Facile synthesis of azaarene-2-substituted chromanone derivatives via tandem sp3 C–H functionlization/decarboxylation of azaarenes with 4-oxo-4H-chromene-3-carboxylic acid

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Supporting Information

CONTENTS

1. General Information……………………………………………………………………………………………………2
2. Experimental Procedures ……………………………………………………………………………………………2
3. Characterization of Products……………………………………………………………………………………2
4. 1H- and 13C-NMR Spectra……………………………………………………………………………………9
1. General Methods

All the chemical reagents were purchased from commercial companies and all the solvents were dried according to standard procedures before use. All reactions were performed in pressure-proof pipe and monitored by TLC with 0.2 mm silica gel-coated HSGF 254 plates. The reaction mixtures were purified by flash column chromatography (200-300 mesh silica gel) eluted with the gradient of petroleum ether and ethyl acetate.

Proton nuclear magnetic resonance spectra (1H NMR) were recorded on a Bruker AMX 500 spectrophotometer (CDCl3 as solvent). Chemical shifts were reported in ppm using tetramethylsilane (TMS, δ (ppm) = 0.00 ppm) as the internal standard, and relative to the signal of chloroform-d (δ 7.26, singlet). The number of protons (n) for a given resonance is indicated by nH. Coupling constants are reported as a J value in Hz. The following abbreviations are used to indicate the multiplicity: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), and multiplet (m). Carbon nuclear magnetic resonance spectra (13C NMR) were reported in parts per million using solvent CDCl3 (δ (ppm) = 77.0 ppm) as an internal standard. HRMS analyses were performed on a Waters XEVO QTOF mass spectrometer. The compounds chromone-3-carbaldehyde1,2, chromone-3-carboxylic acid3 and 3-acetyl-chromone4 were prepared according the reported procedures.

2. Experimental Procedures

General Procedure for Synthesis of Azaarenes-Substituted Chromanones

To a 25 mL pressure tube equipped with a magnetic stirrer bar were added dioxane (1 mL), azaarenes 2 (0.75 mmol) and chromanone-3-carboxylic acids 1 (0.3 mmol). The mixture was then stirred at 140 °C and monitored by TLC until 1 was consumed up. Then the reaction was cooled to room temperature and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel to afford the desired product 3.

3. Characterization of Products

3.1 2-((6-Methylpyridin-2-yl) methyl) chroman-4-one

Red-brown solid, yield 67%.

1H NMR (500 MHz, CDCl3) δ 7.87 (dd, J = 7.8, 1.0 Hz, 1H), 7.53 (t, J = 7.7 Hz, 1H), 7.48-7.42 (m, 1H), 7.08-7.02 (m, 2H), 7.00 (t, J = 7.5 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H), 4.97-4.89 (m, 1H), 3.36 (dd, J = 13.8, 7.0 Hz, 1H), 3.15 (dd, J = 13.8, 6.1 Hz, 1H), 2.76 (d, J = 7.7 Hz, 2H), 2.53 (s, 3H). 13C NMR (125 MHz, CDCl3) δ 192.2, 161.4, 158.2, 155.8, 136.7,
135.9, 126.9, 121.5, 121.2, 121.1, 121.0, 117.9, 77.4, 43.4, 42.5, 24.3. **HRMS (ESI):** calcd. for C_{16}H_{16}NO_{2} [M+H]^+: 254.1176, found: 254.1177.

### 3.2 2-((6-Methyl-5-nitropyridin-2-yl)methyl)chroman-4-one

![Structure Image](image)

Brown solid, yield 56%.

**1H NMR** (500 MHz, CDCl₃) δ 8.27 (d, J = 8.4 Hz, 1H), 7.89 (dd, J = 7.9, 1.6 Hz, 1H), 7.49-7.44 (m, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.02 (t, J = 7.5 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 5.05-4.97 (m, 1H), 3.41 (dd, J = 14.1, 7.7 Hz, 1H), 3.25 (dd, J = 14.1, 5.0 Hz, 1H), 2.85 (s, 3H), 2.84-2.80 (m, 2H).

**13C NMR** (125 MHz, CDCl₃) δ 191.6, 161.1, 161.0, 153.7, 144.3, 136.1, 132.9, 127.0, 122.4, 121.6, 120.9, 117.8, 76.6, 43.2, 42.6, 24.0. **HRMS (ESI):** calcd. for C_{16}H_{16}N₂O₄ [M+H]^+: 299.1027, found: 299.1025.

### 3.3 2-(pyridin-2-ylmethyl)chroman-4-one

![Structure Image](image)

Brown viscous liquid, 70%.

**1H NMR** (500 MHz, CDCl₃) δ 8.56 (d, J = 3.9 Hz, 1H), 7.87 (d, J = 7.9 Hz, 1H), 7.66 (t, J = 7.7 Hz, 1H), 7.45 (t, J = 7.7 Hz, 1H), 7.29-7.26 (m, 1H), 7.22-7.16 (m, 1H), 7.00 (t, J = 7.5 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H), 5.00-4.91 (m, 1H), 3.39 (dd, J = 13.9, 6.9 Hz, 1H), 3.20 (dd, J = 13.9, 5.9 Hz, 1H), 2.77 (dd, J = 6.9, 1.6 Hz, 2H).

**13C NMR** (125 MHz, CDCl₃) δ 192.2, 161.4, 156.7, 149.6, 136.6, 136.0, 127.0, 124.3, 122.0, 121.4, 118.0, 77.4, 43.4, 42.6. **HRMS (ESI):** calcd. for C_{15}H_{14}NO_{2} [M+H]^+: 240.1020, found: 240.1020.

### 3.4 2-(1-(pyridin-2-yl)ethyl)chroman-4-one

![Structure Image](image)

Brown viscous liquid, 37%.

**1H NMR** (500 MHz, CDCl₃) δ 8.57 (d, J = 4.3 Hz, 1H), 7.85 (dd, J = 7.9, 1.1 Hz, 1H), 7.69-7.62 (m, 1H), 7.45-7.38 (m, 1H), 7.28-7.25 (m, 1H), 7.18 (dd, J = 7.0, 5.2 Hz, 1H), 6.98 (t, J = 7.5 Hz, 1H), 6.85 (d, J = 8.3 Hz, 1H), 4.88-4.77 (m, 1H), 3.44-3.37 (p, J = 7.0 Hz, 1H), 2.75 (dd, J = 9.8, 8.1 Hz, 2H), 1.45 (d, J = 7.1 Hz, 3H).

**13C NMR** (125 MHz, CDCl₃) δ 192.5, 161.5, 161.4, 149.2, 136.4, 135.8, 126.9, 123.0, 121.9, 121.2, 121.0, 117.9, 80.8, 45.6, 40.1, 15.3. **HRMS (ESI):** calcd. for C_{16}H_{16}NO_{2} [M+H]^+: 254.1176, found: 254.1175.

### 3.5 2-((3-methylpyridin-2-yl)methyl)chroman-4-one
Brown viscous liquid, 57%.

\(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)) \(\delta\) 8.39 (d, \(J = 3.8\) Hz, 1H), 7.88 (dd, \(J = 7.8, 1.2\) Hz, 1H), 7.50 – 7.41 (m, 2H), 7.10 (dd, \(J = 7.4, 4.9\) Hz, 1H), 7.00 (t, \(J = 7.5\) Hz, 1H), 6.91 (d, \(J = 8.4\) Hz, 1H), 5.08-5.00 (m, 1H), 3.44 (dd, \(J = 14.2, 6.6\) Hz, 1H), 3.19 (dd, \(J = 14.2, 6.6\) Hz, 1H), 2.88 – 2.75 (m, 2H), 2.37 (s, 3H). \(^{13}\text{C NMR}\) (125 MHz, CDCl\(_3\)) \(\delta\) 192.3, 161.5, 155.2, 146.8, 137.9, 135.9, 132.1, 127.0, 121.9, 121.2, 121.1, 117.9, 77.5, 42.7, 40.0, 19.0. \(\text{HRMS (ESI)}\): calcd. for C\(_{16}\)H\(_{16}\)NO\(_2\) [M+H]^+: 254.1176, found: 254.1176.

3.6 2-(Pyrimidin-4-ylmethyl)chroman-4-one

Brown viscous liquid, 41%.

\(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)) \(\delta\) 9.17 (s, 1H), 8.70 (d, \(J = 5.0\) Hz, 1H), 7.88 (d, \(J = 7.8\) Hz, 1H), 7.49-7.43 (m, 1H), 7.33 (d, \(J = 5.0\) Hz, 1H), 7.02 (t, \(J = 7.5\) Hz, 1H), 6.90 (d, \(J = 8.3\) Hz, 1H), 5.05-4.97 (m, 1H), 3.33 (dd, \(J = 14.3, 7.8\) Hz, 1H), 3.18 (dd, \(J = 14.3, 5.0\) Hz, 1H), 2.84 – 2.78 (m, 2H). \(^{13}\text{C NMR}\) (125 MHz, CDCl\(_3\)) \(\delta\) 191.4, 165.4, 160.9, 158.8, 156.9, 136.1, 127.0, 121.8, 121.6, 120.9, 117.8, 76.2, 42.7, 42.6. \(\text{HRMS (ESI)}\): calcd. for C\(_{14}\)H\(_{13}\)N\(_2\)O\(_2\) [M+H]^+: 241.0972, found: 241.0972.

3.7 2-(Pyrazin-2-ylmethyl)chroman-4-one

Brown viscous liquid, 25%.

\(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)) \(\delta\) 8.60 (s, 1H), 8.54 (s, 1H), 8.49 (d, \(J = 2.3\) Hz, 1H), 7.88 (dd, \(J = 7.9, 1.5\) Hz, 1H), 7.48-7.43 (m, 1H), 7.02 (t, \(J = 7.5\) Hz, 1H), 6.91 (d, \(J = 8.3\) Hz, 1H), 4.99-4.89 (m, 1H), 3.38 (dd, \(J = 14.3, 7.6\) Hz, 1H), 3.23 (dd, \(J = 14.3, 5.0\) Hz, 1H), 2.83-2.79 (m, 2H). \(^{13}\text{C NMR}\) (125 MHz, CDCl\(_3\)) \(\delta\) 191.6, 161.1, 152.7, 145.6, 144.2, 143.1, 136.1, 127.0, 121.6, 120.9, 117.9, 76.6, 42.6, 40.6. \(\text{HRMS (ESI)}\): calcd. for C\(_{14}\)H\(_{13}\)N\(_2\)O\(_2\) [M+H]^+: 241.0972, found: 241.0973.

3.8 2-(Quinolin-2-ylmethyl)chroman-4-one

Brown liquid, yield 53%.
1H NMR (500 MHz, CDCl₃) δ 8.13 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.88 (dd, J = 7.8, 1.5 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.74-7.68 (m, 1H), 7.52 (t, J = 7.4 Hz, 1H), 7.46-7.37 (m, 2H), 6.99 (t, J = 7.5 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 5.12-5.04 (m, 1H), 3.56 (dd, J = 14.0, 7.1 Hz, 1H), 3.39 (dd, J = 14.0, 5.8 Hz, 1H), 2.87-2.82 (m, 2H). 13C NMR (125 MHz, CDCl₃) δ 192.0, 161.3, 147.9, 136.5, 135.9, 129.6, 128.9, 127.5, 126.9, 126.2, 125.8, 122.2, 121.3, 121.0, 117.9, 77.4, 44.0, 42.6. HRMS (ESI): calcd. for C₁₉H₁₈NO₂ [M+H]⁺: 290.1176, found: 290.1170.

3.9 2-((6-Methylquinolin-2-yl)methyl)chroman-4-one

Brown liquid, yield 45%.

1H NMR (500 MHz, CDCl₃) δ 8.02 (d, J = 8.4 Hz, 1H), 7.92 (d, J = 8.5 Hz, 1H), 7.87 (dd, J = 7.8, 1.4 Hz, 1H), 7.58-7.50 (m, 2H), 7.46-7.40 (m, 1H), 7.34 (d, J = 8.3 Hz, 1H), 6.98 (t, J = 7.5 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 5.09-5.01 (m, 1H), 3.53 (dd, J = 14.0, 7.1 Hz, 1H), 3.35 (dd, J = 13.9, 5.9 Hz, 1H), 2.84-2.80 (m, 2H), 2.52 (s, 3H). 13C NMR (125 MHz, CDCl₃) δ 192.1, 161.3, 146.5, 136.0, 135.9, 135.7, 131.8, 128.5, 126.9, 126.4, 126.3, 122.2, 121.3, 121.0, 117.9, 77.4, 43.9, 42.6, 21.4. HRMS (ESI): calcd. for C₂₀H₁₉NO₂ [M+H]⁺: 304.1333, found: 304.1327.

3.10 2-((6-Bromoquinolin-2-yl)methyl)chroman-4-one

Brown liquid, yield 43%.

1H NMR (500 MHz, CDCl₃) δ 8.04 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 1.9 Hz, 1H), 7.92-7.87 (m, 2H), 7.77 (dd, J = 9.0, 2.0 Hz, 1H), 7.48-7.39 (m, 2H), 7.01 (t, J = 7.5 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 5.12-5.04 (m, 1H), 3.55 (dd, J = 14.1, 7.2 Hz, 1H), 3.38 (dd, J = 14.1, 5.7 Hz, 1H), 2.87-2.83 (m, 2H). 13C NMR (125 MHz, CDCl₃) δ 191.9, 161.2, 157.8, 146.4, 135.9, 135.3, 133.0, 130.6, 129.5, 128.0, 126.9, 123.1, 121.4, 121.0, 120.0, 117.9, 77.1, 43.9, 42.6. HRMS (ESI): calcd. for C₁₉H₁₅BrNO₂ [M+H]⁺: 368.0281, found: 368.0275. C₁₉H₁₅BrNO₂ [M+H+2]⁺: 370.0261, found: 370.0260.

3.11 2-((7-chloroquinolin-2-yl)methyl)chroman-4-one

Brown liquid, yield 39%.

1H NMR (500 MHz, CDCl₃) δ 8.22 (dd, J = 8.0, 1.6 Hz, 1H), 7.92-7.85 (m, 2H), 7.75 (d, J = 8.7 Hz, 1H), 7.46-7.38 (m, 3H), 7.01 (t, J = 7.5 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 5.19-4.98 (m, 1H), 3.55 (dd, J = 14.1, 7.2 Hz, 1H), 3.39 (dd, J = 14.1, 5.7 Hz, 1H), 2.90-2.77 (m, 2H).
$^{13}$C NMR (125 MHz, CDCl$_3$) δ 192.0, 161.3, 158.5, 148.2, 136.0, 135.5, 133.8, 128.7, 127.0, 125.3, 125.24, 122.5, 121.4, 121.0, 118.2, 117.9, 77.2, 43.9, 42.6. HRMS (ESI): calcd. for C$_{19}$H$_{15}$ClNO$_2$ [M+H]$^+$: 324.0786, found: 324.0781. C$_{19}$H$_{15}$ClNO$_2$ [M+H+2]$^+$: 326.0757, found: 326.0458.

3.12 2-((8-hydroxyquinolin-2-yl)methyl)chroman-4-one

Brown liquid, yield 48%.

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.10 (d, $J = 8.3$ Hz, 1H), 7.87 (d, $J = 7.8$ Hz, 1H), 7.47-7.36 (m, 3H), 7.31 (d, $J = 8.2$ Hz, 1H), 7.16 (d, $J = 7.6$ Hz, 1H), 6.99 (t, $J = 7.4$ Hz, 1H), 6.90 (d, $J = 8.3$ Hz, 1H), 5.11-5.02 (m, 1H), 3.53 (dd, $J = 14.1$, 7.2 Hz, 1H), 3.36 (dd, $J = 14.1$, 5.6 Hz, 1H), 2.80 (d, $J = 7.7$ Hz, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 191.7, 161.2, 155.1, 151.7, 137.7, 136.6, 136.0, 127.4, 127.1, 126.9, 122.9, 121.4, 121.0, 117.9, 117.6, 110.2, 77.1, 43.4, 42.5. HRMS (ESI): calcd. for C$_{19}$H$_{16}$NO$_3$ [M+H]$^+$: 306.1125, found: 306.1129.

3.13 2-((8-methoxyquinolin-2-yl)methyl)chroman-4-one

Brown liquid, yield 67%.

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.11 (d, $J = 8.4$ Hz, 1H), 7.88 (d, $J = 6.6$ Hz, 1H), 7.49-7.42 (m, 3H), 7.39 (d, $J = 8.0$ Hz, 1H), 7.07 (d, $J = 7.5$ Hz, 1H), 7.00 (t, $J = 7.4$ Hz, 1H), 6.92 (d, $J = 8.3$ Hz, 1H), 5.11-5.03 (m, 1H), 4.08 (s, 3H), 3.62 (dd, $J = 13.9$, 7.5 Hz, 1H), 3.47 (dd, $J = 13.9$, 5.4 Hz, 1H), 2.84 (d, $J = 7.7$ Hz, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 192.1, 161.4, 156.4, 155.1, 140.0, 136.3, 135.9, 128.2, 127.0, 126.4, 122.9, 121.3, 119.5, 118.0, 108.0, 77.7, 56.1, 44.2, 42.7. HRMS (ESI): calcd. for C$_{20}$H$_{18}$NO$_3$ [M+H]$^+$: 320.1282, found: 320.1280.

3.14 2-((8-(benzyloxy)quinolin-2-yl)methyl)chroman-4-one

Brown liquid, yield 71%.

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.08 (d, $J = 8.3$ Hz, 1H), 7.89 (d, $J = 7.6$ Hz, 1H), 7.49 (d, $J = 7.4$ Hz, 2H), 7.43 (t, $J = 6.8$ Hz, 2H), 7.37-7.31 (m, 4H), 7.30-7.26 (m, 1H), 7.07 (d, $J = 7.0$ Hz, 1H), 7.02-6.97 (m, 1H), 6.92 (d, $J = 8.3$ Hz, 1H), 5.40 (s, 2H), 5.16-5.07 (m, 1H), 3.61 (dd, $J = 14.1$, 7.1 Hz, 1H), 3.47 (dd, $J = 14.1$, 5.7 Hz, 1H), 2.91-2.83 (m, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 192.1, 161.4, 156.3, 154.1, 140.3, 137.1, 136.3, 135.9, 129.0, 128.7, 128.5, 127.7, 126.9, 126.2, 122.8, 121.3, 121.1, 119.9, 117.9, 111.0, 77.5, 71.0, 43.9, 42.6. HRMS
(ESI): calcd. for C_{26}H_{32}NO_{3} [M+H]^+: 396.1595, found: 396.1596.

3.15 2-(benzo[f]quinolin-3-ylmethyl)chroman-4-one

Brown liquid, yield 59%.

^1H NMR (500 MHz, CDCl_3) δ 8.90 (d, J = 8.4 Hz, 1H), 8.60 (d, J = 8.1 Hz, 1H), 8.05-7.85 (m, 4H), 7.72-7.57 (m, 2H), 7.54 (d, J = 8.4 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 6.99 (t, J = 7.5 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 5.18-5.06 (m, 1H), 3.59 (dd, J = 14.0, 7.1 Hz, 1H), 3.43 (dd, J = Hz, 1H), 2.92-2.75 (m, 2H). ^13C NMR (125 MHz, CDCl_3) δ 192.1, 161.4, 156.7, 147.9, 135.9, 131.5, 131.0, 129.5, 128.7, 127.8, 127.1, 126.9, 126.8, 124.0, 122.5, 122.2, 121.3, 121.09, 117.9, 77.4, 43.7, 42.7. HRMS (ESI): calcd. for C_{26}H_{27}NO_{3} [M+H]^+: 396.1596, found: 396.1596.

3.16 2-(isoquinolin-1-ylmethyl)chroman-4-one

Brown liquid, yield 57%.

^1H NMR (500 MHz, CDCl_3) δ 8.46 (d, J = 5.6 Hz, 1H), 8.17 (d, J = 8.5 Hz, 1H), 7.87 (dd, J = 7.9, 1.5 Hz, 1H), 7.84 (d, J = 8.2 Hz, 1H), 7.69 (t, J = 7.5 Hz, 1H), 7.64-7.58 (m, 1H), 7.57 (d, J = 5.7 Hz, 1H), 7.45-7.39 (m, 1H), 6.98 (t, J = 7.5 Hz, 1H), 6.88 (d, J = 8.3 Hz, 1H), 5.24-5.16 (m, 1H), 3.98 (dd, J = 14.5, 6.2 Hz, 1H), 3.66 (dd, J = 14.5, 7.0 Hz, 1H), 2.89-2.83 (m, 2H). ^13C NMR (125 MHz, CDCl_3) δ 192.2, 161.5, 156.6, 141.9, 136.4, 135.9, 130.1, 127.6, 127.5, 127.4, 127.0, 125.1, 121.4, 121.1, 120.1, 118.0, 77.3, 42.9, 40.0. HRMS (ESI): calcd. for C_{19}H_{16}NO_{2} [M+H]^+; 290.1176, found: 290.1170.

3.17 6-methyl-2-(quinolin-2-ylmethyl)chroman-4-one

Brown viscous liquid, 51%.

^1H NMR (500 MHz, CDCl_3) δ 8.13 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 8.3 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.74 - 7.70 (m, 1H), 7.68-7.65 (m, 1H), 7.55 - 7.50 (m, 2H), 7.41 (d, J = 8.4 Hz, 1H), 7.26-7.24 (m, 1H), 6.82 (d, J = 8.4 Hz, 1H), 5.07-5.0 (m, 1H), 3.55 (dd, J = 13.9, 7.2 Hz, 1H), 3.38 (dd, J = 13.9, 5.7 Hz, 1H), 2.85 - 2.79 (m, 2H), 2.29 (s, 3H). ^13C NMR (125 MHz, CDCl_3) δ 192.4, 159.4, 157.4, 147.9, 137.0, 136.5, 130.8, 129.6, 128.9, 127.5, 127.0, 126.5, 126.2, 122.3, 120.6, 117.7, 77.4, 44.1, 42.7, 20.4. HRMS (ESI): calcd. for C_{20}H_{18}NO_{2} [M+H]^+; 304.1333, found: 304.1337.
Reference
4. $^1$H- and $^{13}$C-NMR Spectras

[Diagram of NMR spectra for 3a]

[Diagram of NMR spectra for 3a]