CHEMISTRY LETTERS, pp. 873-874, 1978. Published by the Chemical Society of Japan

DEPENDENCY OF THE RATIO OF THE DIASTEREOMERS, L- AND D-*t*-LEUCYL-L-VALINE, ON THE COUPLING METHODS

Toshifumi MIYAZAWA, Katsumi TAKASHIMA, Takashi YAMADA, Shigeru KUWATA,
and Hiroshi WATANABE
Laboratory of Chemistry, Faculty of Science, Kōnan University, Okamoto,
Higashinada-ku, Kobe 658

In the condensation of *N*-pivaloyl- or *N*-benzyloxycarbonyl-DL-*t*-leucine with methyl L-valinate, the ratio of the resulting diastereomers varied depending upon the coupling method.

In the course of our studies on the asymmetric synthesis of *t*-leucyl peptides,1) samples of methyl *N*-pivaloyl-*t*-leucyl-L-valinate (Piv-Tle-L-Val-OMe: Tle = DL, D and L) were necessary as standards for the gas chromatographic analysis.2) We attempted to prepare the samples by condensing Z-Tle*) (DL, D and L) with L-Val-OMe by the DCC or the DCC-HOBt method and replacing Z with Piv as shown in the following scheme.

$$\text{Z-Tle} \xrightarrow[\text{DCC,THF}]{\text{L-Val-OMe}} \text{Z-Tle-L-Val-OMe} \xrightarrow[\text{MeOH}]{\text{H}_2\text{/Pd-C}} \xrightarrow[\text{EtN(Pr-}i)_2\text{,CH}_2\text{Cl}_2]{\text{Piv-Cl}} \text{Piv-Tle-L-Val-OMe}$$

The condensation of Z-DL-Tle with L-Val-OMe, however, gave a product rich in the L-L-diastereomer, particularly by the DCC-HOBt method.

Apparently this phenomenon reflects kinetic difference between the reaction of Z-L-Tle with L-Val-OMe and that of Z-D-Tle with L-Val-OMe. Stimulated by this fact we further examined the diastereomer ratios in this coupling reaction by various methods commonly used.3)

Table 1 shows the diastereomer ratios in the products obtained by the coupling of Piv-DL-Tle with L-Val-OMe in the molar ratio of 2:1 at room temperature for *ca.* 24 h. By the DCC method the D-L-isomer was produced preferentially, but the use of such additives as HOBt, HOSu, and HONb4) brought about a reverse ratio. Almost the same results were obtained when the active esters of these additives were used. On the other hand by the DPPA method the D-L-isomer was produced in larger excess.5)

The condensation of Z-DL-Tle with L-Val-OMe (molar ratio = 2:1) was carried out under the same conditions (Table 2). In this case even the condensation by DCC alone produced a mixture rich in the L-L-diastereomer, and the additives increased the L-L-diastereomer content greatly. Especially marked was the result of the DCC-HONb method, the condensation product containing *ca.* 80% of the L-L-diastereomer.

This interesting phenomenon, that the ratio of the L-L- and D-L-diastereomers varies strikingly with the coupling method, may be a special case, and seems to be connected with the bulkiness of both the acid and the amine components. Červinka *et al.*6) have also observed a similar phenomenon that in the coupling reaction of Z-DL-amino acids with L-amino acid esters in the molar ratio of 3:2 by the DCC method at room temperature D-L-diastereomers are preferentially formed, though no reference is made to the other coupling methods.

This work was supported by a Grant-in-Aid for Scientific Research (No. 174177) from the Ministry of Education.

Table 1. Condensation of Piv-DL-Tle with L-Val-OMe (2:1)

Method[a]	Yield (%)[d]	Ratio of Diastereomers[e]	
		L-L	D-L
DCC-HONb	70	69	31
Active ester (-ONb)	83	68	32
DCC-HOSu	58	60	40
Active ester (-OBt)	78	60	40
Active ester (-OSu)	45	59	41
DCC-HOBt	88	58	42
MA (ClCOOEt)[b]	-	46	54
MA (ClCOOBu-*i*)[b]	-	45	55
CDI	-	45	55
Chloride	-	44	56
DCC	89	43	57
Active ester (-ONp)	87	42	58
DPPA [c]	-	31	69

a) Unless otherwise noted THF was used as solvent. b) Solvent: THF-$CHCl_3$ c) Solvent: DMF d) The yields, after isolation by a preparative TLC, are overestimated due to contamination. e) Estimated by a Hitachi 063 gas chromatograph: column, 0.5% FFAP on Chromosorb G (ϕ3mm × 2m); column temp, 150°C; carrier gas, N_2 11 ml/min.

Table 2 Condensation of Z-DL-Tle with L-Val-OMe (2:1)

Method[a]	Yield (%)[b]	Ratio of Diastereomers[b]	
		L-L	D-L
DCC-HONb	52	81	19
DCC-HOBt	55	73	27
DCC-HOSu	79[c]	65	35
DCC	79	58	42

a) Solvent:THF b) Estimated after converting the products into Piv-Tle-L-Val-OMe (see the scheme). c) The yield is overestimated due to contamination.

References and Notes

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*) Abbreviations: DCC, dicyclohexylcarbodiimide; Z, benzyloxycarbonyl; HOBt, 1-hydroxybenzotriazole; HOSu, *N*-hydroxysuccinimide; HONb, *N*-hydroxy-5-norbornene-endo-2,3-dicarboximide; MA, mixed anhydride; CDI, carbonyldiimidazole; ONp, *p*-nitrophenyl ester; DPPA, diphenylphosphorylazide.

(Received June 9, 1978)