Supporting Information

Synthesis of Polysubstituted 4,5,6,7-Tetrahydrofuro[2,3-*c*]pyridines by a Novel Multicomponent Reaction

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General procedure for the three-component synthesis of tetrahydro furopyridin (**1**).

A solution of amine (**2**) (1 eq.) and aldehyde (**3**) (1.2 eq.) in dry toluene (0.1 M) was stirred at room temperature in the presence of one equivalent of NH₄Cl for 1h. α -isocyanoacetamide (**4**) (1.2 eq.) was added and the reaction mixture was heated to reflux. The reaction was monitored by TLC (typically 15 h). The reaction mixture was cooled to room temperature and toluene was removed under reduce pressure. After dilution with water, the product was extracted with dichloromethane. The combined organic extracts were washed with brine, dried over Na₂SO₄ and the solvent was removed under reduced pressure. The crude was purified by either preparative TLC (silica gel) or flash chromatography (silica gel). Eluent Heptane/AcOEt (typically 2/1 to 1/1).

Yellow oil, yield: 82 %; IR (CHCl₃) ν 3087, 3065, 2958, 2931, 2859, 1686, 1573, 1449, 1367, 1271, 1115, 1085 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.75 (t, *J* = 6.8 Hz, 3H), 1.14-1.30 (m, 8H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.55-1.61 (m, 2H), 2.43 (m, 1H), 2.65 (m, 2H), 2.94 (m, 1H), 3.29 (t, *J* = 6.3 Hz, 1H), 3.32-3.46 (m, 4H), 3.54 (d, *J* = 13.5 Hz, 1H), 3.69 (d, *J* = 13.5 Hz, 1H), 3.75 (t, *J* = 4.6 Hz, 4H), 4.14 (qd, *J* = 7.1 et 1.6 Hz, 2H), 7.17-7.31 (m, 5H); ¹³C NMR (62.5 MHz, CDCl₃) δ 14.1, 14.4, 21.0, 22.6, 25.7, 29.3, 31.9, 32.9, 44.9, 48.8 (2C), 56.4, 57.3, 59.5, 66.7 (2C), 94.3, 115.9, 126.9, 128.0 (2C), 128.8 (2C), 139.6, 143.3, 161.2, 164.2; MS (IE) *m/z* 369 [M-C₆H₁₃]⁺, 455 [M+1]⁺; HRMS *m/z calcd. for*: [M-1]⁺ 453.2753, [M] 454.2832, *m/z found for*: [M-1]⁺ 453.2736, [M] 454.2808; MICRO-ANALYSE: *calcd. for* C₂₇H₃₈N₂O₄: % C 71.34 % H 8.43 % N 6.16, *found*: % C 71.23 % H 8.47 % N 5.93.

Yellow oil, yield: 65 %; IR (CHCl₃) ν 3003, 2942, 2863, 1687, 1573, 1450, 1272, 1171, 1115, 1084, 1070 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.47 (t, J = 7.0 Hz, 3H), 2.15 (m, 2H), 2.64-2.93 (m, 5H), 3.20 (m, 1H), 3.53-3.69 (m, 5H), 3.79 (d, J = 13.4 Hz, 1H), 3.94 (d, J = 13.4 Hz, 1H), 3.98 (m, 4H), 4.38 (q, J = 7.0 Hz, 2H), 7.25-7.56 (m, 10H); ¹³C NMR (62.5 MHz, CDCl₃) δ 14.4, 21.0, 31.9, 34.6, 44.9, 48.8 (2C), 56.2, 57.4, 59.5, 66.6 (2C), 94.3, 116.4, 125.6, 127.0, 128.3, 128.4, 128.9, 139.5, 142.5, 142.7, 161.2, 164.2; MS (ESI) 473.3 [M-H]⁺, 475.3 [M+1]⁺; MS (IE) m/z 369 [M-C₂H₄Ph]⁺, 474 [M]⁺; HRMS m/z *calcd. for*: [M+1]⁺ 475.2597, [M+Na]⁺ 497.2416, m/z *found for*: [M+1]⁺ 475.2583, [M+Na]⁺ 497.2408.

Yellow oil, yield: 80 %; IR (CHCl₃) ν 2960, 2867, 1686, 1573, 1494, 1448, 1367, 1296, 1271, 1171, 1115, 1087 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.81 (d, J = 6.7 Hz, 3H), 0.93 (d, J = 6.7 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H), 1.81 (m, 1H), 2.40 (m, 1H), 2.63-2.73 (m, 2H), 2.87 (d, J = 8.2 Hz, 1H), 2.92 (m, 1H), 3.32-3.47 (m, 4H), 3.57 (s, 2H), 3.75 (t, J = 4.7 Hz, 4H), 4.15 (q, J = 7.2 Hz, 2H), 7.17-7.31 (m, 5H); ¹³C NMR (62.5 MHz, CDCl₃) δ 14.6, 19.5, 20.7, 20.9, 32.7, 44.3, 48.9 (2C), 57.9, 59.8, 63.1, 66.8 (2C), 94.4, 116.6, 127.0, 128.2 (2C), 128.9 (2C), 139.9, 143.2, 161.3, 164.4; MS (ESI) 413.2 [M+H]⁺; HRMS m/z *calcd. for*: [M+Na]⁺ 435.2260, m/z *found*: 435.2259; MICRO-ANALYSE: *calcd. for* C₂₄H₃₂N₂O₄: % C 69.88 % H 7.82 % N 6.79, *found*: % C 69.77 % H 8.04 % N 6.61.

Yellow oil, yield: 78 %; IR (CHCl₃) ν 2940, 2859, 1732, 1684, 1642, 1572, 1445, 1261, 1084, 1916 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.86 (t, J = 6.9 Hz, 3H), 1.22-1.37 (m, 8H), 1.30 (t, J = 7.2 Hz, 3H), 1.59-1.70 (m, 8H), 2.49 (m, 1H), 2.70 (m, 2H), 3.01 (m, 1H), 3.34 (t, J = 5.8

Hz, 1H), 3.36-3.41 (m, 4H), 3.61 (d, $J = 13.5$ Hz, 1H), 3.76 (d, $J = 13.5$ Hz, 1H), 4.21 (qd, $J = 7.1$ et 1.4 Hz, 2H), 7.24-7.38 (m, 5H); ^{13}C NMR (62.5 MHz, CDCl_3) δ 14.1, 14.5, 21.1, 22.5, 24.6, 25.7 (2C), 29.3, 31.7, 32.9, 45.0, 49.9 (2C), 56.4, 57.3, 59.2, 92.9, 115.7, 126.8, 128.4 (2C), 128.7 (2C), 139.7, 142.4, 161.1, 164.4; MS (ESI) 453.3 $[\text{M}+\text{H}]^+$; HRMS m/z *calcd. for*: $[\text{M}+\text{H}]^+$ 453.3117, m/z *found*: 453.3115.

Yellow oil, yield: 64 %; IR (CHCl_3) ν 3045, 3022, 2981, 2875, 1681, 1647, 1575, 1453, 1341, 1260, 1148, 1084 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 0.81 (d, $J = 6.7$ Hz, 3H), 1.00 (d, $J = 6.7$ Hz, 3H), 1.31 (t, $J = 7.2$ Hz, 3H), 1.90-1.95 (m, 5H), 2.45 (m, 1H), 2.68-2.81 (m, 2H), 2.90 (d, $J = 8.2$ Hz, 1H), 3.03 (m, 1H), 3.57 (m, 4H), 3.64 (s, 2H), 4.20 (q, $J = 7.2$ Hz, 2H), 7.23-7.38 (m, 5H); ^{13}C NMR (62.5 MHz, CDCl_3) δ 14.7, 19.2, 20.8, 20.9, 25.6 (2C), 33.0, 44.4, 49.8 (2C), 57.9, 59.1, 62.1, 88.9, 116.2, 126.9, 128.2 (2C), 129.2 (2C), 140.1, 141.2, 160.2, 164.8; MS (ESI) 397.1 $[\text{M}+\text{H}]^+$; HRMS m/z *calcd. for* $[\text{M}+\text{H}]^+$ 397.2491, m/z *found*: 397.2479.

Yellow oil, yield: 55 %; IR (CHCl_3) ν 2934, 1685, 1602, 1572, 1448, 1261, 1084 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 0.86 (t, $J = 6.8$ Hz, 3H), 1.17 (t, $J = 7.1$ Hz, 6H), 1.22-1.36 (m, 8H), 1.30 (t, $J = 7.0$ Hz, 3H), 1.59-1.68 (m, 2H), 2.49 (m, 1H), 2.69 (m, 2H), 3.02 (m, 1H), 3.34 (t, $J = 6.1$ Hz, 1H), 3.37-3.53 (m, 4H), 3.59 (d, $J = 13.5$ Hz, 1H), 3.78 (d, $J = 13.5$ Hz, 1H), 4.20 (q, $J = 7.1$ Hz, 2H), 7.24-7.38 (m, 5H); ^{13}C NMR (62.5 MHz, CDCl_3) δ 13.3 (2C), 14.1, 14.5, 21.5, 22.6, 25.7, 29.3, 31.9, 32.9, 44.7 (2C), 45.3, 56.5, 57.3, 59.1, 92.1, 115.9, 126.8, 128.4 (2C), 128.8 (2C), 139.8, 141.9, 161.2, 164.4; MS (ESI) 441.2 $[\text{M}+\text{H}]^+$; HRMS m/z *calcd. for*: $[\text{M}+\text{H}]^+$ 441.3117, m/z *found*: 441.3077.

Yellow oil, yield: 61 %; IR (CHCl₃) ν 2958, 2864, 1724, 1688, 1573, 1450, 1367, 1171, 1115, 1084, 1070 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.24 (t, J = 7.2 Hz, 3H), 1.28-1.50 (m, 4H), 1.57-1.63 (m, 2H), 1.96 (s, 3H), 2.43 (m, 1H), 2.60-2.69 (m, 2H), 2.92 (m, 1H), 3.27 (t, J = 6.3 Hz, 1H), 3.32-3.45 (m, 4H), 3.54 (d, J = 13.5 Hz, 1H), 3.66 (d, J = 13.5 Hz, 1H), 3.74 (t, J = 4.6 Hz, 4H), 3.93 (t, J = 7.1 Hz, 2H), 4.14 (qd, J = 7.2 et 1.5 Hz, 2H), 7.15-7.29 (m, 5H); ¹³C NMR (62.5 MHz, CDCl₃) 14.6, 19.0, 21.0, 28.6, 32.5, 44.9, 48.9 (2C), 51.2, 56.2, 57.4, 59.6, 64.6, 66.7 (2C), 94.4, 116.3, 127.1, 128.3 (2C), 128.9 (2C), 139.6, 143.0, 161.3, 164.3, 171.3; MS (ESI) 485.3 [M+H]⁺, 507.3 [M+Na]⁺; HRMS m/z *calcd. for*: [M+23] 507.2471, m/z *found for*: [M+23] 507.2491.

Yellow solid, Mp: 132-134 °C; yield: 59 %; IR (CHCl₃) ν 2862, 1685, 1573, 1450, 1271, 1116, 1086 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.24 (t, J = 7.0 Hz, 3H), 2.47-2.56 (m, 1H), 2.64 (m, 2H), 2.86-2.97 (m, 1H), 3.16-3.24 (m, 2H), 3.32-3.41 (m, 2H), 3.38 (d, J = 13.5 Hz, 1H), 3.66 (m, 4H), 3.72 (d, J = 13.5 Hz, 1H), 4.14 (qd, J = 7.0 et 1.8 Hz, 2H), 4.38 (s, 1H), 7.25-7.56 (m, 10H); ¹³C NMR (62.5 MHz, CDCl₃) δ 14.6, 22.9, 46.6, 48.7 (2C), 57.9, 59.7, 62.3, 66.7 (2C), 94.2, 117.5, 127.1, 127.7, 128.3 (2C), 128.4 (2C), 128.8 (2C), 128.9 (2C), 139.5, 140.5, 141.3, 161.7, 164.3; MS (ESI) 447.2 [M+H]⁺; MS (IE) m/z 369 [M-C₆H₁₃]⁺, 455 [M+1]⁺; HRMS m/z *calcd. for*: [M+1]⁺ 447.2284, [M+Na]⁺ 469.2103, m/z *found*: [M+1]⁺ 447.2259, [M+Na]⁺ 469.2071.

Orange oil, yield: 66 %; IR (CHCl₃) ν 2984, 2924, 2967, 2863, 1690, 1575, 1523, 1448, 1349, 1269, 1115, 1085, 1070 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.31 (t, J = 7.0 Hz, 3H), 2.60-2.75 (m, 3H), 2.99 (m, 1H), 3.23-3.33 (m, 2H), 3.40-3.46 (m, 2H), 3.48 (d, J = 13.5 Hz, 1H), 3.75 (m, 5H), 4.22 (q, J = 7.0, 2H), 4.54 (s, 1H), 7.24-7.34 (m, 5H), 7.53 (d, J = 8.6 Hz, 2H), 8.18 (d, J = 8.6 Hz, 2H); ¹³C NMR (62.5 MHz, CDCl₃) δ 14.4, 22.5, 46.7, 48.5 (2C), 58.0, 59.7, 61.4, 66.5 (2C), 94.0, 118.3, 123.53 (2C), 127.3, 128.4 (2C), 128.6 (2C), 129.3 (2C), 138.6, 139.5, 147.5, 148.4, 161.7, 164.0; MS (ESI) 492.2 [M+H]⁺, 514.4 [M+Na]⁺; HRMS m/z calcd. for: [M+Na]⁺ 514.1954, m/z found: 514.1948.

Yellow oil, yield: 47 %; IR (CHCl₃) ν 3036, 3021, 3014, 1688, 1602, 1573, 1511, 1231, 1223, 1212, 1195, 1190 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.24 (t, J = 7.1 Hz, 3H), 2.45-2.56 (m, 1H), 2.63 (m, 2H), 2.92 (m, 1H), 3.17-3.24 (m, 2H), 3.33-3.40 (m, 3H), 3.67-3.72 (m, 5H), 3.72 (s, 3H), 4.14 (q, J = 7.1, 2H), 4.33 (s, 1H), 6.77 (d, J = 8.7 Hz, 2H), 7.15 (d, J = 8.7 Hz, 2H), 7.16-7.27 (m, 5H); ¹³C NMR (62.5 MHz, CDCl₃) δ 14.4, 22.8, 46.5, 48.6 (2C), 55.2, 57.6, 59.5, 61.6, 66.6 (2C), 94.1, 113.5 (2C), 117.2, 126.9, 128.2 (2C), 128.7 (2C), 129.7 (2C), 132.3, 139.4, 141.4, 159.0, 161.5, 164.2; MS (ESI) 499.0 [M+Na]⁺; HRMS m/z calcd. for: [M+H]⁺ 477.2389, m/z found: 477.2375.

Yellow oil; yield: 87 %; IR (CHCl₃) ν 3014, 2962, 2840, 1664, 1603, 1495, 1453, 1374, 1114, 1016 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.74 (d, *J* = 6.5 Hz, 3H), 1.08 (d, *J* = 6.5 Hz, 3H), 1.93 (t, *J* = 2.5 Hz, 1H), 2.22-2.35 (m, 3H), 2.38-2.48 (m, 1H), 2.91 (m, 1H), 2.97 (m, 4H), 3.22 (d, *J* = 14.0 Hz, 1H), 3.25 (d, *J* = 14.0 Hz, 1H), 3.74 (m, 4H), 3.85 (s, 2H), 3.94 (d, *J* = 15 Hz, 1H), 5.30 7.19-7.37 (m, 10H); ¹³C NMR (62.5 MHz, CDCl₃) δ 18.4, 20.2 (2C), 28.5, 31.7, 49.4, 51.1 (2C), 55.4, 65.0, 66.7 (2C), 69.0, 82.9, 124.1, 126.0, 126.9, 128.2 (2C), 128.3 (4C), 128.8 (2C), 139.5, 139.7, 151.7, 158.2; MS (ESI) 480.2 [M+Na]⁺, 496.1 [M+K]⁺; HRMS *m/z* *calcd. for*: [M+Na]⁺ 480.2627, *m/z found*: 480.2590.

Procedure leading to oxazole (5a).

Oxazole **5a** was isolated in 47 % yield when reaction was carried out at 80°C in toluene for 15h or in 51 % yield in MeOH at reflux for 3h (see **Table 1**, entry 1 and 6).

Yellow oil; IR (CHCl₃) ν 2929, 2859, 2236, 1703, 1495, 1453, 1368, 1266, 1114, 1072 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.86 (t, *J* = 6.5 Hz, 3H), 1.23 (m, 7H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.42 (m, 1H), 1.84 (m, 2H), 2.37 (m, 2H), 2.62 (m, 1H), 2.92 (m, 1H), 2.97 (m, 4H), 3.43 (d, *J* = 14.0 Hz, 1H), 3.69 (t, *J* = 7.5 Hz, 1H), 3.74 (m, 4H), 3.84 (s, 2H), 3.88 (d, *J* = 14.0 Hz, 1H), 4.21 (q, *J* = 7.2, 2H), 7.18-7.36 (m, 10H); ¹³C NMR (62.5 MHz, CDCl₃) δ 13.0, 13.1, 17.9, 21.6, 25.3, 27.9, 29.4, 30.7 (2C), 47.6, 50.0 (2C), 54.5, 57.0, 60.7, 65.9 (2C), 72.8, 86.7, 123.2, 125.1, 126.1, 127.2 (2C), 127.3 (2C), 127.4 (2C), 127.7 (2C), 138.4, 138.6, 150.7,

152.7, 158.0; MS (ESI) 594 $[M+Na]^+$; HRMS m/z *calcd. for:* $[M+Na]^+$ 594.3308, m/z *found:* 594.3286.

Deprotection procedure of furopyridin (**1a**)

Product **1a** (12 mg, 0.026 mmol) was dissolved in EtOH (0.4 mL) and 10 % (mass) of Pd(OH)₂ was added. The mixture was stirred under H₂ atmosphere for 5h at room temperature. After celite filtration, washing with EtOH and evaporation of the solvent in vacuo, the residue was purified by preparative TLC (silica gel), eluent AcOEt.

Yellow oil, yield: 58 %; IR (CHCl₃) ν 2929, 2859, 1780, 1732, 1686, 1573, 1448, 1368, 1270, 1171, 1115, 1086 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.88 (t, J = 7.0 Hz, 3H), 1.25-1.35 (m, 10H), 1.42 (m, 1H), 1.73-1.91 (m, 2H), 2.62 (m, 2H), 2.87 (m, 1H), 3.19 (m, 1H), 3.45 (m, 4H), 3.76 (m, 1H), 3.81 (m, 4H), 4.21 (q, J = 7.1 Hz, 2H); ¹³C NMR (62.5 MHz, CDCl₃) δ 14.1, 14.4, 22.6, 25.2, 25.7, 29.4, 31.8, 33.7, 42.3, 48.8 (2C), 52.3, 59.5, 66.6 (2C), 94.7, 116.8, 143.8, 160.9, 164.1; MS (ESI) 365.0 $[M+H]^+$; HRMS m/z *calcd. for:* $[M+H]^+$ 365.2440, m/z *found:* 365.2429.