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SOLID PHASE SYNTHESIS OF PEPTIDE AMINOALKYLAMIDES DEVELOPMENT AND APPLICATION OF NEW LINKING AGENTS

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Abstract: A new method for the preparation of peptide aminoalkylamides by solid phase synthesis using a modified Fmoc strategy is described. Key step is the synthesis of compound 6 as acid labile linker.

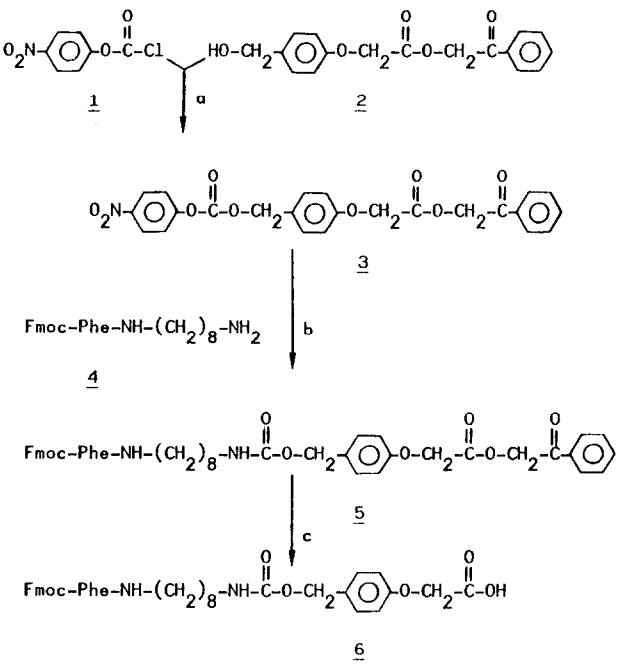
Introduction of an aminoalkylamide group at the carboxy-terminal end of a biologically active peptide improved in some cases metabolic stability as well as biological activity [1,2]. Aminoalkylamides of peptides have been synthesized either by classical solution synthesis [1,2] or by a combination of solid phase synthesis with following coupling of the monoprotected diaminoalkylresidue to the protected peptide in solution and subsequent cleavage of the protecting groups [3].

We report here a new method to prepare peptide aminoalkylamides directly by solid phase synthesis. Key step is the attachment of the known linkage agents [4] with their benzylalcohol moiety to amino acid aminoalkylamides thereby forming an easily cleavable urethane group of the Z(OMe)-type [5].

These new linkers liberate the aminoalkylamides by treatment with trifluoroacetic acid or catalytic hydrogenolysis. The linkage agent 6 can be attached to virtually every commercially available resin commonly used in solid phase synthesis. We prefer resins with an amino anchor group such as aminomethyl or benzhydrylamine resins [6].

Synthesis of the new linkers is straightforward as outlined in scheme I [7]. The phenacylester of the linkage agent 2 is reacted with a phosgene derivative like 4-nitrophenylchloroformate 1 and the obtained mixed carbonate 3 is coupled to the N-α Fmoc-protected amino acid aminoalkylamide resulting the fully protected compound 5. Deprotection of the carboxy moiety by treatment with zinc in acetic acid yields the key compound 6 which is coupled to the resin using diisopropylcabodiimide.

Scheme I

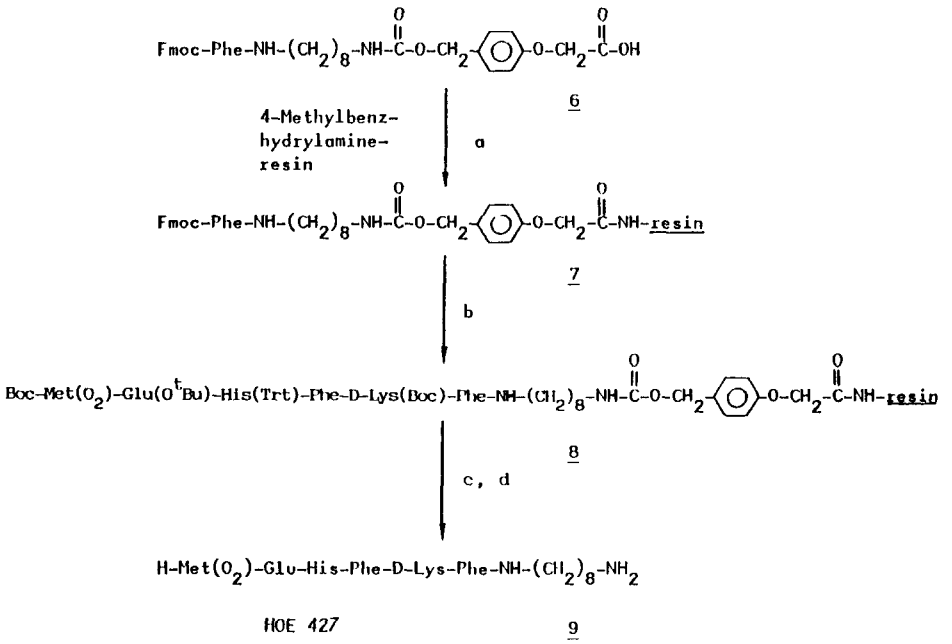


(a) DMF, pyridine 1:1, -20°C → RT, 93 %
(b) DMF, RT → 40°C, 89 %
(c) Zn/AcOH, RT, 83 %

Peptide synthesis follows our generally applied solid phase procedure using N-α Fmoc-protected amino acid derivatives which are coupled either as preformed or in situ generated HOObt esters [8,9].

As an example the synthesis of a biologically active ACTH(4-9) analogue 9 HOE 427) [2] is reported in scheme II. Starting with a N-α-Fmocphenyl alanine 8-aminooctylamide resin the aminoacids are coupled stepwise onto this support in the manner described in scheme II using an Applied Biosystems 430A peptide synthesizer. After the synthesis is finished the resin is washed and dried. Then, the side chain protecting groups and the peptide aminoalkylamide are cleaved simultaneously from the resin with trifluoroacetic acid under addition of thioanisol and ethanedithiol as scavengers.

Scheme II



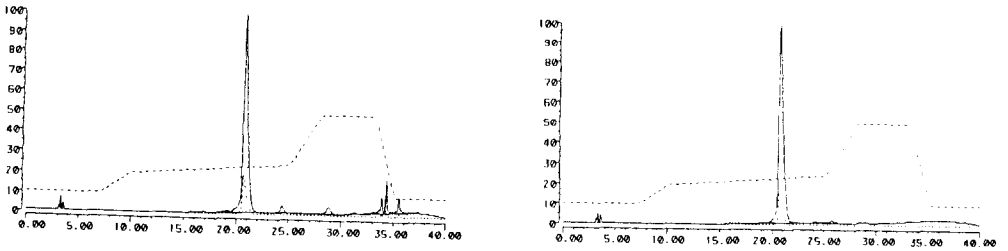
(a) diisopropylcarbodiimide/HOBt, DMF, 2fold excess of reagents and 8 ; (b) couplings cycles consisting of the following: 20 % piperidine in DMF ; washings with DMF ; coupling of preformed or preactivated amino acid-OObt esters ; washings with DMF ; (c) trifluoroacetic acid/ethanedithiol/thioanisole 85/10/5 ; (d) desalting by gel chromatography

The hplc trace of the crude peptide (a) and an authentic sample (b) of HOE 427 9 obtained by classical synthesis [2] is shown in figure 1.

The results described above show, that it is convenient to prepare peptide aminoalkylamides directly by solid phase synthesis using the new anchor group of structure 6. Peptide aminoalkylamides with different chain length and modified C-terminal amino acid have been synthesized.

Figure I

a) b)



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6) These resins are commercially available from several suppliers.

7) All new compounds were characterized by ^{1}H-NMR and MS.

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