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Studies on Reactions of the *N*-Phosphonium Salts of Pyridines. V. The Preparation of Carboxylic Amides and Esters by Means of the One-electron-transfer Oxidation of Phosphorous Acid and Its Esters in the Presence of Tertiary Amines

Noboru YAMAZAKI and Fukuji HIGASHI

Department of Polymer Science, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo 152

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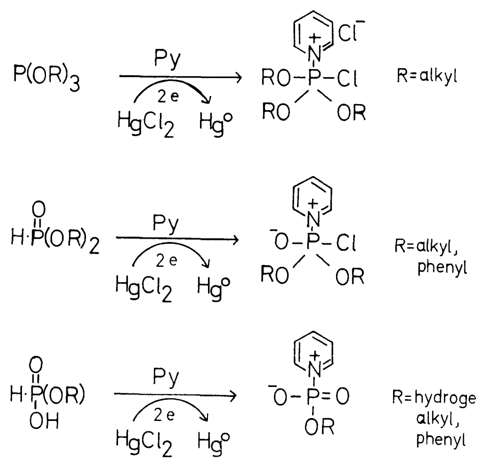
The oxidation of phosphorous acid and its esters with an equimolar amount of mercurous chloride and half an equimolar amount of mercuric chloride was carried out in tertiary amines. On the treatment of the oxidation mixture with carboxylic acids, amines, and alcohols, followed by aminolysis, alcoholysis, or acidolysis, the corresponding carboxylic amides and esters were obtained in good yields, together with a nearly quantitative yield of metallic mercury. The yield was affected by the tertiary amines, the alkyl groups in the dialkyl phosphites, and the steric effect of the carboxylic acids. The reaction was proposed to proceed through the activation of carboxylic acids, amines, and alcohols *via* the *N*-phosphonium salts prepared by the oxidation. The electron-transfer processes involved in the oxidation were discussed on the basis of the yield of the amides obtained. These procedures were successfully extended to the preparation of peptides and active esters of amino acids, using diphenyl phosphite in pyridine.

In previous papers,[1-4)] we showed a convenient method for the preparation of carboxylic amides and esters through the activation of carboxyl, amino, and hydroxyl groups by means of the *N*-phosphonium salts of pyridines given by the oxidation of phosphorous acid and its esters with mercuric salts in pyridines.

In these reactions, mercuric salts were used in amounts equimolar with the phosphorous compounds; the amount of liberated mercury after the reactions was nearly quantitative. Obviously, these facts show that the mercuric salts accepted two electrons from the phosphorous compounds, were changed into metallic mercury, and reversely oxidized the phosphorus(III) compounds into the phosphorus(V) compounds. Hence, the reactions can be described as the oxidation by a two-electron transfer:[1)]



We have also found[5)] that the oxidation products prepared from phosphorus compounds with an equimolar amount of mercurous chloride or half an equimolar amount of mercuric chloride in pyridine could cause coupling reactions between carboxylic acids and amines, and alcohols to produce the carboxylic amides and esters. It has been assumed[5)] that the phosphorus (III) compounds are oxidized by an one-electron transfer to the corresponding phosphorus(IV) compounds, which then form the corresponding *N*-phosphonium salts of pyridine similar to those obtained by the two-electron-transfer oxidation

This paper will describe in detail the results of the oxidations of phosphorous acid and its esters with mercurous and mercuric chlorides in pyridines, and of application of the process to the syntheses of carboxylic amides and esters. It will also show a successful extension of this procedure to the preparation of peptides and active esters of amino acids.

Results and Discussion

Such as in the two-electron oxidation, phosphorous acid and its esters (25 mmol) was oxidized in refluxing pyridine with an equimolar amount of mercurous chloride (25 mmol) or half an equimolar amount of mercuric chloride (12.5 mmol). When the oxidation mixture (I) thus formed was treated with a carboxylic acid and then with aniline, the corresponding anilide was obtained in the yield shown in Table 1, together with a nearly quantitative yield of metallic mercury (Method A). In Method B, I was refluxed first with aniline and then acidolized with carboxylic acids.

Furthermore, the reaction of I with carboxylic acids and then with alcohols gave the corresponding carboxylic esters (Method C). The esters were also prepared by adding the two components in the reverse order, that is, by the reaction of I initially with alcohols and then with carboxylic acids (Method D). Several anilides and esters thus obtained are listed in Tables 1 and 2.

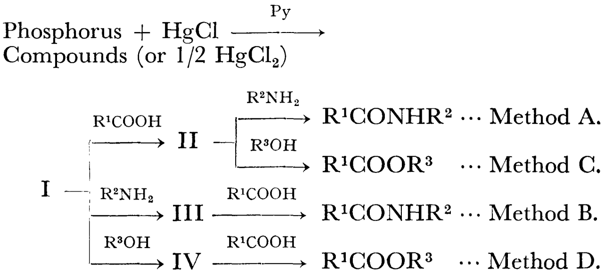


Table 1. Preparation of anilides by means of the one-electron oxidation of phosphorus compounds with mercurous and mercuric chlorides in pyridine

Phosphorus compounds	Yield of anilides obtained (%)			
	Method A		Method B	
	Acetanilide[a)]	Pivalanilide	Acetanilide[a)]	Pivalanilide
Phosphorous acid	79 (53)	0	61 (66)	9
Monophenyl ester	45 (51)	—	65 (61)	—
Diisopropyl ester	80 (81)	63	85 (93)	58
Triisopropyl ester	50 (48)	—	57 (58)	—

a) Values in the parentheses are those obtained by the oxidation with half an equivalent of mercuric chloride.

Table 2. Preparation of carboxylic esters by means of the one-electron oxidation of phosphorus compounds with mercurous chloride in pyridine

Phosphorus compounds	Carboxylic esters	Yield (%)	
		Method C	Method D
Phosphorous acid	Phenyl acetate	60	65
Diisopropyl ester	*n*-Butyl *n*-butyrate	59	56

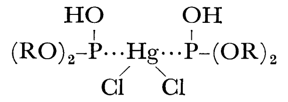
There are two possible ways of electron transfer, in principle, in the oxidation of the phosphorus(III) compounds with an equimolar amount of mercurous chloride or with half an equimolar amount of mercuric chloride. One is the one-electron-transfer oxidation of the phosphorus(III) compounds to yield the corresponding phosphorus(IV) compounds, and the other is two-electron transfer to the phosphorus(V) compounds.

The type of oxidation process involved in the oxidation of phosphorus(III) compounds was examined in terms of the yield of the acetanilide obtained (Table 1).

In the case of the oxidation of phosphorus(III) compounds with mercurous chloride, phosphorous acid and its diisopropyl ester gave acetanilide in excellent yields. The yields higher than 50% indicate that mercurous chloride can oxidize one equivalent of the phosphorus compounds by one-electron transfer to yield the corresponding active product (I), which could then condensate one equivalent of acetic acid and aniline to give the anilide in the high yields. The reactions with the monophenyl and triisopropyl esters, which gave yields of nearly 50% or more of acetanilide, possibly support the involvement of the one-electron-transfer oxidation in the reactions.

Similar situations were encountered in the oxidation with half an equivalent of mercuric chloride (Table 1). Especially, the diisopropyl ester gave acetanilide in a surprisingly high yield (93%). It is also the case with the reactions yielding carboxylic esters in yields higher than 50%.

In one-electron-transfer oxidation with mercuric chloride, the oxidation may not proceed step-by-step *via* one-electron oxidation, first with mercuric chloride and then with the resultant mercurous chloride, since mercuric chloride can undergo two-electron oxidation under these conditions. Therefore, the oxidation might take place between two moles of phosphorus(III) compounds and one mole of mercuric chloride *via* an intermediate, as is shown below;



$$(RO)_2\text{-}\overset{\text{HO}}{\overset{|}{P}}\cdots\underset{\text{Cl}\quad\text{Cl}}{\text{Hg}}\cdots\overset{\text{OH}}{\overset{|}{P}}\text{-}(OR)_2$$

The reaction producing amides by way of one-electron-transfer oxidation with mercurous chloride in pyridine was investigated in detail using phosphorous acid and its diesters. The reaction has been proposed[5)] to proceed *via* the quaternary *N*-phosphonium salt of pyridine (I in the scheme), similar to that given by the two-electron oxidation, though the formation of quaternary phosphonium salts has been known only in the reactions of phosphorus(III) compounds with nucleophiles. If the *N*-phosphonium salt has a similar structure, the yield of anilides would be influenced by the alkyl groups of the phosphites, tertiary amines, and carboxylic acids, as in the cases of the two-electron-transfer oxidation.

Table 3. Effect of ester residues of the dialkyl and diphenyl phosphites upon the yield

Diester	Yield of acetanilide (%)
Dimethyl	33
Diethyl	75
Diisopropyl	80
Di-*n*-butyl	72
Diphenyl	79

Table 4. Effect of tertiary amines upon the yield

Tertiary amine	pK_a	Yield of acetanilide[a)] (%)
Pyridine	5.23	79 (92)
3-Methylpyridine	5.52	50 (90)
2-Methylpyridine	5.97	39 (64)
4-Methylpyridine	6.02	45 (67)
2,6-Dimethylpyridine	6.99	30 (0)

a) Values in the parentheses are those obtained by two-electron oxidation[2)].

The effect of alkyl groups upon the yield of acetanilide in the reactions using several dialkyl and diphenyl phosphites may be in the following order: methyl<ethyl≈*n*-butyl<isopropyl≈phenyl. This was similar to that observed in the reaction by two-electron oxidation. In addition, among the diesters of phos-

phorous acid examined, diphenyl phosphite with electron-attracting phenyl groups was found to be most effective for the reaction at low temperatures and so was used for peptide synthesis, as will be discussed below.

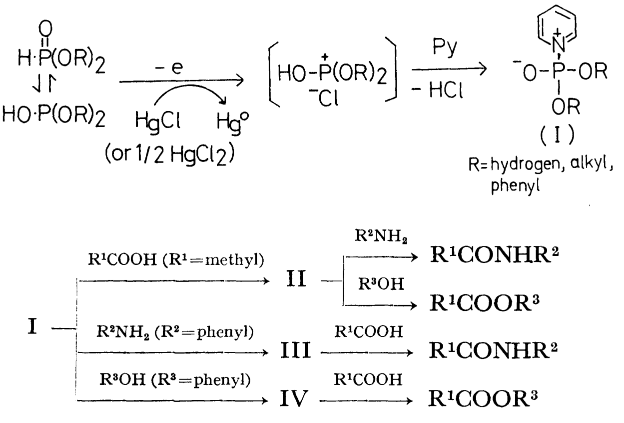
In Table 4 the effect of tertiary amines upon the reaction is compared with that in the two-electron oxidation. An increase in the basicity of amines decreases the yield of acetanilide, as in the latter case. However, the effect is not explicable only by the basicity, because a small difference in pK_a value between pyridine and other pyridine derivatives had an unexpectedly large effect upon the yield. The facts that the yield in 2-methylpyridine was nearly equal to that in 4-methylpyridine, and that even in 2,6-dimethylpyridine acetanilide was obtained in a 30% yield, suggested the presence of a slight steric effect.

The steric effect of carboxylic acids upon the yield was reflected by the yields of pivalanilide, lower than those of acetanilide in both one- and two-electron oxidations.

The proposed reaction mechanism was investigated using diethyl phosphite, since the diester of phosphorous acid proceeded predominantly *via* one-electron-transfer oxidation, as has been discussed above. The salts, I, II, III, and IV, were separated according to previously described procedures,[1–4] though their amounts were not satisfactory.

The IR spectrum of I showed a band at 1630 cm^{-1} due to the $\nu_{C=N^+}$ of the *N*-phosphonium salts of pyridine.[1] II, III, and IV exhibited bands due to the $\nu_{C=O}$ of the acetoxy group, the $\nu_{C=C}$ of the anilino group, and the $\nu_{C=C}$ of the phenoxy group respectively, together with the band due to the $\nu_{C=N^+}$ of the *N*-phosphonium salt.

On the basis of the experimental results obtained, the reaction may be explained by assuming the initial formation of the *N*-phosphonium salt (I) by the one-electron-transfer oxidation of phosphorus compounds. Salt I reacts with carboxylic acids, amines, and alcohols to yield the corresponding products, II, III, and IV. The carboxyl, amino, and alkoxy groups carried by these products are activated enough to be converted into carboxylic amides and esters on further aminolysis, alcoholysis, and acidolysis (see the scheme).



Scheme

As has been discussed above, simple carboxylic amides and esters were synthesized by way of the one-electron-transfer oxidation of the phosphorus compounds with mercurous and mercuric chlorides in pyridines.

Then this method for the preparation of the amides and esters were applied in the syntheses of peptides and active esters of amino acids, using diphenyl phosphite in pyridine. The coupling reactions between carboxyl and amino components, and hydroxyl components were carried out at 45 °C by mixing the reactants with the oxidation product (I) obtained from diphenyl phosphite in order to prevent racemization.

Several peptides and an active ester were obtained in good yields without any detectable racemization within the limits of experimental error (see Table 5).

The presence of the free side chains of glutamic acid, glutamine, and methionine in the carboxyl component, and of tyrosine in the amino component, did not cause any difficulties in the reactions as have been observed in two-electron oxidation.[3] In the case of glutamic acid, the α-carboxyl group was activated in preference to the γ-carboxyl group, yielding the α-peptide in a good yield. Similarly, a peptide of glutamine was obtained without any accompanying side reactions such

TABLE 5. PREPARATION OF PEPTIDES AND AN ACTIVE ESTER BY MEANS OF THE OXIDATION OF DIPHENYL PHOSPHITE WITH MERCUROUS CHLORIDE IN PYRIDINE

Peptide and an active ester	Reaction time (hr)	Yield (%)	(Mp °C)	[α]$_D$
Z–Gly–Gly–OEt	12	91[a]	80	
Z–Gly–Gly–OEt	6	92	—	
Z–Gly–Gly–Gly–OEt	6	82	163—164	
Z–Phe–Gly–OEt(L)	6	80	108—109	−17.5° (*c* 5, EtOH)
Z–Phe–Gly–OEt(L)	12	91	—	
Z–Gly–Tyr–OEt(L)	6	77	125—126	+18.9° (*c* 5, EtOH)
Z–Gly–Tyr–OEt(L)	12	91	—	
Z–Met–Gly–OEt(DL)	12	93	72—73	
Z–Glu(NH$_2$)–Gly–OEt(L)	12	81	166—168	− 6.5° (*c* 1, DMF)
Z–α–Glu–Gly–OEt(L)	6	72	122—123	
Z–Gly–O–C$_6$H$_5$–NO$_2$(*p*)	20	82	128	
Z–Gly–O–C$_6$H$_5$–NO$_2$(*p*)	20	84[a]	—	

a) Half an equivalent of mercuric chloride was used in the place of mercurous chloride.

as nitrile formation. In the reaction of ethyl tyrosinate, with both amino and hydroxyl groups, the amino group was preferably activated to produce the corresponding amide with the glycine.

Experimental

The salts (I, II, III, and IV), carboxylic amides and esters, peptides, and active esters were prepared according to previously reported procedures,[1-4] except for the use of one equivalent of mercurous chloride and half an equivalent of mercuric chloride in the place of one equivalent of mercuric chloride.

References

1) Part I; N. Yamazaki and F. Higashi, This Bulletin, **46**, 1235 (1973).

2) Part II; N. Yamazaki and F. Higashi, *ibid.*, **46**, 1239 (1973).

3) Part III; N. Yamazaki and F. Higashi, *ibid.*, **46**, 3824 (1973).

4) Part IV; N. Yamazaki and F. Higashi, *J. Amer. Chem. Soc.*, submitted for publication.

5) N. Yamazaki and F. Higashi, presented at the 26th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1972.