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THE SYNTHESES OF N-FREE α-DEHYDROAMINO ACID ESTER AND N-ACETYL DEHYDRODIPEPTIDE ESTER FROM N-CARBOXY α-DEHYDROAMINO ACID ANHYDRIDE

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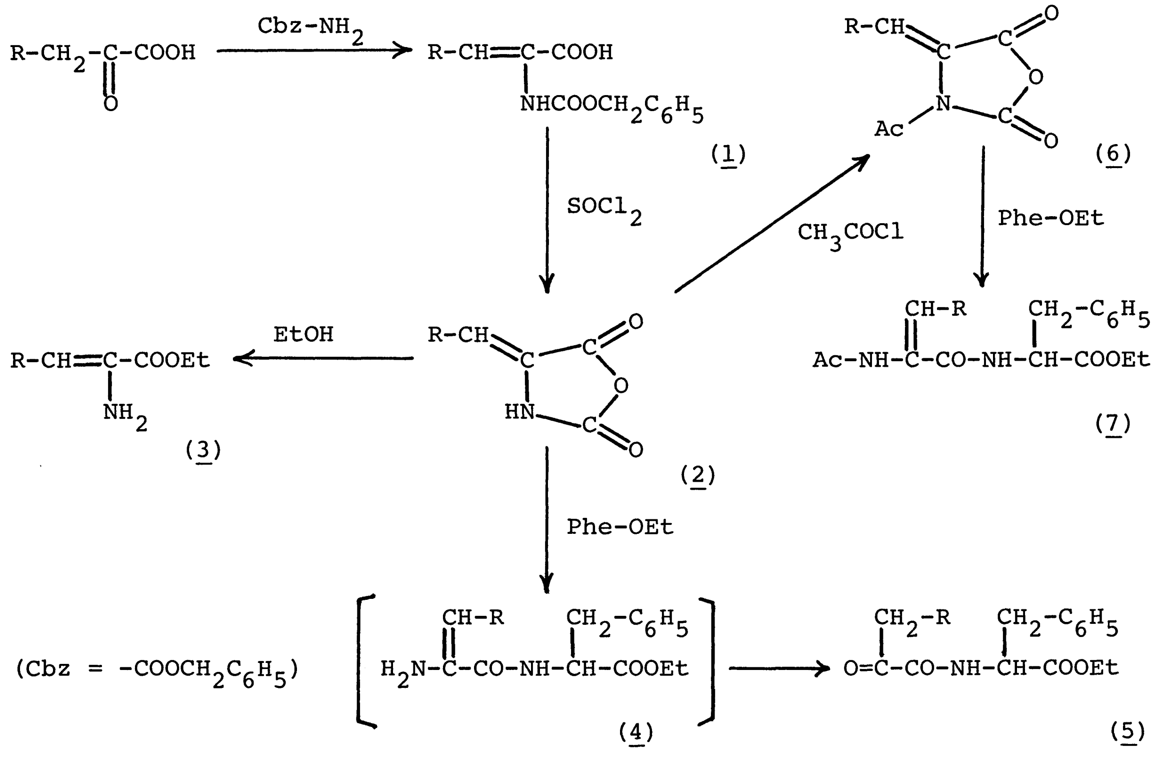
N-Carboxy α-dehydroamino acid anhydride, derived from N-benzyloxycarbonyl α-dehydroamino acid (DHA) and thionyl chloride, was found to be very useful for the synthesis of N-free DHA ester by alcoholysis and N-acetyl dehydrodipeptide ester by coupling was α-amino acid ester.

In previous papers,[1-3)] we reported on the useful syntheses of the currently interesting N-benzyloxycarbonyl (Cbz) α-dehydroamino acid (DHA) (1), N-free DHA ester (3), and their dehydropeptides, which were very important constituents or moieties of antibiotic and phytotoxic peptides containing DHA residue.[4-6)] So far, compound 3 has been derived only from α,β-unsaturated carboxylic ester *via* the corresponding α-azidoolefin ester by us.[2,7,8)]

In the present paper, we wish to report a facile synthesis of several N-carboxy α-dehydroamino acid anhydrides (ΔNCA)[9)] (2), other than N-carboxy α-dehydroalanine anhydride,[10)] and the application for the preparations of 3 and N-acyl dehydrodipeptide esters (7).

The starting compound (Z)-1 (a; R=CH_3, b; R=C_2H_5, c; R=n-C_3H_7, d; R=i-C_3H_7, e; R=C_6H_5), prepared by the condensation of α-oxocarboxylic acid with benzyl carbamate as in our earlier works,[1,2)] was treated with three molar $SOCl_2$ (15 ml) in CH_3COCl (30 ml)[11)] as a solvent at room temperature for 2 hours to give readily the desired 2 as colorless needles in an almost quantitative yield (Table 1). Compared with the common saturated N-carboxy α-amino acid anhydrides (NCA), ΔNCA (2) were found to be surprisingly stable and not to polymerize even after they were allowed to stand at room temperature for several months. Furthermore, alcoholysis of 2 (30 mmol) with EtOH (15 ml) in the presence of small amount of Et_3N at room temperature for an hour proceeded smoothly to give a colorless oil, identified as ethyl (Z)-2-amino-2-alkenoate (3) in about 74% yield. The compounds 3 thus obtained was in complete agreement with the DHA ester prepared by the reduction of ethyl (Z)-2-azido-2-alkenoates with aluminum-amalgam.[2)]

Generally, it is well-known that the conditions for the preparation of dipeptides by the direct coupling of NCA with α-amino acid ester, except glycine ester, are very delicate because of extreme tendency of NCA for polymerization. In order to examine the reactivity, ΔNCA was subjected to the coupling with α-amino acid ester. When solution of 2 (20 mmol) in dry THF (15 ml) were treated with an equimolar phenylalanine ethyl ester (Phe-OEt) at room temperature for half an hour, colorless syrup or crystals, which were identified as Phe-OEt N-protected with alkylethanedioyl group (5), were obtained in about 50% yield (Table 2). The reaction of 2 with Phe-OEt would to give initially the desired



a; $R=CH_3$, b; $R=C_2H_5$, c; $R=n\text{-}C_3H_7$, d; $R=i\text{-}C_3H_7$, e; $R=C_6H_5$

Scheme 1

N-free dehydrodipeptides (4), which are converted to 5 by subsequent hydrolysis, during purification on silica gel columns. Similarly, compound 2 reacted with primary amines such as cyclohexylamine and benzylamine to give the corresponding α-oxocarboxamides in good yields.

On the other hand, ΔNCA (2) were subjected to the acetylation, followed by

Table 1. The yields, melting points, and NMR data of ΔNCA (2 and 6)

	Yield (%)	Mp °C	^{1}H NMR (DMSO-d_6) -CH= δ (Hz)		Yield (%)	Mp °C	^{1}H NMR (DMSO-d_6) -CH= δ (Hz)
2a	95	136-138 (dec.)$^{a)}$	5.80q (7.5)	6a	92	82-85 (dec.)$^{c)}$	6.47q (7.5)
2b	90	97-98$^{a)}$	5.82t (8.0)	6b	90	55-56 (dec.)$^{c)}$	6.36t (7.5)
2c	93	116-117$^{a)}$	5.82t (8.0)	6c	93	syrup	6.40t (7.5)
2d	94	91-92$^{a)}$	5.74d (10.0)	6d	90	82-84 (dec.)$^{c)}$	6.18d (10.0)
2e	93	229-232 (dec.)$^{b)}$	6.66s	6e	87	105-108 (dec.)$^{c)}$	7.17s

a) Colorless needles from cyclohexane. b) Colorless needles from $CHCl_3$.
c) Colorless needles after successive washing with water and ethyl ether.

Table 2. The yields, melting points, and NMR data of 5 and 7

	Yield (%)	^{1}H NMR ($CDCl_3$) -CH_2CO-	α-H δ (Hz)		Yield (%)	Mp °C	^{1}H NMR ($CDCl_3$) -CH= δ (Hz)
5a	50$^{a)}$	2.85q (7.0),	4.75dt (8.2, 6.3)	7a	95	138-140$^{c)}$	6.38q (7.1)
5b	53$^{a)}$	2.60t (7.0),	4.76dt (8.2, 6.3)	7b	97	162-163$^{c)}$	6.38t (7.0)
5c	57$^{a)}$	2.84t (7.0),	4.76dt (8.2, 6.3)	7c	92	137-138$^{d)}$	6.26t (7.0)
5d	51$^{a)}$	2.74d (7.0),	4.78dt (9.0, 6.7)	7d	94	150-152$^{d)}$	6.10d (10.0)
5e	65$^{b)}$	4.14d (1.1),	4.75dt (8.0, 6.2)	7e	98	152-154$^{e)}$	6.88s

a) Colorless syrup. b) Mp 126-127 °C. c) Colorless needles from CCl_4.
d) Colorless needles from CCl_4-ethyl acetate. e) Colorless needles from benzene-isopropyl alcohol.

the coupling with α-amino acid ester, in order to prepare N-blocked dehydrodipeptides. Compounds 2 (20 mmol) were treated with CH_3COCl (45 mmol) in dry THF (50 ml) at pH 4.0 with dropwise addition of Et_3N for an hour to give the expected N-acetyl ΔNCA (6) as colorless needles in fairly good yields (Table 1).

It is noteworthy that compound 6 is comparatively unstable and gradually polymerizes in DMSO solution within a few hours to give resinous substance, while 6 is readily converted in water to the authentic N-acetyl DHA quantitatively.

The subsequent coupling of 6 (20 mmol) with an equimolar Phe-OEt in dry THF (40 ml) was conducted at room temperature for 40 minutes and colorless needles, identified as N-acetyl (Z)-dehydroaminoacylphenylalanine ethyl esters (7), were obtained in almost quantitative yields (Table 2). The structural and configurational assignment of 7e was confirmed by the independent coupling of N-acetyl (Z)-2-dehydrophenylalanine with Phe-OEt.3) The structure of all new compounds (2, 5, 6, and 7) were supported by spectroscopic data and satisfactory results in elemental analysis.

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9) In this paper, the symbol Δ indicates an exocyclic double bond of 5-position in oxazolidinedione (2 and 6).
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11) N-Carboxy α-dehydroalanine anhydride was first synthesized by the treatment of benzyloxycarbonylaminoacrylic acid with PCl_5 in dry ethyl ether in a 70% yield.10)

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