Synthesis of Chiral Triamines and Diamines from Amino Acids

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Selectively protected (2S)-1,2,6-triaminohexane 4 was prepared from L-lysine by reduction of the amino acid, replacement of the hydroxy group by an azido group and selective reduction. Following the same method vicinal diamines 11 and 13 bearing a third functional group were synthesized from L-glutamic acid.

In recent years N-protected α-amino alcohols, which are easily obtained from α-amino acids,1 have been used as starting materials for the synthesis of optically active α-amino aldehydes,2 1,2,3 and 1,3-diamines,4 2-substituted taurines,5 lipidic 1,2-diamines,6 α-methylamines,7 β-substituted aminoethane sulfonamide and sulfonamides5 and iodoamines.9 Natural α-amino acids with one functional group in the side chain may be modified in several ways, due to the presence of three different functional groups, and may be regarded as a useful source for the synthesis of 1,2-diamines bearing a third functional group.10,2bc Triamines and vicinal diamines are important intermediates in the synthesis of ligands used for radiolabelling and imaging,11 in chelation chemistry12 and exhibit interesting biological properties.13 Although there are many approaches for the preparation of racemic compounds, only a few for the enantiomerically pure forms exist.14,15 A method for the synthesis of selectively protected chiral triamines and vicinal diamines starting from L-lysine and L-glutamic acid is presented here.

Boc-Lys(Z)-OH (1) was converted into the alcohol 2 by chemoselective reduction of its corresponding mixed anhydride with sodium borohydride16 (Scheme 1). The hydroxy group of 2 was activated as its methanesulfonate and was converted directly into azide 3 by treatment with sodium azide in dimethylformamide at 60 °C in high yield. The selective reduction of the azido group of 3 was carried out using sodium borohydride in the presence of 10% Pd-C in aqueous methanol at room temperature. The reduction of the azido group was rapid in high yield, while the Z protecting group remained unaffected under the conditions employed. The amine obtained was isolated and characterized as the Fmoc derivative 4. Each protecting group of the selectively protected (2S)-1,2,6-triaminohexane 4 can be easily and preferentially removed according to known standard procedures.

Z-Glu(OMe)-OH (5) was reduced to alcohol 6 and following the same procedure as described for lysine, was converted to azide 7 (Scheme 2). Reduction of the azido group of 7 by NaBH₄ in the presence of 10% Pd-C afforded the cyclic derivative 8, due to spontaneous lactamization. A mixture of N-protected compound 9 (38%) and 8 (28%) was obtained when the reduction was performed in the presence of di-tert-butyl dicarbonate at room temperature. Reduction of the acid 10, obtained by alkaline hydrolysis of methyl ester 7, followed by subsequent treatment with benzyl chloroformate afforded N⁴,N⁵-dibenzoxycarbonyl-4,5-diaminovaleric acid (11). Chemoselective reduction of 10 by the mixed anhydride sodium borohydride method16 led to the corresponding alcohol 12, while the azido group remained unaffected. Reduction of 12 by NaBH₄/10% Pd-C in the presence of di-tert-butyl dicarbonate gave the 4,5-diamino protected pentan-1-ol 13 with selectively protected amino groups.

In conclusion, the present procedure reported for the conversion of lysine and glutamic acid into amines is free of racemization as indicated by comparison of the specific rotation value for one of the final products {11: [α]D = -7.5 (c = 1, in EtOH)} with that reported.15b {[α]D = -7.8 (c = 1 in EtOH)}. Furthermore, it is facile and may be applied to other basic or acidic α-amino acids in order to prepare a variety of chiral triamines and diamines bearing selectively protected amino groups.
Melting points were determined on a Buchi micro melting point apparatus and are uncorrected. Specific rotations were determined with a Perkin-Elmer 141 polarimeter using a 10 cm cell. NMR spectra were recorded on a Bruker AM-200 spectrometer. FAB-MS spectra were obtained on a VG Analytical ZAB-SE. All amino acids (i.e., configuration) were purchased from Fluka Chemical Co. Analytical TLC plates (silica gel 60 F254) and silica gel 60 (230–400 mesh) for column chromatography were purchased from Merck. THF was passed through a column of aluminum oxide, distilled over CaH2 and stored over molecular sieves. All other solvents and chemicals were of reagent grade and used without further purification. Petroleum ether used had bp 40–60°C. Compounds 2–13 gave satisfactory microanalyses: C ± 0.24, H ± 0.21, N ± 0.29.

(2S)-6-Benzoxycarbonylamino-2-tert-butoxycarbonylamino-hexan-1-ol (2):

This compound was prepared according to literature,1,2 and purified by column chromatography using hexane/EtOAc (8:2) as eluent; white crystals; yield: 72%, mp 67–68°C; [α]D 0 = -10.3 (c = 0.6, CHCl3).

MS (FAB): m/z (%) = 389 (M + Na+, 5), 315 (100).

1H NMR (CDCl3): δ = 7.35 (5H, s, C5H5), 5.08 (2H, s, CH2C6H5), 5.03–4.75 (2H, m, 2 × CONH), 3.54 (3H, m, CH, CH2OH), 3.12 (2H, m, CH2NH), 2.85 (1H, m, OH), 1.32–1.20 (15H, m, H-3, 4, 5 + (CH2)3C).

Methyl (4S)-4-Benzoxycarbonylamino-5-hydroxypentanoate (6):

This compound was prepared according to literature,3,4 white solid, yield: 78%, mp 68–65°C (Lit.5 mp 64–66°C); [α]D 0 = -19.3 (c = 1, CHCl3), [Lit.6,7 [α]D 0 = -18.2 (c = 1, CHCl3).

Azides 3,7; General Procedure:

To a stirred solution of N-protected alcohols 2, 6 (1.24 mmol) in CH2Cl2 (3 mL) were added Et3N (0.33 mL, 2.36 mmol) and MeSOCl (0.19 mL, 2.36 mmol) in portions at 0°C. The mixture was stirred at 0°C for 30 min and 30 min at r.t. Brine was added and the organic phase was washed with 1 N HCl, brine, 5% aq NaHCO3, brine, dried (Na2SO4) and evaporated. The addition of petroleum ether (8 mL) under cooling, afforded a solid which after filtration was used in the next step without any further purification. Analytically pure product was obtained after purification by flash chromatography using hexane/EtOAc (8:2) as eluent.

To a stirred solution of the above crude mesylate in DMF (3 mL), was added NaN3 (0.24 g, 3.72 mmol) and the mixture heated at 55°C for 7 h. The solvent was removed the residue taken up in EtOAc (3 × 15 mL). The organic phase was washed with brine (3 × 15 mL), dried (Na2SO4) and evaporated. The residue was purified by column chromatography (hexane/EtOAc, 1:1).

(2S)-6-Benzoxycarbonylamino-2-tert-butoxycarbonylaminohexyl Methanesulfonate: a yellow solid; yield: 417 mg (86%); mp 65–66°C; [α]D 0 = -50.7 (c = 0.5, CHCl3).

MS (FAB): m/z (%) = 467 (M + Na, 60), 315 (100).

1H NMR (CDCl3): δ = 7.35 (5H, s, C5H5), 5.08 (2H, s, CH2C6H5), 5.00–4.70 (2H, m, 2 × CONH), 4.14 (2H, m, CH2OSO2CH3), 3.72 (1H, m, CH), 3.14 (2H, m, CH2NH), 2.97 (3H, s, SO2CH3), 1.55–1.26 (15H, m, H-3, 4, 5 + (CH2)3C).

(2S)-1-Azido-6-benzoxycarbonylamino-2-butoxycarbonylamino-hexane (3): a white solid; yield: 417 mg (86%); mp 65–66°C; [α]D 0 = -50.7 (c = 0.5, CHCl3).

MS (FAB): m/z (%) = 414 (M + Na, 100), 292 (13).

1H NMR (CDCl3): δ = 7.35 (5H, s, C5H5), 5.07 (2H, s, CH2C6H5),
Methyl (4S)-4-Benzylxycarbonylaminopropanoate: yellow solid; mp 73–76°C; [α]D = -26.4° (c = 0.5, CHCl₃).

MS (FAB): m/z (%) = 360 (M + H, 20), 91 (100).

1H NMR (CDCl₃): δ = 7.32 (5H, t, C₅H₅), 5.08 (2H, s, CH₂C₅H₅), 2.94 (1H, t, J= 8 Hz, CH₂O), 2.93 (2H, s, CH₂CO₂H), 2.47 (2H, m, CH₂CO₂) , 2.05 –1.80 (2H, m, CH₃).

Methyl (4S)-4-Azido-benzylxycarbonylaminopropionate: oil; yield: 326 mg (86%); [α]D = -26.0° (c = 0.5, CHCl₃).

MS (FAB): m/z (%) = 307 (M + H, 36), 91 (100).

1H NMR (CDCl₃): δ = 7.32 (5H, t, C₅H₅), 4.88 (1H, d, J= 8 Hz, OCONH), 3.87 (1H, t, CH₃), 3.62 (3H, s, CH₃CO₂), 3.41 (2H, m, CH₂N₂), 2.40 (2H, m, CH₂CO₂), 2.00–1.70 (2H, m, CH₃).

(2S)-N⁵-Benzylxycarbonyl-N⁵-tert-butoxycarbonyl-N¹-(9-fluorenethylmethoxycarbonyl)-1,2,6-triaminohepane (4A):

To a stirred mixture of Pd/C (20 mg) in H₂O (1 mL) through which N₂ had been passed for 5 min was added a solution of NaN₃ (33 mg, 0.8 mmol) in H₂O (1 mL) followed by a solution of N⁵-protected amino azide (78 mg, 0.28 mmol) in MeOH (2.5 mL) at r.t. The catalyst was filtered 20 min later and the solution was concentrated by evaporation with 1 N HCl. The water phase was mixed with EtOAc (5 mL), neutralized with solid NaHCO₃ and extracted with EtOAc (2 x 5 mL). The solvent was removed by evaporation and the residue was dissolved in diiodomethane (4 mL). A solution of NaN₃ (30 mg) in water (4 mL) was added at 2°C, followed by 9-fluorenethylmethoxycarbonylate (72 mg, 0.28 mmol) in portions. After stirring for 5 h at r.t., the mixture was poured into water and extracted with EtOAc (2 x 10 mL). The organic phase was dried, concentrated and the residue was purified by flash chromatography (EtOAc/MeOH: 1) to give 4 as a white solid; yield: 120 mg (73%); mp 124–126°C; [α]D = 10.1° (c = 0.5, CHCl₃).

MS (FAB): m/z (%) = 588 (M + H, 15), 488 (M – CO₂Bu-t, 85), 413 (100).

1H NMR (CDCl₃): δ = 7.78, 7.65, 7.35 (13 H, 3 m, C₅H₅, Fmoc), 5.25, 4.80, 4.65 (3 H, br, 3 x OCONH), 5.08 (2H, s, CH₂C₅H₅), 3.43 (2H, m, OCH₃), 4.19 (1H, t, CH₂O), 3.60 (1H, t, CHNH), 3.20 (4H, m, CH₂NHfMoc + CH₂NH₂), 1.55–1.30 (15 H, m, H-3,4,5 + (CH₂)₃).
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