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Synthesis of protected pseudopeptides from dicarboxylic amino acids by Mitsunobu condensation

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Abstract—Four protected pseudopeptides from Glu-, Asp- and Gly-derivatives have been prepared via Mitsunobu condensation. It was shown to be a universal and preparative method which allows the formation of different structural molecules containing reduced peptides.

1. Introduction

Replacement of the natural peptide –CONH group with the resistant isosteric ψ(CH_2NH) group has been applied to obtain biologically active peptide analogues, which are more stable towards enzyme action.[1] This type of compound may also be used as a key intermediate in PNA monomer synthesis.[2] The latter are very useful in biology and medicine due to their unique hybridization properties.[3]

The usual procedure for reduced peptide synthesis is reductive *N*-alkylation[4] between an aldehyde and a component with an amino group. Only a few synthetic procedures are known and used at present for obtaining such aldehydes: periodate oxidation;[5] ozonolysis of alkenes;[6] Swern oxidation;[7] alcohol oxidation by Corey and Kim[8] and reduction of the corresponding Weinreb amides.[9] However, many of these methods are not suitable for all amino acids and do not show regioselectivity, that is, it is difficult to prepare *N*-Boc-ω-*O*-benzyl-α-aldehydes from dicarboxylic amino acids. Also aminoaldehydes are unstable compounds; they are inclined to polycondensation reactions and the formation of significant amounts of by-products. Hence, these features do not allow us to consider the reductive *N*-alkylation as a universal preparative procedure. The Mitsunobu condensation between an alcohol and an acidic component[10] serves as another approach for pseudopeptide formation.

The Mitsunobu reaction proceeds under mild and neutral conditions (pH 7, 0 °C) and shows stereospecificity, functional selectivity and regioselectivity. These conditions avoid the formation of by-products and racemization.

In our case, reduced derivatives of amino acids **3b**,**c** and *N*-Boc-ethanolamine **3a** were selected as the alcohol components and *o*-nitrobenzenesulfonic derivatives **4a**–**c** were used as the acidic components (Scheme 1).

Hydroxyl containing compounds **3b** and **3c** were synthesized by reduction of the α-carboxyl groups of *N*-Boc-ω-benzyl-esters of the corresponding carboxylic acids by using a 1 M solution of BH_3 in THF.[11] This method was selected because of its high selectivity and we did not observe any reduction of the Boc-group and the benzyl ester in contrast to reduction by DIBAL-H or $LiAlH_4$. Conventional introduction of the *o*-nitrobenzenesulfonic (*o*-NBS) group in the carboxyl protected amino acid derivatives was effected by the action of *o*-nitrobenzenesulfonyl chloride in dichloromethane in the presence of triethylamine. The *o*-NBS-group increases the electrophility of the nitrogen and therefore

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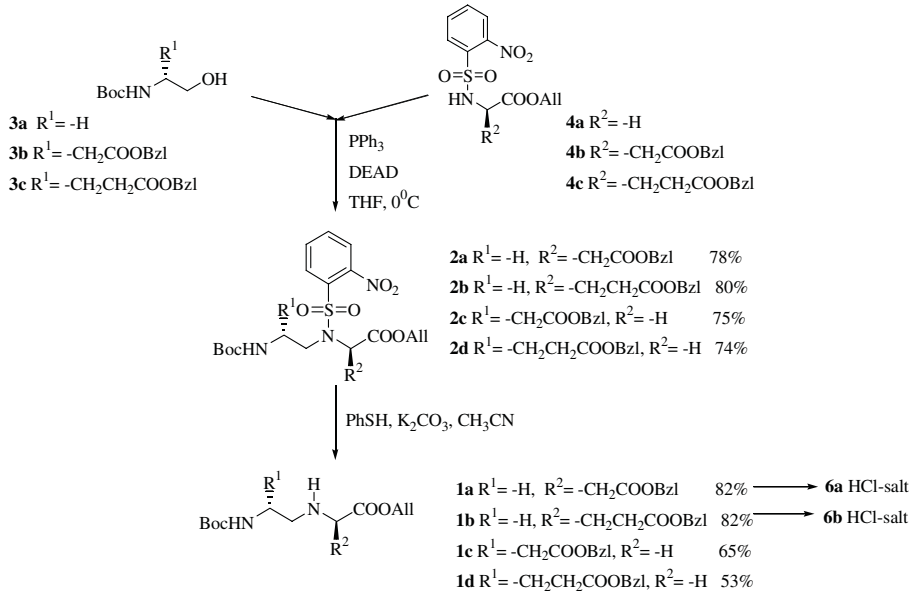


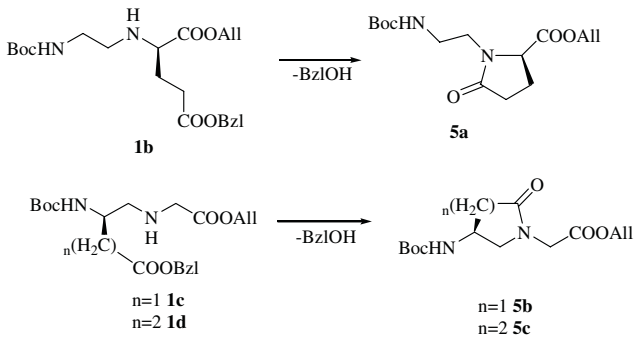
Scheme 1.

facilitates nucleophilic substitution by the S_N2 mechanism. The Mitsunobu reaction was carried out under standard conditions using DEAD and PPh_3 in THF.[10a]

Protected pseudopeptides obtained by this method can be stored for long periods at temperatures below 4 °C. Another way of storing pseudopeptides **1a** and **1b** is as their corresponding HCl salts. We failed to isolate **1c** and **1d** as their salts because of the lower stability of the Boc-group of these compounds in acidic conditions.

The protected pseudopeptides **2a–d** can be used in their free form immediately after removing the *o*-NBS-group using a fivefold excess of thiophenol with a twofold excess of K_2CO_3 in acetonitrile[10b] or after neutralization of the corresponding salt in situ. The thiolysis reaction takes about 5 h with full conversion of *o*-NBS-derivatives into the desired pseudopeptides **1a–d**. It should be noted that compounds **1b–d** are inclined to form the cyclic products **5a–c** under the reaction conditions and this process may be completed after 24 h of storage as the free amines (Scheme 2).

The structures of the *o*-NBS-derivatives of pseudopeptides **2a–d** and the pseudopeptides **1a–b** as their HCl



Scheme 2.

salts were confirmed by ^1H and ^{13}C NMR analysis and from elemental analysis data.

2. Conclusion

The Mitsunobu condensation serves as a general approach for the synthesis of different types of pseudopeptides with the reduced peptide bond in high yields and no racemization. This proposed synthetic strategy has been applied to prepare stable *o*-NBS-derivatives of pseudopeptides in preparative amounts.

3. Experimental

3.1. *o*-NBS pseudopeptide derivative synthesis by Mitsunobu condensation (general procedure)

The *o*-NBS-derivative **4** (1 equiv), amino acid **3** (1.1 equiv) and triphenylphosphine (1 equiv) were dissolved in tetrahydrofuran. The solution was cooled to 0 °C in an ice bath and DEAD (40% solution in toluene) (1.5 equiv) was added dropwise under argon over 30 min. After overnight stirring at room temperature, the solvent was evaporated and the crude oil concentrated in vacuo, redissolved in dry diethyl ether and cooled to 4 °C. The resulting white precipitate was removed by filtration. The filtrate was dried in vacuo and subjected to separation on silica gel (petroleum ether–ethyl acetate 1:1 (v/v)) to give a yellow oil after evaporation and drying in vacuo.

3.2. Removal of the *o*-NBS group (general procedure)

To the solution of the *o*-NBS protected pseudopeptide (1 equiv) in acetonitrile cooled to 0 °C, potassium carbonate (2 equiv) and thiophenol (5 equiv) were added. After 15 min of vigorously stirring at 0 °C and then

5 h at room temperature, the solvent was evaporated. The residue was dissolved in diethyl ether and washed with 20% aqueous citric acid. The water layer was then adjusted to pH 7.0 with solid K_2CO_3 and extracted with dichloromethane. The resulting organic layer was dried over Na_2SO_4, the solvent was evaporated and the remaining oil dried in vacuo.

3.2.1. Boc-Glyψ[CH_2N(*o*-NBS)]Asp(α-OAll,β-OBzl) (2a). Yellow oil, yield 512.90 mg (78%); $[\alpha]_D^{20}$ −13.2 (*c* 1, MeOH); δ_H (200 MHz, $CDCl_3$) 8.07 (1H, d, *J* 7.82, –C*H*–C–N (*o*-NBS)), 7.85 (3H, m, *o*-NBS); 7.35 (5H, s, C_6H_5–), 6.85 (1H, s, N*H*–Boc), 5.62 (1H, m, –O–CH_2–C*H*=CH_2), 5.17 (1H, dd, *J* 1.01, 17.20 Hz, –O–CH_2–CH=CH_2), 5.14 (1H, dd, *J* 1.01, 10.2 Hz, –O–CH_2–CH=CH_2), 5.12 (2H, s, –O–CH_2–Ph), 5.00 (1H, m, α-C*H*), 4.39 (2H, d, *J* 5.70 Hz, –O–CH_2–CH=CH_2), 3.45 (1H, m, Boc–NH–CH_2–CH_2–), 3.12 (3H, m, Boc–NH–CH_2–CH_2–), 2.97 (1H, dd, *J* 4.63, 16.44 Hz, β-C*H*), 2.91 (1H, dd, *J* 5.85, 16.73 Hz, β-C*H*), 1.35 (9H, s, ^{t}Bu); δ_C (62.9 MHz, $CDCl_3$) 167.68, 169.09, 155.96, 148.31, 135.41, 133.89, 132.50, 131.70, 131.30, 131.01, 128.61, 128.50, 128.45, 124.22, 119.44, 79.54, 67.12, 66.71, 57.63, 46.99, 40.47, 36.03, 28.41. Anal. Calcd for $C_{27}H_{33}S_1N_3O_{10}$: C, 54.81; H, 5.62; S, 5.42; N, 7.10. Found: C, 54.57; H, 5.84; S, 5.01; N, 6.90.

3.2.2. Boc-Glyψ[CH_2N(*o*-NBS)]Glu(α-OAll,γ-OBzl) (2b). Yellow oil, yield 334 mg (80%); $[\alpha]_D^{20}$ −2.0 (*c* 1, MeOH); δ_H (200 MHz, $CDCl_3$) 8.05 (1H, d, *J* 7.60 Hz, –C*H*–C–S (*o*-NBS)), 7.62 (3H, m, *o*-NBS), 7.35 (5H, s, C_6H_5–), 5.02 (1H, s, N*H*-Boc), 5.68 (1H, m, –O–CH_2–C*H*=CH_2), 5.21 (1H, dd, *J* 1.01, 17.25 Hz, –O–CH_2–CH=CH_2), 5.15 (1H, dd, *J* 1.01, 9.89 Hz, –O–CH_2–CH=CH_2), 5.12 (2H, s, –CH_2–Ph), 4.73 (1H, m, α-C*H*), 4.48 (2H, d, *J* 5.84 Hz, –O–CH_2–CH=CH_2), 3.51 (1H, m, Boc–NH–CH_2–CH_2–), 3.47 (3H, m, Boc–NH–CH_2–CH_2–), 2.60 (2H, m, γ-CH_2), 2.50 (1H, m, β-C*H*), 2.09 (1H, m, β-C*H*), 1.35 (9H, s, ^{t}Bu); δ_C (50.32 MHz, $CDCl_3$) 172.12, 169.87, 155.91, 148.16, 135.77, 133.78, 132.22, 131.57, 131.29, 131.11, 128.57, 128.28, 124.06, 119.27, 79.50, 66.58, 66.32, 60.17, 46.02, 40.83, 30.45, 28.36, 25.06. Anal. Calcd for $C_{28}H_{35}S_1N_3O_{10}$: C, 55.53; H, 5.82; S, 5.29; N, 6.94. Found: C, 55.48; H, 6.10; S, 4.97; N, 6.4.06.

3.2.3. Boc-Asp(β-OBzl)ψ[CH_2N(*o*-NBS)]Gly(OAll) (2c). Yellow oil, yield 650 mg (75%); $[\alpha]_D^{20}$ −8.3 (*c* 1, MeOH); δ_H (200 MHz, $CDCl_3$) 7.98 (1H, d, *J* 7.58 Hz, –C*H*–C–S (*o*-NBS)), 7.65 (3H, m, *o*-NBS); 7.35 (5H, s, C_6H_5–), 4.35 (1H, d, *J* 9.30 Hz, N*H*–Boc); 5.80 (1H, m, –O–CH_2–C*H*=CH_2), 5.26 (1H, dd, *J* 1.0, 17.20 Hz, –O–CH_2–CH=CH_2), 5.20 (1H, dd, *J* 1.0, 10.53 Hz, –O–CH_2–CH=CH_2), 5.12 (2H, s, –O–CH_2–Ph), 4.50 (2H, d, *J* 5.87 Hz, –O–CH_2–CH=CH_2), 4.20 (1H, m, α-C*H*), 4.05 (2H, m, CH_2Gly), 3.57 (2H, m, CH_2Asp), 2.79 (1H, dd, *J* 4.64, 16.39 Hz, β-C*H*); 2.67 (1H, dd, *J* 5.87, 16.87 Hz, β-C*H*), 1.35 (9H, s, ^{t}Bu); δ_C (62.9 MHz, $CDCl_3$) 171.08, 168.42, 155.37, 148.04, 135.61, 133.72, 133.04, 131.78, 131.39, 131.01, 128.91, 128.64, 128.34, 124.22, 118.97, 79.90, 66.74, 66.07, 51.06, 48.56, 45.43, 36.27, 28.35. Anal. Calcd for $C_{27}H_{33}S_1N_3O_{10}$: C, 54.81; H, 5.62; S, 5.42; N, 7.10. Found: C, 54.95; H, 5.61; S, 4.95; N, 6.85.

3.2.4. Boc-Glu(γ-OBzl)ψ[CH_2N(*o*-NBS)]Gly(OAll) (2d). Yellow oil, yield 860.0 mg (74%); $[\alpha]_D^{20}$ −17.3 (*c* 1, MeOH); δ_H (200 MHz, $CDCl_3$) 8.07 (1H, d, *J* 7.85 Hz, –C*H*–C–S (*o*-NBS)), 7.85 (3H, m, *o*-NBS), 7.35 (5H, s, C_6H_5–), 6.70 (1H, d, *J* 9.30 Hz, N*H*–Boc), 5.78 (1H, m, –O–CH_2–C*H*=CH_2), 5.25 (1H, dd, *J* 1.0, 17.20 Hz, –O–CH_2–CH=CH_2), 5.15 (1H, dd, *J* 1.0, 10.5 Hz, –O–CH_2–CH=CH_2), 5.12 (2H, s, –CH_2–Ph), 4.48 (2H, d, *J* 5.63 Hz, –O–CH_2–CH=CH_2), 4.27 (1H, m, α-C*H*), 4.05 (2H, s, CH_2Gly), 3.45 (2H, m, CH_2Glu), 2.35 (2H, m, γ-CH_2), 1.78 (1H, m, β-C*H*), 1.55 (1H, m, β-C*H*), 1.35 (9H, s, ^{t}Bu); δ_C (50.32 MHz, $CDCl_3$) 172.86, 168.31, 155.94, 147.94, 135.82, 133.63, 133.26, 131.74, 131.29, 130.71, 128.58, 128.25, 124.17, 118.99, 79.76, 66.44, 65.99, 51.79, 47.63, 30.76, 28.30, 27.59. Anal. Calcd for $C_{28}H_{35}S_1N_3O_{10}$: C, 55.53; H, 5.82; S, 5.29; N, 6.94. Found: C, 55.58; H, 6.03; S, 4.92; N, 6.39.

3.2.5. Boc-Glyψ(CH_2NH)Asp(α-OAll,β-OBzl) (1a). Yellow oil, yield 112.2 mg (82%).

3.2.6. Boc-Glyψ(CH_2NH)Glu(α-OAll,γ-OBzl) (1b). Yellow oil, yield 113.0 mg (82%).

3.2.7. Boc-Glu(γ-OBzl)ψ[(CH_2NH)]Gly(OAll) (1c). Yellow oil, yield 105.6 mg (65%).

3.2.8. Boc-Asp(β-OBzl)ψ[CH_2NH]Gly(OAll) (1d). Yellow oil, yield 73.1 mg (53%).

3.2.9. Boc-Glyψ(CH_2NH)Asp(α-OAll,β-OBzl) HCl salt (6a). Colourless solid; mp 124–126 °C; $[\alpha]_D^{20}$ +9.7 (*c* 1, MeOH); δ_H (200 MHz, $CDCl_3$) 10.89 (1H, s, *H*Cl), 9.59 (1H, s, N*H*), 7.35 (5H, s, C_6H_5–), 5.91 (1H, s, N*H*–Boc), 5.75 (1H, m, –O–CH_2–C*H*=CH_2), 5.25 (1H, dd, *J* 1.01, 17.20 Hz, –O–CH_2–CH=CH_2), 5.22 (1H, dd, *J* 1.01, 10.2 Hz, –O–CH_2–CH=CH_2), 5.15 (2H, s, –O–CH_2–Ph), 4.61 (2H, d, *J* 5.70 Hz, –O–CH_2–CH=CH_2), 4.35 (1H, m, α-C*H*), 3.65 (2H, d, *J* 4.63 Hz, β-CH_2), 3.50 (1H, m, Boc–NH–CH_2–CH_2–), 3.21 (3H, m, Boc–NH–CH_2–CH_2–), 1.35 (9H, s, ^{t}Bu). Anal. Calcd for $C_{21}H_{31}N_2O_6Cl_1$: C, 56.95; H, 7.01; N, 6.33. Found: C, 57.55; H, 7.55; N, 6.39.

3.2.10. Boc-Glyψ(CH_2NH)Glu(α-OAll,γ-OBzl) HCl salt (6b). Colourless solid; mp 117–120 °C; $[\alpha]_D^{20}$ +4.4 (*c* 1, MeOH); δ_H (200 MHz, $CDCl_3$) 10.51 (1H, s, *H*Cl), 9.59 (1H, s, N*H*), 7.35 (5H, s, C_6H_5–), 6.15 (1H, s, N*H*–Boc); 5.80 (1H, m, –O–CH_2–C*H*=CH_2), 5.35 (1H, dd, *J* 1.0, 17.20 Hz, –O–CH_2–CH=CH_2), 5.25 (1H, dd, *J* 1.0, 10.53 Hz, –O–CH_2–CH=CH_2), 5.10 (2H, s, –O–CH_2–Ph), 4.59 (2H, d, *J* 5.87 Hz, –O–CH_2–CH=CH_2), 4.05 (1H, s, α-C*H*), 3.60 (2H, m, γ-CH_2), 3.21 (2H, d, *J* 2.51 Hz, β-CH_2), 2.75 (1H, m, Boc–NH–CH_2–CH_2–), 2.50 (3H, m, Boc–NH–CH_2–CH_2–), 1.35 (9H, s, ^{t}Bu). Anal. Calcd for $C_{22}H_{33}N_2O_6Cl_1$: C, 57.83; H, 7.23; N, 6.13. Found: C, 58.27; H, 7.78; N, 6.31.

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