IV** and **4a**.

3. Conclusion

In summary, we have developed a simple, mild and efficient method for synthesis of 4-aryl-3,4-dihydrocoumarins. Screening of the reaction conditions implied that the economic perchloric acid was the optimal Brønsted acid. Under the optimized reaction conditions, a variety of 4-aryl-3,4-dihydrocoumarins were efficiently synthesized in good to excellent yields. Considering the reaction mechanism, we proposed that two processes, an SN_1-type alcohol nucleophilic substitution (or Friedel–Crafts alkylation) and a cycloaddition reaction, could be realized in one pot with the aid of perchloric acid.



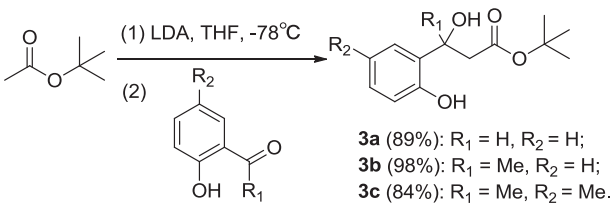
Scheme 1. The plausible mechanism of the formation of **5**.

4. Experimental section

4.1. General considerations

^{1}H NMR spectra were recorded on a VARIAN Mercury-Plus 600 spectrometer in $CDCl_3$ with TMS as the internal reference, ^{13}C NMR spectra were recorded in $CDCl_3$ on a VARIAN Mercury-Plus 600 (151 MHz) spectrometer, and chemical shifts (δ) are given in ppm relative to the centre line of a triplet at 77.0 ppm of $CDCl_3$. The following abbreviations are used to designate multiplicities: s=singlet, d=doublet, t=triplet, dd=doublet of doublets, brs=broad singlet, m=multiplet. MS spectra were determined using a Trace MS 2000 organic mass spectrometry, and the signals were given in *m*/*z*. HRMS was taken on an Agilent 6520 Accurate-Mass Q-TOF instrument. Melting points were taken on a Buchi B-545 melting point apparatus and are uncorrected. Ordinary reagents and solvents were commercially available and treated with standard methods before use. Besides, compounds **4** including 1,3-dimethoxybenzene (**4a**), anisole (**4b**), 1,2-dimethoxybenzene (**4c**), 1,3-dimethoxy-2-methylbenzene (**4d**), 2-methylfuran (**4e**), 2-methylthiophene (**4f**), 1-methyl-1H-indole (**4g**) were also purchased from commercial suppliers.

4.2. General procedure for synthesis of compounds 3a–3c (Scheme 2)



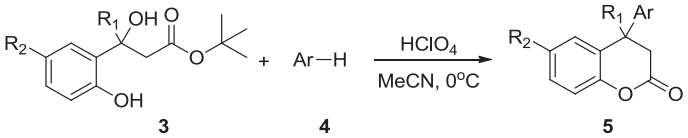
Scheme 2. Synthesis of **3a**–**3c**.

To a solution of diisopropyl amine (55.0 mmol) in THF (60 mL) was added dropwisely *n*-butyl lithium solution (55.0 mmol) at −78 °C under inert atmosphere, and the mixture was stirred for 20 min at the same temperature. Then *t*-butyl acetate (55.0 mmol) was added slowly to the above mixture, followed by dropwise addition of salicylaldehyde (22.0 mmol) after 1 h. Afterwards, the mixture was stirred for additional 1.5 h and 15% citric acid solution (60 mL) was added. The mixture was then extracted with EtOAc (3×60 mL), and the resulted organic layer was washed with water (2×50 mL), brine (50 mL), dried over Na_2SO_4, concentrated, and purified by column chromatography to afford the pure product (**3a**).

Synthesis of **3b** and **3c** was similar with that of **3a**.

4.3. General procedure for synthesis of compounds 5a–5o (Scheme 3)

To a solution of **3** (2.00 mmol) in acetonitrile (3 mL) was added dropwisely $HClO_4$ (6.00 mmol) at 0 °C. Then **4** (4.00 mmol) was added and the reaction mixture was stirred at 0 °C for 10 min.



3 4 5

Scheme 3. Synthesis of **5** from **3** and **4**.

Afterwards, the mixture was directly purified by column chromatography to afford the pure products (**5a**–**5o**).

4.4. Analytical data for compounds 3a–3c and 5a–5o

*4.4.1. tert-Butyl 3-hydroxy-3-(2-hydroxyphenyl)propanoate (**3a**).* White solid: mp 87.5–89.0 °C. Isolated yield: 89%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.31 (s, 1H), 7.18 (dd, J=7.4, 7.2 Hz, 1H), 6.96 (d, J=7.8 Hz, 1H), 6.88 (d, J=8.4 Hz, 1H), 6.83 (dd, J=7.8, 7.7 Hz, 1H), 5.24 (d, J=10.2 Hz, 1H), 4.66 (s, 1H), 2.91–2.86 (m, 1H), 2.66–2.62 (m, 1H), 1.49 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$): 172.57, 155.71, 129.17, 126.60, 125.34, 119.81, 117.38, 82.25, 71.60, 41.75, 28.04; MS (EI): m/z=238.12 (M^+). HRMS (ESI): m/z calcd for $C_{13}H_{18}O_4Na$ $[M+Na]^+$: 261.10973; Found 261.10626.

*4.4.2. tert-Butyl 3-hydroxy-3-(2-hydroxyphenyl)butanoate (**3b**).*[41] Pale yellow oil. Isolated yield: 98%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.35 (s, 1H), 7.15 (dd, J=7.4, 7.2 Hz, 1H), 6.98 (d, J=7.8 Hz, 1H), 6.87 (d, J=7.8 Hz, 1H), 6.79 (dd, J=7.4, 7.2 Hz, 1H), 5.72 (s, 1H), 3.07 (d, J=16.8 Hz, 1H), 2.65 (d, J=16.2 Hz, 1H), 1.61 (d, J=7.2 Hz, 3H), 1.42 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$): 172.72, 156.08, 129.06, 128.89, 124.80, 119.27, 117.81, 82.63, 76.19, 45.21, 28.51, 27.89; MS (EI): m/z=252.06 (M^+).

*4.4.3. tert-Butyl 3-hydroxy-3-(2-hydroxy-5-methylphenyl)butanoate (**3c**).* Pale yellow oil. Isolated yield: 84%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.12 (brs, 1H), 6.95 (d, J=6.6 Hz, 1H), 6.78–6.76 (m, 2H), 5.64 (brs, 1H), 3.06 (d, J=15.6 Hz, 1H), 2.64 (d, J=16.2 Hz, 1H), 2.24 (s, 3H), 1.60 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$): 172.82, 153.76, 129.52, 128.60, 128.16, 125.35, 117.60, 82.58, 76.17, 45.27, 28.54, 28.49, 27.96, 27.91, 20.63; MS (EI): m/z=266.25 (M^+); HRMS (ESI): m/z calcd for $C_{15}H_{22}O_4Na$ $[M+Na]^+$: 289.14103; Found: 289.13871.

*4.4.4. 4-(2,4-Dimethoxyphenyl)chroman-2-one (**5a**).* White solid: mp 81.5–83.0 °C. Isolated yield: 99%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29–7.28 (m, 1H), 7.11 (d, J=7.8 Hz, 1H), 7.07 (dd, J=7.4, 7.2 Hz, 1H), 7.03 (d, J=6.6 Hz, 1H), 6.74 (d, J=8.4 Hz, 1H), 6.48 (s, 1H), 6.38 (d, J=7.8 Hz, 1H), 4.59 (t, J=6.6 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.09–3.06 (m, 1H), 2.98–2.94 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): 168.11, 160.25, 157.73, 151.95, 128.66, 128.31, 125.29, 124.39, 121.14, 116.81, 104.18, 98.83, 55.25, 55.09, 35.30, 34.92; MS (EI): m/z=284.12 (M^+). HRMS (ESI): m/z calcd for $C_{17}H_{17}O_4$ $[M+H]^+$: 285.11214; Found: 285.10972.

*4.4.5. 4-(4-Methoxyphenyl)chroman-2-one (**5b**).*[26] White solid: mp 130.6–132.1 °C. Isolated yield: 84%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31–7.28 (m, 1H), 7.12 (d, J=7.8 Hz, 1H), 7.10–7.07 (m, 3H), 6.98 (d, J=7.8 Hz, 1H), 6.88 (d, J=9.0 Hz, 2H), 4.30 (t, J=7.2 Hz, 1H), 3.80 (s, 3H), 3.07–2.97 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$): 167.77, 158.94, 151.62, 132.15, 128.68, 128.59, 128.25, 126.18, 124.60, 117.05, 114.43, 55.27, 39.84, 37.16; MS (EI): m/z=254.11 (M^+).

*4.4.6. 4-(3,4-Dimethoxyphenyl)chroman-2-one (**5c**).*[42] White solid: mp 108.7–110.0 °C. Isolated yield: 88%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30 (dd, J=7.8, 7.6 Hz, 1H), 7.13 (d, J=8.4 Hz, 1H), 7.09 (dd, J=8.0, 7.8 Hz, 1H), 7.00 (d, J=7.8 Hz, 1H), 6.83 (d, J=7.8 Hz, 1H), 6.69 (d, J=8.4 Hz, 1H), 6.67 (s, 1H), 4.29 (t, J=7.2 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.09–3.05 (m, 1H), 3.03–2.99 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): 167.62, 151.53, 149.30, 148.39, 132.58, 128.72, 128.27, 126.00, 124.63, 119.66, 117.05, 111.43, 110.52, 55.92, 55.71, 40.29, 37.19; MS (EI): m/z=284.22 (M^+).

*4.4.7. 4-(2,4-Dimethoxy-3-methylphenyl)chroman-2-one (**5d**).* White solid: mp 92.5–94.0 °C. Isolated yield: 99%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28 (dd, J=7.8, 7.6 Hz, 1H), 7.13 (d, J=7.6 Hz, 1H), 7.06 (dd, J=7.4, 7.2 Hz, 1H), 6.96 (d, J=7.2 Hz, 1H), 6.74 (d, J=8.8 Hz, 1H), 6.59 (d, J=8.4 Hz, 1H), 4.65 (t, J=7.2 Hz, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 3.01–3.00 (m, 2H), 2.19 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): 167.94, 158.23, 157.15, 151.89, 128.47, 128.28, 126.28, 125.38, 124.56, 124.38, 119.97, 116.98, 106.51, 61.20, 55.64, 36.49, 34.33, 9.50; MS (EI): m/z=298.24 (M^+); HRMS (ESI): m/z calcd for $C_{18}H_{19}O_4$ $[M+H]^+$: 299.12779; Found: 299.12787.

*4.4.8. 4-(5-Methylfuran-2-yl)chroman-2-one (**5e**).*[43] Pale yellow oil. Isolated yield: 82%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 (dd, J=7.8, 7.6 Hz, 1H), 7.18–7.08 (m, 3H), 5.89–5.86 (m, 2H), 4.33 (t, J=6.0 Hz, 1H), 3.21–3.16 (m, 1H), 3.02–2.97 (m, 1H), 2.24 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): 167.41, 152.37, 151.37, 150.78, 128.94, 128.18, 124.57, 123.47, 117.19, 107.69, 106.17, 34.74, 34.03, 13.52; MS (EI): m/z=228.16 (M^+).

*4.4.9. 4-(5-Methylthiophen-2-yl)chroman-2-one (**5f**).* Pale yellow oil. Isolated yield: 84%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (dd, J=7.4, 7.2 Hz, 1H), 7.18 (d, J=7.2 Hz, 1H), 7.14–7.10 (m, 2H), 6.57 (s, 2H), 4.51 (t, J=6.0 Hz, 1H), 3.09 (d, J=6.0 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): 167.14, 151.22, 140.96, 139.76, 129.02, 128.02, 125.57, 125.11, 125.02, 124.66, 117.23, 37.34, 36.36, 15.29; MS (EI): m/z=244.08 (M^+); HRMS (ESI): m/z calcd for $C_{14}H_{12}O_2SNa$ $[M+Na]^+$: 267.04502; Found: 267.04555.

*4.4.10. 4-(2,4-Dimethoxyphenyl)-4-methylchroman-2-one (**5g**).* White solid: mp 110.4–111.8 °C. Isolated yield: 90%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24 (d, J=7.2 Hz, 1H), 7.08–7.05 (m, 2H), 7.01 (d, J=7.2 Hz, 1H), 6.90 (d, J=8.4 Hz, 1H), 6.46 (s, 1H), 6.40 (d, J=8.4 Hz, 1H), 3.80–3.79 (m, 4H), 3.63 (s, 3H), 2.59 (d, J=15.6 Hz, 1H), 1.73 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): 168.62, 160.34, 158.38, 150.60, 131.29, 128.37, 127.91, 126.07, 124.26, 123.87, 116.92, 103.77, 99.95, 55.23, 54.97, 40.84, 39.92, 26.56. MS (EI): m/z=298.15 (M^+); HRMS (ESI): m/z calcd for $C_{18}H_{19}O_4$ $[M+H]^+$: 299.12779; Found: 299.12839.

*4.4.11. 4-(4-Methoxyphenyl)-4-methylchroman-2-one (**5h**).* Pale yellow oil. Isolated yield: 89%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31 (dd, J=8.0, 7.8 Hz, 1H), 7.22 (d, J=7.8 Hz, 1H), 7.17 (dd, J=8.0, 7.8 Hz, 1H), 7.11–7.08 (m, 3H), 6.82 (d, J=9.0 Hz, 2H), 3.77 (s, 3H), 3.24 (d, J=15.6 Hz, 1H), 2.81 (d, J=15.6 Hz, 1H), 1.72 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): 167.57, 158.44, 151.08, 135.84, 131.03, 128.60, 127.25, 126.50, 124.63, 117.23, 113.95, 55.15, 43.81, 40.47, 27.57; MS (EI): m/z=268.13 (M^+); HRMS (ESI): m/z calcd for $C_{17}H_{17}O_3$ $[M+H]^+$: 269.11722; Found: 269.11735.

*4.4.12. 4-(2,4-Dimethoxy-3-methylphenyl)-4-methylchroman-2-one (**5i**).* White solid: mp 96.2–97.7 °C. Isolated yield: 92%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24 (d, J=7.2 Hz, 1H), 7.10 (d, J=7.8 Hz, 1H), 7.06 (dd, J=8.0, 7.8 Hz, 1H), 6.99–6.94 (m, 2H), 6.57 (d, J=8.4 Hz, 1H), 3.92 (d, J=16.2 Hz, 1H), 3.82 (s, 3H), 3.20 (s, 3H), 2.63 (d, J=16.2 Hz, 1H), 2.11 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): 168.26, 158.59, 158.08, 150.40, 131.93, 128.37, 127.96, 126.61, 124.82, 124.16, 120.26, 116.92, 104.61, 60.00, 55.35, 41.46, 40.10, 27.79, 10.21; MS (EI): m/z=312.17 (M^+); HRMS (ESI): m/z calcd for $C_{19}H_{21}O_4$ $[M+H]^+$: 313.14344; Found: 313.14076.

*4.4.13. 4-Methyl-4-(5-methylthiophen-2-yl)chroman-2-one (**5j**).* Pink oil. Isolated yield: 95%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.32

(dd, *J*=8.0, 7.8 Hz, 1H), 7.28 (d, *J*=7.8 Hz, 1H), 7.17 (dd, *J*=8.0, 7.8 Hz, 1H), 7.10 (d, *J*=8.4 Hz, 1H), 6.54–6.53 (m, 2H), 3.20 (d, *J*=15.6 Hz, 1H), 2.91 (d, *J*=15.6 Hz, 1H), 2.41 (s, 3H), 1.78 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): 167.01, 150.61, 146.47, 139.45, 130.34, 128.93, 125.87, 124.74, 124.69, 124.28, 117.19, 44.59, 39.50, 28.28, 15.21; MS (EI): *m*/*z*=258.08 (M^+); HRMS (ESI): *m*/*z* calcd for $C_{15}H_{15}O_2S$ $[M+H]^+$: 259.07873; Found: 259.07875.

*4.4.14. 4-Methyl-4-(1-methyl-1H-indol-3-yl)chroman-2-one (**5k**).* Pale yellow oil. Isolated yield: 92%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34–7.29 (m, 2H), 7.23–6.98 (m, 6H), 6.83 (s, 1H), 3.77 (s, 3H), 3.54 (d, *J*=15.6 Hz, 1H), 2.78 (d, *J*=16.2 Hz, 1H), 1.82 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): 168.13, 150.80, 137.92, 130.44, 128.39, 127.09, 126.92, 125.02, 124.54, 121.64, 120.48, 118.95, 117.47, 117.01, 109.69, 43.01, 37.31, 32.66, 26.78; MS (EI): *m*/*z*=291.14 (M^+); HRMS (ESI): *m*/*z* calcd for $C_{19}H_{18}NO_2$ $[M+H]^+$: 292.13321; Found: 292.13266.

*4.4.15. 4-(2,4-Dimethoxyphenyl)-4,6-dimethylchroman-2-one (**5l**).* White solid: mp 137.4–138.7 °C. Isolated yield: 93%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.05 (d, *J*=8.4 Hz, 1H), 6.96 (d, *J*=8.4 Hz, 1H), 6.86 (d, *J*=8.4 Hz, 1H), 6.82 (s, 1H), 6.46 (s, 1H), 6.39 (d, *J*=9.0 Hz, 1H), 3.80–3.76 (m, 4H), 3.66 (s, 3H), 2.57 (d, *J*=16.2 Hz, 1H), 2.27 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): 168.63, 160.17, 158.33, 148.52, 133.66, 130.78, 128.37, 128.31, 126.32, 123.90, 116.52, 103.66, 99.86, 55.09, 54.89, 40.80, 39.81, 26.35, 20.74; MS (EI): *m*/*z*=312.16 (M^+); HRMS (ESI): *m*/*z* calcd for $C_{19}H_{21}O_4$ $[M+H]^+$: 313.14344; Found: 313.14060.

*4.4.16. 4-(4-Methoxyphenyl)-4,6-dimethylchroman-2-one (**5m**).* Pale yellow oil. Isolated yield: 86%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.11–7.08 (m, 3H), 7.00–6.98 (m, 2H), 6.82 (d, *J*=9.0 Hz, 2H), 3.78 (s, 3H), 3.21 (d, *J*=15.6 Hz, 1H), 2.78 (d, *J*=16.2 Hz, 1H), 2.33 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): 167.81, 158.38, 149.02, 135.96, 134.22, 130.62, 129.06, 127.27, 126.81, 116.94, 113.91, 55.16, 43.97, 40.41, 27.59, 20.93; MS (EI): *m*/*z*=282.14 (M^+); HRMS (ESI): *m*/*z* calcd for $C_{18}H_{19}O_3$ $[M+H]^+$: 283.13287; Found: 283.13276.

*4.4.17. 4-(2,4-Dimethoxy-3-methylphenyl)-4,6-dimethylchroman-2-one (**5n**).* White solid: mp 117.4–118.7 °C. Isolated yield: 84%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.03 (d, *J*=8.4 Hz, 1H), 6.99 (d, *J*=8.4 Hz, 1H), 6.95 (d, *J*=8.4 Hz, 1H), 6.75 (s, 1H), 6.57 (d, *J*=8.4 Hz, 1H), 3.87 (d, *J*=15.6 Hz, 1H), 3.83 (s, 3H), 3.21 (s, 3H), 2.59 (d, *J*=15.6 Hz, 1H), 2.24 (s, 3H), 2.11 (s, 3H), 1.68 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): 168.45, 158.51, 158.07, 148.32, 133.59, 131.52, 128.45, 128.37, 126.87, 124.80, 120.20, 116.63, 104.58, 59.94, 55.29, 41.54, 40.04, 27.70, 20.60, 10.16; MS (EI): *m*/*z*=326.17 (M^+); HRMS (ESI): *m*/*z* calcd for $C_{20}H_{22}O_4K$ $[M+K]^+$: 365.11497; Found: 365.11168.

*4.4.18. 4,6-Dimethyl-4-(5-methylthiophen-2-yl)chroman-2-one (**5o**).* Pale yellow oil. Isolated yield: 85%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.10 (d, *J*=8.4 Hz, 1H), 7.06 (s, 1H), 6.98 (d, *J*=8.4 Hz, 1H), 6.53–6.52 (m, 2H), 3.16 (d, *J*=15.6 Hz, 1H), 2.86 (d, *J*=15.6 Hz, 1H), 2.41 (s, 3H), 2.33 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): 167.11, 148.56, 146.61, 139.30, 134.30, 129.92, 129.43, 126.17, 124.72, 124.25, 116.94, 44.74, 39.43, 28.29, 20.90, 15.17; MS (EI): *m*/*z*=272.18 (M^+); HRMS (ESI): *m*/*z* calcd for $C_{16}H_{17}O_2S$ $[M+H]^+$: 273.09438; Found: 273.09420.

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Supplementary data

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