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

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Abstract—N-Carboxydehydrotyrosine anhydride (ATyr·NCA) was first
synthesized from p-methoxymethoxybenzaldehyde and 2-azidoacetate
via N-benzyloxy carbonyl-O-methoxymethoxydehydrotyrosine by five
steps. The facile stepwise protections of ATyr·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 bioactiv-
ity,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

So far, we reported the synthesis of several kinds of DHA and ΔNCA which corre-
sponds 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 (N₃), 1630 (C=O) cm⁻¹. NMR (CDCl₃): 6 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 HgCl₂ (14.9 g)] in Et₂O (200 ml) gave O-MOM-ΔTyr-
While the usual acylation of 2 was found to be difficult, the reaction of \(2\) (40 mmol) with benzyloxycarbonyl (Cbz) chloride (80 mmol) in \(\text{CH}_2\text{Cl}_2\) (80 ml) for 24 h proceeded ultimately in the presence of \(\text{NaOH}\) (10 mmol) and \((\text{CH}_3\text{CH}_2)_3\text{N} \cdot \text{HSO}_4\) (0.4 mmol) as a phase transfer catalyst to give \(\text{N-Cbz-0-MOM-ATyr-OEt}\) (1).

Furthermore, the ester \(1\) (11.4 mmol) was hydrolyzed with 1 M-LiOH (13.7 mmol) in dioxane (8 ml) to give \(\text{N-Cbz-0-MOM-ATyr-OH}\) (4). As shown in Scheme 1, the intended cyclization of 4 (0.56 mmol) with \(\text{SOCl}_2\) (27.56 mmol) in \(\text{CH}_2\text{Cl}_2\) (2 ml) for 1.5 h readily took place to give \(\text{ATyr.NCA}\) (2) along with a small amount of \(\text{O-MOM-ATyr.NCA}\). 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\(^{-1}\) (\(>\text{C}=\text{C}<\)) and that of the chemical shift at about 6.50 (\(-\text{CH}=\text{C}-\)) 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 \(\text{NH}_2\) groups of \(\text{ATyr}\) 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 \(\text{ANCA}\) 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 \(\text{N-methylmorpholine (NMM)}\) and was stirred for 1 h to give \(\text{O-Boc-ATyr-OMe}\) (6).
Table 1. Dehydrotyrosine Derivatives (2, 3, 4, and 5)

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Yield (%)</th>
<th>Mp °C</th>
<th>IR (KBr), cm⁻¹</th>
<th>¹H-NMR, δ (CDCl₃)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>NH</td>
<td>COO</td>
</tr>
<tr>
<td>2</td>
<td>95</td>
<td>syrup</td>
<td>3460</td>
<td>1710</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>syrup</td>
<td>3375</td>
<td>1705</td>
</tr>
<tr>
<td>4</td>
<td>85</td>
<td>148-149</td>
<td>3270</td>
<td>1720</td>
</tr>
<tr>
<td>5</td>
<td>83</td>
<td>196 (dec.)</td>
<td>3405</td>
<td>1825</td>
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</table>

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-ATyr-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 ATyr derivatives N,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-ATyr-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-ATyr-OMe (9), as illustrated in Scheme 2 and summarized in Table 2. In addition, it was
Table 2. O- and O,N-Diprotected ΔTyr Derivatives (6-9)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
<th>Mp °C</th>
<th>IR (KBr), cm⁻¹</th>
<th>(^1)H-NMR, δ (CDCl₃)</th>
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<td></td>
<td></td>
<td></td>
<td>NH</td>
<td>COO</td>
</tr>
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<td>7</td>
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<td>93-95</td>
<td>3480</td>
<td>1755</td>
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<tr>
<td>8</td>
<td>46</td>
<td>97-98</td>
<td>3325</td>
<td>1760</td>
</tr>
<tr>
<td>9</td>
<td>52</td>
<td>78-80</td>
<td>3350</td>
<td>1770</td>
</tr>
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</table>

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

3. In this paper, the symbol Δ indicates the double bond of DHA derivatives.

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