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REACTIONS OF THE N-PHOSPHONIUM SALTS OF PYRIDINES AND ITS APPLICATION TO PEPTIDE SYNTHESIS

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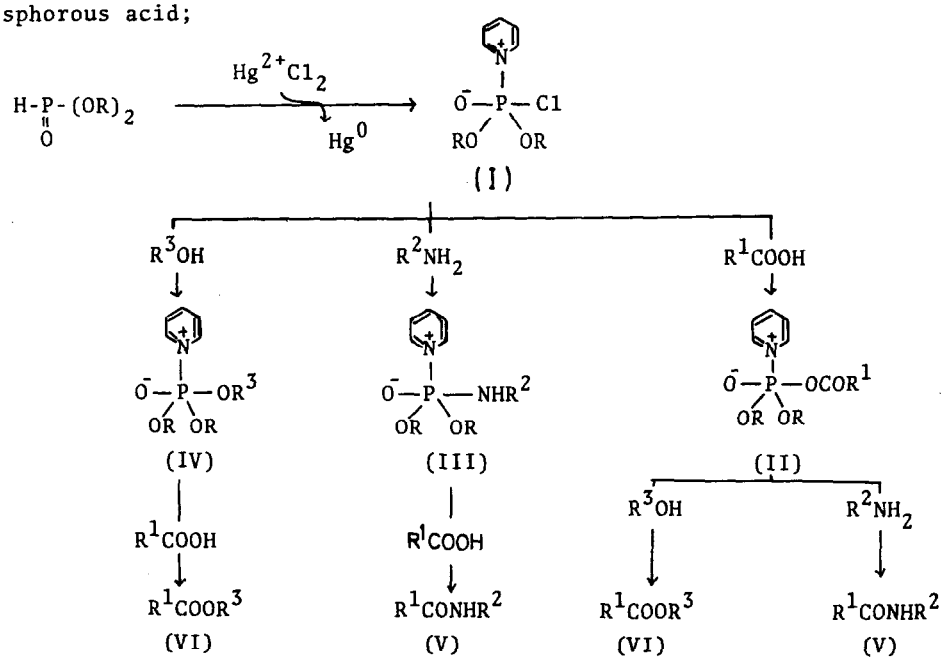
We found that the N-phosphonium salt [1] of pyridine(I) was formed via the oxidation of phosphorous acid and its esters with mercuric chloride in pyridine. The salt(I) was treated with carboxylic acids, amines and alcohols to give the corresponding phosphonium salts(II,III and IV) which were remarkably reactive. These phosphonium salts were possible to react with amines, carboxylic acids and alcohols, resulting in amides(V) and esters(VI) in high yield. The reaction was proposed as shown below in the case of oxidation of diesters of phosphorous acid;



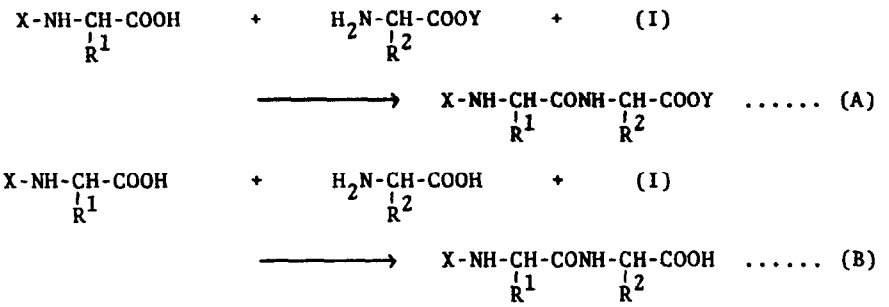
For example, the preparation of acetanilide(V, R^1=CH_3, R^2=C_6H_5) through the activation of acetic acid using phosphorous acid as follows; A mixture of phosphorous acid(25 mmol) and mercuric chloride(25 mmol) in pyridine(20 ml) was refluxed for 1 hr, and then acetic acid(25 mmol) was added to the reaction mixture. After refluxing for 1 hr, the mixture was treated with aniline(28 mmol) under reflux for 2 hr. After separation from the liberated metallic mercury, the solution was evaporated in vacuo and treated with aqueous ammonia, followed by the extraction of the product with acetone. The acetone solution was evaporated to a syrup, from which acetanilide was obtained in 94% yield by treating it with water. In a similar way, by using monoethyl(ammonium salt)[2], diisopropyl and triisopropyl ester, the anilide was obtained in 92, 94 and 73% yield, respectively.

When alcohols were treated with II instead of amines under reflux for 1 hr, the corresponding ester(VI) were prepared. Actually, phenyl acetate(VI, R^1=CH_3, R^3=C_6H_5) as well as n-butyl-n-butyrate[3] was obtained in 72% yield by the reaction of II(R^1=CH_3) with phenol by the use of phosphorous acid.

Amines were activated in a similar manner to those of carboxylic acids to give III. Compound III was more reactive than II, and in the case of oxidation of phosphorous acid, for example, the acidolysis of III(R^2=C_6H_5) with acetic acid for only 1 hr gave acetanilide in 97% yield, whereas more than 2 hr was required to complete the reaction of II(R^1=CH_3) with aniline. Similarly, by employing the monoethyl and diisopropyl ester, acetanilide was obtained in 33 and 97% yield, respectively.

Esters(VI) were prepared by the reaction of IV with carboxylic acids under reflux for 1 hr. Thus phenyl acetate and n-butyl-n-butyrate were prepared in 76 and 78% yield, respectively, by using phosphorous acid.

Then this reaction was applied to peptide synthesis in the following two types of reaction;



The reactive N-phosphonium salt(I) was prepared by the oxidation of the diphenyl ester of phosphorous acid with mercuric chloride in pyridine as mentioned above.

In the reactions of type A, for example, benzyloxycarbonyl-glycine(12.5 mmol) and ethyl glycinate hydrochloride(12.5 mmol) in pyridine(20 ml) were added at 45°C to a pyridine solution of I which was prepared from equimolar amounts of the diphenyl esters of phosphorous acid and mercuric chloride. After stirring for 12 hr, the solution was separated from the liberated metallic mercury and evaporated to a syrup in vacuo. The residue was taken up in ethyl acetate, washed with 2N-hydrochloric acid, saturated sodium bicarbonate solution, water, dried over sodium sulfate and the solvent was evaporated. From the residue, Z-Gly-Gly-OEt was obtained by treating it with petroleum ether, 3.4g(94%), mp. 79-80°C[4].

It is noteworthy to describe that the peptides with side chain, such as carboxyl or hydroxyl groups, are prepared directly in high yields with high optical purity without protection of these functional groups.

Peptide synthesis without protection has also been achieved by this method (type B). In a typical experiment, Z-glycine(12.5 mmol) in pyridine(10 ml) was added at 70°C to a pyridine solution of I. After stirring for 30 minutes, glycine(12.5 mmol) and pyridine(10 ml) were added to the mixture. The solution was kept at 70°C for 3 hr, and treated in a similar manner to those in type A. The residue was taken up in ethyl acetate, washed with 2N-hydrochloric acid, water, dried over sodium sulfate. By recrystallization from water, Z-Gly-Gly-OH was obtained in 50%(1.7g) yield, mp. 173°C[4].

Of oxidizing agents examined, various mercuric salts, mercurous salts and halogens proved to be also effective for these reactions and peptide synthesis.

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