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A NEW SYNTHETIC METHOD FOR DEHYDROALANINE PEPTIDES THROUGH HOFMANN DEGRADATION OF α,β-DIAMINOPROPIONYL RESIDUE

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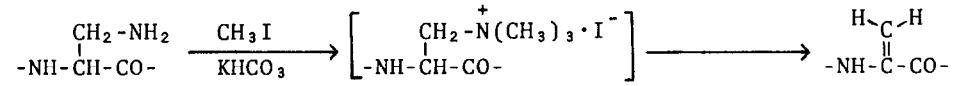
Dehydroamino acid[1] occurred frequently in nature particularly in antibiotic peptides and plant pathogenic toxins.[2] It has been postulated that the dehydroamino acid plays an important role in giving the definite peptide conformation that is required for exhibition of biological activities[3] and could be presumably an intermediate for the biosynthesis of an unusual amino acid or D-amino acid in many natural peptides. Although several methods for synthesis of dehydroalanine peptides[4] have been reported, there are not known conversion reactions of the precursor into dehydroalanine peptide without protections of functional groups in other amino acid residues. We report here a novel useful method for the synthesis of dehydroalanine peptides by means of Hofmann degradation of α,β-diaminopropionyl (A_2pr)[5] residue as shown below:



In a general procedure, a protective group for β-amino function of A_2pr residue in an intermediate peptide was removed *prior to* Hofmann degradation at an adequate step in peptide synthesis. The free amino group of A_2pr was then quaternized according to Chen's procedure[6] as follows: a solution of the deprotected peptide (1 mmol) in methanol (20 ml) was stirred for 15 - 25 hr at room temperature with methyl iodide (2 ml) and $KHCO_3$ (1.5 g). After an addition of ethyl acetate (ca. 100 ml), the reaction mixture was filtered and evaporated to dryness. After ethyl acetate and water had been added to the residue, the organic layer was washed with 10 % aqueous citric acid, saturated aqueous $NaHCO_3$ and water successively, and then dried over $MgSO_4$. Evaporation of the solvent gave a dehydroalanine peptide without any other purification procedures. $N^{\beta},N^{\beta},N^{\beta}$-Trimethyl-$A_2pr$ peptide as an intermediate could not be isolated. Dehydroalanine peptides prepared by this method are summarized in the table.

Several advantages of this new procedure should be pointed out in comparison with the known methods. Other amino acid residues, such as Ser, Asn, and Tyr[7] in the same peptide chain were not methylated under the condition of Hofmann degradation. Although Cys(Me) residue proved to be partially methylated, the formation of sulfonium compounds could be suppressed by a slow addition of methyl

Table[7]

Precursor	Method of deprotection*	Yield(%)	Product**
Z-A_2pr(Boc)-OMe	A	86	Z-ΔAla-OMe
Boc-A_2pr(Z)-Ala-OMe	B	82	Boc-ΔAla-Ala-OMe
Boc-Ala-A_2pr(Z)-OMe	B	68	Boc-Ala-ΔAla-OMe
Boc-Ala-A_2pr(Z)-Ala-OMe	B	61	Boc-Ala-ΔAla-Ala-OMe
Boc-Ser-A_2pr(Z)-Ala-OMe	B	76	Boc-Ser-ΔAla-Ala-OMe
Boc-Tyr(Bzl)-A_2pr(Z)-OMe	B	83	Boc-Tyr-ΔAla-OMe
Z-A_2pr(Boc)-Cys(Me)-OMe	C	78	Z-ΔAla-Cys(Me)-OMe
Boc-Asn-A_2pr(Z)-Ala-OMe	B	77	Boc-Asn-ΔAla-Ala-OMe

* A; HCl-THF, B; H_2-Pd black, C; 99% HCOOH.

** Structures of the products were confirmed by NMR analyses.

iodide. These facts make this method useful for the preparation of complex dehydroalanine peptides containing different kinds of free functional groups. Furthermore, a base-catalyzed rearrangement of Asn[7] residue between α- and β-amides was not detected in the synthesis of Boc-Asn-ΔAla-Ala-OMe.[7]

Since this reaction proceeds under very mild condition in which the other functional groups were not affected in a peptide, this novel and simple procedure may provide a versatile synthetic method for dehydroalanine peptides. Further studies in order to demonstrate the utility of this method are now in progress.

REFERENCES AND FOOTNOTES

1) Dehydroamino acid denotes an amino acid containing a double bond in its side chain especially at α position.

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7) Abbreviations: A_2pr, α,β-diaminopropionic acid; Ala, alanine; Ser, serine; Asn, asparagine; Tyr, tyrosine; Cys(Me), S-methyl-cysteine; ΔAla, dehydroalanine; Z, benzyloxycarbonyl; Boc, *t*-butoxycarbonyl.

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