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A NEW METHOD FOR THE PREPARATION OF ACTIVE ESTERS OF VARIOUS AMINO ACIDS BY OXIDATION-REDUCTION CONDENSATION

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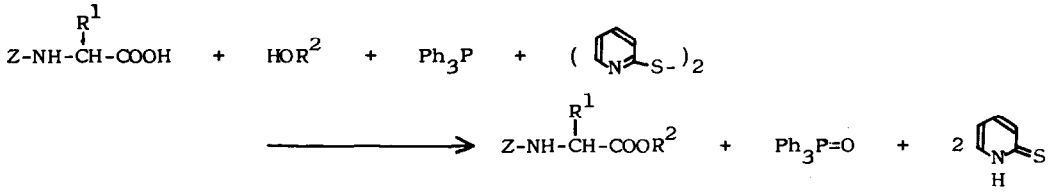
It was recently found in our laboratory that peptides with high optical purities are synthesized in excellent yields by oxidation-reduction condensation starting from free N-protected amino acids and free amino acid esters[1,2].

In the present experiment, the preparation of active esters of various amino acids was tried with the expectation that ester bond could be formed by the use of alcohols in place of free amino acid esters in the above reaction.



First, the preparation of benzyloxycarbonyl-L-glutamine pentachlorophenyl ester was attempted. A solution of triphenylphosphine in dry acetone was added with stirring to an ice-cooled acetone solution of equimolar amounts of benzyloxycarbonyl-L-glutamine, pentachlorophenol and 2,2'-dipyridyl disulfide. After stirring for 5 hr, the precipitate was collected by filtration, washed with acetone and ether, and dried in vacuo to give the analytically pure active ester in 72% yield. In a similar way, several N-protected amino acid esters were prepared, and these results are shown in Table I.

In this communication, next abbreviations were used; Z: benzyloxycarbonyl, NPS: o-nitrophenylsulfenyl, Su: N-hydroxysuccinimide residue, PCP: pentachlorophenyl, Q: 8-hydroxyquinoline residue.

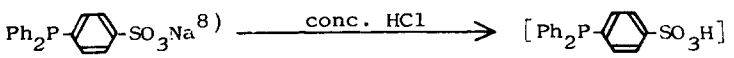
Table I

Active esters	Yield %	mp °C	$[\alpha]_D^{t°}$ (c solv.)
Z-L-Glu(NH_2)-OPCP*	72	182-184.5	$[\alpha]_D^{20}$ -17.3° (c1 DMF)
NPS-L-Glu(NH_2)-OSu[3-a)]	74	146-147	$[\alpha]_D^{23}$ -59.8° (c2 DMF)
Z-L-Asp(NH_2)-OPCP*	74	167-168.5	$[\alpha]_D^{20}$ -26.7° (c1 DMF)
Z-L-Arg(NO_2)-OPCP[3-b)]	71	109-111	$[\alpha]_D^{30}$ -14.0° (c1 DMF)

* Benzyloxycarbonyl-L-asparagine pentachlorophenyl ester was a new compound and the specific rotation of benzyloxycarbonyl-L-glutamine pentachlorophenyl ester was different from the value described in the literature[3-b)], so these esters were allowed to react with glycine ethyl ester and identified from the physical properties of the dipeptides produced[4)].

It is noteworthy that the pure active esters of glutamine and asparagine, which are known to give nitriles[5)] by ordinary methods, were exclusively produced by such a simple procedure. Also, favorable result was obtained in the case of nitroarginine which is known to form the lactam[6)] by ordinary methods.

Next, in order to check the degree of racemization during the preparation of active esters of peptide fragments by Young test[7)], the preparation of benzoyl-L-leucine succinimide ester was tried by the same procedure described above. However, this ester was unstable and decomposed during separation from triphenylphosphine oxide, so a phosphine whose oxide is soluble in water and easily removable by washing with water was devised. An introduction of acidic or basic substituents on benzene ring of triphenylphosphine would be sufficient for this purpose. From the viewpoints of both racemization and non-participation of this group to the reaction, sulfo group was introduced as the form of its salt with base. The diphenylphosphine-p-benzenesulfonic acid N-ethylpiperidine salt was synthesized according to the following method.



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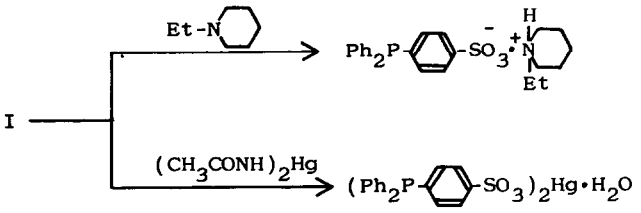
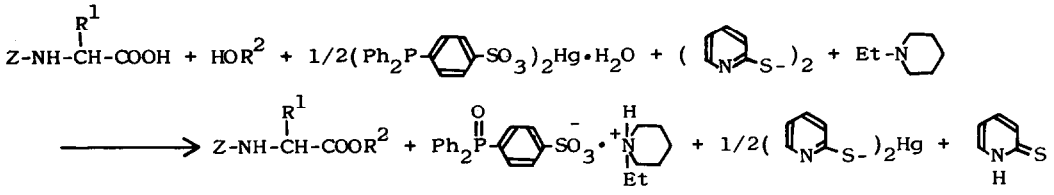


mp	211-212°C		
Anal.			
Calcd.	47.97	3.36	6.87
Found	48.15	3.50	6.66

This phosphine and the oxide were found to be very soluble both in water and in organic solvents, but unfortunately this phosphine is unstable toward air oxidation. After several investigations, this phosphine was proved to be safely stored in the form of mercuric salt, and no difficulties were encountered when it was used in the presence of tertiary amines.

Then the preparation of active esters of leucine, phenylalanine, valine and alanine by using diphenylphosphine-p-benzenesulfonic mercury and 2,2'-dipyridyl disulfide was studied.



For example, N-ethylpiperidine in methylene chloride was added at room temperature to a methylene chloride solution of benzoyl-L-leucine, N-hydroxysuccinimide, diphenylphosphine-p-benzenesulfonic mercury and 2,2'-dipyridyl disulfide. After stirring for 4 hr, the precipitates were filtered off, and solution was washed with aquous sodium hydrogen carbonate solution and water, and dried over sodium sulfate. After evaporation of the solvent in vacuo, the crude ester obtained was once recrystallized, from ethyl acetate-petroleum ether (30-50°C) to give the analytically pure benzoyl-L-leucine succinimide ester in 59% yield. Further this ester was allowed to react with glycine ethyl ester to give benzoyl-L-leucylglycine ethyl ester in 83% yield, $[\alpha]_D^{20}$ -32.3° (c3.1 EtOH), L-isomer 95%[7].

In a similar way, the active esters of phenylalanine, valine and alanine were prepared (See Table II).

Table II

Active esters	Yield %	mp °C	$[\alpha]_D^{t°}$ (c solv.)
Bz-L-Leu-OSu[9-a]	59	168-169	
Z-L-Phe-OSu[9-b]	75	136-137.5	$[\alpha]_D^{24}$ -54.2° (c1 DMF)
Z-L-Val-OSu[9-b]	61	116-117.5	$[\alpha]_D^{25}$ -25.8° (c2 Dioxane)
Z-L-Phe-OPCP[3-b]	86	157.5-158	$[\alpha]_D^{24}$ -51.4° (c1 DMF)
Z-L-Val-OPCP[3-b]	82	140	$[\alpha]_D^{24}$ -22.6° (c1 DMF)
Z-L-Phe-OQ[9-c]	70	138.5-139.5	$[\alpha]_D^{25}$ -70.6° (c2 DMF)
Z-L-Ala-OQ[9-c]	72	101-102	$[\alpha]_D^{26}$ -67.7° (c1 DMF)

In conclusion, it is noted that this oxidation-reduction condensation reaction can be successfully applied for the preparation of various amino acids and peptides of high optical purity in good yields by an extremely simple procedure without accompanying the side reactions.

REFERENCES

1) T. Mukaiyama, M. Ueki, H. Maruyama and R. Matsueda, J. Amer. Chem. Soc., 90, 4490 (1968).

2) T. Mukaiyama, R. Matsueda and M. Suzuki, Tetrahedron Lett., 1901 (1970).

3) (a) C. Meyers and R. T. Havran, Chemistry and Industry, 136 (1969).
(b) J. Kovacs, M. Q. Ceprini, C. A. Dupraz and G. N. Schmit, J. Org. Chem., 32, 3696 (1967).

4) E. Schnabel, Liebigs Ann. Chem., 688, 238 (1965).

5) C. Ressler and H. Ratzkin, J. Org. Chem., 26, 3356 (1961).

6) M. Bodanszky and J. T. Sheehan, Chemistry and Industry, 1268 (1960).

7) M. W. Williams and G. T. Young, J. Chem. Soc., 881 (1963).

8) H. Schindlbauer, Monatsh. Chem., 96, 2051 (1965).

9) (a) G. W. Anderson, F. M. Callahan and J. E. Zimmerman, J. Amer. Chem. Soc., 89, 178 (1967).
(b) G. W. Anderson, J. E. Zimmerman and F. M. Callahan, ibid, 86, 1839 (1964)
(c) Hans-Dieter Jakubke and Arno Voigt, Chem. Ber., 99, 2419 (1966).