

FACILE AND USEFUL ONE-POT SYNTHESIS OF DEHYDROOLIGOPEPTIDES USING ΔNCA

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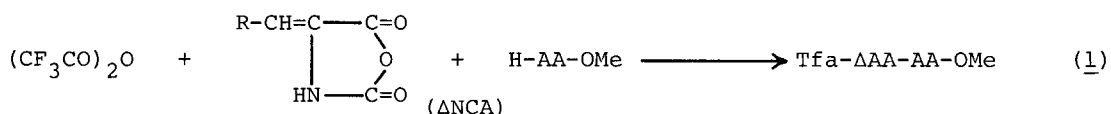
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Summary: One-pot coupling of ΔNCA with N- and C-terminus α-amino acid, peptide, or dehydropeptide was achieved to give various types of dehydrooligopeptides.

Recently, much attention has come to be focused on the synthesis of naturally occurring dehydropeptides (DHP) and their analogs, and on the correlation between the structure and the bioactivity of DHP.

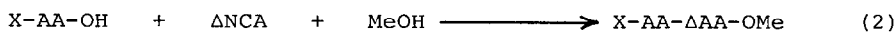
In the preceding papers,^{1,2)} we reported briefly the synthesis of N-carboxy α-dehydroamino acid anhydride (ΔNCA) and the application to the synthesis of acetyl-DHP. Here, we will report very useful one-pot synthesis of versatile DHP by using ΔNCA as the building block of α-dehydroamino acid (DHA, ΔAA) residue.

Δ¹-Dehydrodipeptide³⁾ N-protected with trifluoroacetyl (Tfa) group was synthesized by the reaction of ΔNCA (3.20 mmol), (CF₃CO)₂O (3.84 mmol) with an equimolar α-amino acid (AA) methyl ester in THF (5 ml) at -10 °C, followed by the addition of pyridine (9.60 mmol) at room temperature. Since it is known that only Tfa group attached directly to N-terminus DHA residue can be readily removed by treating with primary amines,^{4,5)} it is worthwhile to synthesize Tfa-DHP.



Tfa-ΔLeu-(L)-Phe-OMe	98%	103-104 °C	[α] _D -15.6° (c 1.01) ⁵⁾
Tfa-ΔPhe-(L)-Thr-OMe	70%	syrup	[α] _D 29.0° (c 0.95)

On the other hand, N-protected Δ²-dehyrodipeptide ester (2)³⁾ was synthesized from an equimolar N-blocked AA-OH (3.20 mmol) and ΔNCA in the presence of DCC (3.87 mmol) and 3 molar pyridine in THF (5 ml) below -10 °C, followed by the addition of MeOH (30 ml) and triethylamine to pH 8 at room temperature.



Cbz-(L)-Ala-ΔBut-OMe	88%	136-137 °C	[α] _D -10.5° (c 0.65)
Boc-(L)-Phe-ΔBut-OMe	85%	97-98 °C	[α] _D -14.2° (c 0.90)

Furthermore, surprisingly, the similar coupling between three building blocks of N-protected AA-OH, Δ NCA, and H-AA-OMe was worked up in one-pot to give the expected N-blocked Δ^2 -dehydrotripeptide ester (3).

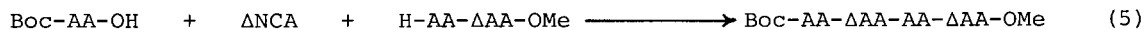


Cbz-Gly- Δ Phe-(L)-Ser-OMe	60%	syrup	$[\alpha]_D$ -21.9 $^\circ$ (c 1.16)
Boc-(L)-Ala- Δ norVal-(L)-Ser-OMe	65%	syrup	$[\alpha]_D$ -34.5 $^\circ$ (c 1.03)
Boc-Gly- Δ Phe-(L)-Met-OMe	85%	161-162 $^\circ\text{C}$	$[\alpha]_D$ -50.9 $^\circ$ (c 0.95)

In order to apply the above reaction to versatile DHP synthesis, the coupling between α -amino acid, Δ NCA, and dipeptide or dehydrodipeptide was performed. The similar treatment of Δ NCA with successive Boc-AA-OH and dipeptide or Δ^2 -dehyrodipeptide ester was worked up to give the expected Δ^2 -dehydrotetrapeptide (4) and $\Delta^{2,4}$ -dehydrotetrapeptide esters (5)³⁾ respectively.



Boc-(L)-Leu- Δ Phe-Gly-(L)-Ala-OMe	80%	82-84 $^\circ\text{C}$	$[\alpha]_D$ -80.0 $^\circ$ (c 0.90)
Boc-(D)-Ala- Δ But-(L)-Phe-(L)-Leu-OMe	84%	157-158 $^\circ\text{C}$	$[\alpha]_D$ 21.1 $^\circ$ (c 0.93)



Boc-Gly- Δ Leu-Gly- Δ Leu-OMe	72%	syrup	
Boc-(D)-Ala- Δ Phe-(L)-Leu- Δ Val-OMe	78%	syrup	$[\alpha]_D$ 23.8 $^\circ$ (c 0.82)

It is noteworthy that the coupling proceeds successfully in the presence of pyridine. In addition, based on the NMR spectral data, the configuration of all the new DHP obtained was confirmed to be (Z)-geometric structure.⁷⁾

In conclusion, it was found that the synthetic method of DHP developed by us was very available and applicable for the synthesis of the desired DHP, e. g., the highly unsaturated DHP and various combination of DHA in DHP.

Further work including β -elimination of DHP thus obtained is now in progress.

References

- 1) C. Shin, Y. Yonezawa, and J. Yoshimura, *Chemistry Lett.*, 1981, 1635.
- 2) Y. Yonezawa, T. Yamada, and C. Shin, *Chemistry Lett.*, 1982, 1567.
- 3) In this paper, the symbols Δ^1 , Δ^2 , and $\Delta^{2,4}$ indicate one or two double bonds of DHA residues and their position numbers from N-terminus in sequence.
- 4) E. G. Breitholle and C. H. Sattmer, *J. Org. Chem.*, 41, 1344 (1976).
- 5) C. Shin, Y. Yonezawa, K. Watanabe, and J. Yoshimura, *Bull. Chem. Soc. Jpn.*, 54, 3811 (1981).
- 6) Measured in MeOH at 25 $^\circ\text{C}$.
- 7) C. Shin, Y. Yonezawa, T. Yamada, and J. Yoshimura, *Bull. Chem. Soc. Jpn.*, 55, 2147 (1982).