A Facile Route to Polysubstituted *N*-Benzyl Pyroglutamates

Pei-Pei Sun, Meng-Yang Chang, Michael Y. Chiang and Nein-Chen Chang*

Supporting Information

Experimental Section

Before use, THF was distilled from a deep blue solution resulting from sodium and benzophenone under nitrogen. All reagents and solvents were obtained from commercial sources and used without further purification. Thin layer chromatography (TLC) analysis was performed with precoated silica gel (60 f₂₅₄ plates) and column chromatography was carried out on silica (70~230 mesh). All reactions were performed under an atmosphere of nitrogen in dried (except those concerned with aqueous solutions) spherical flasks and stirred with magnetic bars.

General procedure of [3+2] cycloaddition to pyroglutamates 9. To a suspension of sodium hydride (360mg, 60% dispersion in oil, 9 mmole, was washed three times with dry hexane) in dry THF (30 mL) was added 2-sulfonylacetamide **1** (3 mmol) in portions. After 20 min, ethyl 2-bromo-2-propeoate **4** (6 mmol) in THF (30 mL) were added to the suspension mixture over a period of 30 min. The mixture was stirred for 12 h at room temperature. The reaction was quenched with H₂O. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried, filtered, and concentrated. The residue was purified by column chromatography on silica gel (elution with hexane/ethyl acetate) to give pyroglutamates **9**.

Compound Data

(9a): ethyl 1-benzyl-3-(dimethoxymethyl)-4-[(4-methylphenyl)sulfonyl]-5-oxo-2-pyrrolidinecarboxylate; mp 103-104 °C; ^1H NMR (500 MHz, CDCl_3) δ 7.85 (d, J = 8.5 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.29-7.24 (m, 3H), 7.15-7.13 (m, 2H), 5.14 (d, J = 15.0 Hz, 1H), 4.30-4.18 (m, 4H), 4.00 (d, J = 3.0 Hz, 1H), 3.86 (d, J = 2.5 Hz, 1H), 3.52-3.50 (m, 1H), 3.30 (s, 3H), 3.27 (s, 3H), 2.46 (s, 3H), 1.33 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 169.9, 165.4, 145.3, 139.4, 134.3, 129.6 (2C), 129.4 (2C), 128.6 (2C), 128.5 (2C), 127.8, 104.6, 66.6, 62.0, 57.5, 55.2, 55.0, 46.4, 39.3, 21.7, 14.1; MS (EI, 70 eV): m/z : 476 ($M^+ + 1$, 3), 320 (71), 91 (100); HRMS calcd for $\text{C}_{24}\text{H}_{29}\text{NO}_7\text{S}$ (M^+) 475.1665, found 475.1672; Anal. calcd for $\text{C}_{24}\text{H}_{29}\text{NO}_7\text{S}$: C, 60.61; H, 6.15; N, 2.95; S, 6.74; Found: C, 60.76; H, 6.65; N, 2.82; S, 6.65.

(9b): ethyl 1-benzyl-3-methyl-4-[(4-methylphenyl)sulfonyl]-5-oxo-2-pyrrolidinecarboxylate; mp 140-141 °C; ^1H NMR (500 MHz, CDCl_3) δ 7.84 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 7.29-7.25 (m, 3H), 7.11-7.01 (m, 2H), 5.11 (d, J = 15.0 Hz, 1H), 4.26-4.17 (m, 2H), 4.12 (d, J = 15.0 Hz, 1H), 3.60 (d, J = 5.5 Hz, 1H), 3.42 (d, J = 2.3 Hz, 1H), 3.21-3.17 (m, 1H), 2.45 (s, 3H), 1.29 (t, J = 7.0 Hz, 3H), 1.28 (d, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 169.46, 165.20, 145.38, 134.90, 134.39, 129.61 (2C), 129.49 (2C),

128.83 (2C), 128.52 (2C), 128.05, 71.90, 63.35, 61.84, 46.09, 32.43, 21.74, 20.66, 14.09; MS (EI, 30 eV): m/z : 416 ($M^+ + 1$, 1), 260 (19), 91 (100); HRMS calcd for $C_{22}H_{25}NO_5S$ ($M^+ + 1$) 416.1531, found 416.1532; Anal. calcd for $C_{22}H_{25}NO_5S$: C, 63.59; H, 6.06; N, 3.37; S, 7.72; Found: C, 63.65; H, 6.39; N, 3.18; S, 7.64.

(9c): ethyl 1-benzyl-4-[(4-methylphenyl)sulfonyl]-5-oxo-3-propyl-2-pyrrolidinecarboxylate; mp 90-91 °C; 1H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J = 8.5 Hz, 2H), 7.38 (d, J = 8.5 Hz, 2H), 7.31-7.26 (m, 3H), 7.14-7.13 (m, 2H), 5.14 (d, J = 15.0 Hz, 1H), 4.29-4.19 (m, 2H), 4.15 (d, J = 15.0 Hz, 1H), 3.65 (d, J = 3.5 Hz, 1H), 3.53 (d, J = 2.5 Hz, 1H), 3.22-3.18 (m, 1H), 2.46 (s, 3H), 1.49-1.42 (m, 2H), 1.32 (t, J = 7.5 Hz, 3H) 1.29-1.21 (m, 2H), 0.86 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.81, 165.25, 145.34, 135.01, 134.43, 129.63 (2C), 129.41 (2C), 128.81 (2C), 128.49 (2C), 128.06, 70.90, 61.99, 61.85, 46.27, 37.42, 36.54, 21.74, 19.14, 14.09, 13.46; MS (EI, 30 eV): m/z : 444 ($M^+ + 1$, 3), 288 (17), 91 (100); HRMS calcd for $C_{24}H_{29}NO_5S$ ($M^+ + 1$) 444.1839, found 444.1838.

(9d): ethyl 1-benzyl-4-[(4-methylphenyl)sulfonyl]-5-oxo-3-phenyl-2-pyrrolidinecarboxylate; mp 135-136 °C; 1H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.31-7.17 (m, 8H), 6.91-6.89 (m, 2H), 5.27 (d, J = 14.5 Hz, 1H), 4.37-4.22 (m, 3H), 4.27 (d, J = 14.5 Hz, 1H), 3.97 (d, J = 3.0 Hz, 1H), 3.95 (d, J = 3.5 Hz, 1H), 2.45 (s, 3H), 1.34 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

169.3, 164.9, 145.5, 141.2, 135.0, 134.2, 129.7 (2C), 129.5 (2C), 129.2 (2C), 129.0 (2C), 128.9 (2C), 128.3, 127.9, 126.3 (2C), 73.0, 63.7, 62.1, 46.7, 41.7, 21.8, 14.1; MS (EI, 70 eV): m/z : 478 ($M^+ + 1$, 1), 322 (18), 91 (100); HRMS calcd for $C_{27}H_{27}NO_5S$ (M^+) 477.1610, found 477.1607; Anal. calcd for $C_{27}H_{27}NO_5S$: C, 67.90; H, 5.70; N, 2.93; S, 6.71; Found: C, 68.00; H, 6.01; N, 2.80; S, 6.75.

(**9e**): ethyl 1-benzyl-3-[(benzyloxy)methyl]-4-[(4-methylphenyl)sulfonyl]-5-oxo-2-pyrrolidinecarboxylate; mp 115-116°C; 1H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 7.31-7.08 (m, 10H), 5.13 (d, J = 15 Hz, 1H), 4.46 (d, J = 11.5 Hz, 1H), 4.39 (d, J = 11.5 Hz, 1H), 4.25-4.13 (m, 2H), 4.16 (d, J = 15 Hz, 1H), 4.05 (d, J = 5.5 Hz, 1H), 3.84 (d, J = 4.0 Hz, 1H), 3.65-3.57 (m, 2H), 3.35-3.32 (m, 1H), 2.46 (s, 3H), 1.27 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.83, 165.36, 145.38, 137.20, 134.74, 134.29, 129.62 (2C), 129.53 (2C), 128.61 (2C), 128.42 (2C), 128.40 (2C), 127.85, 127.80, 127.59 (2C), 73.08, 69.96, 67.30, 61.84, 58.83, 46.18, 37.43, 21.75, 14.08; MS (FAB): m/z : 522 ($M^+ + 1$, 6), 366 (1), 91 (100); HRMS calcd for $C_{29}H_{31}NO_6S$ ($M^+ + 1$) 522.1950, found 522.1953; Anal. calcd for $C_{29}H_{31}NO_6S$: C, 66.77; H, 5.99; N, 2.69; Found: C, 66.85; H, 6.07; N, 2.51.

(**9f**): ethyl 1-benzyl-3-[3-(benzyloxy)propyl]-4-[(4-methylphenyl)sulfonyl]-5-oxo-2-pyrrolidinecarboxylate; 1H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, J = 8.5 Hz, 2H), 7.38-7.23 (m, 10H), 7.14-7.12 (m, 2H), 5.143 (d, J = 15 Hz, 1H), 4.43 (s, 2H), 4.29-4.17 (m, 2H), 4.15 (d, J = 15 Hz, 1H), 3.69 (d, J = 3.5 Hz, 1H), 3.55 (d, J = 3.0 Hz, 1H), 3.40 (t, J = 6 Hz, 2H), 3.23-3.19 (m, 1H), 2.45 (s, 3H), 1.64-1.54 (m, 4H), 1.30 (t, J = 7.5

Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 169.67, 165.15, 145.32, 138.18, 134.92, 134.34, 129.60 (2C), 129.38 (2C), 128.79 (2C), 128.44 (2C), 128.32 (2C), 128.03, 127.56, 127.52 (2C), 72.85, 70.77, 69.03, 61.97, 61.83, 46.24, 36.62, 32.03, 26.19, 21.69, 14.05; MS (EI, 30 eV): m/z : 550 ($\text{M}^+ + 1$, 1), 394 (20), 91 (100); HRMS calcd for $\text{C}_{31}\text{H}_{35}\text{NO}_6\text{S}$ ($\text{M}^+ + 1$) 550.2213, found 550.2217.

(9g): ethyl 1-benzyl-3-(3,4-dimethoxyphenyl)-4-[(4-methylphenyl)sulfonyl]-5-oxo-2-pyrrolidinecarboxylate; ^1H NMR (500 MHz, CDCl_3) δ 7.82 (d, $J = 8.5$ Hz, 2H), 7.37 (d, $J = 8.5$ Hz, 2H), 7.30-7.25 (m, 5H), 6.67 (d, $J = 8$ Hz, 1H), 6.51 (dd, $J = 8$ Hz, 2H, 1H), 6.32 (d, $J = 2$ Hz, 1H), 5.27 (d, $J = 14.5$ Hz, 1H), 4.37-4.29 (m, 3H), 4.26 (d, $J = 14.5$ Hz, 1H), 4.01 (d, $J = 2.5$ Hz, 1H), 3.94 (d, $J = 3.5$ Hz, 1H), 3.81 (s, 3H), 3.60 (s, 3H), 2.45 (s, 3H), 1.36 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 169.35, 164.96, 149.50, 148.60, 145.46, 135.16, 134.23, 133.81, 129.63 (2C), 129.41 (2C), 129.00 (2C), 128.90 (2C), 128.22, 118.59, 111.34, 108.74, 73.12, 63.82, 62.05, 55.85, 55.67, 46.56, 41.33, 21.71, 14.14; MS (FAB): m/z : 538 ($\text{M}^+ + 1$, 1), 308 (2), 91 (100); HRMS calcd for $\text{C}_{29}\text{H}_{31}\text{NO}_7\text{S}$ (M^+) 538.1849, found 538.1852.

(9h): ethyl 1-benzyl-4-[(4-methylphenyl)sulfonyl]-3-(4-nitrophenyl)-5-oxo-2-pyrrolidinecarboxylate; mp 138-139°C; ^1H NMR (500 MHz, CDCl_3) δ 8.05 (d, $J = 8.5$ Hz, 2H), 7.82 (d, $J = 8.5$ Hz, 2H), 7.39 (d, $J = 8.5$ Hz, 2H), 7.34-7.33 (m, 3H), 7.25-7.23 (m, 2H), 7.05 (d, $J = 8.5$ Hz, 2H), 5.29 (d, $J = 15$ Hz, 1H), 4.49 (t, $J = 3.5$ Hz, 1H), 4.37-4.27 (m, 2H), 4.27 (d, $J = 15$ Hz, 1H), 3.95 (d, $J = 3$ Hz, 1H), 3.89 (d, $J = 4$ Hz, 1H), 2.47 (s, 3H), 1.35 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 168.74, 164.32, 147.85, 147.46, 145.94, 134.76, 133.77, 129.80 (2C), 129.51 (2C), 129.09 (2C), 128.98 (2C), 128.62, 127.55 (2C), 124.51

(2C) 72.54, 62.91, 62.47, 46.77, 41.47, 21.79, 14.15; MS (EI, 30 eV): m/z : 523 ($M^+ + 1$, 1), 367 (12), 91 (100); HRMS calcd for $C_{27}H_{26}N_2O_7S$ ($M^+ + 1$) 523.1539, found 523.1540.

H493-1