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Lewis acid promoted construction of chromen-4-one and isoflavone scaffolds *via* regio- and chemoselective domino Friedel–Crafts acylation/Allan–Robinson reaction†‡

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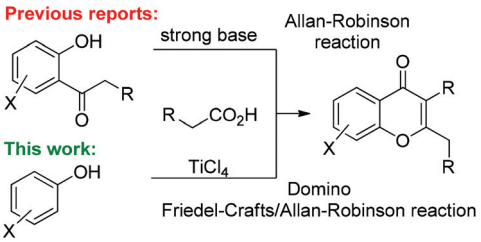
A facile and efficient synthesis of chromen-4-one and isoflavone frameworks is achieved by the domino C-acylation/O-acylation/aldolization sequence. This operationally simple one-pot elegant strategy provides structurally unique chromen-4-ones and isoflavones directly from phenols *via* concomitant formation of multiple C–C and C–O bonds in a single operation. The outcomes of the buttressing effect, substituent dependence, and catalyst and solvent specificity during the course of the Friedel–Crafts acylation reactions are demonstrated and supported by fitting experiments.

Introduction

Chromones and isoflavones are of widespread chemical and biological significance and are present in a large number of molecules of medicinal importance.[1] Chromones are often very active as estrogen receptor modulators[2a,b] and thymidine phosphorylase inhibitors.[2c] They have also been employed as insecticidal[2d] and antifungal[2e] agents possessing high target affinity and specificity. Substituted isoflavones serve as S-nitrosoglutathione reductase (GSNOR) inhibitors[3a] and have been shown to have osteogenic activity.[3b] The above biological properties have stimulated considerable interest toward the synthesis of natural and unnatural analogues of isoflavones.[4] Among the reported methods for the synthesis of chromones the most common one is the base catalyzed Allan–Robinson reaction of *ortho*-acylphenols and carboxylic acid derivatives[5] (Scheme 1). In fact the most significant route to fabricate chromones is actually a two-step process consisting of Friedel–Crafts acylation of the corresponding phenol followed by the Allan–Robinson reaction.

In recent years, complex molecular architectures of natural products have been obtained from structurally simplified building blocks through a series of carefully choreographed synthetic operations. Thus, a new cascade protocol to construct chromone and isoflavone derivatives with pot, step, and atom economy is highly desirable. As a part of our research programme to devise new domino protocols for the synthesis of biologically relevant molecules,[6] here we describe the use of phenols directly for the synthesis of chromones *via* the Lewis acid promoted domino Friedel–Crafts acylation/Allan–Robinson reaction for the first time.



Scheme 1 Synthesis of chromones.

The choice of substrates and reaction conditions in this regard is the crucial factor as the Friedel–Crafts acylation reaction is highly sensitive toward substituents.[7] The substituent dependence of this reaction was not properly justified in the early literature[8] as it was believed to be irreversible in nature. However, later on the reversibility of this reaction was established by a number of experiments disclosing the substituent effects to a good extent.[9] The reversibility of Friedel–Crafts acylation *via* acetyl exchange was first examined by Gore and coworkers.[10] Herein, we discuss the effects of substituents, scope, and limitations of the Lewis acid mediated Friedel–

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†This paper is dedicated to Prof. H. Ila on the occasion of her 70th birthday.

‡Electronic supplementary information (ESI) available: Elaborate reaction procedure; characterization data; scanned spectra of all the products. CCDC 932483 and 970761. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ob01743a

Crafts acylation reaction. A variety of substrates and acylating agents were employed, and it was observed that under varying conditions highly chemo- and regioselective outcomes were achieved.

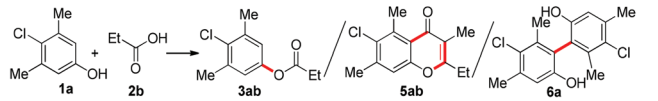
Results and discussion

We started our investigation by taking 4-chloro-3,5-dimethylphenol **1a** and propionic acid **2b** as the model substrates under different Lewis acid mediated Friedel–Crafts acylation conditions[11] (Table 1). Initially, a neat mixture of **1a** (1 mmol), **2b** (10 mmol), and anhydrous $AlCl_3$ (2.5 mmol) was heated at 100 °C under an argon atmosphere. No reaction took place even after 12 h of heating and the starting phenol **1a** was recovered unconsumed (Table 1, entry 1). Next, the above reaction was performed in nitromethane (CH_3NO_2) at 50 °C for 18 h. Notably, the reaction proceeded smoothly and an unexpected C–C coupled product **6a** was obtained in 86% yield (Table 1, entry 2). Neither our expected product **5ab** nor the C-acylated product 4-chloro-3,5-dimethyl-2-propionylphenol was formed. A similar result was obtained when $SnCl_4$ (2.5 mmol) was used as the promoter in nitromethane (Table 1, entry 3). Formation of **6a** proceeds *via* a six-coordinated sigma-type EDA complex of phenolic derivative **1a** with $AlCl_3$ or $SnCl_4$ where nitromethane plays the dual role of solvent and oxidant.[12] When the above model reaction was carried out with 2.5 mmol of $SnCl_4$ under solvent-free conditions, interestingly, chemoselective O-acylation of **1a** took place instead of C-acylation affording 4-chloro-3,5-dimethylphenyl propionate **3ab** in 92% yield (Table 1, entry 5). Having found optimum reaction conditions for chemoselective O-acylation, we next examined the scope of this reaction by synthesizing some O-acylated derivatives **3** (Table 2). The above $SnCl_4$ mediated O-acylation of phenols having a specific substitution pattern may be applicable as an alternative to the other existing methods.[13]

Next, a mixture of **1a** (1 mmol) and **2b** (10 mmol) was treated with 2.5 mmol of $TiCl_4$ under solvent-free inert conditions. The workup of the reaction afforded the expected chromone derivative **5ab**[14] (Fig. 1) in quantitative yield involving C-acylation, O-acylation, and aldol condensation as key steps (Table 1, entry 6). This unique result prompted us to explore the scope of this $TiCl_4$ promoted cascade reaction. In this regard, various substituted phenols **1a–h** and different α-substituted acetic acids **2a–h** were selected as counter substrates for the synthesis of chromen-4-ones and isoflavones **5**.

Out of a broad range of substituted phenols used, only the phenolic derivatives substituted at both the *meta*-positions (**1a–f**) were found to be capable of providing the desired product chromen-4-ones **5**. Propionic acid **2b**, its higher homo-

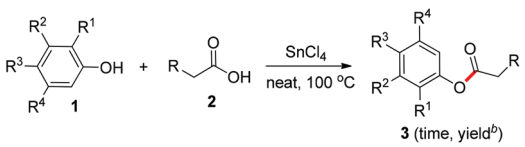
Table 1 Attempted Friedel–Crafts acylation of **1a**[a]

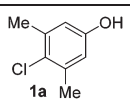
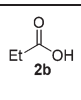
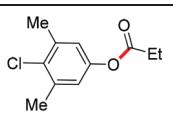
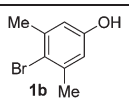
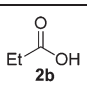
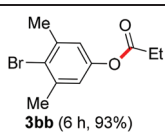
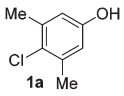
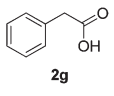
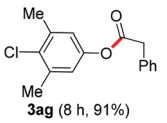
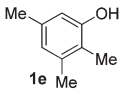
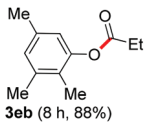


Entry	Catalyst (mmol)	Solvent	Temp. (°C)	Time (h)	Product[b] (yield)
1	$AlCl_3$ (2.5)	None	100	12	—[c]
2	$AlCl_3$ (2.5)	$MeNO_2$	50	18	**6a** (86)
3	$SnCl_4$ (2.5)	$MeNO_2$	50	18	**6a** (82)
4	$TiCl_4$ (2.5)	$MeNO_2$	50	18	**6a** (45)
5	$SnCl_4$ (2.5)	None	100	8	**3ab** (92)
6	$TiCl_4$ (2.5)	None	100	2	**5ab** (96)
7	$TiCl_4$ (2.5)	None	80	6	**5ab** (88)[d]
8	$TiCl_4$ (1.5)	None	100	6	**5ab** (65)[e]
9	$TiCl_4$ (0.3)	None	100	6	**5ab** (10)[f]

[a] Reaction conditions: a mixture of **1a** (1 mmol) and **2b** (10 mmol) with different Lewis acids was heated under an argon atmosphere. [b] Isolated pure yield in %. [c] No reaction. [d] 10% of **1a** was recovered. [e] 30% of **1a** was recovered. [f] 85% of **1a** was recovered.

Table 2 $SnCl_4$ mediated O-acylation of substituted phenols **1**[a]



Entry	1	2	3	Entry	1	2	3
1				3			
	1a	2b	**3ab** (8 h, 92%)		1b	2b	**3bb** (6 h, 93%)
2				4			
	1a	2g	**3ag** (8 h, 91%)		1e	2b	**3eb** (8 h, 88%)

[a] Reaction conditions: a mixture of **1** (1 mmol), **2** (10 mmol), and $SnCl_4$ (2.5 mmol) was heated at 100 °C under an argon atmosphere. [b] Isolated pure yield.

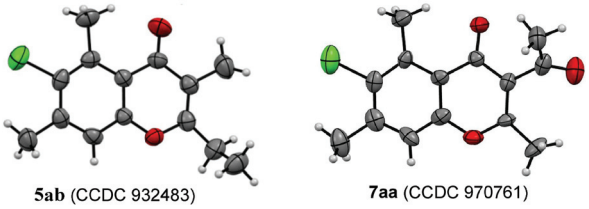
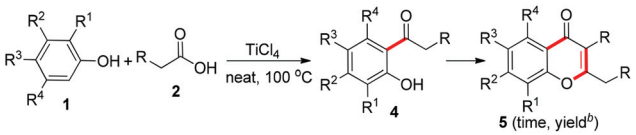


Fig. 1 ORTEP diagrams of **5ab** and **7aa**.

logues **2c–f**, and substituted phenyl acetic acids **2g–i** as reaction partners were also tolerated well affording the desired product **5** in high yields (Table 3, entries 1–12). However, acetic acid **2a** along with **1a** under similar reaction conditions gave an inseparable mixture of 6-chloro-2,5,7-trimethyl-4*H*-chromen-4-one **5aa**, 5′-chloro-2′-hydroxy-4′,6′-dimethyl acetophenone[15] **4aa**, and 3-acetyl-6-chloro-2,5,7-trimethyl-4*H*-chromen-4-one[14] **7aa** (Fig. 1) along with the unreacted **1a** (Scheme 2).

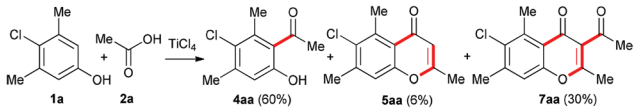
When the substrate **1b** was treated with **2b** under similar optimized reaction conditions, surprisingly, only a trace of the desired product **5bb** was obtained along with O-acylated product **3bb** in 85% yield (Table 3, entry 13). This anomalous result could be due to the buttressing effect of the large bromine atom flanked by two methyl groups. Next, **1g** and **1h** were treated separately with excess of **2b** in the presence of

Table 3 Synthesis of chromen-4-ones and isoflavones **5**[a]



Entry	1	2	Product	Entry	1	2	Product
1	**1a**	**2b**	**5ab** (3 h, 96)	9	**1c**	**2b**	**5cb** (8 h, 68)
2	**1a**	**2c**	**5ac** (6 h, 83)	10	**1d**	**2b**	**5db** (5 h, 97)
3	**1a**	**2d**	**5ad** (6 h, 91)	11	**1e**	**2b**	**5eb** (5 h, 98)
4	**1a**	**2e**	**5ae** (8 h, 82)	12	**1f**	**2b**	**5fb** (6 h, 75)
5	**1a**	**2f**	**5af** (6 h, 86)	13	**1b**	**2b**	**5bb** (12 h, trace) + **3bb** (85)
6	**1a**	**2g**	**5ag** (6 h, 84)	14	**1g**	**2b**	**4gb** (6 h, 94)
7	**1a**	**2h**	**5ah** (8 h, 76)	15	**1h**	**2b**	**4hb** (6 h, 92)
8	**1a**	**2i**	**5ai** (10 h, 72)				

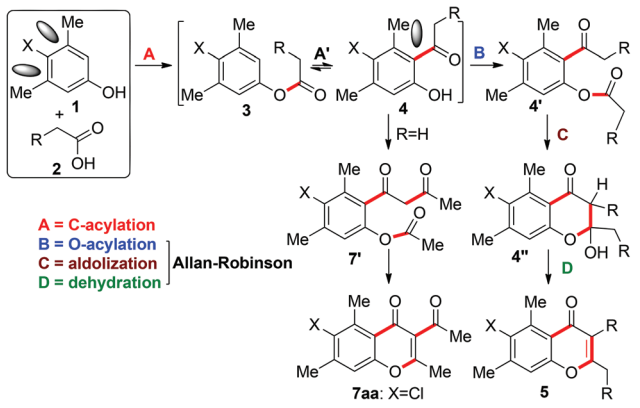
[a] A mixture of 1 mmol of **1**, excess of **2** (10 mmol) and 2.5 mmol of $TiCl_4$ was heated at 100 °C under argon. [b] Isolated pure yield in %.



Scheme 2 Fate of acetic acid **2a** in Friedel–Crafts acylation/Allan–Robinson reaction.

$TiCl_4$ under previously optimized conditions. The workup of the reaction mixture furnished the *ortho*-acylated products **4gb**[16a] and **4hb**,[16b] respectively, in quantitative yields (Table 3, entries 14 and 15).

The reversibility of Friedel–Crafts reaction, which is somehow substituent dependent, has a key role in the above domino reaction for the formation of chromen-4-ones **5** (Scheme 3). Initial C-acylation yielded *ortho*-acylated phenols **4**, which are thermodynamically stable due to hydrogen bonding. However, in the case of substrates **1a–1f** intermediate **4** would become relatively unstable because the acyl group suffers steric repulsion by the adjacent methyl group and by its neighbouring substituent X. Consequently, the acyl group becomes tilted from the plane of the aromatic ring, resulting redundancy in resonance, thus making the bond between the acyl group and the aromatic ring quite labile.[17a] Hence, 4,6-disubstituted *ortho*-acyl phenol becomes relatively unstable and an equilibrium between C-acylated product **4** and O-acylated product **3** was established (Scheme 3). Intermediates **4** and **3** appear to have similar energy and are present side by side in the reaction medium.[9a] Next, *in situ* O-acylation of **4** provided intermediate **4′**, which is cyclized *via* aldol condensation to give the desired chromen-4-ones **5**. Compound **5** is planar hence steric destabilization is minimized to some extent. As soon as the intermediate **4** is converted to **5**, to maintain the equilibrium, **3** is converted to **4** and the reaction moves toward completion. As a control experiment and to emphasize our statement about the reversibility between **3** and **4**, we performed the reaction of **3ab** (1 mmol) with excess of **2b** (10 mmol) in the presence of 2.5 mmol of $TiCl_4$ under the optimized reaction conditions. As per our expectations, **5ab** was formed in 92% yield after 10 h of heating.

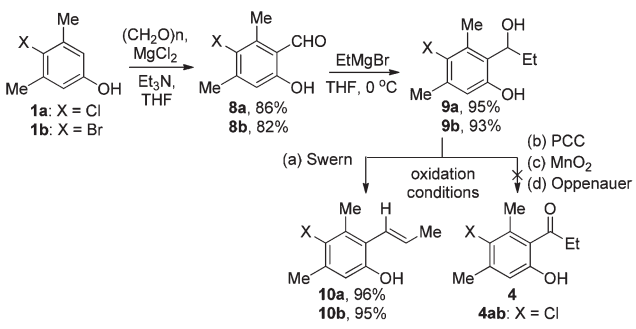


Scheme 3 Mechanism for the synthesis of chromen-4-ones **5** and **7**.

The destabilizing steric factor is absent in intermediates **4gb** and **4hb** making them stable due to their intramolecular hydrogen bonding. Thus, the equilibrium mentioned earlier is not possible, therefore, substrates **1g** and **1h** provided the expected single regioisomer of *ortho*-acylated product **4** (**4gb** and **4hb**, respectively) in quantitative yield. However, in the case of substrate **1b** only a trace of the desired domino product **5bb** was obtained along with 85% of O-acylated product **3bb**. Here, the large size of the Br atom exerts a massive buttressing effect[17] that strongly disfavours the formation of *ortho*-C-acylated intermediate **4bb**, hence the equilibrium mentioned earlier entirely moved towards the direction where the steric crowding can be minimized and provided **3bb** almost exclusively.

Fascinatingly, when acetic acid **2a** was used as the acylating reagent, the desired chromone **5aa** was obtained in trace (6%) along with *ortho*-C-acylated product **4aa** in 60% yield (Scheme 2). While the substituent 'R' becomes 'H' instead of 'Me' or its sterically higher analogues (Scheme 3), destabilization of the C–C bond between the aryl ring and the associated acyl group rather decreased, stabilizing the intermediate **4aa** to some extent. Under similar reaction conditions $SnCl_4$ might not be able to trigger the condensation steps B and C mentioned in Scheme 3, hence only the O-acylated products were obtained. These observations provided insight into the reaction mechanism and the substituent dependent reversibility of Friedel–Crafts acylation reaction. Suitable size and co-ordinating properties of $TiCl_4$ facilitate the condensation steps (steps B and C mentioned in Scheme 3) and the reaction advanced forward towards formation of highly substituted chromone frameworks **5** and thus making this domino protocol specific to $TiCl_4$.[18]

To validate our mechanistic hypothesis, we attempted to synthesize the intermediate 4-chloro-3,5-dimethyl-2-propionylphenol (**4ab**) *via* different strategies and further wished to employ it as an initial substrate along with **2b** to produce **5ab**. We succeeded to synthesize 4-halo-2-(1-hydroxypropyl)-3,5-dimethylphenol **9** but failed to oxidize the hydroxyl group of the secondary alcohol **9** to transform it to **4**. Several different reported methods of oxidation were performed but none was found to be successful (Scheme 4; for detailed discussion, see ESI‡). This observation again supported the presence of a



Scheme 4 Attempted strategy for the synthesis of C-acylated product **4**.

strong steric effect and the buttressing effect exerted by the methyl and halogen groups present on the phenyl ring of **9**, which provided the main obstacle to oxidize the sp^3-C centre of **9** to sp^2-carbonyl carbon of **4** (Scheme 4).

Conclusions

In conclusion, we have designed and developed an operationally simple, highly efficient, and straightforward method for the synthesis of highly functionalized and structurally unique chromone and isoflavone derivatives from phenols for the first time. This one-pot domino protocol involves the Lewis-acid promoted Friedel–Crafts acylation/Allan–Robinson reaction creating two C–C and one C–O new bonds in a single operation. We also established the substituent dependent reversibility of Friedel–Crafts acylation through experimental observations. Furthermore, how the buttressing effect guided the outcomes of this reaction is thoroughly assessed and supported by appropriate experiments. The scope and diversity of the tolerated substrates in this work is rather broad in comparison with the reported ones. A plausible reaction mechanism was proposed to account for the cascade reaction.

Experimental section

General experimental details

^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Chemical shift (δ) values are given in parts per million (ppm) with reference to tetramethylsilane (TMS) as the internal standard. Coupling constant (J) values are given in hertz (Hz). High resolution mass spectra were recorded using the ESI method. Organic solvents were dried by standard methods prior to use. Commercially obtained reagents were used after further purification when needed. All these reactions were monitored by TLC with silica gel coated plates. Column chromatography was carried out whenever needed, using silica gel of 100/200 mesh. A mixture of hexane–ethyl acetate in appropriate proportion (determined by TLC analysis) was used as the eluent.

General procedure for the synthesis of 3

A mixture of 1 mmol of **1**, excess of **2** (10 mmol), and 2.5 mmol of $SnCl_4$ was heated at 100 °C under an argon atmosphere for the stipulated period of time mentioned in Table 2 (completion of the reaction was monitored *via* TLC analysis). As in some cases the boiling point of the initial substrate **2** was less than 100 °C, a cold circulatory bath fitted with a condenser was used to minimize the evaporation of the concerned substrate. After completion of the reaction, the residue obtained was dissolved in ethyl acetate (100 mL) and washed with 4% aqueous HCl (100 mL × 2) followed by water, dilute $NaHCO_3$, and brine. Ethyl acetate was evaporated and the crude was purified by column chromatography whenever needed using a mixture of EtOAc and hexane in an appropriate proportion as the eluent to provide pure **3**.

4-Chloro-3,5-dimethylphenylpropionate (3ab). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.81 (s, 2H), 2.59 (q, J = 7.5 Hz, 2H), 2.35 (s, 6H), 1.27 (t, J = 7.5 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.9, 148.3, 137.3, 131.5, 121.3, 27.6, 20.7, 8.9; HRMS (ESI-TOF) of $C_{13}H_{11}ClO_2$ (m/z) = 235.0504 [M + Na^+] (calculated = 235.0502).

4-Chloro-3,5-dimethylphenyl-2-phenylacetate (3ag). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.25–7.19 (m, 5H), 6.67 (s, 2H), 3.70 (s, 2H), 2.21 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 169.8, 148.2, 137.3, 133.2, 131.6, 129.1, 128.6, 127.2, 121.1, 41.2, 20.6; HRMS (ESI-TOF) of $C_{16}H_{15}ClO_2$ (m/z) = 275.0838 [M + H^+] (calculated = 275.0839).

4-Bromo-3,5-dimethylphenylpropionate (3bb). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.81 (s, 2H), 2.593 (q, J = 7.5 Hz, 2H), 2.38 (s, 6H), 1.27 (t, J = 7.2 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.8, 149.0, 139.3, 123.9, 121.1, 27.6, 23.8, 8.9.

2,3,5-Trimethylphenylpropionate (3eb). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.83 (s, 1H), 6.65 (s, 1H), 2.62 (q, J = 7.5 Hz, 2H), 2.25–2.23 (m, 6H), 2.00 (s, 3H), 1.29 (t, J = 7.5 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.8, 148.9, 137.9, 135.7, 128.2, 125.2, 119.7, 27.5, 20.6, 19.8, 11.8, 9.1; HRMS (ESI-TOF) of $C_{12}H_{16}O_2$ (m/z) = 193.1228 [M + H^+] (calculated = 193.1229).

General procedure for synthesis of 5

A similar procedure as above for the synthesis of **3** was utilized except in place of $SnCl_4$, $TiCl_4$ was used.

6-Chloro-2,5,7-trimethyl-4*H*-chromen-4-one.[19] (5aa). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.15 (s, 1H), 6.06 (s, 1H), 2.96 (s, 3H), 2.47 (s, 3H), 2.30 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 179.6, 163.9, 142.0, 138.0, 137.2, 132.3, 117.2, 111.8, 111.7, 21.8, 19.8, 18.0.

6-Chloro-2-ethyl-3,5,7-trimethyl-4*H*-chromen-4-one (5ab). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.12 (s, 1H), 2.97 (s, 3H), 2.70 (q, J = 7.65 Hz, 2H), 2.44 (s, 3H), 2.00 (s, 3H), 1.30 (t, J = 7.65 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 179.4, 163.8, 155.2, 141.4, 137.8, 131.7, 119.8, 117.0, 116.6, 25.2, 21.7, 18.0, 11.2, 9.7; CCDC 932483; HRMS (ESI-TOF) of $C_{14}H_{15}ClO_2$ (m/z) = 251.0838 [M + H^+] (calculated m/z = 251.0839).

6-Chloro-3-ethyl-5,7-dimethyl-2-propyl-4*H*-chromen-4-one (5ac). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.11 (s, 1H), 2.98 (s, 3H), 2.64–2.45 (m, 5H), 1.80–1.72 (m, 2H), 1.29–1.25 (m, 2H), 1.13 (t, J = 7.5 Hz, 3H), 1.04 (t, J = 7.5 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 178.9, 162.9, 155.2, 141.3, 137.8, 131.7, 123.3, 121.3, 120.3, 117.0, 33.2, 21.7, 20.7, 18.0, 13.8, 13.7; HRMS (ESI-TOF) of $C_{16}H_{19}ClO_2$ (m/z) = 279.1152 [M + H^+] (calculated = 279.1154).

6-Chloro-2-heptyl-3-hexyl-5,7-dimethyl-4*H*-chromen-4-one (5ad). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.07 (s, 1H), 2.94 (s, 3H), 2.61 (t, J = 7.5 Hz, 2H), 2.41 (broad, 5H), 1.73–1.63 (m, 2H), 1.27–1.22 (broad, 15H), 0.86 (broad, 7H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 179.0, 163.3, 155.2, 141.3, 137.8, 131.7, 121.9, 120.2, 116.9, 31.6, 31.4, 29.5, 29.3, 29.2, 28.9, 28.8, 27.3, 24.8, 22.6, 22.5, 21.7, 18.1, 18.0, 14.0; HRMS (ESI-TOF) of $C_{24}H_{35}ClO_2$ (m/z) = 391.2401 [M + H^+] (calculated 391.2398).

6-Chloro-5,7-dimethyl-2-nonyl-3-octyl-4*H*-chromen-4-one (5ae). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.11 (s, 1H), 2.98 (s, 3H), 2.64 (t, J = 7.5 Hz, 2H), 2.45 (broad, 5H), 1.71–1.66 (m, 2H), 1.27 (broad, 23H), 0.87–0.85 (broad, 7H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 179.0, 163.3, 155.2, 141.3, 137.9, 131.7, 122.0, 120.3, 117.0, 31.8, 31.4, 29.9, 29.4, 29.3, 27.3, 24.8, 22.6, 21.7, 18.1, 14.0; HRMS (ESI-TOF) of $C_{28}H_{43}ClO_2$ (m/z) = 447.3033 [M + H$^+$] (calculated 447.3024).

6-Chloro-3-(2-chloroethyl)-2-(3-chloropropyl)-5,7-dimethyl-4*H*-chromen-4-one (5af). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.15 (s, 1H), 3.79 (t, J = 6.3 Hz, 2H), 3.65 (t, J = 6.3 Hz, 2H), 3.00–2.90 (m, 7H), 2.47 (s, 3H), 2.62–2.21 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 178.6, 163.4, 155.2, 142.1, 138.0, 132.3, 119.9, 118.4, 117.0, 43.9, 43.3, 29.8, 28.9, 28.6, 21.8, 18.0; HRMS (ESI-TOF) of $C_{16}H_{17}Cl_3O_2$ (m/z) = 389.0810 [M + Na$^+$] (calculated 389.0816).

2-Benzyl-6-chloro-5,7-dimethyl-3-phenyl-4*H*-chromen-4-one (5ag). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.46–7.14 (m, 11H), 3.82 (s, 2H), 2.94 (s, 3H), 2.47 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 178.7, 161.7, 155.2, 142.1, 138.4, 135.9, 133.1, 132.3, 131.0, 130.6, 128.6, 127.0, 124.9, 120.8, 117.3, 38.6, 21.8, 18.2; HRMS (ESI-TOF) of $C_{24}H_{19}ClO_2$ (m/z) = 375.1153 [M + H$^+$] (calculated 375.1152).

6-Chloro-2-(4-fluorobenzyl)-3-(4-fluorophenyl)-5,7-dimethyl-4*H*-chromen-4-one (5ah). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.24–6.93 (m, 9H), 3.78 (s, 2H), 2.92 (s, 3H), 2.47 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 178.3, 164.1, 163.5, 161.8, 160.8, 160.2, 155.2, 142.4, 138.4, 132.5, 132.3, 132.2, 131.5, 130.1, 130.0, 128.7, 123.8, 120.5, 117.2, 115.7, 115.4, 37.4, 21.8, 18.0; HRMS (ESI-TOF) of $C_{14}H_{17}ClF_2O_2$ (m/z) = 411.0964 [M + H$^+$] (calculated 411.0958).

6-Chloro-2-(3,4-dichlorobenzyl)-3-(3,4-dichlorophenyl)-5,7-dimethyl-4*H*-chromen-4-one (5ai). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 8.4 Hz, 1H), 7.35–7.32 (m, 2H), 7.25–7.18 (m, 2H), 7.09 (d, J = 8.1 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 3.77 (s, 2H), 2.92 (s, 3H), 2.49 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 177.7, 166.8, 160.9, 155.1, 142.9, 138.6, 135.5, 133.1, 132.9, 132.8, 132.8, 132.6, 132.5, 132.4, 130.7, 130.5, 129.9, 127.9, 123.1, 117.2, 117.2, 37.4, 21.9, 18.1; HRMS (ESI-TOF) of $C_{24}H_{15}Cl_5O_2$ (m/z) = 534.9376 [M + Na$^+$] (calculated 534.9383).

6-Bromo-2-ethyl-3,5,7-trimethyl-4*H*-chromen-4-one (5bb). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.17 (s, 1H), 3.05 (s, 3H), 2.71 (q, J = 7.5 Hz), 2.51 (s, 3H), 2.01 (s, 3H), 1.26–1.25 (m, 3H); HRMS (ESI-TOF) of $C_{14}H_{15}BrO_2$ (m/z) = 294.0237 [M$^+$] (calculated 294.0255).

2-Ethyl-3,5,7-trimethyl-4*H*-chromen-4-one (5cb). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.98 (s, 1H), 6.84 (s, 1H), 2.81 (s, 3H), 2.68 (q, J = 7.5 Hz, 2H), 2.35 (s, 3H), 1.99 (s, 3H), 1.29 (t, J = 7.5 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 179.9, 163.8, 157.3, 142.5, 140.1, 128.2, 118.5, 116.2, 115.3, 25.1, 22.5, 21.2, 11.1, 9.3; HRMS (ESI-TOF) of $C_{14}H_{16}O_2$ (m/z) = 239.1046 [M + Na$^+$] (calculated 239.1043).

2-Ethyl-3,5,6,7-tetramethyl-4*H*-chromen-4-one (5db). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.01 (s, 1H), 2.84 (s, 3H), 2.68 (q, J = 7.5 Hz, 2H), 2.34 (s, 3H), 2.21 (s, 3H), 2.00 (s, 3H), 1.29 (t, J = 7.5 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 180.4, 163.3, 155.3, 141.9, 137.9, 132.1, 118.9, 116.3, 115.7, 25.2, 21.5, 17.1, 15.1, 11.2, 9.7; HRMS (ESI-TOF) of $C_{15}H_{18}O_2$ (m/z) = 253.1193 [M + Na$^+$] (calculated 253.1199).

2-Ethyl-3,5,7,8-tetramethyl-4*H*-chromen-4-one (5eb). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.86 (s, 1H), 2.78–2.68 (m, 5H), 2.32–2.29 (m, 6H), 2.00 (s, 3H), 1.33 (t, J = 7.5 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 180.6, 163.6, 155.3, 140.8, 136.8, 128.7, 122.3, 118.8, 115.9, 25.2, 22.5, 20.0, 11.3, 9.4; HRMS (ESI-TOF) of $C_{15}H_{18}O_2$ (m/z) = 231.1381 [M + H$^+$] (calculated 231.1385).

2-Ethyl-3,5,7,8-tetramethyl-4-oxo-4*H*-chromen-6-yl propionate (5fb). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.73–2.64 (m, 7H), 2.35 (s, 3H), 2.16 (s, 3H), 2.00 (s, 3H), 1.35–1.25 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 180.5, 172.4, 163.7, 153.1, 144.2, 134.4, 128.2, 123.8, 119.1, 116.0, 27.3, 25.2, 13.8, 13.6, 11.8, 11.2, 9.5, 9.2; HRMS (ESI-TOF) of $C_{18}H_{22}O_2$ = 325.1410 [M + Na$^+$] (calculated 325.1410); HRMS (ESI-TOF) of $C_{18}H_{22}O_2$ (m/z) = 325.1410 [M + Na$^+$] (calculated 325.1410).

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