A Mild and Efficient Protocol for the Protection of 3-Hydroxychromones Under Phase-Transfer Catalysis

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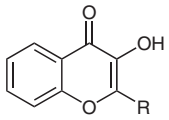
Abstract: A mild and efficient protocol for the introduction of different protecting groups on 3-hydroxychromones (3-HCs) under phase-transfer catalysis conditions in toluene or dichloromethane/aqueous potassium hydroxide system in the presence of crown ether has been developed. The method is useful for the protection of base-sensitive chromone derivatives. Protected chromones are easier to handle and to purify, and therefore suitable for further chemical transformations. The protecting groups were cleaved cleanly using standard conditions.

Key words: 3-hydroxychromone, phase-transfer catalysis, protecting groups, acylation, alkylation, cleavage

3-Hydroxychromones (Figures 1, 3-HCs) are oxygen-containing heterocyclic compounds mainly found in natural products. This important family of compounds has attractive properties for different applications. For instance, molecules containing the 3-HC core display a wide range of biological activities.[1] In addition, 2-aryl-3-HCs demonstrate striking fluorescent properties. 3-HCs are multiparametric photophysical probes that are highly sensitive to the environmental change. These unique properties have been applied for probing lipid bilayers, cell membranes, proteins and nucleic acids, and in fluorescence cell imaging in microbiology.[2]



3-HC

Figure 1 3-Hydroxychromone core structure

The development of new 3-HCs is hampered by the fact that synthetic manipulations are made complex by several factors. The solubility of many 3-HCs is low in commonly used organic solvents. Together, the carbonyl and hydroxy groups make 3-HC a good bidentate ligand able to coordinate metal ions and make chromatography purification more difficult likely due to metallic species contaminating silica gel. Therefore, manipulation of 3-HCs requires the utilization of acceptable protecting groups, not only to mask the intrinsic reactivity of the hydroxy group, but also to improve their chemicophysical properties. In the literature, the most common approach for protection is based on acylation of the hydroxy group of 3-HC. Treatment of 3-HCs with anhydrides or acid chlorides in basic media (pyridine, NaOH, or Et_3N) takes significant time,[2f] and often gives unsatisfactory yields.[3] In addition, none of these protocols are of broad applicability. Furthermore, in a program aimed to label oligonucleotides (ODNs) with 3-HC-containing fluorescent nucleosides,[4] we had to face the problem of compatibility of the hydroxy protecting group for 2-bromo-3-hydroxychromone (Figure 1, R = Br) amenable to transformation into the target nucleoside analogue[4] and incorporation in ODNs.[5] Treatment of 2-bromo-3-HC with acylating reagent (CbzCl) in polar aprotic solvents such as pyridine or DMF in the presence of trialkylamines or potassium carbonate gave poor results due to the slow conversion rate and to the instability of the starting compound in such basic media. Silyl-based protecting groups (TBDMS, SEM) were unstable while the MEM was found too resistant and problematic during acidic treatment of labeled ODNs due to strand cleavage. Altogether, these examples show that a mild and general protocol for introducing hydroxy protecting groups on 3-HCs compatible with chemical manipulation and transformation would be of great interest for this important family of compounds. Herein, we describe an easy protocol for the hydroxy protection of different 3-HCs, including the base sensitive 2-bromo-3-HC, using phase-transfer catalysis[6] and various acylating and alkylating reagents. The conditions to cleave the protecting groups and an example illustrating the usefulness of protected 2-bromo-3-HC in the preparation of the fluorescent 3-hydroxy-2-thienyl-chromone are also given.

The investigation was started with the unsubstituted 3-HC (**1a**) and benzyl chloroformate as a model reaction in different phase-transfer catalysis (PTC) conditions (Table 1).

The different conditions tested were selected from literature reports on phenols with acylating or alkylating reagents.[7] One classical approach consists in reacting phenols with acyl or alkyl halides using quaternary amine salts such as benzyltriethylammonium chloride (TEBAC) as phase-transfer catalyst.[7b] Using a mixture of 3-HC (**1a**) in toluene/aqueous sodium hydroxide with 1.5 equivalents of benzyl chloroformate and a catalytic amount of TEBAC furnished the corresponding carbonate product **2a** in a modest 40% isolated yield after 30 minutes, al-

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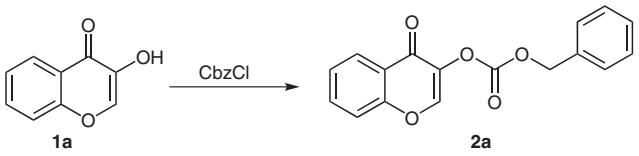
Table 1 Survey of the Reaction Conditions with CbzCl



1a **2a**

Entry	Solvent, base[a]	Catalyst[b]	Time (min)	Yield (%)[c]
1	toluene, NaOH	TEBAC[d]	30 min	40
2	CH_2Cl_2, NaOH	TEBAC	30 min	89
3	CH_2Cl_2, KOH	18-crown-6	10 min	95
4	toluene, KOH	18-crown-6	10 min	97
5	toluene, KOH	Kryptofix222[e]	30 min	96
6	toluene, KOH	tris-DHA	>24 h	–[f]

[a] The bases were used as 25% solution in H_2O.
[b] Catalyst (5 mol%).
[c] Isolated yield.
[d] Benzyltriethylammonium chloride.
[e] Potassium binding cryptand.
[f] No conversion.

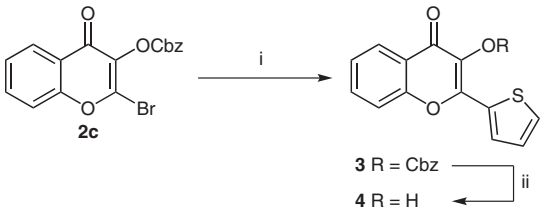
though the conversion was not completed (Table 1, entry 1). In contrast, when toluene was changed to dichloromethane, the conversion rate was improved and the product **2a** was obtained in 89% yield (entry 2). Moreover, when the reaction was conducted in either dichloromethane or toluene and aqueous potassium hydroxide with 18-crown-6 as the potassium-transfer catalyst,[7b] we found that it gave the best results for 3-HC protection (95 and 97%, 10 min conversion, entries 3 and 4). Proceeding under the same reaction conditions, but in the presence of Kryptofix 222 as the catalyst,[7c] did not give any more advantage (entry 5). Using tris-dioxaheptylamine as the phase-transfer catalyst[7b] no conversion of the starting material was observed even with excess of acylating reagent and prolonged reaction time (3 equiv, >24 h, entry 6).

In the second step of this investigation, the scope of the optimized conditions set up for the model compound for the preparation of three series of 3-hydroxychromones protected with different acylating and alkylating groups was extended.[8] The results are presented in Table 2.

Typical experiments were conducted with 5 mol% of crown ether, 3-HC (1–10 mmol scale) and organic halide in a mixture of toluene and aqueous potassium hydroxide. In several cases (Table 2, entries 10, 11, 12, and 15) toluene–dichloromethane mixture or dichloromethane were used as the organic phase instead of toluene to improve the solubility of the final product. We observed that the conversion rate depends on the organic halide used. Fast couplings were observed with chloroformates (entries 1–9), while the reaction with benzoyl chloride (entries 10–12) and benzyl bromide (entries 13–15) required prolonged reaction times, couplings with the latter displaying the slowest rates. In all cases, good to excellent yields of protected chromones were obtained with only 1.5 equivalents of halide reagent except for **2m** and **2o** where 3 equivalents were employed. Thus, the PTC conditions described herein allow the introduction of different orthogonal protecting groups on the 3-HCs tested including the base sensitive bromo derivative **1c** (entries 3, 6, 9, 12, and 15). Furthermore, the protecting groups were cleaved cleanly using standard conditions: the benzyl carbonate and benzyl groups of **2b** and **2n** with hydrogen and catalytic Pd/C (10%), the Alloc protecting group of **2e** with diethylamine and catalytic $Pd(PPh_3)_4$, and the ethyl carbonate and benzoate groups of **2h** and **2k** with ammonium hydroxide in ethanol–water.[8]

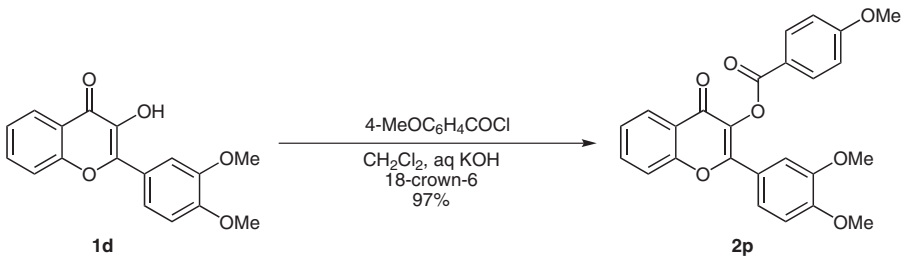
These conditions were also applied for several other compounds. For example, compound **2p** was described as a blood fat decreasing agent and was synthesized previously in 47% yield.[3a] When the flavone **1d** was reacted under the aforementioned PTC conditions with 4-methoxybenzoyl chloride, compound **2p** was obtained now in near quantitative yield (Scheme 1).

The protected bromo derivative proved to be a suitable intermediate to introduce molecular diversity at position 2. For example, the benzyloxycarbonate protected compound **2c** is a convenient building block in Pd(0)-catalyzed carbon–carbon bond formation using Stille coupling conditions (Scheme 2).



2c

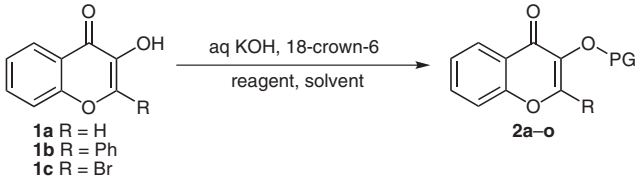
Scheme 2 Coupling reaction with protected HC. *Reagents and conditions*: i: 2-tributylstannylthiophene, $Pd(PPh_3)_4$, CuI, toluene, reflux, 1 h, 95%; ii) NH_4OH, EtOH–H_2O, r.t., 3 h, 97%.



1d **2p**

Scheme 1 Application of the PTC conditions to the preparation of the methoxybenzoyl ester **2p**

Table 2 Reaction Conditions for the Synthesis of Protected Chromones **2a–o**



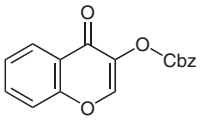
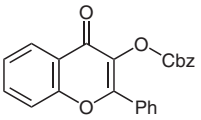
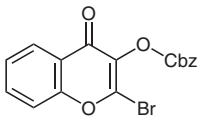
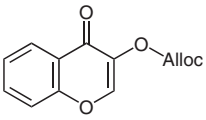
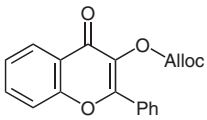
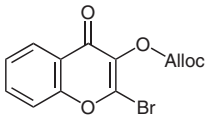
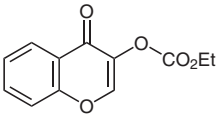
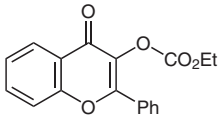
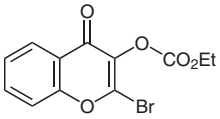
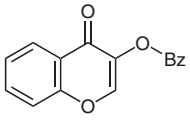
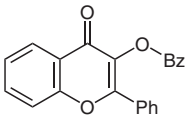
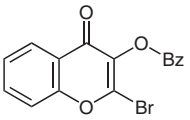
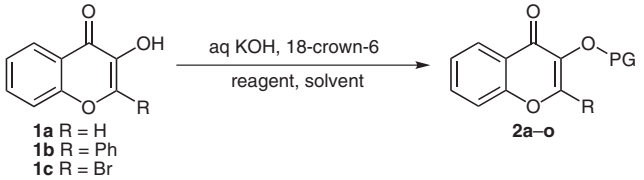
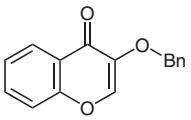
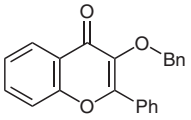
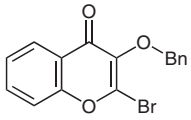
Entry	Reagent[a]	Solvent	Product	Time (min)	Yield (%)[b]
1	BnOCOCl	toluene	**2a** 	10	97
2	BnOCOCl	toluene	**2b** 	10	95
3	BnOCOCl	toluene	**2c** 	20	88
4	H_2C=$CHCH_2OCOCl$	toluene	**2d** 	5	93
5	H_2C=$CHCH_2OCOCl$	toluene	**2e** 	5	98
6	H_2C=$CHCH_2OCOCl$	toluene	**2f** 	20	75
7	EtOCOCl	toluene	**2g** 	5	90
8	EtOCOCl	toluene	**2h** 	5	99
9	EtOCOCl	toluene	**2i** 	20	91
10	PhCOCl	toluene–CH_2Cl_2[c]	**2j** 	240	76
11	PhCOCl	toluene–CH_2Cl_2	**2k** 	5	96
12	PhCOCl	toluene–CH_2Cl_2	**2l** 	90	73

Table 2 Reaction Conditions for the Synthesis of Protected Chromones **2a–o** (continued)



Entry	Reagent[a]	Solvent	Product		Time (min)	Yield (%)[b]
13	BnBr[d]	toluene	**2m**		480	71
14	BnBr	toluene	**2n**		360	92
15	BnBr[d]	CH_2Cl_2	**2o**		360	94

[a] Reaction conditions: reagent (1.5 equiv) and 18-crown-6 (5 mol%).
[b] Yield of pure isolated product.
[c] Ratio = 1:1 (v/v).
[d] BnBr (3 equiv) and 18-crown-6 (10 mol%) were used in this case to accelerate the reaction (see text).

Thus, the reaction of **2c** with 2-tributylstannylthiophene in the presence of catalytic $Pd(PPh_3)_4$ in refluxing toluene afforded the coupling product **3** in 95% yield. Removal of the protecting group by treatment with ammonia in aqueous ethanol solution gave quantitatively the fluorescenting compound, 3-hydroxy-2-thienylchromone (**4**). The fluorescence spectra of **4** is displayed in Figure 2.[9] It should be mentioned that this approach complements the main methods of obtaining 3-hydroxychromones.[10]

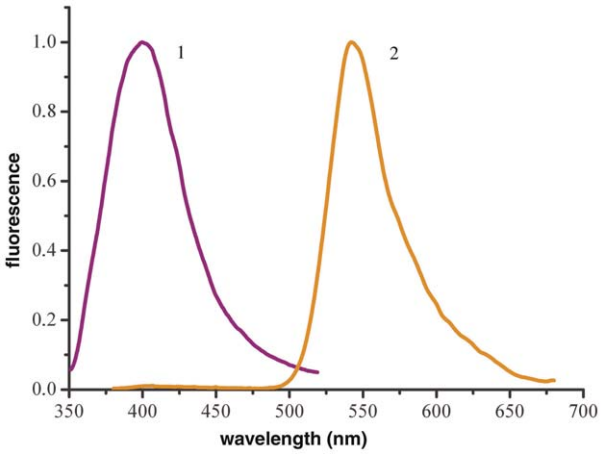


Figure 2 Normalized fluorescence spectra: (1) protected **3** in MeOH (exc. = 330 nm), (2) deprotected **4** in CH_2Cl_2 (exc. = 360 nm). In CH_2Cl_2, 3-HC **4** exhibits two emission bands: the low emissive normal band centered at 417 nm and the highly emissive and red shifted tautomer band centered at 542 nm resulting from excited state intramolecular proton transfer (ESIPT).[2b,4]

In summary, a convenient phase-transfer catalysis protocol for the introduction of different protecting groups on 3-HCs has been developed. The protected chromones are easier to handle and to purify and therefore suitable for further chemical transformations. Removal of the protected groups was achieved conveniently using standard conditions.

Standard column chromatography was performed on 230–400 mesh silica gel using flash column chromatography techniques.[11] Analytical TLC was performed on Merck precoated silica gel 60 F254 plates. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Avance Spectrometer 200 (200 MHz for ^1H and 50 MHz for ^{13}C). Chemical shifts are reported in ppm relative to residual $CHCl_3$ signal as an internal reference (7.26 ppm for ^1H and 77.16 for ^{13}C). Spin-spin coupling constants are reported in hertz (Hz). High-resolution mass spectra (HRMS) were recorded on Hybride LTQ Orbitrap (Thermoscientific) apparatus. Compounds **1a**, **1c**, and **1d** were synthesized according to known procedures.[4,6c]

Protection of 3-HCs with Organic Halides; General Procedure

A stirring bar and 3-HC **1** (1 mmol) were placed in a 15 mm diameter test tube. Then, solvent (toluene or CH_2Cl_2, 4 mL), organic halide (1.5 to 3 mmol), and 18-crown-6 (5–10% mol) were added. After that, aq KOH (25%, 1 mL) was added at once and the mixture was kept under intense stirring at r.t. In the binary system used, the conversion of the 3-HC was easily monitored. Indeed, the unprotected 3-HC was poorly soluble in either the organic and aqueous phases while the product was only soluble in the organic phase. Thus the disappearance of the precipitate in the reaction vessel indicated complete conversion of the starting material as further evidenced by TLC (cyclohexane–EtOAc, 7:3). After completion of the reaction, the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2×5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuum. The

crude product was purified by silica gel flash chromatography with cyclohexane–EtOAc (Table 2).

Benzyl 4-Oxo-4*H*-chromen-3-yl Carbonate (2a)
Yield: 288 mg (97%); R_f = 0.40 (cyclohexane–EtOAc, 7:3).

^{1}H NMR: δ = 8.28 (dd, *J* = 8.1, 1.5 Hz, 1 H), 8.09 (s, 1 H), 7.71 (m, 1 H), 7.35–7.59 (m, 7 H), 5.31 (s, 2 H).

^{13}C NMR: δ = 171.72, 156.15, 152.74, 148.44, 137.65, 134.52, 134.22, 128.95, 128.81, 128.65, 126.32, 125.58, 124.58, 118.44, 71.24.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{13}O_5$: 297.0758; found: 297.0762.

Benzyl 4-Oxo-2-phenyl-4*H*-chromen-3-yl Carbonate (2b)
Yield: 354 mg (95%); R_f = 0.39 (cyclohexane–EtOAc, 7:3).

^{1}H NMR: δ = 8.29 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.97–7.82 (m, 2 H), 7.79–7.66 (m, 1 H), 7.61–7.32 (m, 10 H), 5.29 (s, 2 H).

^{13}C NMR: δ = 172.27, 156.38, 155.61, 152.46, 134.68, 134.18, 134.01, 131.51, 129.64, 128.82, 128.69, 128.49, 128.27, 126.13, 125.39, 123.72, 118.22, 70.99.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{17}O_5$: 373.1071; found: 373.1075.

Benzyl 2-Bromo-4-oxo-4*H*-chromen-3-yl Carbonate (2c)
Yield: 331 mg (88%); R_f = 0.44 (cyclohexane–EtOAc, 7:3).

^{1}H NMR: δ = 8.24 (dd, *J* = 8.2, 1.5 Hz, 1 H), 7.82–7.65 (m, 1 H), 7.57–7.34 (m, 7 H), 5.34 (s, 2 H).

^{13}C NMR: δ = 170.08, 156.45, 151.76, 142.69, 136.37, 134.50, 134.38, 128.89, 128.76, 128.40, 126.53, 126.22, 123.51, 117.89, 71.39.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{12}BrO_5$: 374.9863; found: 374.9868.

Allyl 4-Oxo-4*H*-chromen-3-yl Carbonate (2d)
Yield: 229 mg (93%); R_f = 0.37 (cyclohexane–EtOAc, 7:3).

^{1}H NMR: δ = 8.28 (dd, *J* = 8.0, 1.7 Hz, 1 H), 8.10 (s, 1 H), 7.80–7.62 (m, 1 H), 7.57–7.37 (m, 2 H), 6.14–5.85 (m, 1 H), 5.54–5.27 (m, 2 H), 4.85–4.70 (m, 2 H).

^{13}C NMR: δ = 171.75, 156.18, 152.59, 148.42, 137.66, 134.23, 130.90, 126.35, 125.60, 124.60, 119.86, 118.45, 70.03.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}O_5$: 247.0601; found: 247.0603.

Allyl 4-Oxo-2-phenyl-4*H*-chromen-3-yl Carbonate (2e)
Yield: 316 mg (98%); R_f = 0.41 (cyclohexane–EtOAc, 7:3).

^{1}H NMR: δ = 8.28 (dd, *J* = 8.0, 1.4 Hz, 1 H), 8.00–7.86 (m, 2 H), 7.80–7.66 (m, 1 H), 7.63–7.38 (m, 5 H), 6.18–5.72 (m, 1 H), 5.57–5.13 (m, 2 H), 4.87–4.54 (m, 2 H).

^{13}C NMR: δ = 172.31, 156.39, 155.69, 152.27, 134.21, 134.08, 131.57, 131.00, 129.76, 128.89, 128.59, 126.22, 125.41, 123.77, 119.40, 118.26, 69.85.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{15}O_5$: 323.0914; found: 323.0918.

Allyl 2-Bromo-4-oxo-4*H*-chromen-3-yl Carbonate (2f)
Yield: 244 mg (75%); R_f = 0.44 (cyclohexane–EtOAc, 7:3).

^{1}H NMR: δ = 8.17 (dd, *J* = 7.9, 1.4 Hz, 1 H), 7.77–7.60 (m, 1 H), 7.52–7.36 (m, 2 H), 6.09–5.85 (m, 1 H), 5.57–5.21 (m, 2 H), 4.95–4.62 (m, 2 H).

^{13}C NMR: δ = 170.00, 156.38, 151.48, 142.59, 136.26, 134.47, 130.68, 126.43, 126.17, 123.41, 119.66, 117.84, 70.09.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{10}BrO_5$: 324.9706; found: 324.9710.

Ethyl 4-Oxo-4*H*-chromen-3-yl Carbonate (2g)
Yield: 211 mg (90%); R_f = 0.34 (cyclohexane–EtOAc, 7:3).

^{1}H NMR: δ = 8.24 (dd, *J* = 8.0, 1.7 Hz, 1 H), 8.08 (s, 1 H), 7.80–7.58 (m, 1 H), 7.55–7.31 (m, 2 H), 4.33 (q, *J* = 7.1 Hz, 2 H), 1.38 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR: δ = 171.74, 156.09, 152.64, 148.38, 137.59, 134.13, 126.21, 125.48, 124.51, 118.38, 65.75, 14.17.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{11}O_5$: 235.0601; found: 235.0602.

Ethyl 4-Oxo-2-phenyl-4*H*-chromen-3-yl Carbonate (2h)
Yield: 309 mg (99%); R_f = 0.38 (cyclohexane–EtOAc, 7:3).

^{1}H NMR: δ = 8.27 (dd, *J* = 8.0, 1.6 Hz, 1 H), 8.03–7.83 (m, 2 H), 7.82–7.64 (m, 1 H), 7.63–7.36 (m, 5 H), 4.32 (q, *J* = 7.1 Hz, 2 H), 1.36 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR: δ = 172.39, 156.33, 155.69, 152.39, 134.18, 134.10, 131.51, 129.83, 128.87, 128.56, 126.19, 125.37, 123.77, 118.24, 65.71, 14.21.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{15}O_5$: 311.0914; found: 311.0915.

Ethyl 2-Bromo-4-oxo-4*H*-chromen-3-yl Carbonate (2i)
Yield: 284 mg (91%); R_f = 0.45 (cyclohexane–EtOAc, 7:3).

^{1}H NMR: δ = 8.23 (dd, *J* = 8.0, 1.4 Hz, 1 H), 7.81–7.65 (m, 1 H), 7.59–7.39 (m, 2 H), 4.38 (q, *J* = 7.1 Hz, 2 H), 1.42 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR: δ = 170.01, 156.29, 151.52, 142.51, 136.20, 134.41, 126.32, 126.09, 123.33, 117.77, 65.97, 14.08.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{10}BrO_5$: 311.0914; found: 311.0915.

4-Oxo-4*H*-chromen-3-yl Benzoate (2j)
Yield: 203 mg (76%); R_f = 0.41 (cyclohexane–EtOAc, 7:3).

^{1}H NMR: δ = 8.30 (dd, *J* = 7.9, 1.4 Hz, 1 H), 8.26–8.18 (m, 2 H), 8.15 (s, 1 H), 7.81–7.60 (m, 2 H), 7.59–7.34 (m, 4 H).

^{13}C NMR: δ = 171.83, 164.18, 156.14, 148.55, 137.41, 134.04, 130.61, 128.68, 128.45, 126.30, 125.43, 124.57, 118.38.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{11}O_4$: 267.0652; found: 267.0656.

4-Oxo-2-phenyl-4*H*-chromen-3-yl Benzoate (2k)
Yield: 329 mg (96%); R_f = 0.41 (cyclohexane–EtOAc, 7:3).

^{1}H NMR: δ = 8.29 (dd, *J* = 8.0, 1.4 Hz, 1 H), 8.25–8.16 (m, 2 H), 8.00–7.88 (m, 2 H), 7.81–7.39 (m, 9 H).

^{13}C NMR: δ = 172.30, 164.04, 156.51, 155.83, 134.12, 133.98, 131.39, 130.69, 130.19, 128.85, 128.78, 128.73, 128.45, 126.36, 125.36, 123.84, 118.26.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{15}O_4$: 343.0965; found: 343.0965.

2-Bromo-4-oxo-4*H*-chromen-3-yl Benzoate (2l)
Yield: 251 mg (73%); R_f = 0.48 (cyclohexane–EtOAc, 7:3).

^{1}H NMR: δ = 8.37–8.14 (m, 3 H), 7.82–7.62 (m, 2 H), 7.61–7.40 (m, 4 H).

^{13}C NMR: δ = 170.35, 163.18, 156.64, 142.76, 136.35, 134.41, 134.26, 130.79, 128.79, 128.23, 126.72, 126.20, 123.64, 117.94.

HRMS: *m/z* [M + H]$^+$ calcd for $C_{16}H_{10}BrO_4$: 344.9757; found: 344.9755.

3-Benzyloxy-4*H*-chromen-4-one (2m)
Yield: 180 mg (71%); R_f = 0.47 (cyclohexane–EtOAc, 7:3).

^{1}H NMR: δ = 8.30 (dd, *J* = 7.9, 1.2 Hz, 1 H), 7.71 (s, 1 H), 7.70–7.58 (m, 1 H), 7.50–7.29 (m, 7 H), 5.17 (s, 2 H).

^{13}C NMR: δ = 174.05, 155.84, 144.59, 143.14, 136.43, 133.51, 128.76, 128.47, 128.25, 126.16, 124.76, 124.50, 118.22, 73.14.

HRMS: *m/z* [M + H]$^+$ calcd for $C_{16}H_{13}O_3$: 253.0859; found: 253.0862.

3-Benzyloxy-2-phenyl-4*H*-chromen-4-one (2n)
Yield: 304 mg (92%); R_f = 0.6 (cyclohexane–EtOAc, 7:3).

^{1}H NMR: δ = 8.29 (dd, *J* = 8.0, 1.3 Hz, 1 H), 8.06–7.93 (m, 2 H), 7.70–7.56 (m, 1 H), 7.54–7.20 (m, 10 H), 5.12 (s, 2 H).

^{13}C NMR: δ = 175.14, 156.42, 155.29, 139.85, 136.61, 133.45, 130.97, 130.62, 128.84, 128.29, 128.21, 128.10, 125.76, 124.71, 124.19, 118.05, 74.08.

HRMS: *m/z* [M + H]$^+$ calcd for $C_{22}H_{17}O_3$: 329.1172; found: 329.1174.

3-Benzyloxy-2-bromochromen-4-one (2o)
Yield: 311 mg (94%); R_f = 0.38 (cyclohexane–EtOAc, 7:3).

NMR and MS analytical data fit satisfactorily with the previously published data.[4]

2-(3,4-Dimethoxyphenyl)-4-oxo-4*H*-chromen-3-yl 4-Methoxybenzoate (2p)
Yield: 419 mg (97%); R_f = 0.26 (cyclohexane–EtOAc, 6:4).

NMR and MS analytical data fit satisfactorily with the previously published data.[3a]

Benzyl 4-Oxo-2-thiophen-2-yl-4*H*-chromen-3-yl Carbonate (3)
A solution of compound **2c** (375 mg, 1 mmol) in anhyd toluene was degassed three times with argon. Then tributylstannylthiophene (0.35 mg, 1.1 mmol, 1.1 equiv), $Pd(PPh_3)_4$ (58 mg, 5 mol%), and CuI (19 mg, 10 mol%) were added at once and the reaction mixture was refluxed for 1 h at 120 °C. The mixture was cooled down to r.t. and filtered. The organic phase was concentrated in vacuum and purified by silica gel flash chromatography (eluent: cyclohexane–EtOAc, 9:1). The product **3** was obtained as a pale yellow solid; yield: 360 mg (95%); R_f = 0.41 (cyclohexane–EtOAc, 7:3).

^{1}H NMR: δ = 8.26 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.92 (dd, *J* = 3.9, 1.2 Hz, 1 H), 7.80–7.30 (m, 9 H), 7.20 (dd, *J* = 5.0, 3.9 Hz, 1 H), 5.37 (s, 2 H).

^{13}C NMR: δ = 171.61, 155.21, 155.21, 152.14, 151.77, 134.72, 134.14, 132.14, 131.74, 131.09, 128.84, 128.77, 128.48, 128.24, 126.16, 125.37, 123.75, 118.02, 71.31.

HRMS: *m/z* [M + H]$^+$ calcd for $C_{21}H_{15}O_5S$: 379.0635; found: 379.0635.

3-Hydroxy-2-thiophen-2-yl-4*H*-chromen-3-one (4)
Aqueous ammonia solution (4 mL) was added to a suspension of compound **3** (200 mg, 0.53 mmol) in EtOH (6 mL). The mixture was stirred at r.t. for 3 h in a capped flask. After that, it was acidified with AcOH and concentrated in vacuum to a volume of about 3 mL. The solution was cooled down to 4 °C. The yellow precipitate was filtered, washed with H_2O (5 mL), and dried under high vacuum in a desiccator over P_2O_5; yield: 125 mg (97%).[9]

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