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A NEW METHOD FOR THE PREPARATION OF PEPTIDES AND ACTIVE ESTERS OF AMINO ACIDS BY MEANS OF PHOSPHOROUS ACID AND ITS ESTERS IN THE PRESENCE OF TERTIARY AMINES

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In a previous paper[1], we showed that phosphorous acid and its esters gave the N-phosphonium salts of pyridine on oxidation with mercuric salts in pyridine and that the salts thus produced were able to activate carboxylic acids, amines and alcohols, resulting in the corresponding amides and esters followed by either aminolysis, acidolysis or alcoholysis.

Mitin et al[2] have reported that triphenyl phosphite causes a coupling reaction between carboxylic acids and amines in the presence of imidazole to yield the corresponding amides, diphenyl phosphite and phenol, but they have not discussed further coupling reactions with the resulted diphenyl phosphite.

In the course of our studies on application of electrolytic process for the oxidation of the phosphorous compounds in the reaction, we found that the yield of peptides was independent of the current passage, that is, the oxidation was not always necessary to accomplish the coupling reaction in tertiary amines using phosphorous acid, its mono- and di-esters. Especially diphenyl phosphite gave peptides in excellent yields in a short period at room temperature. It was also found that the phosphorous compounds could bring about coupling reaction between carboxylic acids and alcohols in pyridine, resulting in the corresponding esters.

In this paper we describe a brief study on the convenient method which is applicable to the syntheses of peptides and active esters of amino acids by means of phosphorous acid and its esters in pyridine in the absence of oxidizing

agents.

The coupling reactions with diphenyl phosphite were summarized in the following equation;

$$H\text{-}\underset{\overset{\|}{O}}{P}(OPh)_2 + Z\text{-}NH\text{-}R^1\text{-}COOH + NH_2\text{-}R^2\text{-}COOX \text{ (or } R^3\text{-}OH)$$

$$\xrightarrow[\text{in pyridine}]{} Z\text{-}NH\text{-}R^1\text{-}CONH\text{-}R^2\text{-}COOX \text{ (or } Z\text{-}NH\text{-}R^1\text{-}COOR^3) + H\text{-}\underset{\overset{\|}{O}}{P}(OPh)(OH) + PhOH$$

In a typical experiment, equivalents of benzyloxycarbonyl-glycine(12.5 mmol) and ethyl glycinate hydrochloride in 20 ml of pyridine were added at room temperature to a pyridine(20 ml) solution of diphenyl phosphite(12.5 mmol). After stirring for 30 min, the solution was evaporated to a syrup in vacuo at a temperature below 30° C. The residue was taken up in ethyl acetate, washed with 2N-hydrochloric acid, saturated aqueous sodium bicarbonate and water, and dried over sodium sulfate. After evaporation of the solvent, benzyloxycarbonyl ethyl glycylglycinate was obtained in 92% yield(3.4 g) by treating the residue with petroleum ether, mp 79-80°.

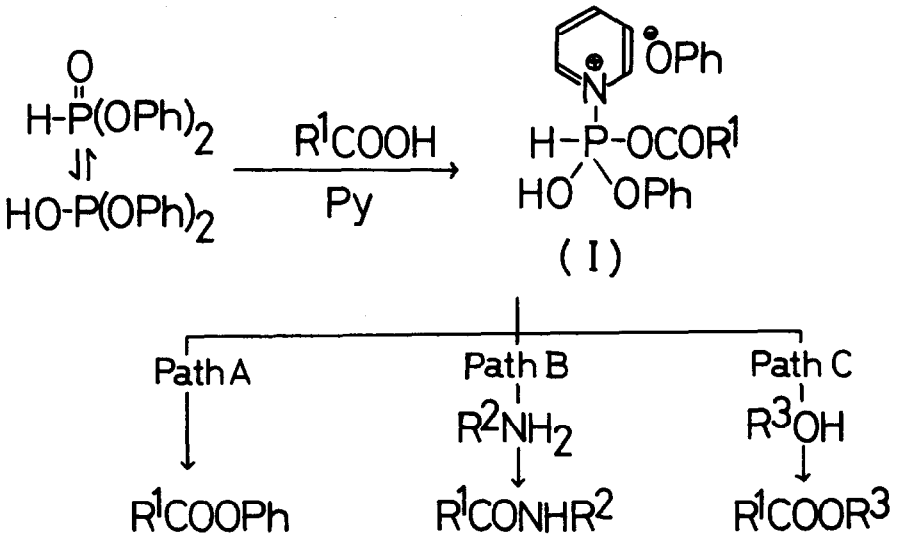
In the same way, various peptides were synthesized in high yields with high optical purity. No difficulties were observed when the side chains of glutamine and methionine in the carboxyl component and of tyrosine in the amino component were present.

The high reactivity of this system can be explained by assuming initial formation of acyloxy N-phosphonium salts of pyridine(I) by releasing phenolate anion from the phosphite according to a similar mechanism in a previous paper[1]. This salt undergoes two types of reactions, amide synthesis by intermolecular reaction with the incoming amino component(path B in the scheme) and the phenyl ester formation by intramolecular reaction with the phenolate anion released from the phosphorus atom(path A). The two reactions(path A and B) competed with each other and were governed by tertiary amines employed in the reaction. For instance, intermolecular reaction(path B) was almost exclusive in pyridine to yield the amide, whereas intramolecular reaction(path A) occurred simultaneous-

ly to give both the amide and the phenyl ester in the presence of imidazole.

The reaction was affected by the amount of tertiary amines and the phosphite. More than two equivalent pyridine and one equivalent diphenyl phosphite gave excellent results, indicating that pyridine and the phosphite were involved stoichiometrically in the reaction.

The reaction was proposed to proceed in the following way;



Scheme

The preparation of active esters of amino acids were attempted by a coupling reaction between carboxylic acids and alcohols(path C). A mixture of equivalents of benzyloxycarbonyl-glycine(12.5 mmol), p-nitrophenol and 1.5 equivalent diphenyl phosphite was kept at 40°C under stirring for 12 hr, and evaporated in vacuo at a temperature below 30°C. The residue was taken up in ethyl acetate, washed and dried in the same way as described above. Benzyloxycarbonyl p-nitrophenyl glycinate was obtained in 77% yield(3.2 g) by treating the residue with petroleum ether and ethyl ether, mp 123-124°. Similarly, various active esters of amino acids were synthesized in good yields(70-80%).

In conclusion, this method produces peptides and active esters of amino acids in high yields with high optical purity with respect to various kinds of amino acids by simply mixing the reactants in pyridine without accompanying any practical side reactions.

A more detailed investigation of this method will be reported in the near future.

References

1) N. Yamazaki and F. Higashi, Tetrahedron Letters, 415(1972).

2) Yu. V. Mitin and O. V. Glinskaya, ibid., 5267(1969).