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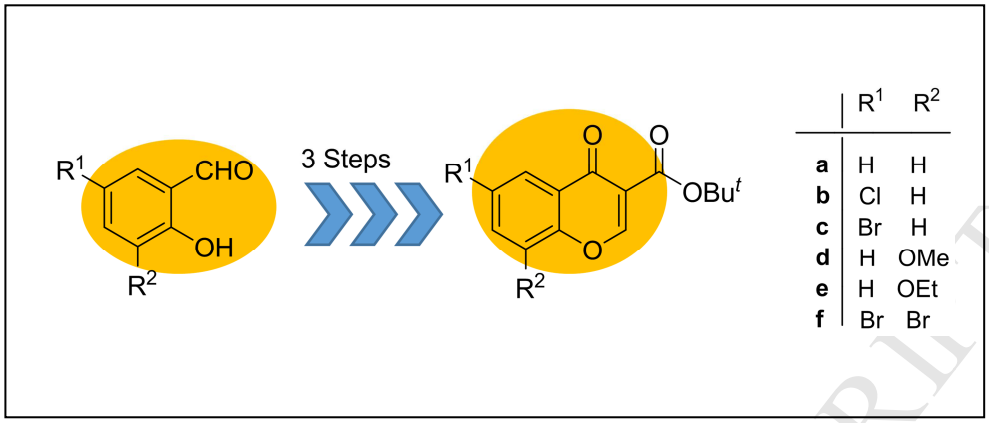

Application of Baylis-Hillman Methodology in the Direct Construction of Chromone Derivatives

Faridoon,[a] Temitope.O. Olomola,[a,b] Rosalyn Klein[a] and Perry.T. Kaye[a]*

[a]*Department of Chemistry and Centre for Chemico- and Biomedicinal Research, Rhodes University, Grahamstown, 6140, South Africa.* [b]*Department of Chemistry, Obafemi Awolowo University, Ile-Ife, 220005, Nigeria.*

ABSTRACT. Pyridinium chlorochromate oxidation of Baylis-Hillman-derived *tert*-butyl 2*H*-chromene-3-carboxylates affords chromone-3-carboxylate esters, providing the first application of Baylis-Hillman methodology in a direct and convenient three-step synthesis of chromone derivatives.

Key Words:

Chromones
Benzopyran-4-ones
chromone-3-carboxylate esters
Baylis-Hillman

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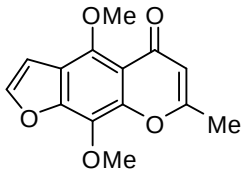
* Corresponding author: Prof Perry Kaye. Tel. +27 46 6037030;
Fax. +27 466225109. E-mail. P.Kaye@ru.ac.za
Dept. of Chemistry, Rhodes University,
Grahamstown, 6140, South Africa.

1. Introduction.

Chromone (benzopyran-4-one) derivatives are widely distributed in nature, and many of them exhibit interesting biological activity.[1] For example, the furanochromone khellin **1**, isolated from *Amni visnaga* has long been used in the treatment of asthma,[2] while the synthetic chromone derivative, disodium cromoglycate, now finds clinical use as an anti-asthmatic.[3] Gaspar *et al*.[4] have shown that chromone-3-carboxamides, such as compound **2** prepared from chromone-2-carboxylic acid, exhibit selective inhibition of monoamine oxidase-B (MAO-B) with IC_{50} values in the nano- and low micromolar range, and have, even more recently, published a comprehensive review on the chromone nucleus as a "valid scaffold in medicinal chemistry".[5]



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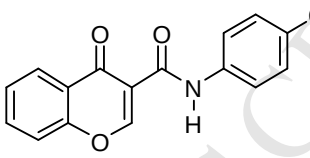
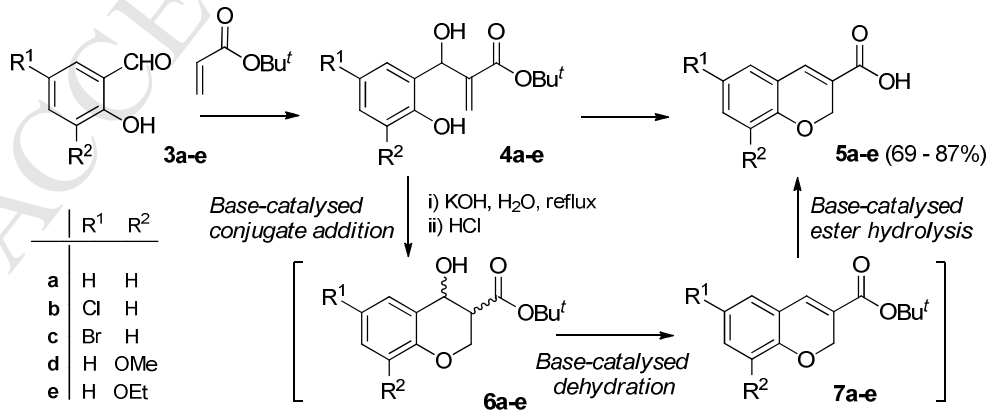


2

We have previously reported seminal contributions to the application of Baylis-Hillman methodology in the construction of benzannulated heterocyclic systems,[6] including indolizines,[7] quinolines[8] and coumarins.[9,10] However, attempts to extend this methodology to access 4-oxygenated derivatives has proved frustrating since cyclisation of appropriate Baylis-Hillman adducts is typically effected under acidic or neutral conditions and is accompanied by loss of the 4-hydroxyl group in a dehydration step. We have recently shown[11] how base-catalysed cyclisation of the salicylaldehyde-derived Baylis-Hillman adducts **4a-e** (Scheme 1) not only permits *chemoselective* access to the 2*H*-chromene-3-carboxylic acids **5a-e**, but that the overall transformation proceeds through three discrete steps, *viz*., base-catalysed intramolecular conjugate addition, base-catalysed dehydration and, finally, base-catalysed ester hydrolysis. The intermediates (**6**) and (**7**) are isolable in some cases and, in this communication, we discuss their use as chromone precursors–to our knowledge, the first reported application of Baylis-Hillman methodology in the direct construction of the chromone nucleus.

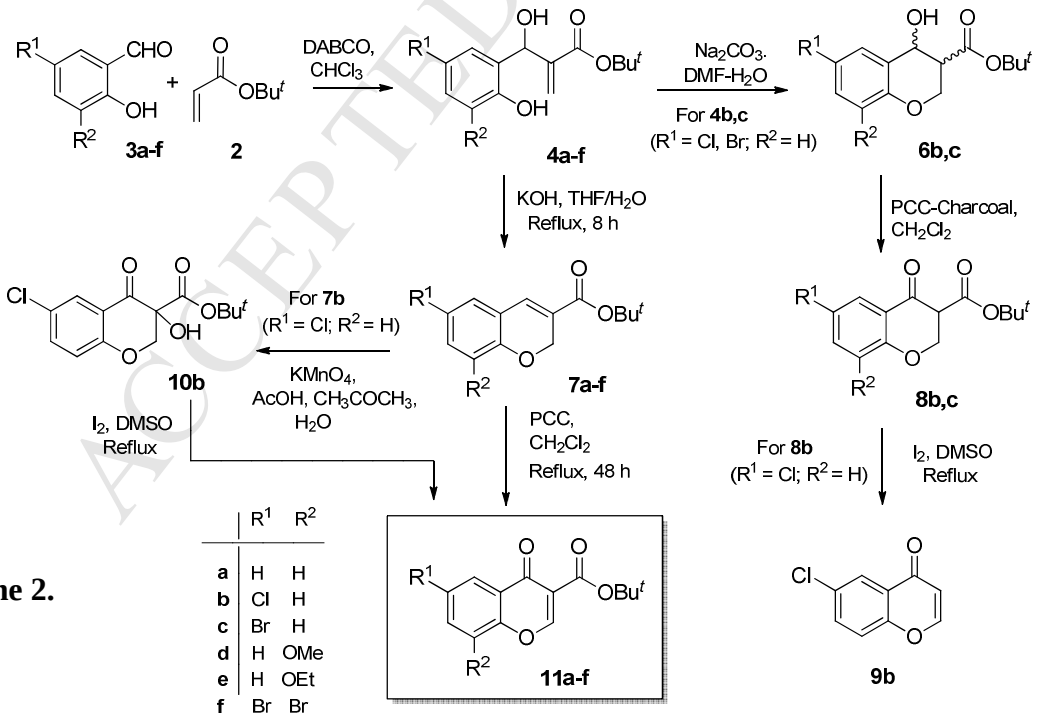


Scheme 1.

2. Results and Discussion.

Oxidation (including aromatization) of the 2,3-dihydro-4-hydroxybenzopyran-2-carboxylate esters **6a-e** (as diastereomeric pairs) appeared to present the most obvious approach to chromone derivatives. However, only the 6-chloro- (**6b**) and 6-bromo- (**6c**) analogues could be isolated in practicable yields using Na_2CO_3 in DMF-H_2O rather than KOH in THF-H_2O as reported previously.[11] Of the various bases (KOH, pyridine, Na_2CO_3, and $NaHCO_3$) examined, Na_2CO_3 (0.25 eq.) in DMF-H_2O proved most efficient, affording, in each case, combined yields of both diastereomers of ≥ 85%. Even after 15 days, the remaining adducts (**6a, d-f**) failed to exhibit useful transformation to the corresponding 4-hydroxychroman-3-carboxylate esters. In our hands, the reaction of 5-chlorosalicylaldehyde **3b** with *tert*-butyl acrylate in the presence of K_2CO_3, following the method reported by Satoh *et al.*,[12] gave compound **6b** in only 20% yield.

Following various unsatisfactory attempts to effect oxidation (including the use of: MnO_2 in dry acetone; acidified $KMnO_4$; and H_2CrO_4), use of pyridinium chlorochromate (PCC) supported on charcoal, as reported by Al-Hamdany and Jihad,[13] finally provided practicable access to the 4-oxo derivatives **8b,c**. Thus, PCC oxidation of diastereomeric mixtures of both analogues afforded the corresponding 4-oxo derivatives **8b** (44%) and **8c** (50%) (Scheme 2), the NMR spectra of which appear to be complicated by tautomerism of the β-keto ester moiety. Subsequent treatment of the 6-chloro derivative **8b** with DMSO-I_2 led, with concomitant elimination of the carboxylate ester moiety, to 6-chlorochromone **9b** in 44% yield. Given the apparent lack of generality in using this strategy, attention was turned to the 2*H*-chromene-3-carboxylate esters **7a-f** as possible chromone precursors.



Scheme 2.

Refluxing mixtures of the Baylis-Hillman adducts **4a-f** and KOH in THF–H_2O for 8 h afforded the corresponding 2*H*-chromene-3-carboxylate esters **7a-f** in yields of up to 48%. In attempts to improve the yield, the 5-chloro adduct **4b** was refluxed with KOH (1 eq.) in *tert*-butyl alchohol for 8 hours, but the cyclised product was collected in 46% yield which represented no improvement on the yield obtained in THF-H_2O. [Use of Bu^{t}OK (in different molar ratios) in *tert*-butyl alchohol, also failed to improve the yield.] Oxidation of the 6-chloro analogue **7b** with $KMnO_4$ gave the α-hydroxy ketone **10b**, dehydration of which was achieved using molecular iodine (20 mol%) in DMSO at 100 ºC to afford the desired chromone-2-carboxylate ester **11b** in 41% yield.

It was found, however, that the target compounds **11a-f** could be obtained more efficiently in a single step (and in up to 88% yield!) from the corresponding 2*H*-chromene-3-carboxylate esters **7a-f**, using PCC in CH_2Cl_2 – a reagent system used by Kim *et al.*[14] to generate 3-benzoylchromone from a 3-benzylidenylchromone precursor in the final step of a five-step sequence. The chromone derivatives **11a-f**, five of which are new, were thus obtained in only three steps from the Baylis-Hillman substrates **3a-f**.

While further optimisation of individual steps may well be expected, it is clear that the methodology developed here offers a new, viable and convenient approach to important chromone scaffolds.

3. Experimental

^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 400 or 600 MHz spectrometers at 303 K, and were calibrated using the solvent signals; coupling constants are given in Hertz (Hz). High resolution electrospray ionisation accurate mass measurements (HRMS) were recorded on a Waters API Q-TOF Ultima spectrometer with an ESI source (Central Analytical Facility, University of Stellenbosch).

Preparation of the Baylis-Hillman adducts **4a-f**,[10] the diastereomeric 4-hydroxychroman-3-carboxylate esters **6c**[11] and the *tert*-butyl 2*H*-chromene-3-carboxylate esters **7a-c**[11] has been described previously.

3.1. General procedure for synthesis of the *tert*-butyl 4-hydroxychroman-3-carboxylates 6b,c.

A solution of Na_2CO_3 (0.186 g, 1.75 mmol) in water (3 mL) was added to a solution of **4b** (2.0 g, 7.02 mmol) in DMF (15 mL) and the mixture was stirred for 4 days. Addition of ice gave a creamy solid which was filtered off, dried and flash chromatographed [on silica gel; elution with hexane–Et_2O (4:1)] to afford the following two diastereomers.

tert-***Butyl (3S*,4S*)-6-chloro-4-hydroxychroman-3-carboxylate*** **6b$_1$** as a white solid (0.38 g, 19%), m.p. 126-127 °C; ν/cm^{-1} 3436 (OH) and 1706 (C=O); (Found: MH$^+$ - Bu^{t}OH, *m/z* 211.0167. $C_{14}H_{18}O_3{}^{35}Cl$ - Bu^{t}OH requires 211.0162.); δ_H (600 MHz; $CDCl_3$) 1.49 (9H, s, Bu^t), 2.93 (1H, dd, *J* = 6.1, 3.9 Hz, CHC*H*CH$_2$), 3.26 (1H, d, *J* = 5.5 Hz, CHC*H*O), 4.40-4.27 (2H, m, CHC*H*$_2$O), 4.94 (1H, s, OH), 6.77 (1H, d, *J* = 8.8 Hz, ArH), 7.14 (1H, dd, *J* = 8.7, 1.9 Hz, ArH) and 7.32 (1H, d, *J* = 1.7 Hz, ArH); δ_C (150 MHz; $CDCl_3$) 28.2, 44.9, 62.8, 64.1, 82.8, 118.3, 124.7, 125.7, 129.7, 129.9, 152.9 and 170.2.

tert-*Butyl (3S*,4R*)-6-chloro-4-hydroxychroman-3-carboxylate* 6b$_2$ as a white solid (1.30 g, 65%), m.p. 92-93 °C; ν/cm^{-1} 3470 (OH) and 1700 (C=O); (Found: MH$^+$ - Bu^{t}OH, *m/z* 211.0152. $C_{10}H_8O_3{}^{35}Cl$ requires 211.0162.); δ_H (600 MHz; $CDCl_3$) 1.46 (9H, s, Bu^t), 2.87 (1H, td, *J* = 8.6, 3.6 Hz, CHC*H*CH$_2$), 3.04 (1H, d, *J* = 4.4 Hz, CHO*H*), 4.16 (1H, dd, *J* = 11.2, 9.1 Hz, CHC*H*$_a$H$_b$O), 4.40 (1H, dd, *J* = 11.3, 3.6 Hz, CHCH$_a$*H*$_b$O), 5.01 (1H, dd, *J* = 7.6, 4.4 Hz, C*H*OH), 6.74 (1H, d, *J* = 8.8 Hz, ArH), 7.12 (1H, dd, *J* = 8.7, 2.4 Hz, ArH) and 7.44 (1H, d, *J* = 2.2 Hz, ArH); δ_C (150 MHz; $CDCl_3$) 28.1, 46.9, 64.6, 65.5, 82.7, 118.0, 125.2, 126.1, 128.1, 129.3, 152.5 and 170.3.

3.2. General procedure for synthesis of the *tert*-butyl 4-chromanone-3-carboxylates 8b,c.

A mixture of PCC supported on charcoal (1.7 g) was suspended in DCM (15 mL) and stirred for 2 min. A solution of (3*S**,4*R**)-*tert*-butyl 6-bromo-4-hydroxychroman-3-carboxylate **6b** (0.5 g, 1.5 mmol) in DCM (2 mL) was then added in one portion, and the mixture stirred for *ca*. 24 h. After being left to stand for 3 h, the resulting mixture was shaken with dry Et_2O and filtered. The filtrate was concentrated *in vacuo* and flash chromatographed [on silica gel; elution with hexane–Et_2O (4:1)] to afford tert-*butyl 6-chloro-4-chromanone-3-carboxylate* **8b** as a red solid (0.25 g, 50.3%), comprising a 2:1 mixture of keto and enol tautomers, m.p. 72-74 °C; [Found: MH$^+$, *m/z* 281.0567. $C_{14}H_{15}O_4{}^{35}Cl$ requires 281.0581]; ν/cm^{-1} 1746 and 1712 (C=O); δ_H (600 MHz; $CDCl_3$; data cited for major, keto tautomer) 1.47 (9H, s, Bu^t), 3.61 (1H, dd, *J* = 7.5, 4.2 Hz, C*H*CH$_2$O), 4.60 (1H, dd, *J* = 11.7, 4.2 Hz, C*H*$_a$H$_b$O), 4.78 (1H, dd, *J* = 11.7, 7.5 Hz, CH$_a$*H*$_b$O), 6.96 (1H, d, *J* = 8.8 Hz, ArH), 7.45 (1H, dd, *J* = 8.8, 2.6 Hz, ArH) and 7.88 (1 H, d, *J* = 2.6 Hz, ArH).

3.2.1. tert-*Butyl 6-bromo-4-chromanone-3-carboxylate* 8c, a red solid (0.22 g, 44.3%) comprising a 2:1.4 mixture of the keto and enol tautomers, m.p. 86-88 °C (Found: MH$^+$, *m/z* 325.0062. $C_{14}H_{15}O_4{}^{79}Br$ requires 325.0075.); δ_H (600 MHz; $CDCl_3$; data cited for major, keto tautomer) 1.46 (9 H, s, Bu^t), 3.60 (1H, dd, *J* = 7.5, 4.3 Hz, C*H*CH$_2$O), 4.59 (1H, dd, *J* = 11.7, 4.2 Hz, C*H*$_a$H$_b$O), 4.77 (1H, dd, *J* = 11.7, 7.5 Hz, CH$_a$*H*$_b$O), 6.90 (1H, d, *J* = 8.8 Hz, ArH), 7.56 (1H, dd, *J* = 8.8, 2.5 Hz, ArH) and 8.02 (1H, d, *J* = 2.5 Hz, ArH).

3.3. Preparation of *6-chlorochromone* 9b

A mixture of compound **8b** (25 mg, 0.09 mmol) and molecular iodine (25 mol%) in DMSO was stirred at 100 ºC for 12 h. The cool reaction mixture was poured into sat. aq. sodium thiosulphate and extracted with EtOAc. The organic fraction was washed with H_2O and dried using anhydr. $MgSO_4$. Concentration *in vacuo* and column chromatography [on silica gel; elution with hexane–EtOAc (8:1)] gave 6-chlorochromone **9b** as a white solid (7 mg, 44 %), m.p. 129-132 °C (Lit.[15] 137 °C).

3.4. Preparation of *tert*-butyl 6-chloro-3-hydroxychroman-4-one-3-carboxylate 10b

A solution of $KMnO_4$ (250 mg, 1.7 mmol) in acetone (3 mL) and H_2O (1 mL) was added drop-wise to a solution of compound **7b** (284.7 mg, 1 mmol) in acetone (8 mL), H_2O (2 mL) and acetic acid (0.4 mL). After stirring at r.t. for 30 min, the mixture was filtered through a pad of Celite, which was washed several times with CH_2Cl_2. The filtrate and washings were washed with aq. $NaHCO_3$ and dried (anhydr. $MgSO_4$). The solvent was evaporated *in vacuo*, and the crude product chromatographed [on silica gel; elution with $CHCl_3$–petroleum ether (3:2)] to give tert-*butyl 6-chloro-2-hydroxy-chroman-4-one-3-carboxylate* **10b** as a white solid (251 mg, 84%), m.p. 78-80 °C; [Found: M-1, *m/z* 299.0676. $C_{14}H_{16}O_5Cl$ requires 299.0686]; ν/cm^{-1} ca. 2400-3200 (OH), 1653 and 1633 (C=O); δ_H (600 MHz; $CDCl_3$) 1.39

(9H, s, Bu^t), 4.09 (1H, s, OH), 4.34 (1H, d, J = 11.8 Hz, CH_aH$_b$O), 4.67 (1 H, d, J = 11.8 Hz, CH$_a$$H_b$O), 6.97 (1H, d, J = 8.9 Hz, ArH), 7.46 (1H, dd, J = 8.9, 2.7 Hz, ArH), 7.87 (1H, d, J = 2.7 Hz, ArH); δ_C (150 MHz; $CDCl_3$) 27.9, 72.1, 74.7, 85.1, 119.7, 120.3, 126.9, 127.6, 136.6, 160.0, 168.1 and 188.3.

3.5. Synthesis of the *tert*-butyl 2*H*-chromene-3-carboxylates 7a-f was effected following the reported method,[11] but increasing the reaction time from 5 h to 8 h.

3.5.1. tert-*Butyl 8-methoxy-2*H-*chromene-3-carboxylate* 7d, a yellow oil (176 mg, 39%); [Found: M-1, *m/z* 261.1128. $C_{15}H_{17}O_4$ requires 261.1127]; ν/cm^{-1} 1696 (C=O); δ_H (600 MHz; $CDCl_3$) 1.52 (9 H, s, Bu^t), 3.87 (3H, s, CH_3O), 5.01 (2H, s, CH_2O), 6.76 (1H, t, J = 6 Hz, ArH), 6.86 (2H, 2 x overlapping d, J = 6 Hz, ArH) and 7.31 (1H, s, CH=C); δ_C (150MHz; $CDCl_3$): δ_C 28.3, 56.2, 65.1, 81.4, 114.4, 120.9, 121.5, 121.9, 124.5, 132.6, 144.1, 148.0 and 164.0.

3.5.2. tert-*Butyl 8-ethoxy-2*H-*chromene-3-carboxylate* 7e, a yellow oil (204 mg, 37%); [Found: M-1, *m/z* 275.1287. $C_{16}H_{19}O_4$ requires 275.1283]; ν/cm^{-1} 1694 (C=O); δ_H (600 MHz; $CDCl_3$) 1.44 (3H, t, J = 7.0 Hz, CH_3CH$_2$), 1.52 (9H, s, Bu^t), 4.09 (2H, q, J = 7.0 Hz, CH$_3$CH_2O), 5.00 (2H, s, CH_2O), 6.75 (1H, dd, J = 7.2 and 1.8 Hz, ArH), 6.82-6.87 (2H, 2 x overlapping m, ArH) and 7.31 (1H, s, CH=C); δ_C (150 MHz; $CDCl_3$) 15.0, 28.3, 64.7, 65.0, 81.3, 115.9, 121.0, 121.4, 122.1, 124.4, 132.7, 144.4, 147.3, 164.0.

3.5.3. tert-*Butyl 6,8-dibromo-2*H-*chromene-3-carboxylate* 7f, a white solid (351 mg, 45%), m.p. 122-124 °C; [Found: M-1, *m/z* 388.9386. $C_{14}H_{15}O_3{}^{79}Br_2$ requires 388.9388]; ν/cm^{-1} 1717 (C=O); δ_H (600 MHz; $CDCl_3$) 1.52 (9H, s, Bu^t), 5.07 (2H, s, CH_2O), 7.19 (1H, d, J = 2.2 Hz, ArH), 7.20 (1H, s, CH=C), 7.54 (1 H, d, J = 2.2 Hz, ArH); δ_C (150 MHz; $CDCl_3$) 28.2, 65.8, 82.1, 111.0, 113.6, 123.7, 126.2, 130.2, 130.6, 136.8, 151.0 and 163.1.

3.6. *tert*-Butyl 6-chlorochromone-3-carboxylate 11b (*Method A*). A mixture of compound **10b** (0.25 mmol, 75 mg) and molecular iodine (20 mol%) in DMSO was stirred overnight at 100 ºC. On cooling, the reaction mixture was poured into a saturated aqueous solution of sodium thiosulphate. The resulting mixture was extracted with EtOAc and the organic fraction was washed with water and dried (anhydr. $MgSO_4$). Concentration *in vacuo* followed by column chromatography [on silica gel; elution with $CHCl_3$–petroleum ether (2:3)] afforded compound **11b** as a white solid (29 mg, 41%).

3.7. General procedure (*Method B*) **for the synthesis of the *tert*-butyl chromone-3-carboxylates 11a-f.**

PCC (2 mmol) was added to a stirred solution of the chromene ester (**7**) (0.5 mmol) in CH_2Cl_2 (10 mL). After refluxing for 48 h, the reaction mixture was cooled to r.t., filtered through a silica pad, which was thoroughly washed with CH_2Cl_2. Evaporation of the filtrate *in vacuo* and column chromatography of the residue [on silica gel; elution with $CHCl_3$–petroleum ether (2:3) for **11a-c,f** and $CHCl_3$ for **11d,e**] gave the target compounds.

3.7.1. *tert*-Butyl chromone-3-carboxylate 11a, a white solid (86 mg, 70%), m.p. 103-105 °C (Lit.[16] 101-105 °C); ν/cm^{-1} 1736 and 1706 (C=O); δ_H (600 MHz; $CDCl_3$) 1.60 (9H, s, Bu^t), 7.30-7.34 (2H, m, ArH), 7.58-7.63 (2H, m, ArH) and 8.39 (1 H, s, C=CHO); δ_C (150 MHz; $CDCl_3$) 28.2, 83.0, 116.8, 118.1, 119.7, 124.8, 129.4, 134.1, 147.7, 155.1, 157.0 and 162.0.

3.7.2. tert-*Butyl 6-chlorochromone-3-carboxylate* 11b, a white solid (109 mg, 77%), m.p. 152-154 °C; [Found: M-1, *m/z* 281.0569. $C_{14}H_{14}O_4{}^{35}Cl$ requires 281.0561]; ν/cm^{-1} 1730 and 1698 (C=O); δ_H (600 MHz; $CDCl_3$) 1.60 (9H, s, Bu^t), 7.30 (1H, d, J = 8.8 Hz, ArH), 7.56 (1H, dd, J = 8.8, 2.4 Hz, ArH), 7.58 (1H, d, J = 2.4 Hz, ArH) and 8.31 (1H, s, C=CH-O); δ_C

(150 MHz; $CDCl_3$) 28.1, 83.3, 118.2, 119.0, 120.9, 128.3, 130.0, 133.8, 146.0, 153.4, 156.2 and 161.6.

3.7.3. tert-*Butyl 6-bromochromone-3-carboxylate* 11c, a white solid (120 mg, 74%), m.p. 169-170 °C; [Found: MH^+- C_4H_9, *m/z* 268.9434. $C_{10}H_4O_4{}^{79}Br$ requires 268.9449]; ν/cm^{-1} 1749 and 1705 (C=O); δ_H (600 MHz; $CDCl_3$) 1.60 (9H, s, Bu^t), 7.24 (1H, d, *J* = 8.8 Hz, ArH), 7.70 (1H, dd, *J* = 8.8, 2.3 Hz, ArH), 7.74 (1H, d, *J* = 2.3 Hz, ArH) and 8.30 (1H, s, C=CH-O); δ_C (150 MHz; $CDCl_3$) 28.1, 83.3, 117.2, 118.5, 119.5, 120.9, 131.4, 136.6, 145.9, 153.8, 156.4 and 161.5.

3.7.4. tert-*Butyl 8-methoxychromone-3-carboxylate* 11d, a yellow solid (87 mg, 63%), m.p. 70-71 °C; [Found: M-1, *m/z* 277.1070. $C_{15}H_{17}O_5$ requires 277.1076] ν/cm^{-1} 1697 and 1696 (C=O); δ_H (600 MHz; $CDCl_3$) 1.59 (9H, s, Bu^t), 3.96 (3H, s, OCH_3), 7.15 (2H, d, *J* = 8.0 Hz, ArH), 7.22-7.25 (1H, m, ArH) and 8.36 (1H, s, C=CHO); δ_C (150 MHz; $CDCl_3$) 28.2, 56.4, 82.9, 115.6, 118.7, 119.9, 120.6, 124.6, 144.9, 147.2, 147.8, 156.4 and 162.0.

3.7.5. tert-*Butyl 8-ethoxychromone-3-carboxylate* 11e, a yellow solid (96 mg, 66%), m.p. 64-65 °C; [Found: M-1, *m/z* 291.1218. $C_{16}H_{19}O_5$ requires 291.1232]; ν/cm^{-1} 1757 and 1704 (C=O); δ_H (600 MHz; $CDCl_3$) 1.47 (3H, t, *J* = 6.7 Hz, CH_2CH_3), 1.58 (9H, s, Bu^t), 4.16 (2H, q, *J* = 6.8 Hz, CH_3CH_2O), 7.12 (2H, 2 x overlapping d, ArH), 7.19 (1H, t, *J* = 6.7 Hz, ArH) and 8.32 (1H, s, C=CHO); δ_C (150 MHz; $CDCl_3$) 14.8, 28.2, 65.2, 82.8, 117.0, 118.7, 119.8, 120.5, 124.6, 145.1, 146.5, 147.7, 156.6 and 162.0.

3.7.6. tert-*Butyl 6,8-dibromochromone-3-carboxylate* 11f, a white solid (178 mg, 88%), m.p. 142-144 °C; [Found: M-1, *m/z* 402.9162. $C_{14}H_{13}O_4{}^{79}Br_2$ requires 402.9161]; ν/cm^{-1} 1742 and 1700 (C=O); δ_H (600 MHz; $CDCl_3$) 1.60 (9H, s, Bu^t), 7.68 (1H, d, *J* = 2.2 Hz, ArH), 7.95 (1H, d, *J* = 2.1 Hz, ArH) and 8.24 (1H, s, C=CHO); δ_C (150 MHz; $CDCl_3$) 28.2, 83.7, 111.4, 117.2, 120.3, 121.8, 130.7, 139.3, 145.6, 151.0, 155.1 and 161.3.

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