A New Approach to the Synthesis of Selectively Protected (2*S*)-1,2,4-Triaminobutane Derivatives

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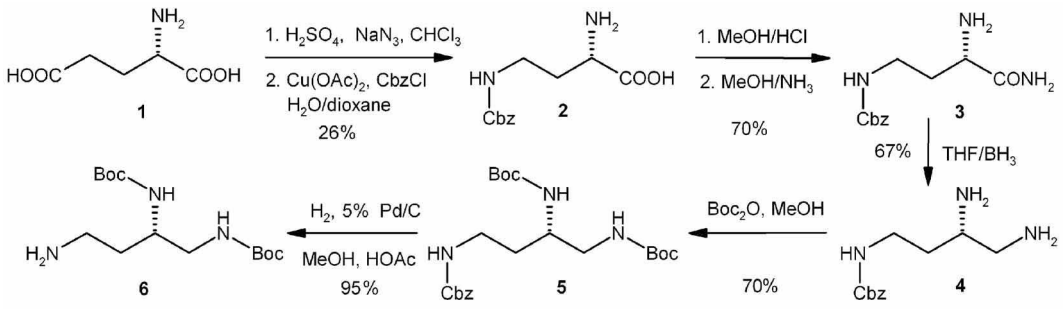
Abstract: An efficient synthesis of selectively protected (2*S*)-1,2,4-triaminobutane from L-glutamic acid via (2*S*)-N^4-benzyloxycarbonyl-2,4-diaminobutanamid is described.

Key words: amides, amines, amino acids, protecting groups, reductions

Vicinal diamines are important ligands for metal complexes[1–5] and useful substrates for heterocyclic compound synthesis.[5–8] 1,2,4-Triaminobutane derivatives were previously applied for preparation of dicarboxylic acids bis(1,2,4-triaminebutane-N^4)amides with two vicinal diamines. These compounds were used for synthesis of bis[platinum(II)] complexes capable of interstrand-DNA binding.[9–12] It is known, however, that only one method for chiral and selectively protected 1,2,4-triaminobutane has been reported.[9–11] The final products were obtained as a result of multi-step synthesis from L- or D-pyroglutamic acid methyl ester via L- or D-(5-hydroxymethyl)-2-pyrrolidone and L- or D-4,5-diaminopentanoic acid derivatives.

Natural α-amino acids with one functional group in the side chain may be regarded as a useful source for the synthesis of 1,2-diamines bearing a third functional group.[5,6,13] We have developed a novel method for the preparation of selectively protected (2*S*)-1,2,4-triaminobutane starting from L-glutamic acid as a source of chirality via (2*S*)-N^4-benzyloxycarbonyl-2,4-diaminobutanoic acid derivatives (Scheme 1). These compounds may be directly used for the preparation of heterocyclic compounds.

(2*S*)-N^4-benzyloxycarbonyl-2,4-diaminobutanoic acid (**2**) was obtained directly from L-Glu (**1**) by a modification of the reported procedures applying Schmidt rearrangement conditions[14,15] and copper complexes method.[15–18] In the second step of the reaction, there was no need to use the pure (2*S*)-2,4-diaminobutanoic acid. In order to avoid the laborious isolation of (2*S*)-2,4-diaminobutanoic acid, a crude mixture of (2*S*)-2,4-diaminobutanoic acid and L-Glu was converted into copper complexes and reacted with benzyl chloroformate. Pure **2** was precipitated from the reaction mixture after decomposition of the copper complexes with EDTA in 1 M HCl[18] when pH was adjusted to 4–5. (2*S*)-N^4-Benzyloxycarbonyl-2,4-diaminobutanoic acid methyl ester[16] was prepared under standard reaction conditions and converted into (2*S*)-N^4-benzyloxycarbonyl-2,4-diaminobutanamide (**3**), applying the reported amino acids amides preparation method.[7,8] Then, (2*S*)-N^4-benzyloxycarbonyl-2,4-diaminobutanamide (**3**) was reduced with diborane in THF (diborane selectively reduces amides[2,7,8,19–25] in the presence of alkoxycarbonyl groups[22–25]) yielding the selectively N^4-protected (2*S*)-1,2,4-triaminobutane derivative **4**. The diborane reduction of **3**, however under reported amino acids reductions conditions,[7,8] gave a complex mixture of various reaction products. In fact, the amide was reduced but also a significant loss of the benzyloxycarbonyl protecting group was



Scheme 1

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unavoidable. Ultimately, it was found that reaction time (5 h) and slightly lowered temperature (55 °C) were sufficient for completion of this reaction. Due to a good solubility of the free diamine in the aqueous phase, (2*S*)-N^4-benzyloxycarbonyl-1,2,4-triaminobutane (**4**) was extracted with Et_2O from saturated NaCl solution. The free amino groups in **4** were protected with *tert*-butoxycarbonyl groups using di-*tert*-butoxycarbonyldicarbonate (Boc_2O) yielding (2*S*)-N^4-benzyloxycarbonyl-N^1,N^2-di-*tert*-butoxycarbonyl-1,2,4-triaminobutane (**5**). The product was finally purified by column chromatography. The benzyloxycarbonyl group was removed by hydrogenolysis (5% Pd/C) to afford (2*S*)-N^1,N^2-*di*-*tert*-butoxycarbonyl-1,2,4-triaminobutane (**6**).

In conclusion, we have developed a five-step method for the preparation of selectively protected (2*S*)-1,2,4-triaminobutane derivatives from L-glutamic acid which is shorter than the reported method starting from L-pyroglutamic acid methyl ester.[9–11] The total yield of the selectively protected triamine synthesis was 13% in comparison to the reported 27%. The yield was mainly limited by the first reaction (Schmidt rearrangement) but commercially available selectively protected (2*S*)-2,4-diaminobutanoic acid derivatives could be used as well. Moreover, the reaction conditions can be easily adapted to the preparation of (2*S*)-1,2,4-triaminobutane derivatives as well as their (*R*)-isomer in large quantities.

^{1}H NMR spectra were recorded on Varian Unity Plus 500 MHz spectrometer. ^{13}C NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer. The optical rotations were measured on a POLAMAT A Carl Zeiss Jena Polarimeter. Microanalyses were performed on a Carlo Erba CHNS-O-EA1180 instrument for C, H, N. Melting points are uncorrected.

(2*S*)-N^4-Benzyloxycarbonyl-2,4-diaminobutanoic Acid (2)

L-Glu (1, 12.5g, 85 mmol) was dissolved in concd H_2SO_4 (43 mL) and $CHCl_3$ (26 mL) was added. To the stirred solution of amino acid NaN_3 (6.8 g, 105 mmol) was added in small portions over 3 h. The obtained solution was warmed for 5–6 h at 50–60 °C. After cooling the reaction mixture was poured on ice and the organic phase was removed. The water phase was neutralized with hot saturated solution of $Ba(OH)_2$. The precipitate of $BaSO_4$ was filtered, washed with water and the filtrate was concentrated to ca. 50 mL. Copper(II) acetate (10 g, 50 mmol) was added and the solution was refluxed for 1 h and then cooled to r.t. The deep blue solution was neutralized to pH = 7.4 and filtered. The filtrate was mixed with dioxane (50 mL) and benzyl chloroformate (6.3 mL, 44 mmol) was added followed by solid NaOH (to adjust the pH to 9). The mixture was stirred for 24 h at r.t. The blue precipitate of amino acids copper complexes was filtered and washed with water, EtOH and Et_2O. The blue solid was dissolved in a solution of EDTA (6.32 g, 17 mmol) in 1 M HCl (100 mL). The insoluble residue was removed by filtration. The pH of the filtrate was adjusted to 5–6 with 10 M NaOH and the solution was kept in a refrigerator overnight. The slightly blue precipitate was filtered and the operation of copper complexes decomposition with EDTA (1.5 g, 4 mmol) in 1 M HCl (70 mL) was repeated. The white solid product was precipitated when pH of the solution was again adjusted to 4–5. Yield: 5.65 g (26.4%); mp 225–227 °C (Lit.[16] mp 223 °C).

^{1}H NMR (500 MHz, DMSO-d_6–TFA): δ = 1.82–2.00 (m, 2 H, CHCH_2), 3.15 (ddd, J_1 = 7.4 Hz, J_2 = 13.7 Hz, J_3 = 8.3 Hz, 2 H, CH_2CH_2), 3.92 (dd, J_1 = 5.3 Hz, J_2 = 10.9 Hz, 1 H, CH_2C*H*), 5.05 (s, 2 H, CH_2Ph), 7.28–7.33 (m, 6 H, C_6H_5, NH), 8.08–8.17 (br s, 3 H, NH_3^+).

^{13}C NMR (200 MHz, D_2O–TFA): δ = 32.7, 39.1, 53.2, 70.0, 130.6, 131.2, 131.6, 139.1, 161.4, 174.4.

Anal. Calcd for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.10. Found: C, 57.04; H, 6.43; N, 10.97.

(2*S*)-N^4-Benzyloxycarbonyl-2,4-diaminobutanamide (3)

(2*S*)-N^4-Benzyloxycarbonyl-2,4-diaminobutanoic acid (**2**, 5.13 g, 20 mmol) was dissolved in 5.7 M absolute MeOH–HCl (27 mL) and absolute MeOH (15 mL). The reaction mixture was kept for 48 h at r.t. The volatiles were evaporated under reduced pressure. The residue was dissolved in $CHCl_3$ (200 mL) and washed with sat. Na_2CO_3 solution to adjust pH of the water to about 9. The organic phase was separated, dried ($MgSO_4$) and evaporated yielding an oily ester (4.07 g, 75%). The oil was dissolved in 24% MeOH–NH_3 (40 mL) and kept for 72 h at r.t. under TLC control. The volatiles were evaporated under reduced pressure yielding a white precipitate of the amide. It was crystallized from MeOH–Et_2O–hexane. Yield: 3.84 g (94%); mp 112–114 °C; $[\alpha]_D^{24}$ +4.3 (*c* = 2, EtOH).

^{1}H NMR (500 MHz, DMSO-d_6–TFA): δ = 1.80–1.92 (m, 2 H, CHCH_2), 3.03–3.17 (m, 2 H, CH_2CH_2), 3.72 (dd, J_1 = 5.8 Hz, J_2 = 11.8 Hz, 1 H, CH_2C*H*), 5.03 (s, 2 H, CH_2Ph), 6.95 (s, 1 H, NH), 7.28–7.39 (m, 5 H, C_6H_5), 7.61 (s, 1 H, NH), 7.87 (br s, 1 H, NH), 8.11 (s, 3 H, NH_3^+).

^{13}C NMR (200 MHz, DMSO-d_6): δ = 35.5, 38.0, 52.9, 65.5, 128.0, 128.6, 137.5, 156.4, 177.6.

Anal. Calcd for $C_{12}H_{17}N_3O_3$: C, 57.36; H, 6.82; N, 16.72. Found: C, 57.23; H, 6.70; N, 16.65.

(2*S*)-N^4-Benzyloxycarbonyl-1,2,4-triaminobutane (4)

(2*S*)-N^4-Benzyloxycarbonyl-2,4-diaminobutanamide (**3,** 2.09 g, 8.33 mmol) was added to anhyd THF (48 mL). The reaction flask was flushed with Ar and cooled in an ice bath. Next 2.8 M THF–BH_3 (15 mL, 42 mmol) was slowly added. The reaction mixture was warmed in 55 °C for 5 h. The solution was cooled in an ice bath and absolute MeOH (15 mL) was added. The mixture was kept at r.t. overnight. Next 5.7 M absolute MeOH–HCl (3.7 mL) was added and the volatiles were evaporated under reduced pressure. The oily residue was dissolved in absolute MeOH (15 mL) and evaporated. The last action was repeated three times to remove the volatile boron compounds. The residue was dissolved in H_2O (10 mL), acidified to pH = 2 with concd HCl and washed with Et_2O (3 × 5 mL). Next the water phase was saturated with NaCl, alkalized with 10 M NaOH and extracted with Et_2O (8 × 15 mL). The ethereal phase was dried with Na_2CO_3 and evaporated under reduced pressure yielding an oil of crude (2*S*)-N^4-benzyloxycarbonyl-1,2,4-triaminobutane (1.32 g, 67%). The product was pure enough for further step of the synthesis. It was stored as dichloride salt. Small samples of the product (tens to hundreds mg) were purified by ion exchange chromatography (Amberlit IRC 50/NH_4^+ in a gradient of Et_3N (0.005–0.4 M). The product was also separated by column chromatography (Sephadex LH-20, MeOH); $[\alpha]_D^{24}$ –3.4 (*c* = 2, EtOH).

^{1}H NMR (500 MHz, DMSO-d_6–TFA): δ = 1.68–1.82 (m, 2 H, CHCH_2), 3.02–3.07 (m, 2 H, CH_2CH), 3.12–3.17 (m, 2 H, CH_2CH_2), 3.34–3.43 (m, 1 H, CH_2C*H*), 5.05 (s, 2 H, CH_2Ph), 7.25–7.40 (m, 6 H, C_6H_5, NH), 7.83–8.25 (br s, 6 H, 2 × NH_3^+).

^{13}C NMR (200 MHz, DMSO-d_6): δ = 30.7, 36.5, 41.1, 47.3, 65.7, 128.0, 128.7, 137.3, 156.4.

Anal. Calcd for $C_{12}H_{21}Cl_2N_3O_2$: C, 46.46; H, 6.82; N, 13.55. Found: C, 46.50; H, 6.74; N, 13.67.

(2*S*)-N^4-Benzyloxycarbonyl-N^1,N^2-di-*tert*-butoxycarbonyl-1,2,4-triaminobutane (5)

(2*S*)-N^4-Benzyloxycarbonyl-1,2,4-triaminobutane (**4**, 1.55 g, 6.5 mmol) was dissolved in MeOH (30 mL) and di-*tert*-butyldicarbonate (2.85 g, 13.1 mmol) was added, followed by Et_3N (1.8 mL, 13.1 mmol). The reaction mixture was stirred for 24 h at r.t. The volatiles were evaporated under reduced pressure and the residue was dissolved in EtOAc (100 mL) and washed with 1 M $KHSO_4$ (3 × 30 mL). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure yielding a white precipitate. The product was purified by column chromatography (silica gel, EtOAc–petroleum ether, 1:1,5) and crystallized from EtOAc–hexane. Yield: 1.99 g (70%); mp 118–120 °C (Lit.[10] mp 122–123 °C); $[\alpha]_D^{24}$ –23.9 (*c* = 2, EtOH) {Lit.[10] $[\alpha]_D^{23}$ –23.8, (*c* = 2, EtOH)}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.40 [s, 9 H, $(CH_3)_3C$], 1.42 [s, 9 H, $(CH_3)_3C$] 1.65–1.74 (m, 2 H, $CHCH_2$), 2.95–3.04 (m, 1 H, CH_2CH_2), 3.08–3.27 (m, 2 H, CH_2CH), 3.44–3.54 (m, 1 H, CH_2CH_2), 3.63–3.72 (m, 1 H, CH_2CH), 4.76–4.85 (br s, 1 H, NH), 4.96–5.03 (br s, 1 H, NH), 5.1 (AB system, J_1 = 12.2 Hz, J_2 = 23.4 Hz, 2 H, CH_2Ph), 5.63–6.71 (br s, 1 H, NH), 7.28–7.38 (m, 5 H, C_6H_5).

^{13}C NMR (200 MHz, MeOD): δ = 29.1, 33.9, 39.1, 45.7, 50.3, 67.7, 80.4, 129.1, 129.2, 129.7, 138.7, 158.7, 158.9, 159.0.

Anal. Calcd for $C_{22}H_{35}N_3O_6$: C, 60.39; H, 8.06; N, 9.60. Found: C, 60.24; H, 8.00; N, 9.71.

(2*S*)-N^1,N^2-Di-*tert*-butoxycarbonyl-1,2,4-triaminobutane (6)

(2*S*)-N^4-Benzyloxycarbonyl-N^1,N^2-di-*tert*-butoxycarbonyl-1,2,4-triaminobutane (**5**, 1.70 g, 3.89 mmol) was dissolved in MeOH (40 mL) and AcOH (0.8 mL) was added. The solution was hydrogenated for 5 h (5% Pd/C). When the reaction was finished, the catalyst was filtered and the volatiles were evaporated under reduced pressure. The residue was dissolved in 1 M $KHSO_4$ (40 mL) and washed with Et_2O (20 mL). The water phase was saturated with NaCl, alkalized with 1 M NaOH and extracted with Et_2O (4 × 40 mL). The ethereal phase was dried ($MgSO_4$) and evaporated under reduced pressure yielding a white solid product (1.12 g, 95%); mp 75–77 °C (Lit.[10] mp 78–80 °C). The product was also turned into acetate by dissolving in Et_2O and adding appropriate equivalent of AcOH. The (2*S*)-N^1,N^2-di-*tert*-butoxycarbonyl-1,2,4-triaminobutane acetate was precipitated as a white solid; mp 130–131 °C; $[\alpha]_D^{24}$ –7.2 (*c* = 2, EtOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.40 [s, 9 H, $(CH_3)_3C$], 1.43 [s, 9 H, $(CH_3)_3C$], 1.52–1.58 (m, 1 H, $CHCH_2$), 1.81–1.90 (m, 1 H, $CHCH_2$), 2.00 (s, 3 H, CH_3COO^-), 2.82–2.88 (m, 1 H, CH_2CH_2), 2.95–3.05 (m, 1 H, CH_2CH_2), 3.15–3.30 (m, 2 H, CH_2CH), 3.65–3.78 (m, 1 H, CH_2CH), 4.95–5.20 (br s, 4 H, NH), 5.43–5.48 (br s, 1 H, NH).

^{13}C NMR (200 MHz, MeOD): δ = 24.4, 29.0, 32.3, 38.3, 45.3, 49.3, 80.6, 80.8, 159.0, 180.4.

Anal. Calcd for $C_{16}H_{33}N_3O_6$: C, 52.87; H, 9.15; N, 11.56. Found: C, 52.90; H, 9.05; N, 11.48.

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