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A New Synthetic Route to Dehydrodipeptides Containing ΔAsp Residue from Oxazine-2,4-dione Derivatives

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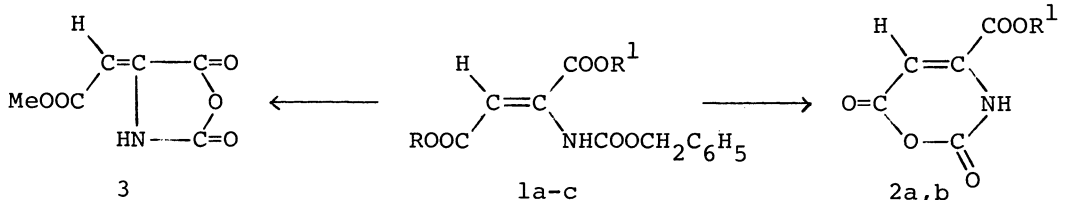
Reaction of N-benzyloxycarbonyl-dehydroaspartic acids with $SOCl_2$ gave N-carboxy dehydroaspartic acid anhydride or oxazine-2,4-dione-6-carboxylic acids depending on the starting materials. The latter were found to be very useful compounds for the synthesis of various dehydropeptides.

Recently, we have accomplished the convenient syntheses of various kinds of N-benzyloxycarbonyl (Cbz)-(E)- and (Z)-dehydroaspartic acids [Cbz-ΔAsp(OR)-OR^1: 1a; R=R^1=H, 1b; R=H, R^1=Me, 1c; R=Me, R^1=H] from both α-(N-Cbz)-aminomaleic acid anhydride and hydroxyaspartic acid dimethyl ester.[1] Here, we would like to report on the new and facile synthetic method for dehydrodipeptides (DHP) containing (E)- or (Z)-ΔAsp residue by using 1, although the similar DHP was so far synthesized by the base-catalyzed β-elimination of hydroxyaspartyldipeptides.[2]

It was already reported that N-carboxy α-dehydroamino acid anhydride (ΔNCA) was very effective for the coupling with α-amino acid both as an N- and C-components.[3] Therefore, according to the method reported previously,[3] an attempt to convert (Z)-1a with $SOCl_2$ to the corresponding ΔAsp·NCA was carried out to obtain colorless crystals. Unexpectedly, it was found that the product did not show the characteristic absorption band at about 1870 cm^{-1} due to five-membered acid anhydride (-CO-O-CO-), even the satisfactory elemental analysis ($C_5H_3NO_5$) was obtained. In addition, the reaction of (Z)-1b also occurred to give similar colorless crystals. As a result of the independent preparation by the condensation of dimethyl oxaloacetate with methyl carbamate[4] and comparison of the IR spectral data, the crystals obtained from 1a,b were found to be oxazine-2,4-dione-6-carboxylic acids [2a; yield 55%, mp 172 °C (dec.). IR (KBr): 1800 (-CO-O-CO-) cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.10 (-CH=), 11.56 (NH). 2b; 98% 150-151 °C. 1800 cm^{-1}. δ 6.16, 11.78] being different from the expected ΔNCA. On the other hand, in the



3 1a-c 2a,b

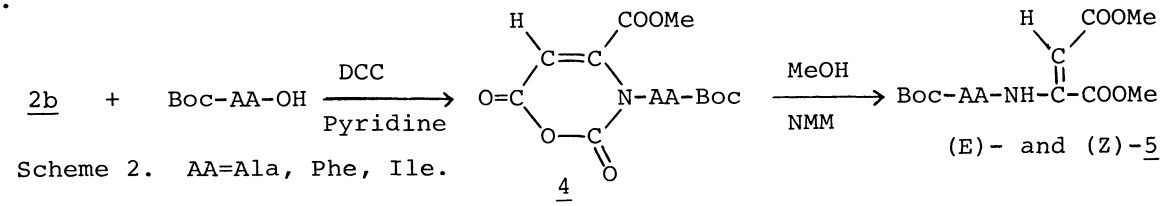
a; R=R^1=H, b; R=H, R^1=Me, c; R=Me, R^1=H

Scheme 1.

case of 1c, the reaction with $SOCl_2$ gave the expected ΔAsp(OMe)·NCA [3; yield 65%, mp 161-163 °C. IR (KBr): 1870 (-CO-O-CO-) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.70 (-CH=), 11.81 (NH)].

From the results, in the case of 1a, it can be seen that the ring closure between Cbz and the β-carboxyl groups, not α-carboxyl, took place predominantly to give 2a, as shown in Scheme 1.

More interestingly, as shown in Scheme 2, subsequent coupling of 2b with Boc-AA-OH (Ala, Phe, Ile) in the presence of DCC in pyridine proceeded to form the corresponding N-acyloxazinedione derivatives (4), which were treated *in situ* with MeOH in the presence of N-methylmorpholin (NMM) to give a mixture of (Z)- and (E)-Δ^2-dehydroaspartyldipeptides (5) in good yields. The isomers thus obtained could be separated by column chromatography, as summarized in Table 1. Since the olefin proton signal of (E)-isomer of α-dehydroamino acid residue is always observed in lower magnetic field,[5] the stereochemistry of the two geometric isomers could be readily determined. In addition, the (E)-5 is thought to be derived by the isomerization of (Z)-5, yielded after the ring cleavage of 4, with strong base such as NMM.



Scheme 2. AA=Ala, Phe, Ile.

Table 1. Yields, Mp, and Physical Constants of 5

Compound 5 (AA)	Geometry of ΔAsp	Yield %	Mp/°C	IR, $\tilde{\nu}$/cm^{-1} (KBr) C=C	^1H NMR, δ ($CDCl_3$) -CH=
Ala	E	6	syrup	1640	6.44s
	Z	67	121-122	1640	5.54s
Phe	E	8	169-170	1635	6.54s
	Z	61	105-107	1638	5.52s
Ile	E	7	112-114	1630	6.43s
	Z	60	syrup	1630	5.52s

In conclusion, it is worth noting that the oxazinediones (2), thus obtained, are versatile compounds for the syntheses of DHP including an important segment of phomopsin A[6] and its analogs.

References

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