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CONVENIENT SYNTHESES AND REACTIONS OF TWO KINDS OF BASIC α-DEHYDROAMINO ACID DERIVATIVES

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Summary: Two kinds of basic N-carboxy α-dehydroamino acid anhydrides (ΔNCA) were synthesized by the cyclization of N-benzyloxycarbonyl (Cbz)-α-dehydro-ornithine and -lysine (DHA), derived from Cbz-aminoaldehydes and N-Cbz-2-(diethoxyphosphinyl)glycine esters. Moreover, facile conversion of Cbz as N^{α}-protecting group in DHA to Boc via ΔNCA was also successful.

In the course of our work on the synthesis of α-dehydroamino acid (DHA),[1,2] which seems to be an important residue in naturally occurring and synthetic dehydropeptides (DHP),[3-5] we already reported several useful synthetic methods for DHA and DHP.[6-8] Recently, the DHA and DHP have been utilized for the studies on both the structure-biological activity correlation[9] and the asymmetric hydrogenation.[10] So far, the syntheses of several kinds of neutral and acidic DHA derivatives, which are supposed to be originated from various aliphatic, aromatic, and acidic α-amino acids, have been reported.[11,12] As an another category, basic DHAs such as α-dehydroornithine (ΔOrn) and α-dehydrolysine (ΔLys) are also postulated to be come from ornithine and lysine, but the synthetic method has not yet appeared in the literature.

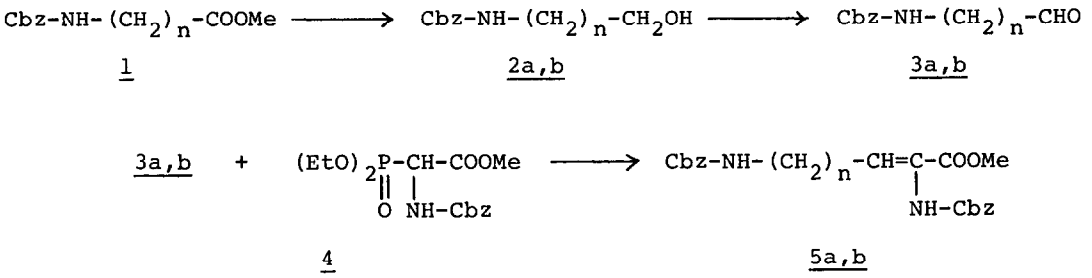
This paper reports the convenient synthesis and facile conversion of N-benzyloxycarbonyl (Cbz)-ΔOrn and Cbz-ΔLys derivatives to the corresponding N-carboxy α-dehydroamino acid anhydrides (ΔNCA), which are further interconverted to the DHA derivatives N^{α}-protected with t-butoxycarbonyl (Boc) group.

According to the method reported recently by Schmidt and co-workers,[13] we took advantage of the reaction of Wittig-Horner reagent with an appropriate aminoaldehyde. First of all, in order to prepare the two desirable aminoaldehydes in high yields, the starting N-Cbz-aminoalcohols (2a,b),[14] derived by the acylation of 3-amino-1-propanol with Cbz-Cl and by the reduction of methyl 4-Cbz-aminobutanoate (1) with $NaBH_4$ or $LiAlH_4$ respectively, were subjected to the following oxidation. In particular, the oxidation of 3-Cbz-amino-1-propanol (2a) was thoroughly examined under various conditions, as summarized in Table 1. As a result, it was found that the yields of the expected 3-Cbz-amino-1-propanal [3a; IR (KBr): 3350 (NH), 1710, 1700 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 5.40 (bs, 1H, NH), 9.64 (s, 1H, CHO)] and 4-Cbz-amino-1-butanal [3b; IR: 3424 (NH), 1710, 1695 (C=O) cm^{-1}. ^{1}H-NMR: δ 5.48 (bs, 1H, NH), (s, 1H, CHO)] reached to 85 and 84% respectively.

Table 1. Oxidation of 2a,b to 3a,b

Substrate No.	Reaction conditions: Oxidizing agent/solvent	Molar ratio[a]	Reaction time (h)	Yield of 3 (%)
2a	$C_5H_5N \cdot SO_3$/DMSO	4.0	72	41
	$(C_5H_5N)_2 \cdot Cr_2O_7/CH_2Cl_2$	1.5	72	39
	CrO_3/C_5H_5N	6.0	1.5	60
	$C_5H_6N \cdot ClCrO_3/CH_2Cl_2$	2.0	1.5	75
	$C_5H_6N \cdot ClCrO_3/CH_2Cl_2$	5.0	1.5	85
	$(COCl)_2$/DMSO	1.1	1.0	69
	$C_5H_6N \cdot ClCrO_3/CH_2Cl_2$	5.0	1.5	79[b]
2b	$C_5H_6N \cdot ClCrO_3/CH_2Cl_2$	5.0	1.5	65
	$(COCl)_2$/DMSO	1.1	1.0	84

a) Oxidizing agent/Substrate. b) Boc-NH$(CH_2)_2$CHO from Boc-NH$(CH_2)_2CH_2$OH.[15]



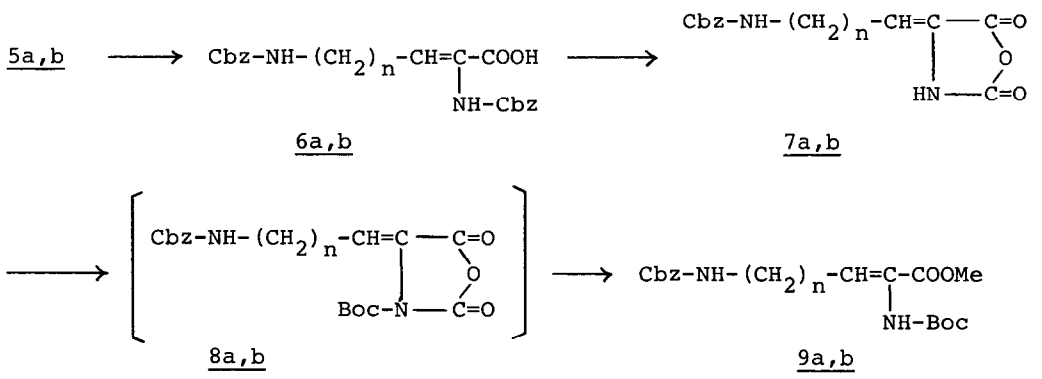
Scheme 1.

Subsequently, condensation of an equimolar 3a,b (4.52 mmol) with N-Cbz-2-(diethoxyphosphinyl)Gly-OMe (4)[13] was carried out in the presence of t-BuOK (4.52 mmol) in CH_2Cl_2 (11 ml) at -60 °C for 1 h and then at room temperature for 3 h to give the desired Cbz-ΔOrn(Cbz)-OMe (5a) and Cbz-ΔLys(Cbz)-OMe (5b) in almost quantitative yields. Hydrolysis of 5a,b (2.43 mmol) with 1 M LiOH aqueous solution (122 ml) at room temperature for 3 h was also performed to give the corresponding, free acids, Cbz-ΔOrn(Cbz)-OH (6a) and Cbz-ΔLys(Cbz)-OH (6b), in fairly high yields respectively (see Table 2).

Moreover, for the synthesis of ΔNCA of both ΔOrn and ΔLys, the compound 6

thus obtained was submitted to the intramolecular cyclization. According to the method reported previously,[7,8] treatment of 6a,b (2.50 mmol) with $SOCl_2$ (5 ml) in ethyl ether (10 ml) below 0 °C for 30 min and then at room temperature for 1 h gave N-carboxy N^{δ}-Cbz-α-dehydroornithine and N^{ε}-Cbz-α-dehydrolysine anhydrides [ΔOrn(Cbz)·NCA (7a) and ΔLys(Cbz)·NCA (7b)] almost quantitatively.

In case of basic amino acids, it is usually neccessary to protect two amino groups with different protecting groups for peptide synthesis. Therefore, in order to protect the basic DHA thus obtained with Boc group at N-terminus, the acylation of 7a,b (3.45 mmol) with di-t-butyl carbonate [$(Boc)_2O$; 4.14 mmol] was carried out to form Boc-ΔOrn(Cbz)·NCA (8a) and Boc-ΔLys(Cbz)·NCA (8b) as unstable intermediates. Subsequent ring cleavage of 8a,b with methanol (5 ml) in the presence of N-methylmorpholin (10.35 mmol) in one-pot gave the expected Boc-ΔOrn(Cbz)-OMe (9a) and Boc-ΔLys(Cbz)-OMe (9b) in 50 and 55% yields respectively, as shown in Scheme 2 and summarized in Table 2.



a; n=2, b; n=3

Scheme 2.

It is noteworthy that the yields of all the new DHA derivatives are very high. Moreover, the structures of all the compounds thus obtained were characterized spectroscopically (IR and ^{1}H-NMR) and gave satisfactory results in elemental analysis. In particular, in the IR spectra of 7a,b, the appearance of the characteristic absorption band at 1860-1850 cm^{-1} region due to the acid anhydride (CO-O-CO) showed clearly the formation of ΔNCA ring. Furthermore, based on the chemical shifts of the γ-methylene and β-olefin proton signals, which appeared in comparatively higher magnetic fields (ca. 2.30 and 6.36 ppm, respectively),[16] the configurations of 5, 6, 7, and 9 could be tentatively concluded to be (Z)-geometry.

Table 2. Yields, melting points, and spectral data of 5-7 and 9

Compound No.	Yield (%)	Mp °C	IR, cm^{-1} in KBr CO (CO-O-CO)		C=C	^{1}H-NMR, δ in $CDCl_3$ γ-H	-CH= (β) (J_{Hz})
5a	90	syrup[a]	1725	1715	1650	2.42q	6.36t (8.0)
5b	85	syrup[a]	1720	1710	1660	2.24q	6.56t (7.5)
6a	80	121-123[b]	1725	1710	1650	2.30q	6.40t (7.0)[c]
6b	85	126-128[b]	1710	1690	1660	2.15q	6.64t (7.5)[c]
7a	93	87-89[b]	(1860)	1810	1650	2.42q	5.90t (8.0)[c]
7b	85	147-149[b]	(1850)	1790	1650	2.24q	5.82t (8.0)[c]
9a	50	syrup[a]	1730	1698	1665	2.44q	6.53t (7.5)
9b	55	syrup[a]	1730	1710	1665	2.22q	6.48t (7.5)

a) Colorless. b) Colorless needles. c) Measured in DMSO-d_6.

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