Electrophilic Amination of Amino Acids with N-Boc oxaziridines: Efficient Preparation of N-orthogonally diprotected Hydrazino Acids and Piperazic Acid Derivatives.

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Reagents were commercially available and used without further purification unless otherwise stated. NMR spectra were recorded at 300 K on a spectrometer operating at 200.13 MHz for ^1H and 50.34 MHz for ^{13}C with the solvent as internal standard.¹ Melting points were measured by means of a microcalorimeter, with simultaneous check of purity. Specific rotations $[\alpha]$ (in $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$) were measured in a 1-dm thermostated quartz cell (25°C). Chromatographic separations were performed over silica gel 60 (0.040–0.063 mm). Anhydrous solvents were distilled from the appropriate drying reagents² immediately before use. Oxaziridine **7** and N_α , N_β -diprotected hydrazino acid derivative **1j** were prepared as previously described.³ N-benzyl amino acids **6a**, **6b**, **6e** and **6l** were prepared as described.⁴

¹ Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512-7515.

² Amarego, W. L. F.; Perrin, D.D. *Purification of Laboratory Chemicals*, 4th ed.; Butterworth-Heinemann, **1997**.

³ Vidal, J.; Hannachi, J-C.; Hourdin, G.; Mulatier, J-C.; Collet, A. *Tetrahedron Lett.* **1998**, *39*, 8845-8848.

⁴ Quitt, P.; Hellerbach, J.; Vogler, K. *Helv. Chim. Acta* **1963**, *46*, 327-333.

L- δ -hydroxynorvaline⁵ **5m:** To a suspension of L-GluOMe **5j** (8.05 g, 50 mmol) in anhydrous CHCl₃ (75 mL) and CH₃CN (12 mL) was added under argon ClSiMe₃ (6.6 mL, 52 mmol). The resulting mixture was refluxed for 5 h. After cooling at room temperature, Et₃N (14.2 mL, 102 mmol) was added dropwise and then a solution of trityl chloride (13.94 g, 50 mmol) in anhydrous CHCl₃ (50 mL). After stirring at room temperature overnight, methanol (10 mL) was added. The resulting mixture was concentrated *in vacuo*. To the residue was added ether (250 mL) and cold aqueous citric acid. After extraction of the aqueous phase, the combined organic phases were dried over MgSO₄, concentrated to 100 mL and then treated by Et₂NH (5.2 mL, 50 mmol). The resulting solid was filtered and washed by Et₂O to give L-TrtGluOMe, Et₂NH salt (20.33 g, 85% from L-GluOMe **5j**): mp 152 °C (lit.^{5a} 155-156 °C); [α]_D²⁵ + 14.9 (c 1, MeOH) (lit.^{5a} [α]_D²⁵ + 13.7 (c 1, MeOH)).

To a solution of L-TrtGluOMe, Et₂NH salt (9.18 g, 19.26 mmol) in anhydrous THF (100 mL) at 4 °C was added dropwise a 1 M solution of LiAlH₄ in THF (25 mL, 25 mmol). The resulting mixture was stirred at 4 °C for 2 h, treated by AcOEt (2 mL) and then concentrated *in vacuo*. The residue was diluted with CHCl₃ (200 mL) and then washed at 0 °C with cold aqueous H₂SO₄ (0.5 M, 200 mL). The organic phase was washed with water, dried over Na₂SO₄ and then concentrated *in vacuo*. The resulting oil was dissolved in a mixture of AcOH (15 mL) and water (5 mL). After stirring for 24 h at room temperature, the resulting suspension was concentrated *in vacuo*, diluted by water (100 mL) and then filtered. The solid was washed three times by water. The combined aqueous phases were extracted by CHCl₃ and then lyophilized. The resulting solid was recrystallized two times in a boiling H₂O/EtOH mixture (1:5) and gave L- δ -hydroxynorvaline **5m** (1.36 g, 45% from L-GluOMe **5j**) as a white solid: dec. 224 °C (lit.^{5a}

⁵ (a) Barlos, K.; Mamos, P.; Papaioannou, D.; Patrianakou, S. *J. Chem. Soc., Chem. Commun.* **1987**, 1583-1584. (b) for a preparation of **5m** from glutamic acid, see: Garcia, M.; Serra, A.; Rubiralta, M.; Diez, A.; Segarra, V.; Lozoya, E.; Ryder, H.; Palacios, J. M. *Tetrahedron: Asymmetry* **2000**, *11*, 991-994.

231 °C). $[\alpha]_D^{25} + 27.5$ (c 2, HCl 5M) (lit.^{5a} $[\alpha]_D^{25} + 22.6$ (c 2, HCl 5M); lit.⁶ $[\alpha]_D^{25} + 28.8$ (c 2, HCl 5M)); ¹H NMR (D₂O) δ 1.45-1.58 (m, 2H), 1.73-1.85 (m, 2H), 3.50 (t, $J = 6$ Hz, 2H), 3.63 (t, $J = 6$ Hz, 1H); ¹³C NMR (D₂O) δ 28.0, 28.1, 55.4, 61.8, 175.4.

L-N-Benzyltryptophane 6d: was prepared from L-tryptophane (4.08 g, 20 mmol) according to Quitt's procedure.⁴ Recrystallization from a boiling mixture of water (20 mL) and AcOH (40 mL) afforded **6d** as a beige solid (4.15 g, 72 %): dec. 256 °C (lit.⁷ 237-240 °C); $[\alpha]_D^{25} + 10.7$ (c 1, HCl 6M); ¹H NMR (D₂O/NaOH) δ 2.93 (d, $J = 7$ Hz, 2H), 3.30 (t, $J = 7$ Hz, 1H), 3.42 and 3.61 (AB system, $J = 12.5$ Hz, 2H), 6.97-7.51 (m, 10H); ¹³C NMR (D₂O/NaOH) δ 29.5, 51.9, 64.4, 111.5, 112.5, 119.6, 119.8, 122.5, 124.9, 128.1, 129.3, 129.4, 137.0, 139.8, 182.5; Anal. Calcd for C₁₈H₁₈N₂O₂ (294.3): C, 73.45; H, 6.16; N, 9.52. Found C, 73.46; H, 6.13; N, 9.39.

L-N,O-Dibenzyltyrosine 6f: was prepared from L-O-benzyltyrosine (2.72 g, 10 mmol) according to Quitt's procedure.⁴ Recrystallization from boiling AcOH afforded **6f** (1.9 g, 52 %) as a colorless solid: dec. 249 °C; $[\alpha]_D^{25} + 29.5$ (c 1.3, HCl 6M/AcOH 1:1); ¹H NMR (DMSO-*d*₆, 330 K) δ 2.83-3.02 (m, 2H), 3.30 (m, 1H), 3.58-3.80 (m, 2H), 5.04 (broad s, 2H), 6.85-7.38 (m, 14 H); ¹³C NMR (D₂O/NaOH) δ 39.0, 51.9, 65.3, 71.2, 116.1, 128.1, 129.0, 129.2, 129.5, 129.7, 131.3, 132.0, 137.5, 139.7, 157.2, 182.0. Anal. Calcd for C₂₃H₂₃NO₃ • 0.25 H₂O (365.9): C, 75.49; H, 6.47; N, 3.83. Found: C, 75.75; H, 6.62; N, 3.84.

L-N-Benzyl-(RS)-S-oxide methionine 6g: L-N-Benzylmethionine was prepared from L-methionine (3 g, 20 mmol) according to Quitt's procedure.⁴ Recrystallization from a boiling mixture of water (40 mL) and AcOH (40 mL) afforded L-N-Benzylmethionine as a colorless solid (3.55 g, 75 %): dec. 226

⁶ Greenstein, J. P.; Winitz, M. Chemistry of the amino acids, 1986, 2612-2619, Krieger.

⁷ Baggaley, K. H.; Fears, R.; Ferres, H.; Geen, G. R.; Hatton, I. K.; Jennings, L. J. A.; Tyrrell, A. W. R. *Eur. J. Med. Chem.* **1988**, 23, 523-531.

°C (lit.⁸ 228-230 °C); $[\alpha]_D^{25} + 26.7$ (c 1.2, HCl 6M) (lit.⁸ $[\alpha]_D + 24.7$ (c 1.2, HCl 2M)); ¹H NMR (D₂O/NaOH) δ 1.68 (m, 2H), 1.92 (s, 3H), 2.34 (t, $J = 8$ Hz, 2H), 3.00 (t, $J = 6.5$ Hz, 1H), 3.42 and 3.61 (AB system, $J = 12.5$ Hz, 2H), 7.20-7.28 (m, 5H); ¹³C NMR (D₂O/NaOH) δ 14.9, 30.6, 33.3, 52.1, 63.1, 128.3, 129.5, 139.6, 182.3; Anal. Calcd for C₁₂H₁₇NO₂S (239.3): C, 60.22; H, 7.16; N, 5.85; S, 13.40. Found: C, 60.10; H, 7.31; N, 5.86; S, 13.48. A mixture of aqueous hydrogen peroxide (7.15 M, 2.5 mL, 17.9 mmol) in AcOH (mL) was added at 4 °C to a solution of L-N-Benzylmethionine (3.55g, 14.8 mmol) in AcOH. After stirring for 2 h at room temperature, the solvent was removed *in vacuo* to give **6g** as a solid and colorless mixture of diastereomers (3.78 g, 100 %): $[\alpha]_D^{25} + 29.7$ (c 1.1, HCl 6M); ¹H NMR (D₂O/NaOH) δ 1.85 (m, 2H), 2.53 and 2.54 (two s, 3H), 2.75 (m, 2H), 3.03 (m, 1H), 3.47 and 3.65 (AB system, $J = 12.5$ Hz, 2H), 7.25 (m, 5H); ¹³C NMR (D₂O/NaOH; major diastereomer) δ 26.4, 37.3, 50.3, 52.1, 62.6, 128.3, 129.6, 129.6, 139.6, 181.5; Anal. Calcd for C₁₂H₁₇NO₃S (255.3): C, 56.45; H, 6.71; N, 5.49; S, 12.56. Found C, 56.36; H, 6.64; N, 5.40; S, 12.89.

L-N-Benzylasparagine 6h: was prepared from L-asparagine (9 g, 60 mmol) according to Quitt's procedure.⁴ Recrystallization from boiling water (warning: some decomposition of **6h** may happen at 100 °C) afforded **6h** as a colorless solid (7.04 g, 53 %): mp. 202 °C; $[\alpha]_D^{25} + 7.5$ (c 1, HCl 6M); ¹H NMR (D₂O) δ 2.21-2.44 (m, 2H), 3.23 (t, $J = 6$ Hz, 1H), 3.44 and 3.61 (AB system, $J = 12.5$ Hz, 2H), 7.18-7.27 (m, 5H); ¹³C NMR (D₂O/NaOH) δ 39.9, 51.9, 60.8, 128.2, 129.5, 129.5, 139.7, 177.2, 181.1; Anal. Calcd for C₁₁H₁₄NO₃ (222.2): C, 59.45; H, 6.35; N, 12.60. Found C, 59.16; H, 6.23; N, 12.30.

L-N-Benzyl glutamic acid 6i: Triethylamine (2.8 mL, 20 mmol) was added to a stirred mixture of L-glutamic acid (1.47 g, 10 mmol), benzaldehyde (1.2 mL, 12 mmol) and dry methanol (20 mL). After an hour, the mixture became limpid and NaBH₄ (0.378 g, 10 mmol) was slowly added at 4° C. After two hours at 4 °C, the solvent was concentrated *in vacuo*. The residue was dissolved in water (50 mL) and

⁸ Ohfuné, Y.; Kurokawa, N.; Higuchi, N.; Saito, M.; Hashimoto, M.; Tanaka, T. *Chem. Lett.* **1984**, 441-444.

acidified to pH = 3 with aqueous 6 M HCl. After filtration, **6j** was obtained as a colorless solid (1.73 g, 73%); mp 145 °C (lit.⁸ 156-157 °C, lit.⁹ 162-163 °C) $[\alpha]_D^{25} + 19.0$ (c 1, HCl 6M) (lit.⁸ $[\alpha]_D^{25} + 17.5$ (c 1, HCl 2M)); ¹H NMR (D₂O+NaOH) δ 1.70-1.77 (m, 2H), 2.09 (t, $J = 8$ Hz, 2H), 3.08 (t, $J = 6.5$ Hz, 1H), 3.61 and 3.75 (AB system, $J = 13$ Hz, 2H), 7.29 (m, 5H); ¹³C NMR (D₂O/NaOH) δ 27.4, 34.9, 51.3, 62.9, 130.0, 130.1, 130.6, 132.8, 175.45, 182.3; Anal. Calcd for C₁₂H₁₅NO₄ (237.2): C, 60.75; H, 6.37; N, 5.90. Found: C, 61.01; H, 6.38; N, 5.79.

L-N-Benzyl-5-(methyl ester)glutamic acid 6j: Triethylamine (5 mL, 36 mmol) was added to a stirred mixture of L-5-(methylester)glutamic acid (4.84 g, 30 mmol), benzaldehyde (3.6 mL, 36 mmol) and dry methanol (60 mL). After an hour, the mixture became limpid and NaBH₄ (1.38 g, 36 mmol) was slowly added at 4° C. After two hours at 4 °C, the mixture was poured onto a cold 5 % acetic acid aqueous solution (400 mL). The resulting suspension was concentrated *in vacuo* to ca 350 mL and quickly heated until the solid was dissolved. After cooling and filtration, **6j** was obtained as a colorless solid (4.32 g, 57 %): mp 163 °C (lit.¹⁰ 165 °C); $[\alpha]_D^{25} + 18.8$ (c 1, HCl 1M); ¹H NMR (D₂O) δ 1.94-2.08 (m, 2H), 2.40 (t, $J = 7.5$ Hz, 2H), 3.52 (t, $J = 7.5$ Hz, 1H), 3.55 (s, 3H), 4.08 and 4.16 (AB system, $J = 13$ Hz, 2H), 7.36 (m, 5H); ¹³C NMR (D₂O/HCl) δ 24.9, 30.2, 51.1, 53.3, 59.1, 130.2, 130.8, 130.9, 131.0, 171.4, 175.6; Anal. Calcd for C₁₃H₁₇NO₄ (251.3): C, 62.14; H, 6.82; N, 5.57. Found: C, 61.98; H, 6.66; N, 5.59.

L-N-Benzyl-4-(benzyl ester)aspartic acid 6k: Triethylamine (2.5 mL, 18 mmol) was added to a stirred mixture of L-4-(benzylester)aspartic acid (3.35 g, 15 mmol), benzaldehyde (1.8 mL, 18 mmol) and dry methanol (50 mL). After an hour, the mixture became limpid and NaBH₄ (0.681 g, 18 mmol) was slowly added at 4° C. After 2.5 hours at 4 °C, the mixture was poured onto a cold 5 % acetic acid aqueous solution (100 mL). After filtration and recrystallization in DMSO (20 mL), **6k** was obtained as

⁹ Petersen, J. S.; Fels, G.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 4539-4547.

¹⁰ Verardo, G.; Geatti, P.; Pol, E.; Giumanini, A. G. *Can. J. Chem.* **2002**, *80*, 779-788.

a colorless solid (4.05 g, 86 %): mp 195 °C; $[\alpha]_D^{25} + 6.7$ (c 0.5, AcOH); ^1H NMR (DMSO- d_6 /HCl) δ 2.87-3.14 (m, 2H), 4.01 (t, $J = 5.5$ Hz, 1H), 4.10 (s, 2H), 5.07 (s, 2H), 7.30-7.45 (10H); ^{13}C NMR (DMSO- d_6 /HCl) δ 34.2, 49.5, 55.0, 66.2, 128.0, 128.1, 128.4, 128.6, 128.8, 129.9, 132.7, 135.7, 169.3, 169.5; Anal. Calcd for $\text{C}_{18}\text{H}_{19}\text{NO}_4$ (313.3): C, 69.00; H, 6.11; N, 4.47. Found: C, 69.06; H, 6.18; N, 4.39.

L-N-Benzyl- δ -hydroxynorvaline 6m: Triethylamine (0.31 mL, 2.2 mmol) was added to a stirred mixture of L- δ -hydroxynorvaline (0.267 g, 2 mmol), benzaldehyde (0.23 mL, 2.3 mmol) and dry methanol (2 mL). The mixture became limpid within 15 min and 2.5 hours later, NaBH_4 (0.048 g, 1.25 mmol) was added at 4° C. After 2.5 hours at 4 °C, the mixture was concentrated *in vacuo* and then diluted with water (1 mL) and AcOH (0.2 mL, 3.5 mmol). After filtration and recrystallization in a 1:1 mixture of water and acetone, **6m** was obtained as a colorless solid (0.318 g, 71 %): dec. 204 °C; $[\alpha]_D^{25} + 20.8$ (c 1.2, HCl 6M); ^1H NMR (D_2O) δ 1.37-1.49 (m, 2H), 1.64-1.79 (m, 2H), 3.42-3.53 (m, 3H), 4.05 and 4.13 (AB system, $J = 13$ Hz, 2H), 7.35 (m, 5H); ^{13}C NMR (D_2O) δ 27.5, 28.0, 51.2, 61.7, 62.3, 130.1, 130.5, 130.9, 131.4, 174.2; Anal. Calcd for $\text{C}_{12}\text{H}_{17}\text{NO}_3 \cdot 0.25 \text{H}_2\text{O}$ (227.8): C, 63.28; H, 7.74; N, 6.15. Found: C, 63.23; H, 7.62; N, 6.17.

Methyl L-N-Benzyl-N-(*tert*-butoxycarbonylamino)- δ -hydroxynorvalinate 8: white crystals, mp 75 °C (Et₂O/hexane 1:3); $[\alpha]_D^{25} + 12.1$ (c 1, MeOH); ^1H NMR (CDCl_3) δ 1.30 (s, 9H), 1.62-1.95 (m, 4H), 2.77 (s, 1H), 3.40-3.65 (m, 3H), 3.71 (s, 3H), 3.97 (q, $J = 10.5$ Hz, 2H), 6.70 (s, 1H), 7.24-7.38 (m, 5H); ^{13}C NMR (CDCl_3) δ 26.3, 28.1, 30.3, 51.6, 61.5, 65.0, 80.1, 127.6, 128.2, 129.6, 136.4, 155.9, 173.9. Anal. Calcd. for $\text{C}_{18}\text{H}_{28}\text{N}_2\text{O}_5$ (352.4): C, 61.35; H, 8.01; N, 7.95. Found: C, 61.46; H, 8.21; N, 8.00.

Methyl L-N-Benzyl-N-(*tert*-butoxycarbonylamino)- δ -(formyloxy)norvalinate 9: colorless oil; IR (CCl_4) 3370, 1731 (broad) cm^{-1} ; ^1H NMR (CDCl_3) δ 1.33 (s, 9H), 1.64-1.79 (m, 3H), 2.09-2.16 (m, 1H), 3.35 (t, $J = 7.5$ Hz, 1H), 3.69 (s, 3H), 3.85-4.10 (m, 4H), 6.60 (s, 1H), 7.20-7.33 (m, 5H), 7.96 (s, 1H);

^{13}C NMR (CDCl_3) δ 25.2, 26.6, 28.1, 51.6, 61.2, 63.5, 63.7, 79.7, 127.6, 128.2, 129.4, 136.7, 155.2, 161.0, 173.6; FAB^+ -LRMS m/z 381.2 (MH^+).

HPLC analysis of hydrazinoalanine derivatives

(Chiralpack OT(+), 12 °C, MeOH, 0.8 mL min⁻¹)