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PHOSPHORYLATION BY OXIDATION-REDUCTION CONDENSATION: PREPARATION AND REACTION OF S-(2-PYRIDYL) PHOSPHOROTHIOATES

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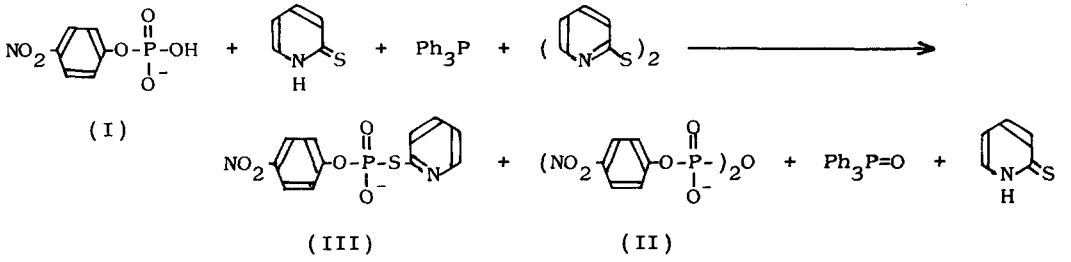
It is well known that active esters of phosphoric acid such as $RO\overset{O}{\overset{\|}{P}}(O^-)-OR'$ [1-3] (diester) and $RO\overset{O}{\overset{\|}{P}}(O^-)-NR'R''$ [4-7] (phosphoramidate) are important intermediates in the synthesis of various kinds of phosphoric acid derivatives. However, there are few reports dealing with $RO\overset{O}{\overset{\|}{P}}(O^-)-SR'$ (thioester) which is expected to be one of the important active esters.

In the present experiment, the preparation of thioester and the reactions of the thioester with alcohols, amines and phosphates were investigated. First, the preparation of aryl and nucleoside S-(2-pyridyl) phosphorothioates, active esters of phosphoric acid, from phosphates and 2-mercaptopyridine was tried according to the general procedure demonstrated in the phosphorylation of alcohols and phosphates with triphenylphosphine and 2,2'-dipyridyl disulfide[8].

For example, 1 equiv of p-nitrophenyl dihydrogen phosphate (I) and excess 2-mercaptopyridine were treated with 3 equiv each of triphenylphosphine and 2,2'-dipyridyl disulfide in acetonitrile at room temperature for 3 hr and III was obtained in 95% yield which was determined by UV absorption after separation with paper chromatography. The effects of solvents are listed in Table 1. The identity of this product was confirmed by isolation as its cyclohexylammonium salt, mp 135°, λmax 275mμ (ε 17760) at pH 7. Anal. Calcd for $C_{17}H_{22}O_5N_3SP$: C, 49.60; H, 5.40; N, 10.22. Found: C, 49.31; H, 5.81; N, 9.92.



(I) (III) (II)

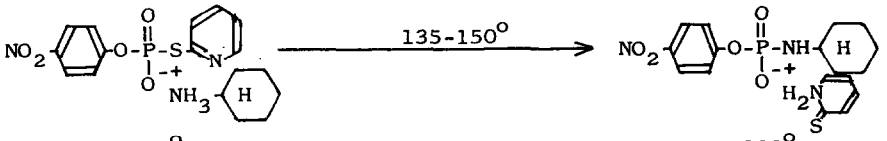
Table 1

Synthesis of p-Nitrophenyl S-(2-Pyridyl) Phosphorothioate[a)]

Solvent	2-Mercaptopyridine	I(%)	II(%)	III(%)[b)]
DMF	——	7	50	43
Pyridine	——	7	47	46
THF	——	5	44	51
CH_3CN	——	—	18	82
DMF	6 equiv	5	37	58
Pyridine	6 equiv	5	42	53
THF	6 equiv	—	18	82
CH_3CN	6 equiv	—	5	95

a) Three equiv each of reagents, triphenylphosphine and 2,2′-dipyridyl disulfide, were used.

b) The 2-mercaptopyridinium salt of p-nitrophenyl phosphorocyclohexylamidate was produced along with a small amount of P^1,P^2-bis(p-nitrophenyl) pyrophosphate by heating the cyclohexylammonium salt of p-nitrophenyl S-(2-pyridyl) phosphorothioate at above its melting point for several minutes as shown in the following equation.



mp 135° mp 203°

In a similar way, p-chlorophenyl ($\lambda_{max}^{pH\ 7}$ 272 mμ), p-tolyl ($\lambda_{max}^{pH\ 7}$ 273 mμ) and adenosine 5′ S-(2-pyridyl) phosphorothioates ($\lambda_{max}^{pH\ 7}$ 265 mμ) were obtained.

Next, the synthesis of pyrophosphates was tried by treating the thioester with various phosphates according to the following procedure; the resulted mixture obtained by the reaction of phosphate, 2-mercaptopyridine, triphenylphosphine and 2,2′-dipyridyl disulfide was treated with 2-equiv of water for 2 hr

at room temperature in order to remove the remaining triphenylphosphine and 2,2'-dipyridyl disulfide completely. By the successive addition of phosphate to the mixture, the reaction took place smoothly to yield the corresponding symmetrical or unsymmetrical pyrophosphates in good yields as summarized in Table 2.

Table 2

Pyrophosphate Synthesis

$ROP(O)(OH)_2$ R:	$R'OP(O)(OH)_2$ R':	$ROP(O^-)-O-P(O^-)-OR'$ [a]	Yield (%)	mp °C
p-nitrophenyl	p-nitrophenyl		95	233
p-nitrophenyl	p-tolyl		90	254
p-chlorophenyl	p-tolyl		90	281.5
p-chlorophenyl	phenyl		88	250.5

a) isolated as cyclohexylammonium salt

Phosphoramidates were also obtained when III was allowed to react with various kinds of amines such as primary or secondary aliphatic and aromatic amines at a temperature range from 10° to boiling point of acetonitrile (Table 3).

Table 3

Phosphoramidate Synthesis

$ROP(O)(OH)_2$ R:	Amine[a]	$ROP(O)NHR'$ [b]	Yield (%)	mp °C
p-nitrophenyl	n-butyl amine		90	—
p-nitrophenyl	benzyl amine		81	186
p-nitrophenyl	cyclohexyl amine		85	225
p-nitrophenyl	morpholine		85	184.5
p-nitrophenyl	aniline		90	214

a) 10 equiv of amine were used. b) isolated as cyclohexylammonium salt

An attempt to synthesize mixed esters of phosphoric acid by the reactions of III with alcohols failed because of the less reactivity of III toward alcohols. As it was found that III was unstable in acidic solution, the synthesis of diester from III and alcohol was tried in the presence of Lewis acids such as boron trifluoride. When III was treated with alcohol in the presence of a catalytic amount of boron trifluoride, the reaction took place rapidly and the

corresponding mixed esters of phosphoric acid were obtained in good yields as listed in Table 4.

Table 4

Disubstituted Phosphate Synthesis

$ROP(O)(OH)_2$ R:	R'OH	$ROP(O)OR'$ O^-	Yield (%)	$\lambda_{max}^{pH\ 7}$ (mμ)
p-nitrophenyl	n-butyl alcohol[a)]		90	290
p-nitrophenyl	n-amyl alcohol[a)]		85	290
p-nitrophenyl	n-octyl alcohol[a)]		80	291
p-nitrophenyl	p-nitrophenol[a)]		85	285
p-nitrophenyl	2',3'-isopropyridene uridine[b)]		30	263
2-cyanoethyl	2',3'-isopropyridene uridine[b)]		45[c)]	262

a) ten equiv of alcohol were used b) two equiv of phosphate were used
c) isolated as barium salt

In conclusion, it is noted that phosphorylation reaction via active intermediates, S-(2-pyridyl) phosphorothioates, affords the corresponding mixed esters of phosphoric acid, phosphoramidates and pyrophosphates in good yields under mild condition. The S-(2-pyridyl) phosphorothioates were prepared from various phosphates and 2-mercaptopyridine with triphenylphosphine and 2,2'-dipyridyl disulfide by oxidation-reduction condensation.

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