"One-pot" Methylation of *N*-Nosyl- α-Amino Acid Methyl Esters with Diazomethane and Their Coupling to Prepare *N*-Methyl Dipeptides

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SUPPORTING INFORMATION

Synthesis of N-Nosyl amino acid methyl esters 2a-e. General Procedure. *p*-Nitrobenzenesulfonyl chloride (0.7 mmol) was added in one portion to a suspension of the appropriate amino acid methyl esters **1a-e** (1 mmol) and pyridine (3 mmol) in dry CH_2Cl_2 (20 mL) at 0° C and the resulting mixture was stirred at room temperature for 2-4 h, monitoring the conversion of **1a-e** by TLC (chloroform/diethyl ether 80:20 v/v). Aqueous HCl 1N was then added and the acidified solution (pH = 2) was extracted with methylene chloride (3 × 10 mL). The organic phase was carefully shaken with a saturated aqueous solution of $NaHCO_3$ (3 × 10 mL) , then dried (Na_2SO_4). The solvent was removed to afford *N*-nosyl amino acid methyl esters **2a-e** as pale yellow solids that were used in the next step without further purification (81-97 % overall yields).

2a. 81% yield, pale yellow solid, mp 111-113 °C. IR (KBr): ν 3257 cm^{-1}, 3114, 1735, 1525, 1350, 1176, 1087, 864, 743. ^{1}H- NMR: δ 1.23 ppm (d, *J*= 7.1 Hz, 3 H), 3.47 (s, 3 H), 3.97-4.03 (m, 1 H), 5.60 (d, *J*= 9.8 Hz, 1 H), 8.01-8.08 (m, 2 H), 8.40-8.46 (m, 2 H). FAB$^+$ MS: *m/z* (%) 289 (60) [(M + H)$^+$], 257 (58), 229 (100), 213 (35), 186 (52). Anal. Calcd. for $C_{10}H_{12}N_2O_6S$: C, 41.66; H, 4.20; N, 9.72; O, 33.30; S, 11.12. Found: C, 41.64; H, 4.22; N, 9.73; S, 11.13.

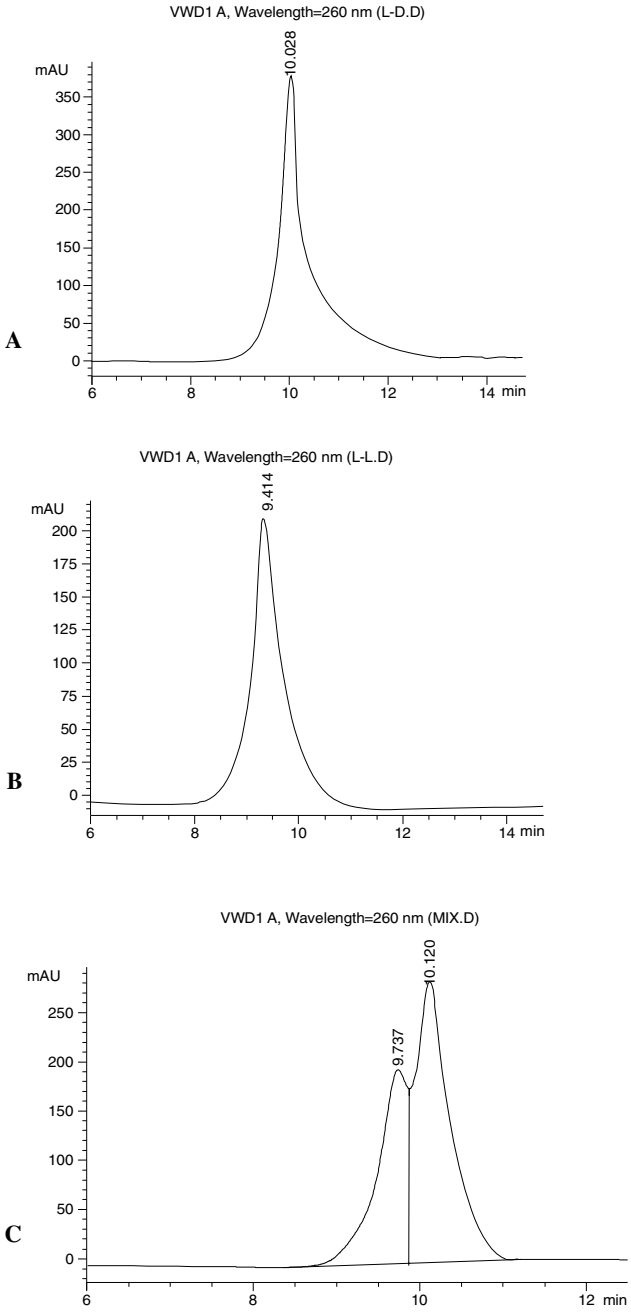
2a'. 86% yield, pale yellow solid, mp 118-120 °C. IR (KBr): ν 3261 cm^{-1}, 3112, 1733, 1530, 1353, 1180, 1085, 860, 741. ^{1}H- NMR: δ 1.23 ppm (d, *J*= 7.1 Hz, 3 H), 3.46 (s, 3 H), 3.98-4.04 (m, 1 H), 5.60 (d, *J*= 9.6 Hz, 1 H), 8.00-8.07 (m, 2 H), 8.40-8.46 (m, 2 H). FAB$^+$ MS: *m/z* (%) 289 (65) [(M + H)$^+$], 257 (52), 229 (100), 213 (33), 186 (48). Anal. Calcd. for $C_{10}H_{12}N_2O_6S$: C, 41.66; H, 4.20; N, 9.72; O, 33.30; S, 11.12. Found: C, 41.64; H, 4.22; N, 9.73; S, 11.13.

2b. 97% yield, pale yellow solid, mp 151-155 °C. IR (KBr): ν 3268 cm^{-1}, 3114, 1721, 1523, 1346, 1168, 1091, 855, 740. ^{1}H- NMR: δ 2.77 ppm (dd, J_1= 9.6 Hz, J_2= 13.5 Hz, 2 H), 2.99 (dd, J_1 = 5.2 Hz, J_2= 13.5 Hz, 2 H), 3.45 (s, 3 H), 4.09 (m,1 H), 5.58 (d, *J* = 9.8 Hz, 1 H), 7.09-7.19 (m, 5 H), 7.75-7.81 (m, 2 H), 8.21-8.28 (m, 2 H). FAB$^+$ MS: *m/z* (%) 365 (32) [(M + H)$^+$], 305 (55), 289 (20), 273 (48), 242 (27), 186 (74), 162 (100), 91 (83). Anal. Calcd. for $C_{16}H_{16}N_2O_6S$: C, 52.74; H, 4.43; N, 7.69; O, 26.35; S, 8.80. Found: C, 52.72; H, 4.45; N, 7.70; S, 8.81.

2c. 84% yield, pale yellow solid, mp 97-100 °C. IR (KBr): ν 3297 cm^{-1}, 3110, 1734, 1529, 1349, 1174, 1089, 859, 741. ^{1}H- NMR: δ 0.88 ppm (d, *J* = 6.8 Hz, 3 H), 0.96 (d, *J*= 6.8 Hz, 3 H), 2.11 (m,1 H), 3.52 (s, 3 H), 3.85 (dd, J_1= 4.9 Hz, J_2= 9.8 Hz, 1 H), 5.56 (d, *J*= 9.8 Hz, 1 H), 8.02-8.09 (m, 2 H), 8.32-8.39 (m, 2 H). FAB$^+$ MS: *m/z* (%) 317 (31) [(M + H)$^+$], 273 (18), 257 (100), 241 (23), 186 (20), 122 (29). Anal. Calcd. for $C_{12}H_{16}N_2O_6S$: C, 45.56; H, 5.10; N, 8.86; O, 30.35; S, 10.14. Found: C, 45.58; H, 5.08; N, 8.89; S, 10.13.

2d. 82% yield, pale yellow solid, mp 96-99 °C. IR (KBr): ν 3276 cm^{-1}, 3104, 1742, 1526, 1350, 1174, 1092, 858, 744. ^{1}H- NMR: δ 0.86- 0.94 ppm (m, 6 H), 1.48-1.55 (m, 2 H), 1.74 (m,1 H), 3.47 (s,3 H), 4,01 (m,1 H), 5.51 (d, *J* =9.9 Hz, 1 H), 8.01-8.07 (m, 2 H), 8.31-8.38 (m, 2 H). FAB$^+$ MS: *m/z* (%) 331 (58) [(M + H)$^+$], 271 (100), 255 (16), 215 (12), 186 (20), 122 (18). Anal. Calcd. for $C_{13}H_{18}N_2O_6S$: C, 47.26; H, 5.49; N, 8.48; O, 29.06; S, 9.71. Found: C, 47.25; H, 5.50; N, 8.51; S, 9.69.

2e. 87% yield, pale yellow solid, mp 94-96 °C. IR (KBr): ν 3295 cm^{-1}, 3105, 2971, 1735, 1537, 1351, 1169, 1092, 863, 746. ^{1}H- NMR: δ 0.83-0.95 ppm (m, 6 H), 1.15 (m, 1 H), 1.37 (m, 1 H), 1.83 (m, 1 H), 3.50 (s, 3 H), 3.89 (m,1 H), 5.62 (d, *J*= 9.8 Hz, 1 H), 8.03-8.08 (m, 2 H), 8.33-8.39 (m, 2 H, Ar-H). FAB$^+$ MS: *m/z* (%) 331 (52) [(M + H)$^+$], 271 (100), 255 (12), 215 (30), 186 (36), 122 (25), 88 (61). Anal. Calcd. for $C_{13}H_{18}N_2O_6S$: C, 47.26; H, 5.49; N, 8.48; O, 29.06; S, 9.71. Found: C, 47.27; H, 5.48; N, 8.50; S, 9.72.



HPLC analyses of *N*-Fmoc dipeptides **6** and **11**:
(A) *N*-Fmoc-L-Leu-D-(Me)-Ala-OMe (**6**);
(B) *N*-Fmoc-L-Leu-L-(Me)-Ala-OMe (**11**);
(C) mixture of **6** and **11**