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RACEMIZATION IN PEPTIDE SYNTHESIS BY THE UGI REACTION

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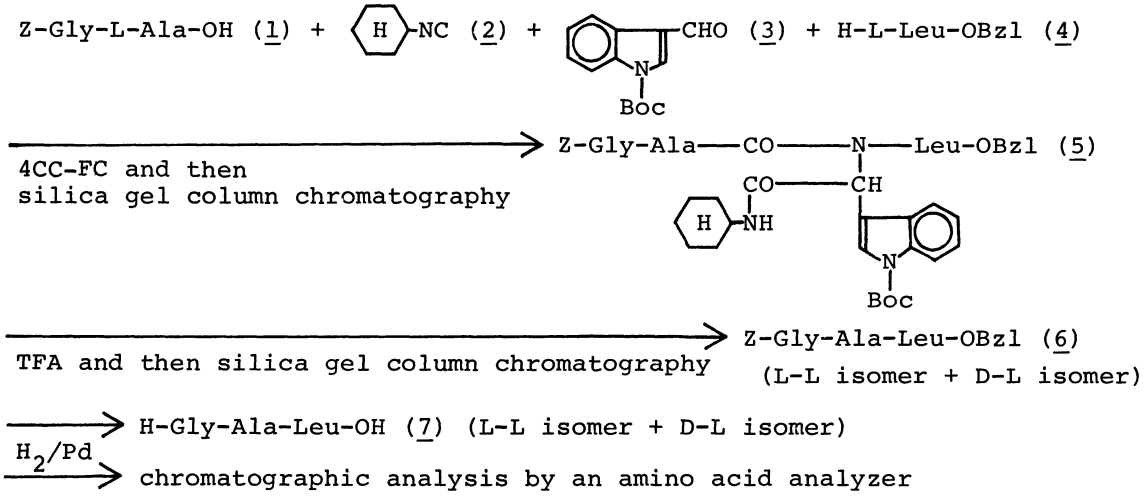
The Izumiya test for racemization in peptide synthesis was applied to examine the effect of solvent and temperature on racemization in the synthesis of a tripeptide derivative by the Ugi reaction (four-component condensation). Almost no racemization was observed under the reaction conditions using methanol and at low temperature.

The Ugi reaction or four-component condensation (4CC) offers a unique and interesting new approach to peptide synthesis.[1] No or very little racemization of an acid component was observed during the 4CC by gas chromatographic analysis.[2] Recently we reported that several model peptides could be synthesized by a fragment condensation strategy of the 4CC (4CC-FC).[3] In the course of the study we observed that the crude tetrapeptide obtained by the 4CC-FC contained small amounts of racemate by high-performance liquid chromatography. This prompted us to examine the racemization behavior of peptide synthesis by the 4CC-FC.

For the detection of possible racemate in the 4CC-FC product, the Izumiya test[4] for racemization in peptide synthesis was applied (Scheme). Crude compound 5[5] obtained by the 4CC-FC was treated with TFA[6] to remove the auxiliary group.[3] Crude tripeptide derivative 6 was directly hydrogenated. The hydrogenated material



Scheme

Table 1. Effect of solvent on racemization in the Scheme[a]

Solvent[b]	Yield of 5 (%)	Extent of racemization (%)[c]
DMF	32	10.3
DMF-MeOH (9:1)	28	9.5
DMF-MeOH (1:1)	45	2.3
DMF-MeOH (1:9)	88	2.0
MeOH	98	1.0

a) The 4CC-FC was carried out at 0.1 M reactant concentration at 0°C for 1 h and then at 25°C for 23 h with equimolar amounts of reactants except for 2 (1.2 equiv). b) All ratios by volume. c) Defined as [100(D-L isomer)]/[(L-L isomer) + (D-L isomer)].

Table 2. Effect of temperature on racemization in the Scheme[a]

Temp and time	Yield of 5 (%)	Extent of racemization (%)
25°C 24 h	70	4.2
0°C 1 h, 25°C 23 h	79	1.0
0°C 24 h	81	0.6

a) The 4CC-FC was carried out at 0.1 M reactant concentration in MeOH with equimolar amounts of reactants.

7 was subjected to an amino acid analyzer, and the amounts of the L-L and D-L diastereomers in 7 were determined according to the literature.[4]

The effect of solvent and temperature on racemization in the 4CC-FC was examined (Tables 1 and 2). Since DMF is frequently used in usual peptide synthesis and MeOH was a suitable solvent for the 4CC,[3] DMF, MeOH and mixtures of these solvents were selected in this study. As shown in Table 1, extensive racemization was observed in DMF, but the increasing concentration of MeOH in DMF sharply reduced the racemization and increased the yield. Table 2 shows that a low temperature at the early stage of the 4CC-FC suppressed the racemization. Thus precautions for reaction conditions must be taken in conducting peptide synthesis by the 4CC-FC.

References and Notes

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3) M. Waki and J. Meienhofer, *J. Am. Chem. Soc.*, 99, 6075 (1977).
4) N. Izumiya, M. Muraoka, and H. Aoyagi, *Bull. Chem. Soc. Jpn.*, 44, 3391 (1971).
5) A part of crude 5 was crystallized from MeOH-petroleum ether to give pure 5; mp 74-76°C, $[\alpha]_D^{20}$ -74.9° (*c* 0.5, MeOH), R_f (TLC with $CHCl_3$:MeOH = 5:1) 0.78. Satisfactory elemental analysis was obtained for the pure 5.
6) Abbreviations: TFA, trifluoroacetic acid; DMF, *N*,*N*-dimethylformamide; Z, benzyloxycarbonyl; Boc, *t*-butyloxycarbonyl; OBzl, benzyl ester.

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