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OXIDATION OF NUCLEOSIDE PHOSPHITES BY MEANS OF 2,2'-DIPYRIDYL DISULFIDE VIA NUCLEOSIDE SILYLPHOSPHITE INTERMEDIATES

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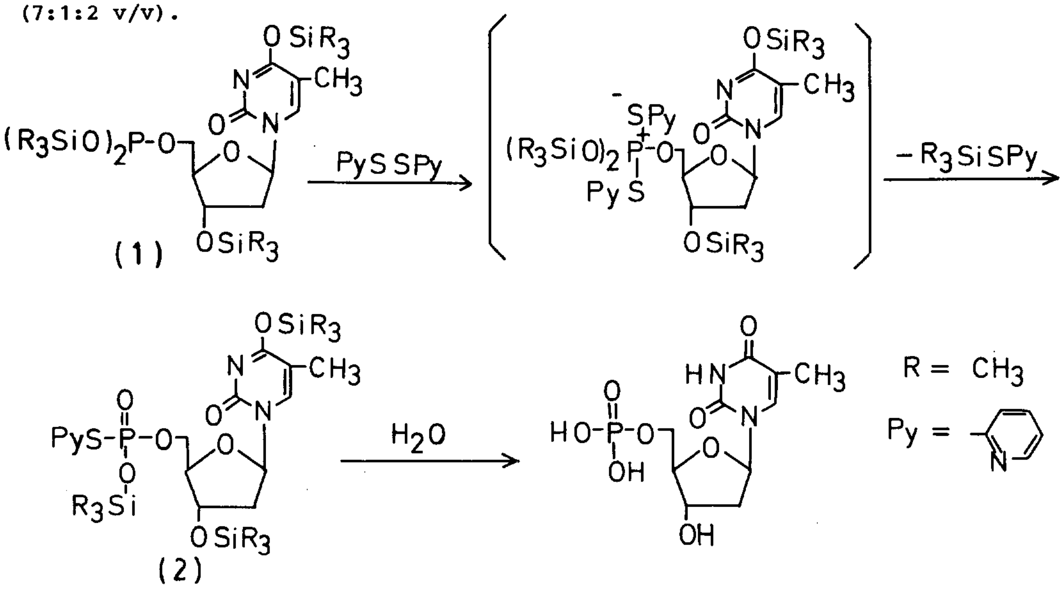
Trialkylphosphines and trialkylphosphites react under mild conditions with the compounds having active oxygen or sulfur atom to give the corresponding phosphoryl or phosphorothioyl derivatives. The driving forces of these reactions are due to the high P=O and P=S bond energies. Owing to such strong tendency of P=O formation, dialkyl- and monalkyl-phosphites exist substantially in the phosphonate form. Therefore, these compounds are much more resistant to the oxidation reactions than trialkylphosphites. Consequently, the oxidation of dialkyl- and monoalkyl-phosphites to the phosphates often involves using relatively strong oxidizing agents,$^{1)}$ which may be detrimental to complex molecule such as nucleotides, except by the use of hexachloroacetone reported by Holy.$^{2)}$ From the facts, the fixation on trivalent form of the phosphites is necessary for their oxidation carried out under mild conditions. Òrlov and Sudakova have reported$^{3)}$ the preparation of alkyl bis(trialkyl)silyl phosphites starting from alkylphosphites and trialkylsilyl chlorides. This will be useful in solving the oxidation problem.

In this paper, we wish to report the oxidation and the sulfurization of nucleoside phosphites via nucleoside silylphosphite intermediates (1) employing the Orlov's technique.

First, the oxidation of nucleoside phosphites[4] by the use of 2,2'-dipyridyl disulfide was tried.[5]

When 5 equiv. of trimethylsilyl chloride (0.125 ml, 1.0 mmole) was added to a mixture of one equiv. of thymidine 5'-phosphite (0.2 mmole) and 5 equiv. of triethylamine (0.141 ml, 1.0 mmole) in dry pyridine (20 ml) at room temperature for 10 min, triethylammonium chloride precipitated immediately. The mixture was further treated with 1.2 equiv. of 2,2'-dipyridyl disulfide (52.8 mg, 0.24 mmole) at room temperature without removing the precipitate. After 1 hr, water was added. Thymidine 5'-phosphate was obtained as a single product detectable by paper chromatography and paper electrophoresis (100% conversion within 1 hr). It was isolated in essentially quantitative yield by paper chromatography using Whatman 3MM paper developed with a solvent consisting of isopropyl alcohol, concentrated ammonium hydroxide and water (7:1:2 v/v).



In a similar manner, 5'-O-tritylthymidine 3'-phosphite, 2',3'-O-isopropylideneuridine 5'-phosphite, and 2',3'-O-isopropylideneadenosine 5'-phosphite were converted to the corresponding nucleotide derivatives in almost quantitative yields respectively.

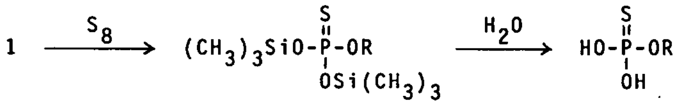
In the above experiments, no reaction was observed when nucleoside 5'-phosphite was treated only with 2,2'-dipyridyl disulfide in the absence of trimethylsilyl chloride and triethylamine.

The reaction seems to proceed through an intermediate, S-pyridyl O-trimethylsilyl thymidine 5'-phosphorothioate derivative (2) which in turn reacts with water to afford thymidine 5'-phosphate as shown in Scheme 1. The formation of 2 as the first reaction product is strongly supported by the reactions in the presence of nucleophiles such as alcohol, phosphate, and amine in place of water. When the reaction was carried out in the presence of methanol (8 equiv.), methyl thymidine 5'-phosphate was obtained in 50% yield. Similarly, thymidine 5'-diphosphate, P^1-p-nitrophenyl P^2-thymidine 5'-pyrophosphate, and thymidine 5'-phosphoromorpholidate were obtained from the reactions with inorganic phosphate (5 equiv.), p-nitrophenyl phosphate (3 equiv.), and morpholine (8 equiv.) in 24%, 42%, and 98% yields, respectively.

Next, the sulfurization of nucleoside phosphites by means of sulfur was examined.

A solution of thymidine 5'-phosphite (0.05 mmole) in dry pyridine (0.5 ml) was treated with triethylamine (0.036 ml, 0.25 mmole) and trimethylsilyl chloride (0.032 ml, 0.25 mmole) and then with pulverized sulfur (3.2 mg, 0.1 mmole). After 15 hr, water was added. Thymidine 5'-phosphorothioate was obtained in 94% yield and was isolated by paper chromatography as described in the above experiments.

In a similar manner, 5'-O-tritylthymidine 3'-phosphorothioate was obtained in 88% yield starting from 5'-O-tritylthymidine 3'-phosphite.



$$1 \xrightarrow{S_8} \mathrm{(CH_3)_3SiO{-}}\underset{\underset{\mathrm{OSi(CH_3)_3}}{|}}{\overset{\overset{\mathrm{S}}{\|}}{\mathrm{P}}}\mathrm{{-}OR} \xrightarrow{H_2O} \mathrm{HO{-}}\underset{\underset{\mathrm{OH}}{|}}{\overset{\overset{\mathrm{S}}{\|}}{\mathrm{P}}}\mathrm{{-}OR}$$

R =nucleoside residue

According to this method, the sulfurization reactions proceeded smoothly without using any catalyst.

In conclusion, it is noted that the methods of the oxidation and the sulfurization have three advantageous points, namely: (1) the yields are essentially quantitative; (2) the reactions proceed smoothly under the mild conditions; (3) no side-reaction is observed.

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References

1) (a) G.W.Kenner, A.R.Todd and F.J.Weymouth, J.Chem.Soc.,3675(1952);
(b) D.M.Brown and P.R.Hammond, ibid.,4229(1960).
2) A.Holy and J.Smrt, Coll.Czech.Chem.Commun.,31,1528(1966).
3) N.F.Orlov and E.V.Sudakova, Zh.Obshch.Khim.,39,222(1969); Chem.Abstr.,70, 87881e(1969).
4) Nucleoside phosphites were prepared in high yields from the corresponding nucleosides and phosphorous acid in dry pyridine by the use of 2,4,6-triisopropylbenzenesulfonyl chloride as a condensing agent.
5) An interest in the active ester, S-pyridyl esters of phosphoric acid developed by T.Mukaiyama and M.Hashimoto, Tetrahedron Lett.,2425(1971), led us to study the oxidation of silylphosphites by means of 2,2'-dipyridyl disulfide.