Practical and Scalable Synthesis of 7-Azetidin-1-yl-4-(hydroxymethyl)coumarin: An Improved Photoremovable Group

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General methods

All reagents were purchased from commercial sources and used as received. Dry solvents were procured from Acros Organics and used as received.

For preparative column chromatography, petroleum ether (Pet. Et.) 40–60 °C was used in place of hexane. Preparative HPLC was carried out using a Hitachi instrument equipped with an autosampler and a diode array detector (DAD) and employing an ACE Excel 5 C18-Amide column (25 cm length, 10 mm internal diameter). Solvent A: H$_2$O, Solvent B: MeCN (flow 4.7 mL min$^{-1}$, 70% A $\rightarrow$ 30 % A).

Automated flash chromatography was carried out using a Büchi Reveleris Prep purification system equipped with a UV and an evaporative light scattering detector, using prepacked Reveleris silica cartridges.

NMR spectra were acquired on Bruker AV300 or Bruker 400 instruments. $^1$H NMR chemical shifts are reported in ppm relative to SiMe$_4$ ($\delta = 0$) and were referenced internally with respect to residual protons in the solvent ($\delta = 2.50$ for (CD$_3$)$_2$SO, $\delta = 7.26$ for CDCl$_3$, and $\delta = 3.31$ for CD$_3$OD). Coupling constants are reported in Hz and multiplicities of signals are described as singlet (s), doublet (d), triplet (t), quartet (q), quintuplet (quint), or multiplet (m). $^{13}$C NMR chemical shifts are reported in ppm relative to SiMe$_4$ ($\delta = 0$) and were referenced internally with respect to solvent signal ($\delta = 39.5$ for (CD$_3$)$_2$SO, $\delta = 77.2$ for CDCl$_3$). Peak assignments are based on calculated chemical shift, multiplicity, and 2D experiments. $^{31}$P NMR with $^1$H decoupling were referenced after addition of triphenylphosphine as internal standard ($\delta = -4.9$ for CDCl$_3$).$^1$

IR spectra were measured on FTIR spectrometer Perkin Elmer Spectrum Two. High-resolution mass spectrometry was conducted by staff at the Molecular and Biomolecular Analysis (MoBiAs) center (ETH Zurich) employing a Bruker maXIS ESI/NanoSpray-Qq-TOF-MS or a Bruker solariX ESI/MALDI-FTICR-MS instrument.

LC/MS were recorded on a Waters Acquity UPLC system, equipped with a Waters Acquity BEH C18 column (5 cm length, 2.1 mm internal diameter), a diode array detector PDA and an SQ Detector 2 ZSPRAY (ESI). The samples were eluted with a MeCN-H$_2$O gradient running from 2% to 98% of MeCN, with a constant 0.1% of HCOOH. Elemental analysis was conducted by staff at the MoBiAs center (ETH Zurich) employing a LECO TruSpec Micro instrument.

IUPAC names of all compounds are provided and were determined using CS ChemDraw Professional 16.0.
Discarded Synthetic Routes

Scheme S1. Route to triflate 7.\(^{2-5}\) Tf = trifluoromethanesulfonate. DIEA: \(N,N\)-diisopropylethylamine. MW= Microwave irradiation.

\[ \text{Resorcinol (2 g, 18.18 mmol) was dissolved in 50 mL of hot toluene (80 °C). Chloroacetacetoacetate (3.5 g, 18.18 mmol, 3 mL) was added and allowed to dissolve. The solution was heated to 110 °C and methanesulfonic acid (1 mL) was added.} \]

the hot toluene containing the product was decanted. The product crystallized upon cooling, it was filtered and dried under vacuum. The resulting gum from the decanting step was re-suspended in toluene, heated and decanted. The procedure was repeated until most of product 5 was recovered as a light brown solid (2.3 g, 60% yield).

\[^{1}\text{H NMR (300 MHz, CD}_3\text{OD): } \delta = 7.67 (d, J = 8.8 \text{ Hz, 1 H, H-3}), 6.84 (dd, J = 8.8, 2.4 \text{ Hz, 1 H, H-2}), 6.73 (d, J = 2.4 \text{ Hz, 1 H, H-1}), 6.37 (t, J = 0.9 \text{ Hz, 1 H, H-4}), 4.81 \text{ (d, J = 0.9 Hz, 2 H, H-5).} \]

HRMS-ESI: \(m/z \ [\text{M + H}]^+ \) calcd for C\(_{10}\)H\(_8\)O\(_3\)Cl: 211.0156; found: 211.0157.

7-Hydroxy-4-(hydroxymethyl)-2\(H\)-chromen-2-one (6)\(^4\) – CAS 151889-83-7

Three batches of compound 5 (500 mg each, total 1.5 g, 7.14 mmol) were inserted in separate microwave vials equipped with a stirrer and suspended in H\(_2\)O (5 mL per vial). The suspensions were irradiated at 160 °C for 1 h. The suspensions turned pale green and gave a precipitate upon cooling with an ice bath.
The precipitates were combined, filtered, washed with cold water and dried under vacuum in a desiccator to give compound 6 as a white solid (1.12 g, 86% yield).

$^1$H NMR (300 MHz, CD$_3$OD): $\delta = 7.51$ (d, $J = 8.7$ Hz, 1 H, H-3), 6.80 (dd, $J = 8.7$, 2.4 Hz, 1 H, H-2), 6.74 (d, $J = 2.4$ Hz, 1 H, H-1), 6.36 (t, $J = 1.5$ Hz, 1 H, H-4), 4.80 (d, $J = 1.5$ Hz, 2 H, H-5).


4-(Hydroxymethyl)-2-oxo-2$H$-chromen-7-yl trifluoromethanesulfonate (7)$^5$ – CAS 736957-95-2

Compound 6 (300 mg, 1.52 mmol) and N,N-phenylbistrifluoromethane-sulfonimide (543 mg, 1.52 mmol) were suspended in MeCN (12 mL). N,N-diisopropylethylamine (245 mg, 1.9 mmol, 0.35 mL) was added and the solution was stirred for 2 h at 25 °C. After 2 h, no more starting material was observed by LC/MS. The solvent was removed under reduced pressure and the crude was dissolved in EtOAc, washed with H$_2$O and brine, and dried over MgSO$_4$. The solvent was removed under reduced pressure. Flash-column chromatography (SiO$_2$, Pet. Et.-EtOAc, 9:1 → 1:1) afforded 6 (300 mg, 60%) as an off-white solid.

$R_f = 0.44$ (SiO$_2$, CH$_2$Cl$_2$-EtOAC, 8:2).

$^1$H NMR (300 MHz, CDCl$_3$): $\delta = 7.64$ (d, $J = 8.8$ Hz, 1 H, H-3), 7.30 (d, $J = 2.4$ Hz, 1 H, H-1), 7.23 (dd, $J = 8.8$, 2.4 Hz, 1 H, H-2), 6.69 (t, $J = 1.6$ Hz, 1 H, H-4), 4.91 (d, $J = 1.6$ Hz, 2 H, H-5).

HRMS-ESI: m/z [M + H]$^+$ calcd for C$_{11}$H$_8$F$_3$O$_6$S: 324.9988; found: 324.9992.

Scheme S2. Buchwald-Hartwig coupling of triflate 7
Buchwald-Hartwig coupling of triflate 7

Compound 3 (30 mg, 0.093 mmol), Cs$_2$CO$_3$ (84 mg, 0.26 mmol), RuPhos (4.3 mg 0.0092 mmol) and RuPhos Pd G3 (7.8 mg, 0.0092 mmol) were added to a Schlenk flask that was evacuated and backfilled with nitrogen three times. Anhydrous 1,4-dioxane or toluene (0.5 mL) was added followed by azetidine (0.10 mmol, 7 µL). The reaction was heated to 80 °C. After 10 min the prominent formation of Tsuji-Trost product 8 over the desired azetidine alcohol 3 was observed.

Figure S1. LC/MS analysis of the Buchwald-Hartwig coupling of triflate 7 in 1,4-dioxane (top and middle) and toluene (bottom).
Scheme S3. Buchwald-Hartwig coupling of TIPS-protected compound 9

2-Oxo-4-(((triisopropylsilyl)oxy)methyl)-2H-chromen-7-yl trifluoromethanesulfonate (9)

Compound 7 (200 mg, 0.61 mmol) was dissolved in CH$_2$Cl$_2$ (0.4 mL). Triisopropylsilyl trifluoromethanesulfonate (377 mg, 1.23 mmol, 0.33 mL) was added and the solution was cooled to 0 $^\circ$C. Imidazole (168 mg, 2.47 mmol) was added in portions and the reaction was allowed to warm up to 25 $^\circ$C. Upon completion (as determined by LC/MS), the mixture was diluted with CH$_2$Cl$_2$ and washed with brine. The organic phase was dried with Na$_2$SO$_4$, filtered, evaporated and the solvent was removed under reduced pressure to yield product 9 as a white solid (220 mg, 75%). The compound was used without further purification.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.54 (d, $J$ = 8.8 Hz, 1 H, H-3), 7.30 (d, $J$ = 2.5 Hz, 1 H, H-1), 7.21 (dd, $J$ = 8.8, 2.5 Hz, 1 H, H-2), 6.74 (t, $J$ = 1.6 Hz, 1 H, H-5), 4.96 (d, $J$ = 1.6 Hz, 2 H, H-5), 1.28 – 1.17 (m, 3 H, H-6), 1.11 (d, $J$ = 6.9 Hz, 18 H, H-7).

MS (ESI): $m/z = 481$ [M + H]$^+$. 

7-(Azetidin-1-yl)-4-(((triisopropylsilyl)oxy)methyl)-2H-chromen-2-one (10)

Compound 9 (15 mg, 0.03 mmol), Cs$_2$CO$_3$ (5.52 mg, 0.04 mmol), RuPhos (1.3 mg 0.003 mmol) and RuPhos Pd G3 (2.5 mg, 0.003 mmol) were added to a Schlenk flask that was evacuated and backfilled with nitrogen three times. Anhydrous 1,4-dioxane (0.2 mL) was added and the suspension was stirred during addition of azetidine (0.03 mmol, 3 $\mu$L). The reaction was heated to 80 $^\circ$C. After 30 min the formation of a new compound was revealed by TLC analysis (SiO$_2$, Pet. Et.-EtOAc, 9:1). The suspension was cooled down, diluted in CH$_2$Cl$_2$ and loaded on a preparatory TLC
The TLC was run twice before recovering compound 10 as a clear oil (3.5 mg, 30%).

$R_f = 0.2$ (SiO$_2$, Pet. Et.-EtOAc, 9:1).

$^1$H NMR (300 MHz, CDCl$_3$): $\delta = 7.22$ (d, $J = 8.4$ Hz, 1 H, H-3), 6.40 (t, $J = 1.6$ Hz, 1 H, H-4), 6.32 – 6.21 (m, 2 H, H-1 and H-2), 4.90 (d, $J = 1.6$ Hz, 2 H, H-5), 3.99 (t, $J = 7.3$ Hz, 4 H, H-6), 2.44 (p, $J = 7.3$ Hz, 2 H, H-7), 1.34 – 1.14 (m, 3 H, H-8), 1.10 (d, $J = 6.3$ Hz, 18 H, H-9).

MS (ESI) $m/z = 388$ [M + H], 410 [M + Na].

**Important note:** A compound generated by the attack of a yet unidentified nucleophile on the azetidine ring was the major product of the Buchwald-Hartwig reaction of 6 in quantities larger than 200 mg. The attack on the azetidine was evident by $^1$H NMR (Figure S2). When the reaction was repeated on a 50 mg scale increasing the temperature to 110 °C, TLC analysis (SiO$_2$, Pet. Et.-EtOAc, 9:1) seemed to show a cleaner reaction mixture. However, product 10 was obtained only in low yield (6 mg, 15% yield) after column chromatography. Repeating the reaction on a 300 mg scale while heating at the same temperature (110 °C) resulted in an even lower yield of (10 mg, 5% yield). In all these cases, the crude was filtered through a silica plug eluted with Pet. Et. The solvent was removed under reduced pressure before separating the mixture by column chromatography.
Figure S2. $^1$H NMR spectrum of the mixture of the open-ring product (marked peaks) and compound 9. The COSY in the inset shows the protons of the propylamino chain coupling two by two, proving the attack at the C–N bond of the azetidine.

Scheme S4. Thermal and photochemical hydrolysis of bromide 4.

**Thermal hydrolysis protocol**

Compound 4 (38 mg, 0.13 mmol) was suspended in 1,4-dioxane (4.7 mL) and sonicated. After addition of H$_2$O (4 mL), the system was heated to reflux and the reaction progress monitored by TLC (SiO$_2$, CH$_2$Cl$_2$-AcOEt, 95:5). Upon completion (as determined by disappearance of the starting material), the mixture was allowed to cool to room temperature and it was extracted four times with EtOAc. The combined organic phases were dried over MgSO$_4$ and the solvent was removed under reduced pressure. The crude was separated by preparative TLC (SiO$_2$, Pet.
Et.-EtOAc, 1:1). LC/MS analysis of the isolated bands suggests that nucleophilic attack of a bromide ion on the azetidine ring took place ($m/z = 312, [M + H]^+$).

**Photolysis protocol**
A 7:3 (mol/mol) mixture of compound 4 and compound 11 (240 mg) was suspended in MeCN (150 mL) and stirred for 1 h. Following addition of H$_2$O (20 mL), the solution was distributed in 20 mL Pyrex test tubes and irradiated in a Rayonet photoreactor equipped with 350 nm emitting lamps and a nitrogen (gas) inlet for cooling. The solution was irradiated for 3 h. During irradiation, the temperature in the reactor reached 45 °C. Most of the MeCN was removed under reduced pressure, and the mixture was then extracted with EtOAc three times. The combined organic phases were dried over MgSO$_4$ and the solvent was removed under reduced pressure. The residue was fixed on Celite and separated by column chromatography (SiO$_2$, CH$_2$Cl$_2$-EtOAc, 85:15). The isolated fraction (30 mg) was found to be a mixture of compounds 3 and 12 as revealed by NMR and LC/MS analysis (Figure S3).

**Figure S3.** Zoom of the high field region of the COSY spectrum of the mixture of 3 and 12 isolated after chromatography. Below the structures are reported the $m/z$ values retrieved by LC/MS analysis.
Scheme S5. Attempted alternative route to 4-halomethylene coumarin derivative.

3-(Azetidin-1-yl)-phenol (13)

Compound 13 was prepared according to the method reported by Grimm et al.\textsuperscript{6} Pd(OAc)\textsubscript{2} (130 mg, 0.57 mmol) was transferred to a flame-dried flask, which was evacuated and backfilled with nitrogen three times. Dry toluene (40 mL) was added. Solutions of 3-bromophenol (2.0 g, 11.6 mmol, 1.23 mL) and 2,8,9-triisobutyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane (“Verkade’s base”, 396 mg, 1.16 mmol, 0.41 mL) in dry toluene (8 mL) were prepared in two different flame-dried flasks kept under positive nitrogen pressure. The two solutions were added in sequence to the palladium suspension, followed by LiHMDS (1 M in THF, 26.6 mmol, 26.6 mL) and azetidine (792 mg, 13.9 mmol, 0.935 mL). The mixture was stirred at 80 °C for 24 h. Upon completion, as determined by TLC, (SiO\textsubscript{2}, Pet. Et.-EtOAc, 7:3), Celite was added and the solvent was evaporated under reduced pressure. The mixture was separated by column chromatography (SiO\textsubscript{2}, Pet. Et.-EtOAc, 1:9 → 1:1), to yield pure compound 13 as a grey powder that gets darker over time (1.3 g, 75% yield).

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta = 7.06 \text{ (t, } J = 8.0 \text{ Hz, } 1 \text{ H, H-2), 6.20 \text{ (ddd, } J = 8.0, 2.4, 0.9 \text{ Hz, } 1 \text{ H), 6.05 \text{ (ddd, } J = 8.1, 2.1, 0.9 \text{ Hz, } 1 \text{ H), 5.91 \text{ (t, } J = 2.3 \text{ Hz, } 1 \text{ H, H-1), 3.84 \text{ (t, } J = 7.3 \text{ Hz, } 4 \text{ H, H-3), 2.34 \text{ (p, } J = 7.3 \text{ Hz, } 2 \text{ H, H-4).}}\)

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta = 156.7, 153.9, 130.1, 105.0, 104.5, 98.9, 52.7, 17.0.\)

HRMS-ESI: \(m/z \ [M + H]^+ \text{ calcd for } C_{9}H_{12}NO: 150.0913; \text{ found: } 150.0914.\)

4-(Chloromethyl)-7-((3-chloropropyl)amino)-2H-chromen-2-one (19)

Compound 13 (100 mg, 0.67 mmol) was transferred to a flame-dried flask. The system was evacuated and backfilled with nitrogen three times. Following addition
of dry toluene (2 mL) and Ti(iOPr)$_3$Cl (1 M in hexanes, 1.4 mL, 1.4 mmol), the solution was stirred at 95 °C for 15 h, before being diluted with 7 mL of CH$_2$Cl$_2$ and 7 mL of a saturated solution of Rochelle’s salt (sodium and potassium tartrate). The emulsion was stirred for 3 h, before being separated by centrifugation (3 min, 3000 rpm). The CH$_2$Cl$_2$ layer was separated and evaporated under reduced pressure. The mixture was separated by preparative TLC (SiO$_2$, Pet. Et.-EtOAc, 7:3) to yield 35 mg of compound 19 as a dark yellow powder. Compound 14, the desired product, was not observed.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.43$ (d, $J = 8.7$ Hz, 1 H, H-3), 6.56 (dd, $J = 8.7, 2.4$ Hz, 1 H, H-2), 6.50 (d, $J = 2.4$ Hz, 1 H, H-1), 6.24 (t, $J = 0.8$ Hz, 1 H, H-4), 4.57 (d, $J = 0.8$ Hz, 2 H, H-5), 3.66 (t, $J = 6.1$ Hz, 2 H), 3.43 (t, $J = 6.7$ Hz, 2 H), 2.22 – 1.97 (m, 2H, H-6).

MS (ESI) $m/z = 286$ [M + H]$^+$. 

**Figure S4.** UV-vis spectra of compounds 16–18 measured in CH$_3$CN-PBS, 7:3 (10 µM).
References


$^{13}$C NMR ((CD$_3$)$_2$SO, 100 MHz) spectrum of compound 3
\(^1\)H NMR (CDCl\(_3\), 400 MHz) spectrum of compound 4

\(^{13}\)C NMR (CDCl\(_3\), 100 MHz) spectrum of compound 4
$^1$H NMR (CD$_3$OD, 300 MHz) spectrum of compound 5

$^1$H NMR (CD$_3$OD, 300 MHz) spectrum of compound 6
$^1$H NMR (CDCl$_3$, 300 MHz) spectrum of compound 7

$^1$H NMR (CDCl$_3$, 300 MHz) spectrum of compound 9
$^1$H NMR (CDCl$_3$, 300 MHz) spectrum of compound 10

$^1$H NMR (CDCl$_3$, 400 MHz) spectrum of compound 11
$^{13}$C NMR (CDCl$_3$, 100 MHz) spectrum of compound 11

$^1$H NMR (CDCl$_3$, 400 MHz) spectrum of compound 13
$^{13}$C NMR (CDCl$_3$, 100 MHz) spectrum of compound 13

$^1$H NMR (CDCl$_3$, 400 MHz) spectrum of compound 16
$^{13}$C NMR (CDCl$_3$, 100 MHz) spectrum of compound 16

$^{31}$P NMR (CDCl$_3$, 162 MHz) spectrum of compound 16.
$\text{H NMR (CDCl}_3$, 400 MHz) spectrum of compound 17

$\text{C NMR (CDCl}_3$, 100 MHz) spectrum of compound 17
$^1$H NMR ([(CD$_3$)$_2$SO, 400 MHz) spectrum of compound 18

$^{13}$C NMR ([(CD$_3$)$_2$SO, 100 MHz) spectrum of compound 18
$^1$H NMR (CDCl$_3$, 300 MHz) spectrum of compound 19