SYNTHESIS OF N-CARBOXYDEHYDROTYROSINE ANHYDRIDE AND ITS TRANSFORMATION TO USEFUL DEHYDROTYROSINE DERIVATIVES

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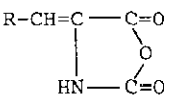
Abstract—— N-Carboxydehydrotyrosine anhydride (ΔTyr·NCA) was first synthesized from p-methoxymethoxybenzaldehyde and 2-azidoacetate *via* N-benzyloxycarbonyl-O-methoxymethoxydehydrotyrosine by five steps. The facile stepwise protections of ΔTyr·NCA gave many useful dehydrotyrosine derivatives.

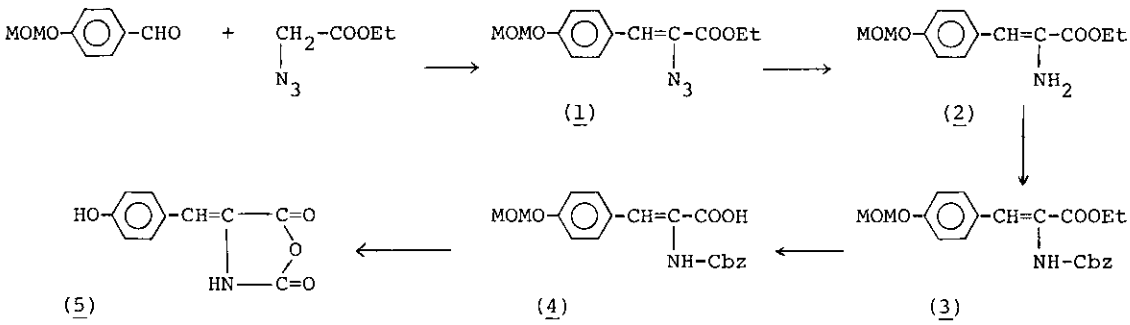
In the course of the study on the synthesis of α-dehydroamino acid (DHA) and its dehydropeptide (DHP), which have been focused on their structure and bioactivity,[1,2] we already pointed out the usefulness of N-carboxy-α-dehydroamino acid anhydride (ΔNCA) for the synthesis of DHA and DHP.[3,4] In fact, recently, N-carboxydehydrophenylalanine anhydride was applied to the facile synthesis of tentoxin.[5]



(ΔNCA)

So far, we reported the synthesis of several kinds of DHA and ΔNCA which corresponds to neutral α-amino acid having no functional groups in their side chains, besides dehydroglutamic acid derivatives.[6] Here, we succeeded in synthesizing dehydrotyrosine (ΔTyr) and its ΔNCA derivatives, the latter of which was subjected to the ring cleavage reaction to other useful ΔTyr derivatives.

According to the Hemetsberger method,[7] p-methoxymethoxybenzaldehyde (200 mmol), derived from p-hydroxybenzaldehyde and methoxymethyl (MOM) chloride, was condensed with ethyl 2-azidoacetate (400 mmol) in the presence of EtONa (400 mmol) in EtOH (200 ml) at 0 °C for 4 h to give ethyl 2-azido-(p-methoxymethoxy)*cinnamate* [1: 57%, syrup. IR (KBr): 2150 (N_3), 1630 (C=C) cm^{-1}. NMR ($CDCl_3$): δ 6.86 (s, -CH=)]. The selective hydrogenolysis of azido group of 1 (32.5 mmol) with aluminum-amalgam [made from Al (14.9 g) and $HgCl_2$ (14.9 g)] in Et_2O (200 ml) gave O-MOM-ΔTyr-



MOM=CH_3OCH_2, Cbz=$C_6H_5CH_2OCO$

Scheme 1

OEt (2) almost quantitatively, according to the procedure reported previously.[8] While the usual acylation of 2 was found to be difficult, the reaction of 2 (40 mmol) with benzyloxycarbonyl (Cbz) chloride (80 mmol) in CH_2Cl_2 (80 ml) for 24 h proceeded ultimately in the presence of NaOH (10 mmol) and $[CH_3(CH_2)_3]_4N\cdot HSO_4$ (0.4 mmol) as a phase transfer catalyst to give N-Cbz-O-MOM-ΔTyr-OEt (3). Furthermore, the ester 3 (11.4 mmol) was hydrolyzed with 1 M-LiOH (13.7 mmol) in dioxane (8 ml) to give N-Cbz-O-MOM-ΔTyr-OH (4). As shown in Scheme 1, the intended cyclization of 4 (0.56 mmol) with $SOCl_2$ (27.56 mmol) in CH_2Cl_2 (2 ml) for 1.5 h readily took place to give ΔTyr·NCA (5) along with a small amount of O-MOM-ΔTyr·NCA. From the result, it seems that the MOM group is effective for the protection of phenolic OH group.

In the IR and NMR spectra of 2-5 summarized in Table 1, the appearance of the absorption at about 1650 cm^{-1} (>C=C<) and that of the chemical shift at about δ 6.50 (-CH=C-) show clearly that the olefinic structure remain unchanged during the consecutive reactions.

On the other hand, to be utilized in a wide variety of the peptide synthesis, both the OH and NH_2 groups of ΔTyr derivatives must be easily and selectively protected with an useful protecting group such as Cbz and t-butoxycarbonyl (Boc) groups. In addition, we were also interested not only in the above protection but also in the reactivity of the ΔNCA ring itself newly obtained.

Treatment of 5 (0.96 mmol) with di-t-butylcarbonate [$(Boc)_2O$; 1.06 mmol] in THF (2 ml) in the presence of a few drops of pyridine for 24 h, followed by the addition of MeOH (5 ml). The resulting solution was then made basic to pH 9 with N-methylmorpholine (NMM) and was stirred for 1 h to give O-Boc-ΔTyr-OMe (6).

Table 1. Dehydrotyrosine Derivatives (2, 3, 4, and 5)

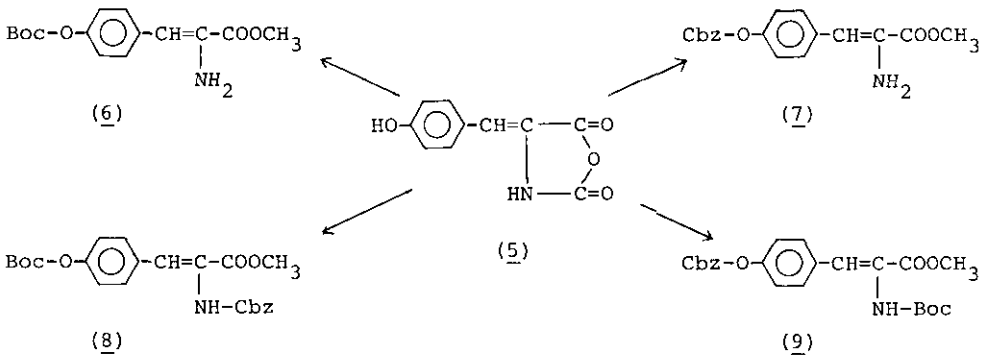
Compound No.	Yield (%)	Mp °C	IR (KBr), cm^{-1}			^{1}H-NMR, δ ($CDCl_3$)	
			NH	COO	C=C	-NH- [OH]	-CH=
2	95	syrup	3460 3375	1710	1645	4.16 (bs)[a]	6.46 (s)[b]
3	60	syrup	3315	1725	1645	6.50 (bs)	7.26-7.40 (+Ph)
4	85	148-149	3270	1720	1640	9.84 (bs)	7.16-7.52 (+Ph)
5	83	196 (dec.)	3405	1825 1770	1660	10.14 (bs) [11.28 (bs)]	6.64 (s)

a) Broad singlet. b) Singlet.

On the other hand, in the case of Cbz-Cl instead of $(Boc)_2O$, the similar reaction gave O-Cbz-ΔTyr-OMe (7) as shown in Scheme 2.

From the results and by comparison with the reactivity of two reaction positions of 5, the phenolic OH group was found to be acylated more preferentially than the ring imino group.

Furthermore, for the one pot synthesis of ΔTyr derivatives O,N-diprotected with different groups, treatment of 5 (0.97 mmol) with $(Boc)_2O$ (1.06 mmol) was similarly carried out for 24 h. To the resulting solution was added successively triethylamine (1.55 mmol) and a solution of Cbz-Cl (1.45 mmol) in THF (1 ml) over 1.5 h. Finally, the reaction mixture was treated with MeOH (5 ml) and then NMM was added to make the mixture to pH 9 to give the expected O-Boc-N-Cbz-ΔTyr-OMe (8). Contrary to the above consecutive reactions, the similar successive treatments of 5 with Cbz-Cl, $(Boc)_2O$, and then MeOH gave N-Boc-O-Cbz-ΔTyr-OMe (9), as illustrated in Scheme 2 and summarized in Table 2. In addition, it was



Scheme 2

Table 2. O- and O,N-Diprotected ΔTyr Derivatives (6-9)

compound No.	Yield (%)	Mp °C	IR (KBr), cm^{-1}			^{1}H-NMR, δ ($CDCl_3$)	
			NH	COO	C=C	-NH- / $-NH_2$	-CH=
6	80	113-115	3455 3380	1760 1700	1630	4.24 (bs)	6.50 (s)
7	84	93-95	3480 3400	1755 1705	1630	4.24 (bs)	6.48 (s)
8	46	97-98	3325	1760 1725	1645	6.48 (bs)	7.12-7.52 (+Ph)
9	52	78-80	3350	1770 1710	1650	6.20 (bs)	7.32 (s)

found that when the above sequential operations were terminated by using water in place of MeOH, the C-free derivatives of 8 and 9 could be obtained in good yields. These results will be reported in detail elsewhere.

REFERENCES AND NOTE

1. U. Schmidt, J. Häusler, E. Öhler, and H. Poisel, Fortschritt. Chem. Org. Naturst., 37, 300 (1979); C. H. Stammer, "Chemistry and Biochemistry of Amino Acid, Peptide and Protein", 6, 34 (1981).
2. K. Noda, Y. Shimohigashi, and N. Izumiya, "The Peptides", Vol. 5, by E. Gross and J. Meienhofer, Academic Press (1983).
3. In this paper, the symbol Δ indicates the double bond of DHA derivatives.
4. C. Shin, T. Yamada, and Y. Yonezawa, Tetrahedron Lett., 24, 2175 (1983). C. Shin and Y. Yonezawa, Chem. Lett., 1985, 519.
5. R. Jacuier and J. Verducci, Tetrahedron Lett., 25, 2775 (1984).
6. C. Shin, Y. Yonezawa, and E. Watanabe, Tetrahedron Lett., 26, 85 (1985).
7. H. Hemetsberger, D. Knittel, and H. Weidmann, Monatsh. Chem., 100, 1599 (1969).
8. C. Shin, Y. Yonezawa, K. Unoki, and J. Yoshimura, Bull. Chem. Soc. Jpn., 52, 1657 (1979).

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