A NEW ROUTE TO (Z)-3-ALKYLIDENE-(S)-6-ALKYL-2,5-PIPERAZINEDIONES VIA N-CARBOXY-α-DEHYDROAMINO ACID ANHYDRIDES

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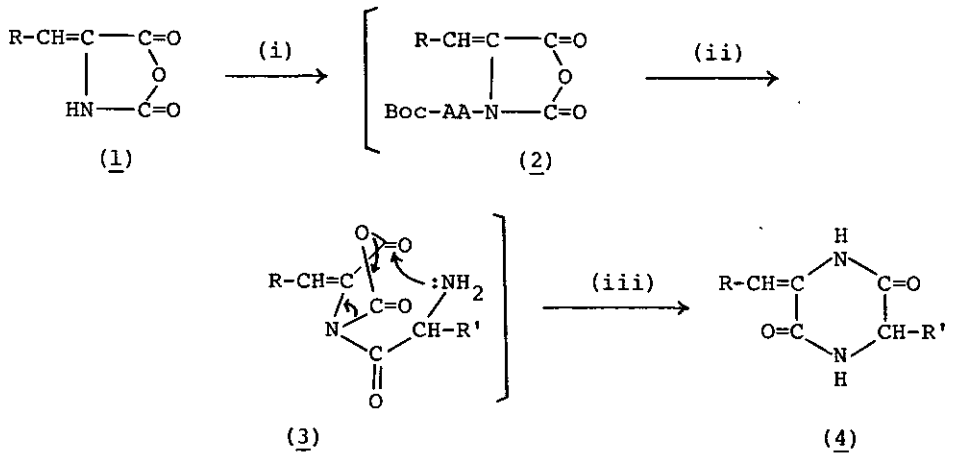
Abstract —— A new synthetic method for (Z)-3-alkylidene-(S)-6-alkyl-2,5-piperazinediones was accomplished by the coupling of N-carboxy-α-dehydroamino acid anhydrides with Boc-α-amino acid, followed by the deprotection of Boc group and by the ring expansion.

Unsaturated unsymmetric 3- and 3,6-disubstituted 2,5-piperazinediones (2,5-piperazinedione ≈ PDO) have been thought to be very important precursor and intermediate for the synthesis of naturally occurring PDO derivatives, such as albonoursin,[1] picroroccelin[2] and bicyclomycin,[3] and interesting substrate for the study of the asymmetric hydrogenation.[4] Although there are many reports on the synthesis of exocyclic unsaturated PDO derivatives, all of them consist of a similar method which is carried out by the condensation of methylene in PDO with various aldehydes.[5] Here, we would like to report a new and facile synthesis of various 3-alkylidene-PDO derivatives (4) by the coupling of N-carboxy-α-dehydroamino acid anhydride (1; ΔNCA)[6] with t-butoxycarbonyl (Boc)-α-amino acid (AA), followed by the cleavage of Boc group and by the ring expansion.
A solution of Boc-AA-OH (7.04 mmol) and dicyclohexylcarbodiimide (DCC) (7.68 mmol) in CH_2Cl_2 (20 ml) was prepared previously at -10 °C. Into the solution was added successively an appropriate 1 (6.40 mmol) and pyridine (7.04 mmol) and then the resulting solution was continuously stirred at -10 °C for 1 h and finally at room temperature for 12 h. After concentrating the reaction solution and removing the dicyclohexylurea precipitated, the residual syrup was dissolved in ethyl acetate (50 ml) and further treated with ethyl acetate (400 ml) saturated with HCl gas and then allowed to stand at room temperature for 2 h. After removal

of the solvent, the colorless crystalline residue thus obtained was dissolved again in dry DMF (300 ml) and the resulting solution was made basic to pH 8 with N-methylmorpholin and then allowed to stand at room temperature for 6 h. Evaporation of the solvent gave crystals, which were recrystallized from ethanol to give colorless needles. The product thus obtained was found to be completely consistent with (Z)-3-alkylidene-(S)-6-alkyl-PDO (4) prepared independently by the condensation of 1,4-diacetyl-(S)-3-alkyl-PDO with an appropriate aldehyde,[7,8] as listed in Table 1.



(i) Boc-AA-OH/DCC. (ii) HCl. (iii) $-CO_2$

ΔNCA = ΔAbu,[7] ΔLeu, ΔPhe. AA = Leu, Phe.

Scheme 1

From the above result and fact, as is shown in Scheme 1, the formation mechanism of 4 is supposed in the following. Namely, N-Boc-AA-ΔNCA (2) formed initially as the intermediate from 1 and Boc-AA-OH was deprotected with HCl to give the corresponding H-AA-ΔNCA (3), which was immediately cyclized with the decarboxylation to give 4.

In conclusion, by comparison with the conventional method mentioned above,[5] the new method developed here was found to be very convenient, because the reaction step is similar in numbers and two substituents can be introduced simultaneously at 3- and 6-positions of PDO.

Table 1. The yields, physical constants, and spectral data of 4

Compound (4)	Yield (%)	Mp (°C)	^{1}H-NMR, δ in TFA[a] -CH= (J_{Hz})	$[\alpha]_D^{25}$ (c 0.2)[b]
cyclo(ΔAbu-Leu)	61	263-265[c]	6.61 q (7.5)	-66.2°
cyclo(ΔLeu-Leu)	76	265-268[d]	6.42 d (10.5)	-89.1°
cyclo(ΔLeu-Phe)	78	242-244	5.98 d (10.5)	-105.0°
cyclo(ΔPhe-Leu)	73	226-228[d]	7.36 s	-197.4°
cyclo(ΔPhe-Phe)	72	276-279[e]	6.97 s	-550.0°

a) TFA = Trifluoroacetic acid. b) Recorded in acetic acid. c) Ref. 8a. d) Ref. 8b. e) Ref. 9.

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7. ΔAbu = 2-Amino-2-butenoic acid residue.
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