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Supporting information

Bi(OTf)₃-Catalyzed Addition of Isocyanides to 2H-Chromene Acetals: An Efficient Pathway for Accessing 2-Carboxamide-2H-Chromenes

Longyun Lyu, ^{*a,b*} Ming Yu Jin, ^{*a*} Qijie He, ^{*a*} Han Xie, ^{*a*} Zhaoxiang Bian^{*b*} and Jun Wang^{*a**} ^{*a*} Department of Chemistry, South University of Science and Technology of China,

Shenzhen, 518055, China; Fax: (+86) 755-88018304; E-mail: wang.j@sustc.edu.cn.

^b School of Chinese Medicine, Hong Kong Baptist University, Hong Kong

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General information

General experimental methods and instruments.

NMR Spectra were recorded on a Bruker DPX-400 or DPX-500 spectrometer at 400 MHz or 500 MHz for ¹H NMR and 100 MHz or 125 MHz for ¹³C NMR in CDCl₃. Chemical shifts are reported in δ (ppm) referenced to an internal tetramethylsilane (TMS) standard or the residual deuterated solvent peaks and coupling constants (*J*) were expressed in Hz. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Flash column chromatograph was carried out using 200-300 mesh silica gel at medium pressure or ODS-A-HG C18 reversed silica gel. High resolution mass spectra (HRMS) were recorded on a LC-TOF spectrometer. ESI-HRMS data were acquired using a Thermo LTQ Orbitrap XL Instrument equipped with an ESI source. All chemicals were purchased from Acros, Alfa Aesar and TCI, and used as received.

General procedure for synthesis of 2-carboxamide-2*H*-chromenes in Table 2 and 3.

To a solution of Bi(OTf)₃ (0.025 mmol, 0.10 equiv) in indicated solvents $(1,4\text{-dioxane:H}_2O = 10:1)$ (1.0 mL) were added chromeme acetals **1** (0.25 mmol, 1.0 equiv) and isocyanides **2** (0.375 mmol, 1.5 equiv) in sequence. Then the result mixtures were stirred at 80 °C for 20 h. After the reactions were completed, the solvent was removed under reduced pressure. The crude products were purified by silica gel chromatography (6-50% EtOAc/PE with 0.1% Et₃N) to give the desired products **3** in 66-95% yields (Table **2** and **3**).



General experimental procedure for synthesis of chromeme acetals.

To a solution of 2-hydroxybenzaldehydes (244.2 mg, 2.0 mmol) in THF (5 mL) was added (formylmethylene)triphenylphosphorane (669.5 mg, 2.2 mmol) at room temperature. The resulting reaction mixture was refluxed at 100 °C for 20 h. The reaction mixture was cooled to room temperature, and extracted with H₂O (3 mL) and EtOAc (3 x 4 mL). The combined organic phase was washed with H₂O (4 mL), brine (4 mL), dried over Na₂SO₄ and concentrated under vacuo to give the desired crude product. The crude product was purified by column chromatography (20% EtOAc/PE) to afford 2-hydroxycinnamaldehyde in 87% yields.

The 2-hydroxycinnamaldehyde was added into a solution (Dioxane:MeOH = 1:1) with 1 mol% $In(OTf)_3$ and stirred at 80 °C for 12 h. After the reactions were completed, the solvent was removed under reduced pressure. The crude products were purified by silica gel chromatography (4-10% EtOAc/PE with 5% Et₃N) to afford the chromeme acetal substrates in 91% yield.



Analytic data for the products in Table 2 and 3.



N-cyclohexyl-2*H*-chromene-2-carboxamide (3aa) was obtained in 95% yield. ¹H NMR (400 MHz, CDCl₃) δ 7.17-7.13 (m, 2H), 7.01-6.99 (m, 1H), 6.94-6.90 (m, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.51 (d, *J* = 7.2 Hz, 1H), 6.45 (dd, *J* = 10.0, 2.8 Hz, 1H), 6.00 (dd, *J* = 10.0, 2.8 Hz, 1H), 5.26 (t, *J* = 2.8 Hz, 1H), 3.87-3.78 (m, 1H), 2.04-1.96 (m, 1H), 1.90-1.86 (m, 1H), 1.77-1.59 (m, 3H), 1.45-1.30 (m, 2H), 1.28-1.12 (m, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 168.36, 151.96, 129.47, 127.02, 124.43, 122.46, 122.39, 121.58, 115.68, 75.24, 48.07, 33.02, 32.99, 25.51, 24.86, 24.83. HRMS (ESI) calcd for C₁₆H₁₉NO₂ (M+H)⁺ 258.1489, found 258.1484.



N-tert-butyl-2*H*-chromene-2-carboxamide (3ab) was obtained in 91% yield. ¹H NMR (500 MHz, CDCl₃) δ 7.16-7.13 (m, 1H), 7.02-6.98 (m, 1H), 6.95-6.91 (m, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.46 (dd, *J* = 10.0, 2.5 Hz, 2H), 6.00 (dd, *J* = 10.0, 3.0 Hz, 1H), 5.18 (d, *J* = 3.0 Hz, 1H), 1.40 (s, 9H). ¹³C NMR (125 MHz, CDCl₃) δ 168.52, 152.02, 129.50, 127.06, 124.42, 122.71, 122.44, 121.67, 115.73, 75.50, 51.36, 28.85. HRMS (ESI) calcd for C₁₄H₁₇NO₂ (M+H)⁺ 232.1332, found 232.1327.



N-butyl-2*H*-chromene-2-carboxamide (3ac) was obtained in 84% yield. ¹H NMR (500 MHz, CDCl₃) δ 7.17-7.13 (m, 1H), 7.02-6.99 (m, 1H), 6.94-6.91 (m, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.62 (s, 1H), 6.46 (dd, *J* = 9.5, 2.5 Hz, 1H), 6.00 (dd, *J* = 10.0, 3.0 Hz, 1H), 5.29 (t, *J* = 2.5 Hz, 1H), 3.37-3.29 (m, 2H), 1.56-1.50 (m, 2H), 1.39-1.32 (m, 2H), 0.93 (t, *J* = 7.5 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 169.43, 152.01, 129.58,

127.13, 124.50, 122.48, 122.39, 121.57, 115.71, 75.39, 39.10, 31.71, 20.14, 13.85. HRMS (ESI) calcd for $C_{14}H_{17}NO_2 (M+H)^+$ 232.1332, found 232.1328.



Methyl (2*H***-chromene-2-carbonyl)glycinate (3ad)** was obtained in 83% yield. ¹H NMR (400 MHz, CDCl₃) δ 7.22-7.12 (m, 2H), 7.05-6.98 (m, 1H), 6.94-6.87 (m, 2H), 6.47 (dd, J = 10.0, 2.4 Hz, 1H), 5.96 (dd, J = 10.0, 2.8 Hz, 1H), 5.35 (t, J = 2.4 Hz, 1H), 4.15 (dd, J = 18.0, 6.4 Hz, 1H), 4.04 (dd, J = 18.4, 5.2 Hz, 1H), 3.75 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 169.87, 169.85, 151.77, 129.61, 127.01, 124.71, 122.39, 121.45, 121.22, 115.73, 75.08, 52.43, 40.89. HRMS (ESI) calcd for C₁₃H₁₃NO₄ (M+H)⁺ 248.0917, found 248.0912.



Ethyl (2*H*-chromene-2-carbonyl)glycinate (3ae) was obtained in 92% yield. ¹H NMR (500 MHz, CDCl₃) δ 7.18-7.14 (m, 2H), 7.01-6.99 (m, 1H), 6.94-6.91 (m, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.48 (dd, J = 9.5, 2.5 Hz, 1H), 5.98 (dd, J = 10.0, 3.0 Hz, 1H), 5.36 (t, J = 3.0 Hz, 1H), 4.23 (q, J = 7.5 Hz, 2H), 4.15 (dd, J = 18.0, 5.5 Hz, 1H), 4.04 (dd, J = 18.5, 5.5 Hz, 1H), 1.29 (t, J = 7.0 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 169.91, 169.51, 151.91, 129.74, 127.14, 124.83, 122.52, 121.61, 121.37, 115.87, 75.22, 61.78, 41.21, 14.25. HRMS (ESI) calcd for C₁₄H₁₅NO₄ (M+H)⁺ 262.1074, found 262.1069.



N-benzyl-2*H*-chromene-2-carboxamide (3af) was obtained in 80% yield. ¹H NMR (400 MHz, CDCl₃) δ 7.34-7.23 (m, 5H), 7.13-7.09 (m, 1H), 7.03-6.95 (m, 2H), 6.93-6.88 (m, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 6.47 (dd, *J* = 9.6, 2.4 Hz, 1H), 6.02 (dd, *J*

= 9.6, 2.8 Hz, 1H), 5.35 (t, J = 2.8 Hz, 1H), 4.57-4.44 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 169.44, 151.86, 137.78, 129.56, 128.80, 127.73, 127.65, 127.06, 124.67, 122.44, 122.03, 115.73, 75.30, 43.17. HRMS (ESI) calcd for C₁₇H₁₅NO₂ (M+H)⁺ 266.1176, found 266.1174.



Diethyl (2*H***-chromene-2-carboxamido)methylphosphonate (3ag)** was obtained in 71% yield. ¹H NMR (500 MHz, CDCl₃) δ 7.18-7.15 (m, 1H), 7.02-6.99 (m, 1H), 6.98-6.91 (m, 2H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.49 (dd, *J* = 9.5, 2.0 Hz, 1H), 5.97 (dd, *J* = 10.0, 3.0 Hz, 1H), 5.38-5.32 (m, 1H), 4.17-4.06 (m, 4H), 3.77 (dd, *J* = 12.0, 7.5 Hz, 2H), 1.34-1.28 (m, 6H). ¹³C NMR (125 MHz, CDCl₃) δ 169.61, 169.56, 151.75, 129.75, 127.11, 124.86, 122.57, 121.45, 121.28, 115.85, 75.13, 62.85, 62.80, 62.75, 35.26, 34.01, 16.49, 16.46. HRMS (ESI) calcd for C₁₅H₂₀NO₅P (M+H)⁺ 326.1152, found 326.1142.



N-(tosylmethyl)-2*H*-chromene-2-carboxamide (3ah) was obtained in 85% yield. ¹H NMR (400 MHz, CDCl₃) δ 7.70-7.65 (m, 2H), 7.45-7.36 (m, 1H), 7.28-7.25 (m, 2H), 7.23-7.18 (m, 1H), 7.04-6.95 (m, 2H), 6.91 (d, J = 8.0 Hz, 1H), 6.44 (dd, J = 9.6, 2.4 Hz, 1H), 5.65 (dd, J = 10.0, 3.2 Hz, 1H), 5.17 (t, J = 2.8 Hz, 1H), 4.80 (dd, J = 14.0, 7.6 Hz, 1H), 4.62 (dd, J = 14.4, 6.4 Hz, 1H), 2.42 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 169.33, 151.49, 145.56, 133.44, 130.06, 130.02, 129.06, 127.19, 124.98, 122.83, 121.10, 120.76, 116.00, 74.82, 59.80, 21.86. HRMS (ESI) calcd for $C_{18}H_{17}NNaO_4S$ (M+Na)⁺ 366.0770 found 366.0768.



N-(2,6-dimethylphenyl)-2*H*-chromene-2-carboxamide (3ai) was obtained in 73% yield. ¹H NMR (500 MHz, CDCl₃) δ 7.88 (s, 1H), 7.20-7.17 (m, 2H), 7.14-7.05 (m, 4H), 6.98-6.95 (m, 1H), 6.93 (d, J = 8.0 Hz, 1H), 6.55 (dd, J = 9.5, 2.5 Hz, 1H), 6.08 (dd, J = 10.0, 3.5 Hz, 1H), 5.50 (t, J = 3.0 Hz, 1H), 2.20 (s, 6H). ¹³C NMR (125 MHz, CDCl₃) δ 168.17, 151.92, 135.55, 132.89, 129.80, 128.40, 127.73, 127.30, 124.82, 122.72, 122.10, 121.50, 115.82, 75.72, 18.42. HRMS (ESI) calcd for C₁₈H₁₇NO₂ (M+H)⁺ 280.1332, found 280.1325.



N-(**4-methoxyphenyl**)-*2H*-chromene-2-carboxamide (**3aj**) was obtained in 76% yield. ¹H NMR (500 MHz, CDCl₃) δ 8.25 (s, 1H), 7.51-7.48 (m, 2H), 7.21-7.17 (m, 1H), 7.05-7.03 (m, 1H), 6.98-6.93 (m, 2H), 6.90-6.87 (m, 2H), 6.52 (dd, *J* = 10.0, 3.0 Hz, 1H), 6.06 (dd, *J* = 10.0, 3.0 Hz, 1H), 5.42 (t, *J* = 3.0 Hz, 1H), 3.80 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 167.32, 156.92, 151.81, 130.14, 129.75, 127.26, 124.89, 122.78, 122.05, 121.94, 121.58, 115.85, 114.37, 75.48, 55.63. HRMS (ESI) calcd for C₁₇H₁₅NO₃ (M+H)⁺ 282.1125, found 282.1125.



N-cyclohexyl-6-methyl-2*H*-chromene-2-carboxamide (3ba) was obtained in 89% yield. ¹H NMR (400 MHz, CDCl₃) δ 6.98-6.92 (m, 1H), 6.82 (d, *J* = 2.0 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.51 (d, *J* = 7.2 Hz, 1H), 6.42 (dd, *J* = 10.0, 2.8 Hz, 1H), 5.98 (dd, *J* = 9.6, 2.8 Hz, 1H), 5.22 (t, *J* = 2.4 Hz, 1H), 3.87-3.77 (m, 1H), 2.26 (s, 3H), 1.99-1.95 (m, 1H), 1.89-1.86 (m, 1H), 1.76-1.60 (m, 3H), 1.45-1.30 (m, 2H), 1.28-1.12 (m, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 168.60, 149.86, 131.76, 129.89,

127.55, 124.63, 122.59, 121.44, 115.43, 75.28, 48.12, 33.10, 33.07, 25.59, 24.89, 20.65. HRMS (ESI) calcd for C₁₇H₂₁NO₂ (M+H)⁺ 272.1645, found 272.1638.



N-cyclohexyl-8-methyl-2*H*-chromene-2-carboxamide (3ca) was obtained in 75% yield. ¹H NMR (400 MHz, CDCl₃) δ 7.03-7.01 (m, 1H), 6.87-6.81 (m, 2H), 6.52 (d, J = 7.2 Hz, 1H), 6.44 (dd, J = 10.0, 2.8 Hz, 1H), 5.98 (dd, J = 10.0, 2.8 Hz, 1H), 5.28 (t, J = 2.8 Hz, 1H), 3.88-3.79 (m, 1H), 2.23 (s, 3H), 2.01-1.94 (m, 1H), 1.92-1.84 (m, 1H), 1.77-1.56 (m, 3H), 1.47-1.32 (m, 2H), 1.28-1.12 (m, 4H). ¹³C NMR (100 MHz, CDCl₃) δ 168.68, 149.91, 131.22, 124.87, 124.78, 124.73, 122.01, 121.83, 121.08, 75.40, 47.92, 33.04, 32.99, 25.59, 24.76, 24.72, 15.60. HRMS (ESI) calcd for C₁₇H₂₁NO₂ (M+H)⁺ 272.1645, found 272.1639.



N-cyclohexyl-7-methoxy-2*H*-chromene-2-carboxamide (3da) was obtained in 86 % yield. ¹H NMR (400 MHz, CDCl₃) δ 6.92 (d, *J* = 8.0 Hz, 1H), 6.51-6.45 (m, 3H), 6.41 (dd, *J* = 10.0, 2.4 Hz, 1H), 5.85 (dd, *J* = 10.0, 4.0 Hz, 1H), 5.23 (t, *J* = 2.8 Hz, 1H), 3.80 (s, 3H), 2.03-1.94 (m, 1H), 1.93-1.84 (m, 1H), 1.79-1.58 (m, 3H), 1.45-1.31 (m, 2H), 1.26-1.12 (m, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 168.57, 160.92, 153.23, 127.74, 124.15, 119.46, 114.90, 107.80, 102.04, 75.42, 55.57, 48.14, 33.12, 33.08, 25.60, 24.93, 24.90. HRMS (ESI) calcd for C₁₇H₂₁NO₃ (M+H)⁺ 288.1594, found 288.1586.



N-cyclohexyl-5-methoxy-2*H*-chromene-2-carboxamide (3ea) was obtained in 73% yield. ¹H NMR (400 MHz, CDCl₃) δ 7.09 (t, J = 8.4 Hz, 1H), 6.80 (dd, J = 10.0, 2.8 Hz, 1H), 6.55-6.45 (m, 3H), 5.92 (dd, J = 10.0, 3.2 Hz, 1H), 5.19 (t, J = 2.8 Hz, 1H), 3.82 (s, 3H), 2.02-1.93 (m, 1H), 1.92-1.83 (m, 1H), 1.78-1.57 (m, 3H), 1.45-1.31 (m, 2H), 1.29-1.11 (m, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 168.52, 155.56, 152.75, 129.45, 120.48, 119.26, 111.14, 108.62, 104.61, 74.85, 55.79, 48.06, 33.05, 33.01, 25.55, 24.88, 24.85. HRMS (ESI) calcd for C₁₇H₂₁NO₃ (M+H)⁺ 288.1594, found 288.1586.



7-bromo-*N***-cyclohexyl-***2H***-chromene-2-carboxamide** (**3fa**) was obtained in 86 % yield. ¹H NMR (500 MHz, CDCl₃) δ 7.24 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.13 (d, *J* = 2.0 Hz, 1H), 6.76 (d, *J* = 7.5 Hz, 1H), 6.44-6.38 (m, 2H), 6.05 (dd, *J* = 10.0, 3.0 Hz, 1H), 5.26 (t, *J* = 2.5 Hz, 1H), 3.86-3.78 (m, 1H), 2.02-1.94 (m, 1H), 1.93-1.84 (m, 1H), 1.80-1.57 (m, 3H), 1.45-1.31 (m, 2H), 1.29-1.12 (m, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 167.89, 151.06, 132.03, 129.55, 123.86, 123.49, 117.50, 114.53, 75.38, 48.25, 33.07, 25.55, 24.89. HRMS (ESI) calcd for C₁₆H₁₈BrNO₂ (M+H)⁺ 336.0594, found 336.0592.



N-cyclohexyl-6-(trifluoromethyl)-2*H*-chromene-2-carboxamide (3ga) was obtained in 23% yield. ¹H NMR (500 MHz, CDCl₃) δ 7.41 (d, *J* = 8.4 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.48 (d, *J* = 10.0 Hz, 1H), 6.42 (d, *J* = 6.5 Hz, 1H), 6.10 (d, *J* =

10.0 Hz, 1H), 5.33 (s, 1H), 3.88-3.78 (m, 1H), 1.99 (d, J = 11.4 Hz, 1H), 1.89 (d, J = 11.6 Hz, 1H), 1.79-1.59 (m, 3H), 1.46-1.32 (m, 2H), 1.28-1.13 (m, 3H). ³C NMR (125 MHz, CDCl₃) δ 167.65, 154.51, 126.67 (q, J = 3.75 Hz), 124.82 (q, J = 32.5 Hz), 124.19 (q, J = 3.75 Hz), 124.11 (q, J = 270.0 Hz), 123.88, 123.50, 116.08, 75.70, 48.33, 33.11, 33.09, 25.55, 24.93, 24.90. HRMS (ESI) calcd for C₁₇H₁₉F₃NO₂ (M+H)+ 326.1362, found 326.1355.



N-cyclohexyl-6-fluoro-2*H*-chromene-2-carboxamide (3ha) was obtained in 66% yield. ¹H NMR (400 MHz, CDCl₃) δ 6.99-6.92 (m, 1H), 6.67-6.95 (m, 2H), 6.43 (dd, J = 10.0, 2.8 Hz, 2H), 5.95 (dd, J = 10.0, 2.8 Hz, 1H), 5.26 (t, J = 2.8 Hz, 1H), 3.87-3.78 (m, 1H), 2.02-1.94 (m, 1H), 1.93-1.84 (m, 1H), 1.80-1.57 (m, 3H), 1.45-1.34 (m, 2H), 1.28-1.13 (m, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 167.97, 164.36, 161.89, 153.12 (d, $J_{CF} = 12.0$ Hz), 127.88 (d, $J_{CF} = 9.0$ Hz), 123.64, 121.21 (d, $J_{CF} = 3.0$ Hz), 117.90 (d, $J_{CF} = 4.0$ Hz), 109.15 (d, $J_{CF} = 21.0$ Hz), 103.86 (d, $J_{CF} = 26.0$ Hz), 75.34, 48.19, 33.04, 33.02, 25.52, 24.88, 24.86. HRMS (ESI) calcd for C₁₆H₁₈FNO₂ (M+H)⁺ 276.1394, found 276.1396.

Copies of ¹H, ¹³C spectra in Table 2 and 3.













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3af (400 Hz, CDCl₃)

























