ONE POT, CATALYST-FREE SYNTHESIS OF SPIROOXINDOLE AND 4H-PYRAN DERIVATIVES

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SUPPORTING INFORMATION

GENERAL

All solvents were purchased from commercial sources and used without further purification. ¹H NMR spectra were recorded on 400 MHz and ¹³C NMR spectra were recorded on 100 MHz in DMSO-*d*₆ or CDCl₃ using 400 MHz spectrometer. Chemical shifts are reported in δ (ppm) relative to TMS. Electrospray ionization (ESI) mass spectra were obtained on Agilent mass spectrometer. Infrared spectra were recorded on a Shimadzu FT-IR instrument (KBr pellet) and the band positions are reported in reciprocal of centimeters (cm⁻¹). Melting points were determined on a melting point apparatus (Inlab Pvt Ltd, India) equipped with a thermometer and were uncorrected. Elemental analyses were performed on a Perkin-Elmer 2400 Series II Elemental CHNS analyzer. Silica gel-G plates (Merck) were used for TLC.

Synthesis of 2-amino-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4-phenyl-4H-chromene-3-carbonitrile (4b)^[1] A mixture of benzaldehyde (0.5 g, 4.7 mmol), malononitrile (0.34 g, 5.2 mmol) and dimedone (0.66 g, 4.7 mmol) in DMSO (7 mL) was stirred at room temperature for 1.5 h. The resulting mixture was poured into ice, stirred for 15 min, the solid obtained was filtered and washed with water and diethyl ether to afford pure product (1.3 g, 96%) as a white powder. Mp 228-230 °C; ESI-m/z calcd for [C₁₈H₁₈N₂O₂ + H]⁺ 295.1, found 295.1.

Synthesis of 2-amino-4-(4-chlorophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile (4c)^[2] A mixture of 4-chloro benzaldehyde (0.5 g, 3.6 mmol),

malononitrile (0.26 g, 3.9 mmol) and dimedone (0.50 g, 3.6 mmol) in DMSO (5 mL) was stirred at room temperature for 1.5 h. The resulting mixture was poured into ice, stirred for 15 min, the solid obtained was filtered and washed with water and diethyl ether to afford pure product (1.2 g, 98%) as a white solid. Mp 238-240 °C; δ_{H} (400 MHz, DMSO- d_6) 0.95 (s, 3H), 1.03 (s, 3H), 2.10 (d, J = 16.1 Hz, 1H), 2.25 (d, J = 16.1 Hz, 1H), 2.45 (s, 2H), 4.19 (s, 1H), 7.08 (s, 2H), 7.17 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H); ESI-m/z calcd for $[\text{C}_{18}\text{H}_{17}\text{ClN}_2\text{O}_2 + \text{H}]^+$ 329.1, found 329.1.

Synthesis of 2-amino-4-(4-nitrophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile (4d)^[2] A mixture of 4-nitro benzaldehyde (0.5 g, 3.3 mmol), malononitrile (0.24 g, 3.6 mmol) and dimedone (0.46 g, 3.3 mmol) in DMSO (5 mL) was stirred at room temperature for 1 h. The resulting mixture was poured into ice, stirred for 15 min, the solid obtained was filtered and washed with water and diethyl ether to afford pure product (1.0 g, 90%) as a yellow solid. Mp 177-179 °C; ESI-m/z calcd for $[\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_4 - \text{H}]^+$ 338.1, found 338.1.

Synthesis of 2-amino-4-(4-methoxyphenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile (4e)^[2] A mixture of p-anisaldehyde (0.5 g, 3.7 mmol), malononitrile (0.27 g, 4.0 mmol) and dimedone (0.51 g, 3.7 mmol) in DMSO (5 mL) was stirred at room temperature for 5 h. The resulting mixture was poured into ice, stirred for 15 min, the solid obtained was filtered and washed with water and diethyl ether to afford pure product (1.0 g, 90%) as a yellow solid. Mp 195-197 °C; ESI-m/z calcd for $[\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_3 + \text{H}]^+$ 325.1, found 325.1.

Synthesis of 2-amino-4-(4-methylphenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile (4f)^[2] A mixture of p-tolualdehyde (0.5 g, 4.2 mmol), malononitrile (0.30 g, 4.6 mmol) and dimedone (0.58 g, 4.2 mmol) in DMSO (7 mL) was stirred at room temperature for 2 h. The resulting mixture was poured into ice, stirred for 15

min, the solid obtained was filtered and washed with water and diethyl ether to afford pure product (1.0 g, 90%) as a light yellow solid. Mp 217-219 °C; IR ν_{max} (KBr) 3425, 3330, 3194, 2192, 1675, 1638, 1602, 1511, 1463, 1440, 1408, 1368 cm^{-1} ; δ_{H} (400 MHz, DMSO- d_6) 0.94 (s, 3H), 1.03 (s, 3H), 2.08 (d, $J = 16.1$ Hz, 1H), 2.25 (d, $J = 16.1$ Hz, 1H), 2.26 (s, 3H), 4.12 (s, 1H), 6.97 (s, 2H), 7.01 (d, $J = 7.9$ Hz, 2H), 7.08 (d, $J = 7.9$ Hz, 2H); ESI-m/z calcd for $[\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_2 - \text{H}]^+$ 307.1, found 307.1.

Synthesis of 3-(2-amino-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4H-chromen-4-yl)benzoic acid (4g) A mixture of 3-carboxy benzaldehyde (0.5 g, 3.3 mmol), malononitrile (0.24 g, 3.7 mmol) and dimedone (0.47 g, 3.3 mmol) in DMSO (7 mL) was stirred at room temperature for 1 h. The resulting mixture was poured into ice, stirred for 15 min, the solid obtained was filtered and washed with water and diethyl ether to afford pure product (1.0 g, 92%) as a whit solid. Mp 238-240 °C; IR ν_{max} (KBr) 3374, 3322, 3192, 2962, 2193, 1706, 1681, 1657 cm^{-1} ; δ_{H} (400 MHz, DMSO- d_6) 0.95 (s, 3H), 1.04 (s, 3H), 2.09 (d, $J = 16.1$ Hz, 1H), 2.26 (d, $J = 16.1$ Hz, 1H), 2.51-2.54 (m, 2H), 4.26 (s, 1H), 7.09 (s, 2H), 7.41-7.43 (m, 2H), 7.72 (s, 1H), 7.76-7.78 (m, 1H), 12.96 (s, 1H); δ_{C} (100 MHz, DMSO- d_6) 26.6, 28.5, 31.9, 35.6, 49.9, 57.9, 112.4, 119.6, 127.7, 128.0, 128.7, 131.0, 131.9, 145.3, 158.6, 162.8, 167.3, 195.7; Anal. Calcd. For $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.48; H, 5.38; N, 8.30%; ESI-m/z calcd for $[\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_4 + \text{H}]^+$ 339.1, found 339.1.

Synthesis of 2-amino-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4-(thiophene-2-yl)-4H-chromene-3-carbonitrile (4h)^[3] A mixture of 2-thiophenecarboxaldehyde (0.5 g, 4.5 mmol), malononitrile (0.32 g, 4.9 mmol) and dimedone (0.63 g, 4.2 mmol) in DMSO (7 mL) was stirred at room temperature for 2 h. The resulting mixture was poured into ice, stirred for 15 min, the solid obtained was filtered and washed with water and diethyl ether to afford pure product (1.1 g, 88%) as a yellow solid. Mp 217-219 °C; ESI-m/z calcd for $[\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2\text{S} + \text{H}]^+$ 301.1, found 301.1.

Synthesis of 4-(1-actyl-1*H*-indol-3-yl)-2-amino-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4*H*-chromene-3-carbonitrile (4i) A mixture of 1-actyl-1*H*-indole-3-carbaldehyde (0.5 g, 2.7 mmol), malononitrile (0.20 g, 2.9 mmol) and dimedone (0.37 g, 2.7 mmol) in DMSO (7 mL) was stirred at room temperature for 3 h. The resulting mixture was poured into ice, stirred for 15 min, the solid obtained was filtered and washed with water and diethyl ether to afford pure product (0.87 g, 87%) as a light yellow solid. Mp 206-208 °C; δ_{H} (400 MHz, DMSO-*d*₆) 0.88 (s, 3H), 1.04 (s, 3H), 2.10 (d, *J* = 16.1 Hz, 1H), 2.25 (d, *J* = 16.1 Hz, 1H), 2.54-2.59 (m, 2H), 2.62 (s, 3H), 4.55 (s, 1H), 7.07 (s, 2H), 7.23-7.27 (m, 1H), 7.29-7.33 (m, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.66 (s, 1H), 8.32 (d, *J* = 8.2 Hz, 1H); δ_{C} (100 MHz, DMSO-*d*₆) 24.3, 27.1, 27.5, 28.8, 32.1, 50.4, 57.1, 111.6, 116.5, 119.2, 120.1, 123.6, 124.2, 124.6, 125.0, 128.8, 135.9, 159.3, 163.1, 169.7, 196.1; Anal. Calcd. For C₂₂H₂₁N₃O₃: C, 70.38; H, 5.64; N, 11.19. Found: C, 70.43; H, 5.66; N, 11.21%; ESI-m/z calcd for [C₂₂H₂₁N₃O₃ + H]⁺ 376.1, found 376.1.

Synthesis of 2-amino-4-(4-chlorophenyl)-5,6,7,8-tetrahydro-5-oxo-4*H*-chromene-3-carbonitrile (4j)^[2] A mixture of 4-chloro benzaldehyde (0.5 g, 3.6 mmol), malononitrile (0.28 g, 4.3 mmol) and cyclohexane-1,3-dione (0.4 g, 3.6 mmol) in DMSO (7 mL) was stirred at 70 °C for 10 h. The resulting mixture was poured into ice, stirred for 15 min, the solid obtained was filtered and washed with water and diethyl ether to afford pure product (0.79 g, 72%) as a white solid. Mp 225-227 °C; δ_{H} (400 MHz, DMSO-*d*₆) 1.90-1.95 (m, 2H), 2.22-2.30 (m, 2H), 2.61 (br, 2H), 4.20 (s, 1H), 7.06 (s, 2H), 7.18 (d, *J* = 7.7 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 2H); δ_{C} (100 MHz, DMSO-*d*₆) 19.8, 26.5, 35.0, 36.3, 57.7, 113.4, 119.6, 128.3, 129.1, 131.1, 143.8, 158.5, 164.6, 195.9; ESI-m/z calcd for [C₁₆H₁₃ClN₂O₂ + H]⁺ 301.1, found 301.1.

Synthesis of 2-amino-4-(4-chlorophenyl)-4,5-dihydro-5-oxopyrano[3,2-*c*]chromene-3-carbonitrile (4k)^[4] A mixture of 4-chloro benzaldehyde (0.5 g, 3.6 mmol), malononitrile (0.28 g, 4.3 mmol) and 4-hydroxycoumarin (0.58 g, 3.6 mmol) in DMSO (7 mL) was stirred

at 70 °C for 3 h. The resulting mixture was poured into ice, stirred for 15 min, the solid obtained was filtered and washed with water and diethyl ether to afford pure product (1.1 g, 88%) as a white solid. Mp 259-261 °C; δ_{H} (400 MHz, DMSO- d_6) 4.49 (s, 1H), 7.30 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.46-7.52 (m, 4H), 7.71-7.75 (m, 1H), 7.70 (dd, J = 7.9 Hz, 1.2 Hz, 1H); ESI-m/z calcd for $[\text{C}_{19}\text{H}_{11}\text{ClN}_2\text{O}_3 + \text{H}]^+$ 350.1, found 350.1.

Synthesis of 2-amino-4,5-dihydro-5-oxo-4-*p*-tolylpyrano[3,2-*c*]chromene-3-carbonitrile (4l)^[4] A mixture of *p*-tolualdehyde (0.5 g, 4.2 mmol), malononitrile (0.33 g, 5.0 mmol) and 4-hydroxycoumarin (0.68 g, 4.2 mmol) in DMSO (10 mL) was stirred at 70 °C for 6 h. The resulting mixture was poured into ice, stirred for 15 min, the solid obtained was filtered and washed with water and diethyl ether to afford pure product (1.1 g, 78%) as a white solid. Mp 254-256 °C; ESI-m/z calcd for $[\text{C}_{20}\text{H}_{14}\text{N}_2\text{O}_3 + \text{H}]^+$ 331.1, found 331.1.

Synthesis of 2-amino-4,5-dihydro-5-oxo-4-phenylpyrano[3,2-*c*]chromene-3-carbonitrile (4m) A mixture of vanillin (0.5 g, 3.3 mmol), malononitrile (0.26 g, 3.9 mmol) and 4-hydroxycoumarin (0.53 g, 3.3 mmol) in DMSO (10 mL) was stirred at 70 °C for 10 h. The resulting mixture was poured into ice, stirred for 15 min, the solid obtained was filtered and washed with water and diethyl ether to afford pure product (0.78 g, 62%) as a yellow solid. Mp 241-243 °C; δ_{H} (400 MHz, DMSO- d_6) 3.73 (s, 3H), 4.36 (s, 1H), 6.59-6.62 (m, 1H), 6.70 (d, J = 8.1 Hz, 1H), 6.81 (d, J = 1.2 Hz, 1H), 7.34 (s, 2H), 7.45-7.51 (m, 2H), 7.69-7.73 (m, 1H), 7.89 (dd, J = 7.9, 1.2 Hz, 1H), 8.93 (br s, 1H); δ_{C} (100 MHz, DMSO- d_6) 36.5, 55.7, 58.3, 104.3, 112.1, 113.1, 115.5, 116.5, 119.4, 119.9, 122.4, 124.6, 132.8, 134.3, 145.7, 147.3, 152.1, 153.0, 157.9, 159.6; Anal. Calcd. For $\text{C}_{20}\text{H}_{14}\text{N}_2\text{O}_5$: C, 66.30; H, 3.89; N, 7.73. Found: C, 66.35; H, 3.90; N, 7.75%; ESI-m/z calcd for $[\text{C}_{20}\text{H}_{14}\text{N}_2\text{O}_5 + \text{H}]^+$ 363.1, found 363.1.

Synthesis of 2-amino-4,5-dihydro-5-oxo-4-phenylpyrano[3,2-*c*]chromene-3-carbonitrile (4n)^[4] A mixture of benzaldehyde (0.5 g, 4.7 mmol), malononitrile (0.37 g, 5.7 mmol) and 4-

hydroxycoumarin (0.76 g, 4.7 mmol) in DMSO (10 mL) was stirred at 70 °C for 10 h. The resulting mixture was poured into ice, stirred for 15 min, the solid obtained was filtered and washed with water and diethyl ether to afford pure product (1.1 g, 78%) as a white solid. Mp 257-259 °C; ESI-m/z calcd for $[C_{19}H_{12}N_2O_3 + H]^+$ 317.1, found 317.1.

Synthesis of 2-amino-4,5-dihydro-5-oxo-4-(thiophene-2-yl)pyrano[3,2-c]chromene-3-carbonitrile (4o)^[5] A mixture of 2-thiophenecarbaldehyde (0.5 g, 4.5 mmol), malononitrile (0.35 g, 5.4 mmol) and 4-hydroxycoumarin (0.72 g, 4.5 mmol) in DMSO (10 mL) was stirred at 70 °C for 10 h. The resulting mixture was poured into ice, stirred for 15 min, the solid obtained was filtered and washed with water and diethyl ether to afford pure product (1.1 g, 78%) as a yellow solid. Mp 229-231 °C; δ_H (400 MHz, DMSO- d_6) 4.84 (s, 1H), 6.98 (t, J = 3.6 Hz, 1H), 7.05 (d, J = 2.9 Hz, 1H), 7.23-7.28 (m, 1H), 7.40-7.55 (m, 4H), 7.67-7.74 (m, 1H), 7.85-7.90 (m, 1H); δ_C (100 MHz, DMSO- d_6) 31.9, 57.8, 104.1, 112.8, 116.7, 119.1, 122.5, 124.8, 125.2, 127.1, 133.1, 147.5, 152.1, 153.0, 158.4, 159.5; ESI-m/z calcd for $[C_{17}H_{10}N_2O_3S + H]^+$ 323.0, found 323.0.

Synthesis of 2-amino-7,7-dimethyl-2',5-dioxo-4,5-dihydrospiro[chromene-4,3'-indoline]-3-carbonitrile (6b)^[6] A mixture of isatin (0.5 g, 3.4 mmol), malononitrile (0.27 g, 4.1 mmol) and cyclohexane-1,3-dione (0.38 g, 3.4 mmol) in DMSO (5 mL) was stirred at 70 °C for 1 h. The resulting mixture was poured into ice, stirred for 15 min, the solid obtained was filtered and washed with water and diethyl ether to afford pure product (0.77 g, 74%) as a pale yellow solid. Mp 252-254 °C, δ_H (400 MHz, DMSO- d_6) 1.91-1.95 (m, 2H), 2.20-2.25 (m, 2H), 2.26 (t, J = 5.7 Hz, 2H), 6.77 (d, J = 7.7 Hz, 1H), 6.88 (t, J = 7.4 Hz, 1H), 6.99 (d, J = 7.2 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 7.22 (s, 2H), 10.39 (s, 1H); ESI-m/z calcd for $[C_{17}H_{13}N_3O_3 + H]^+$ 308.1, found 308.1.

2'-Amino-9'-methyl-2,5'-dioxo-5'H-spiro[indoline-3,4'-pyrano[3,2-c]chromene]-3'-carbonitrile (7a) A mixture of isatin (0.5 g, 3.4 mmol), malononitrile (0.27 g, 4.1 mmol) and

4-hydroxy-6-methyl-coumarin (0.60 g, 3.4 mmol) in DMSO (7 mL) was stirred at 70 °C for 6 h. The resulting mixture was poured into ice, stirred for 15 min, the solid obtained was filtered and washed with water and diethyl ether to afford pure product (0.95 g, 75%) as a white solid. Mp >300 °C; IR $\nu_{\max}$ (KBr) 3458, 3364, 3255, 3135, 2193, 1719, 1707, 1670, 1621, 1591, 1496, 1482, 1471 cm^{-1} ; δ_{H} (400 MHz, DMSO- d_6) 2.44 (s, 3H), 6.86 (d, J = 7.7 Hz, 1H), 6.94 (t, J = 7.4 Hz, 1H), 7.18-7.24 (m, 2H), 7.38 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.66 (s, 2H), 7.76 (s, 1H), 10.69 (s, 1H); δ_{C} (100 MHz, DMSO- d_6) 20.6, 47.65, 57.0, 101.4, 109.5, 112.2, 116.5, 117.0, 122.1, 122.2, 124.1, 128.9, 133.2, 134.4, 134.5, 142.2, 150.3, 155.0, 158.4, 158.5, 177.2; Anal. Calcd. For $\text{C}_{21}\text{H}_{13}\text{N}_3\text{O}_4$: C, 67.92; H, 3.53; N, 11.32. Found: C, 67.98; H, 3.54; N, 11.34%; ESI-m/z calcd for $[\text{C}_{21}\text{H}_{13}\text{N}_3\text{O}_4 + \text{H}]^+$ 372.1, found 372.1.

2'-Amino-2,5'-dioxo-5'*H*-spiro[indoline-3,4'-pyrano[3,2-*c*]chromene]-3'-carbonitrile

(7b)^[7] A mixture of isatin (0.5 g, 3.4 mmol), malononitrile (0.27 g, 4.1 mmol) and 4-hydroxy-coumarin (0.55 g, 3.4 mmol) in DMSO (7 mL) was stirred at 70 °C for 6 h. The resulting mixture was poured into ice, stirred for 15 min, the solid obtained was filtered and washed with water and diethyl ether to afford pure product (0.92 g, 76%) as a white solid. Mp 291-293 °C, ESI-m/z calcd for $[\text{C}_{20}\text{H}_{11}\text{N}_3\text{O}_4 + \text{H}]^+$ 358.1, found 358.1.

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^1H NMR spectrum of **4a**

^{13}C NMR spectrum of **4a**

¹H NMR spectrum of **4g**

¹³C NMR spectrum of **4g**

¹H NMR spectrum of 4m

¹³C NMR spectrum of 4m

¹H NMR spectrum of **6a**

¹³C NMR spectrum of **6a**

¹H NMR spectrum of **7a**

¹³C NMR spectrum of **7a**