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PHOSPHORYLATION OF ALCOHOLS WITH DIETHYL PHOSPHOROCHLORIDODITHIOITE

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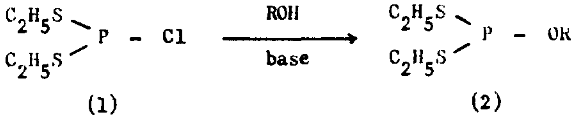
Attempts to prepare monoalkyl phosphates starting from trivalent phosphorus compounds have been investigated in a number of laboratories. For example, nucleoside phosphates were obtained by the reaction of 2',3'-O-isopropylidene nucleosides with phosphorus trichloride followed by oxidation and hydrolysis.1) Honjo, et al.2) have reported that the reaction of nucleosides with phosphorus trichloride in acetone (or methyl ethyl ketone) in an open vessel and subsequent hydrolysis gave nucleoside phosphates.

On the other hand, when protecting group was introduced in a phosphorylating reagent, the phosphate can be easily separated by usual organic techuniques such as extraction or separation by TLC, since the obtaining phosphorus compounds are neutral substances.

In the present study, ethyl mercapto group was chosen as a protecting group for phosphorus compound.

When two equiv ethyl mercaptan was treated with one equiv phosphorus trichloride in petroleum ether, diethyl phosphorochloridodithioite (1) was obtained in 60% yield.3)

The compound (1) was allowed to react with n-propyl alcohol in the presence of dimethylaniline in ethyl ether at 0° for 3 hours, n-propyl diethyl phosphorodithioite (2b) was obtained in a high yield. According to this method, various alkyl diethyl phosphorodithioites (2) were obtained as shown in Table I.



The phosphite (2) was treated with iodine in a mixture of acetone and water for 16 hours by a modification of the procedure of Cook$^{5)}$. And the mixture was concentrated and further treated with ion exchange column. The corresponding alkyl dihydrogen phosphate (6) was obtained in high yield. The results are listed in Table II.

In this experiment, diethyl disulfide (7) was formed quantitatively along with 6. It was easily separated from 6 and determined by UV spectrum. λ_{max}^{EtOH} 251 mμ (ε 420)$^{6)}$.

The reaction seems to be proceed through an intermediate alkyl diethyl phosphorodithioate (4) which in turn with iodine to 6 as sketched below.

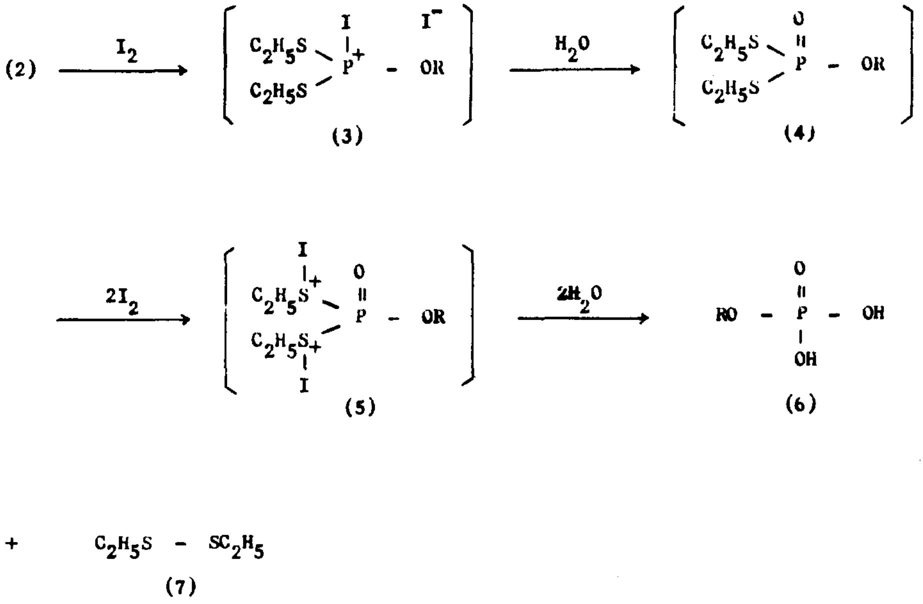


Table I. Preparation of Alkyl Diethyl Phosphorodithioites (2)

Compound R		Yield (%)	$n_D^{°C}$	Formula	Calcd. C	Calcd. H	Calcd. S	Found. C	Found. H	Found. S
2a	ethyl	77	1.5350^{20}	$C_6H_{15}S_2OP$	36.95	7.75	32.56	37.42	7.55	32.41
2b	n-propyl	77	1.5323^{20}	$C_7H_{17}S_2OP$	39.84	8.08	30.91	39.48	8.37	29.57
2c	n-butyl	69	1.5294^{23}	$C_8H_{19}S_2OP$	42.51	8.47	28.86	42.87	8.79	28.19
2d	iso-butyl	65	1.5176^{20}	$C_8H_{19}S_2OP$	42.51	8.47	28.86	43.01	8.56	28.62
2e	n-amyl	73	1.5245^{20}	$C_9H_{21}S_2OP$	45.00	8.75	26.66	45.10	8.76	25.89
2f	cyclohexyl	60	1.5552^{20}	$C_{10}H_{21}S_2OP$	47.61	8.33	25.39	47.01	8.79	25.02

Table II. Preparation of Alkyl Dihydrogen Phosphates (6)[a)]

Compound R		Yield (%)	Mp. (°C)	Rf[b)] value	Formula	Calcd. C	Calcd. H	Calcd. N	Found. C	Found. H	Found. N
3a	ethyl	86	164-165	0.36	$C_8H_{14}NO_4P$	43.84	6.44	6.39	43.94	6.51	6.15
3b	n-propyl	82	137-139	0.45	$C_9H_{16}NO_4P$	46.35	6.87	6.01	45.67	7.01	6.03
3c	n-butyl	72	138-140	0.54	$C_{10}H_{18}NO_4P$	48.44	7.48	5.69	48.55	7.30	5.11
3d	iso-butyl	66	155-156	0.51	$C_{10}H_{18}NO_4P$	48.44	7.48	5.69	48.32	7.38	5.62
3e	n-amyl	70	139-141	0.63	$C_{11}H_{21}NO_4P$	50.57	7.72	5.36	51.72	8.00	5.21
3f	cyclohexyl	65	168-169	0.55	$C_{12}H_{20}NO_4P$	52.74	7.38	5.13	53.01	7.24	5.48

a) The compounds were isolated as a monoanilinium salt.

b) Paper chromatography was carried out by ascending technique using Toyo Roshi No.50 paper. Solvent system used was : n-propyl alcohol, conc. ammonium hydroxide, water (6:3:1 v/v).

According to this method, alcohols were phosphorylated successfully by a simple treatment of $(RS)_2P$-Cl and the obtaining phosphite (2) was easily purified. And alkyl dihydrogen phosphates could be prepared from 2 by oxidation with an aqueous solution of iodine.

References

1) M. Yoshikawa, M. Sakuraba and K. Kusashio, Bull. Chem. Soc. Japan, 43, 456(1970).

2) M. Honjo, R. Marumoto, K. Kobayashi and Y. Yoshida, Tetrahedron Lett., 3851(1966).

3) In this experiment, diethyl phosphorochloridodithioite can be prepared by a modification of the procedure of Zletz[4)]. The reaction was carried out without using any tertiary amine in petroleum ether at room temperature for 15 hours.

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5) A. F. Cook, M. J. Holman and A. L. Nussbaum, J. Amer. Chem. Soc., 91, 1522(1969).

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