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Formation of Bis (Fmoc-amino ethyl)-*N*-glycine derivatives by reductive amination of Fmoc-amino aldehydes with $NaBH_3CN$

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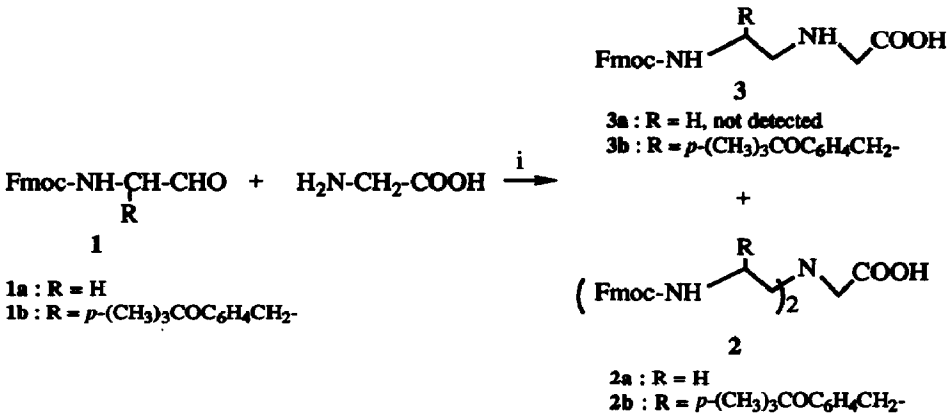
Key-Words : ψ(CH_2NH); Fmoc-amino aldehydes; Bis(Fmoc-amino ethyl)-*N*-glycine; Fmoc-pseudopeptides; reductive amination.

Abstract : *Unexpected results of the reductive amination of Fmoc-amino aldehydes by $NaBH_3CN$ are described. From glycine and Fmoc-4-t-Butoxy-tyrosinal, a small amount of double condensation product was obtained beside the initially desired product Fmoc-Tyr(OtBu)-ψ(CH_2NH)-Gly-OH. From glycine methyl ester and Fmoc-glycinal, we only recovered the reduced peptide bond isostere, but from glycine and Fmoc-glycinal, bis(Fmoc-amino ethyl)-N-glycine was obtained as a major product.*

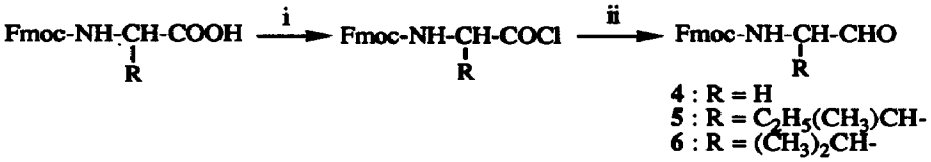
The amino methylene group CH_2NH is often used as an amide bond replacement in peptide analogues[1-3]. As part of our research program[4], we needed such pseudopeptides with a fluoren-9-ylmethyloxycarbonyl (Fmoc) group as amino protection. The incorporation of a ψ(CH_2NH) pseudopeptide bond is usually performed by reductive amination of a Boc-α-amino aldehyde in the presence of $NaBH_3CN$ as reducing agent[1-3]. The preparation of such modified peptides from Fmoc-protected derivatives has not been described, although two recent publications focused on the synthesis of a few Fmoc-amino aldehydes[5,6].

We attempted to synthetize Fmoc-Xxx-ψ(CH_2NH)-Gly-OH under typical conditions[1] described for Boc-amino aldehydes (1.3 equiv of aldehyde and 1 equiv of amine). Surprisingly, further reaction of the amine product with the starting Fmoc-glycinal **1a** occurred mainly, leading to bis(Fmoc-amino ethyl)-*N*-glycine **2a**[7] in 55 % yield from aldehyde (**Scheme 1**). Fmoc-Gly-ψ(CH_2NH)-Gly-OH **3a** was not detected. From Fmoc-4-*t*-butoxy-tyrosinal **1b**, Fmoc-Tyr(OtBu)-ψ(CH_2NH)-Gly-OH **3b** was obtained in 35 % yield and bis-adduct **2b** in 6 % yield[8] (yields from glycine).



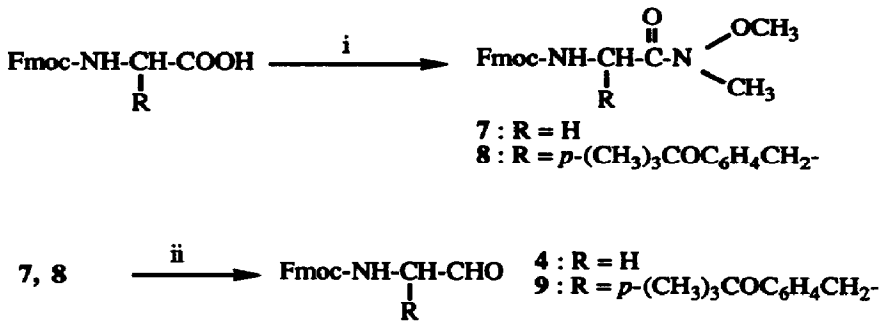
Scheme 1 : i. $NaBH_3CN$; methanol/acetic acid 99/1; r.t.

The first step was the preparation of Fmoc-amino aldehydes. Ho and Ngu[6] synthetized six of them by reduction of Fmoc-AA-*S*-benzylthioesters, while Guichard *et al.*[5] chose the Fehrentz and Castro method[9] in order to obtain Fmoc-Lys(Boc)-H. However, the Fmoc-amino protecting group is stable under acidic conditions and therefore allows the use of Fmoc-amino acid chlorides[10] for the synthesis of aldehyde derivatives. It is known that tributyltin hydride, in the presence of soluble palladium catalysts, reduces acyl chlorides to aldehydes under very mild conditions[11]. We have applied this attractive method to some Fmoc-amino acid chlorides, with tetrakis(triphenyl phosphine) palladium as a catalyst (**scheme 2**).



Scheme 2. i. $SOCl_2$, CH_2Cl_2, reflux, 85 to 90% yield. ii. Bu_3SnH, $(PPh_3)_4Pd$ (cat), THF, rt.

Four and Guibé[9] found that this reduction was quite general and could be carried out with variously substituted acyl chlorides. We have recovered Fmoc-glycinal **4** in 74% yield by this method. Fmoc-isoleucinal **5** and Fmoc-valinal **6** were obtained in only 20 % and 25 % yield from amino acid chlorides, even when a large amount of $(PPh_3)_4Pd$ (*i.e.* 0.1 equiv.) was used. These rather low yields led us to carry out the Fehrentz and Castro method (**scheme 3**).



Scheme 3. i. NEt_3 or DIEA; BOP (benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate); CH_3O-$NHCH_3$, HCl; CH_2Cl_2. ii. $LiAlH_4$, Et_2O.

The conventional use of triethylamine as a base provided Fmoc-Tyr(OtBu)-N(Me)OMe **8** in 80 % yield from Fmoc-Tyr(OtBu)-OH. Diisopropylethylamine DIEA (3.5 equiv.) also allowed the preparation of the Fmoc-protected methyl *N*-methylhydroxamates in very good yields (**7** : 84 % yield, **8** : 87% yield). Reduction of compounds **7** and **8** with 5 equivalents of $LiAlH_4$ gave Fmoc-glycinal **4** and Fmoc-4-*t*-butoxy-tyrosinal **9** in 72% yield and 75% yield from the corresponding hydroxamates. This procedure is very efficient for the preparation of Fmoc-amino aldehydes like Fmoc-4-*t*-butoxy-tyrosinal **9**, since Fmoc and *t*-butyl ether groups remained unaffected.

The reductive amination of aldehydes **9** and **4** with glycine gave the results mentioned above (**scheme 1**). The formation of bis-adducts during reductive amination of carbonyl compounds has been described, especially with ketones when reacting with only one equivalent of amine[12]. However, studies about this side reaction have not, to our knowledge, been reported in relation with reductive amination of α-amino aldehydes by $NaBH_3CN$, although amino aldehydes are typically used in a 2- to 5-fold excess[1,2]. In our case, we have not recovered any amount of the desired product Fmoc-Gly-ψ(CH_2NH)-Gly-OH. Analysis of the proposed reaction mechanism[12] suggests that in this case, the formation of the second iminium moiety proceeds at least as fast as the formation of the first one. In an other hand, we found that the reductive amination of Fmoc-glycinal with a very soluble derivative of glycine, Gly-OMe, only gives the mono-adduct Fmoc-Gly-ψ(CH_2NH)-Gly-OMe[13]. The very low solubility of glycine in the solvent (MeOH/AcOH) can conduced to a very low concentration of the amine compared to the concentration of the aldehyde, and then favoured the bis-adduct formation. However, Fmoc-tyrosinal reacts with glycine to conduce to the major formation of the mono-adduct, which demonstrate that the Fmoc-amino aldehyde side-chain has also a great influence. Preliminar molecular modeling studies (SYBYL modeling system) indicate that a hydrogen bond occurs between an ammonium hydrogen $CH_2N^+H_2$ and the carbonyl moiety of the Fmoc group of Fmoc-Tyr(OtBu)-ψ(CH_2NH)-Gly-OH (not observed in the case of Fmoc-Gly-ψ(CH_2NH)-Gly-OH). This bond could prevent the addition of a second molecule of glycine.

In conclusion, we have found that ψ(CH_2NH) pseudodipeptides could be obtained from Fmoc-amino aldehydes and could therefore be directly used in a Fmoc strategy peptide synthesis. In addition, we have demonstrated that bis(amino ethyl)-*N*-glycine derivatives **2**, which are very useful compounds for

therapeutic purposes[14] or as chelating agents[15], could be synthetized from amino acids. We are presently investigating general reductive amination conditions (pH, number of amine equivalents...) that would lead to the formation of a single product : either the reduced peptide bond isostere, either the bis-adduct.

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References and notes

1. Martinez, J.; Bali, J.P.; Rodriguez, M.; Castro, B.; Magous, R.; Laur, J.; Lignon M.F. *J.Med.Chem.* **1985**, *28*, 1874-1879.
2. Ho, P.T.; Chang, D.; Zhong, J.W.X.; Musso, G.F. *Peptide Res.* **1993**, *6*, 10-12.
3. Couder, J.; Tourwe, D.; Van Binst, G.; Schuurkens, J.; Leysen, J.E. *Int. J. Peptide Protein Res.* **1993**, *41*, 181-184.
4. Hernandez, J.F.; Cretin, F.; Walchshofer, N.; Salvi, J.P.; Gerlier, P.; Rabourdin-Combe, C; Paris, J. in *Peptides 1992*, 844-845, C.H Schneider, A.N. Eberle Eds., ESCOM Science Publishers B.V., Leiden. 1993.
5. Guichard, G.; Briand, J.P.; Friede, M. *Peptide Res.* **1993**, *6*, 121-124.
6. Ho, P.T.; Ngu, K.Y. *J.Org.Chem.* **1993**, *58*, 2313-2316.
7. **2a** : ^{1}H NMR (300 MHz, DMSO d_6) δ : 2.1 (M, 4H, 2x$CH_2C\underline{H}_2NCH_2$); 3.26 (M, 4H, 2x$C\underline{H}_2CH_2NCH_2$); 3.92 (M, 2H, $NC\underline{H}_2COOH$); 4.21 (t, J = 6.32 Hz, 2H, 2xCH of fluorene); 4.33 (d, J = 7.53 Hz, 4H, 2xCH_2OCO); 7.38-7.88 (M, 16H, ArH). Calculated MW : 605. FAB-MS m/e (%) = 606.2 $[M+H]^+$ (69.4), 628.2$[M+Na]^+$ (3.6).
8. **3b** : α_D = +2 (c=0.092, ethanol). Calculated MW : 502. FAB-MS m/e (%) = 503.2 $[M+H]^+$ (100), 1027.8 $[2M+Na]^+$ (2.2). **2b** : α_B = -5 (c=0.058, ethanol). Calculated MW : 929. FAB-MS m/e (%) = 930.4 $[M+H]^+$ (45.3), 952.2 $[M+Na]^+$ (8).
9. Fehrentz, J.; Castro, B. *Synthesis*, **1983**, 676-678.
10. Carpino, L.A.; Cohen, B.J.; Stephens, K.E.; Sadat-Aalaee, S.Y.; Tien, J.H.; Langridge, D.C. *J.Org.Chem.* **1986**, *51*, 3734-3736.
11. Four, P.; Guibe, F. *J.Org.Chem.* **1981**, *46*, 4439-4445.
12. Borch, R.F.; Bernstein, M.D., Dupont Durst, H. *J.Am.Chem.Soc.* **1971**, *93*, 2897-2904.
13. Fmoc-Gly-ψ(CH_2NH)-Gly-OMe: calculated MW : 354. FAB-MS m/e(%) = 355.3$[M+H]^+$(100).
14. Wilson, D.A.; Garlich, J.R.; Frank, R.K.; McMillian, K.; Simon, J. Eur. Patent 89120190.7, 31 oct 1989, 39 pp.
15. Aymes, D.J. ; Suifil, A. ; Collange, E. ; Pâris, M.R. *Bull. Soc. Chim. Fr.* **1990**, *127*, 145-152.

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