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NEW TYPE OF CHEMICAL OXIDATIVE PHOSPHORYLATION: ACTIVATION OF PHOSPHONATE FUNCTION BY USE OF TRIISOPROPYLBENZENESULFONYL CHLORIDE

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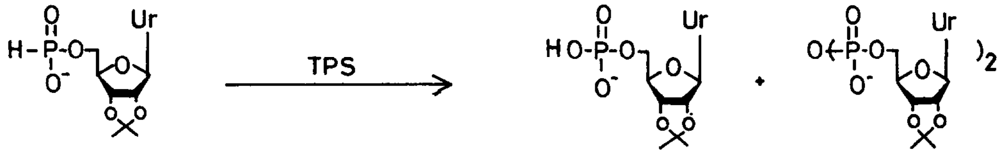
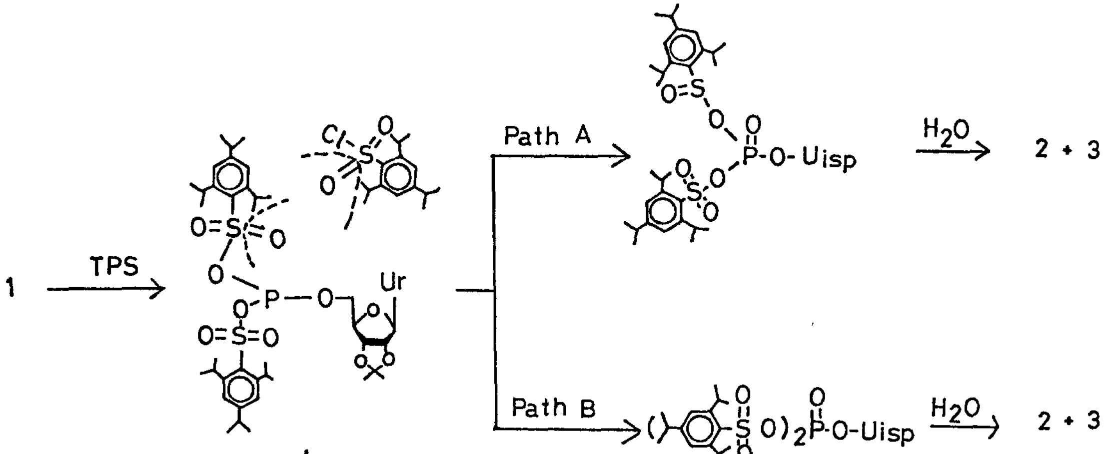
Recently, we have focused on the synthesis of nucleoside phosphonates which have a bright prospect as versatile synthetic intermediates for the synthesis of nucleotide derivatives.1) They were prepared from the reaction of nucleosides and phosphorous acid by use of condensing agents.2) In the course of our experiments, when an excess of 2,4,6-triisopropylbenzenesulfonyl chloride (TPS)3) was employed as the condensing agent, the corresponding nucleotides were obtained unexpectedly along with desired nucleoside phosphonates. In order to clarify the reaction, 2',3'-O-isopropyrideneuridine 5'-phosphonate (1) isolated by paper chromatography was treated with 3 equiv. of TPS in dry pyridine at room temperature for 3 h. 2',3'-O-Isopropyrideneuridine 5'-phosphate (2) and P^1,P^2-di-2',3'-O-isopropyrideneuridine 5'-pyrophosphate (3) were obtained in 60 % and 29 % yields, respectively.



1 2 3

From the above facts, it is clear that the oxidative phosphorylation proceeded by use of excess TPS. The following two reaction pathways to give 2 and 3 can be proposed. One of them involves an intramolecular rearrangement from once-formed bis-sulfonated tervalent intermediate (4) like silyl phosphites (Path A). The other is attributable to an intermolecular deoxygenation between



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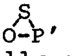
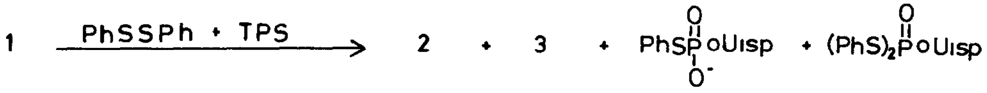
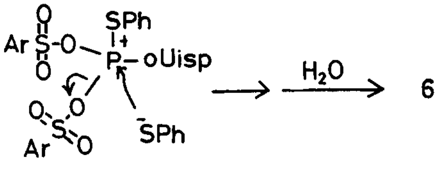
4 and an excess of TPS employed (Path B). However, the later might be exculuded because the remaining TPS molecules could attack hardly on 4 substituted with highly hindered nucleoside and TPS residues and a three membered ring transition state, , which was required for this mechanism might be never built up sterically even if 4 could attack on the sulfur atom or oxygen atom of TPS. In this reaction, when two equiv. of TPS was used, less formation of the oxdized products was observed. Therefore, the rate-determinating step of the reaction seemed to be the bissulfonylation, i.e., the formation of 4 having tervalent phosphorus structure. In addition, it was found that the use of arenesulfonyl azolides such as p-nitrobenzenesulfonyl triazolide, p-toluenesulfonyl imidazolide, and p-toluenesulfonyltriazolide[4,5] gave also nucleotide derivatives. These results suggest strongly the mechanism via the intramolecular rearrangement process. The deoxygenated compound of TPS, i.e., 2,4,6-triisopropybenzenesulfinic acid, was not unfortunately isolated from the reaction mixture. However, the formation of 4 was further supported evidently by the reaction of 1 with TPS in the presence of diphenyl disulfide. When 1 was allowed to react with 3.5 equiv. of TPS in the presence of 5 equiv. of diphenyl disulfide, 2',3'-O-isopropyrideneuridine S-phenyl 5'-phosphorothioate (5) was formed in 12 % yield along with 2 (48 %) and 3 (12 %) and 3 % of 1 was recovered.



$$1 \xrightarrow{\text{PhSSPh} + \text{TPS}} 2 + 3 + \text{PhS}\overset{\text{O}}{\underset{\text{O}^-}{\text{P}}}\text{oUisp} + (\text{PhS})_2\overset{\text{O}}{\text{P}}\text{oUisp}$$

5 6

The yield of 5 increased to 51 % yield, when one equiv. of diphenyl disulfide and 3 equiv. of p-toluenesulfonyl imidazolide were used. However, in this case, the total yield of the nucleotidic products obtained from the aqueous layer did not approach to 100 % and it was found that a neutral nucleotidic substance was isolated from the organic layer and identified as 2',3'-O-isopropyridene-uridine S,S-diphenyl 5'-phosphorodithioate (6)(30 %). Compound 6 seemed to be formed as a result of the decomposition of a phosphonium salt (7) by an attack of a thiolate ion on the phosphorus atom.



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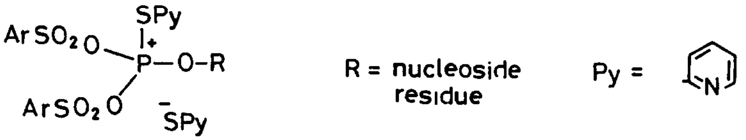
Finally, these findings were applied to the synthesis of thymidylyl thymidine (TpT) from 5'-O-tritylthymidine 3'-phosphonate (9) and 3'-O-acetyl-thymidine (10). In this case, 2,2'-dipyridyl disulfide$^{6)}$ was employed in place of diphenyl disulfide because it could be expected that the bis-sulfonylated derivative of 9 reacted with 2,2'-dipyridyl disulfide to give a highly reactive phosphorylating reagent (8) which could not be isolated but possessed strong leaving groups of two arenesulfonyl groups and two pyridyl groups.



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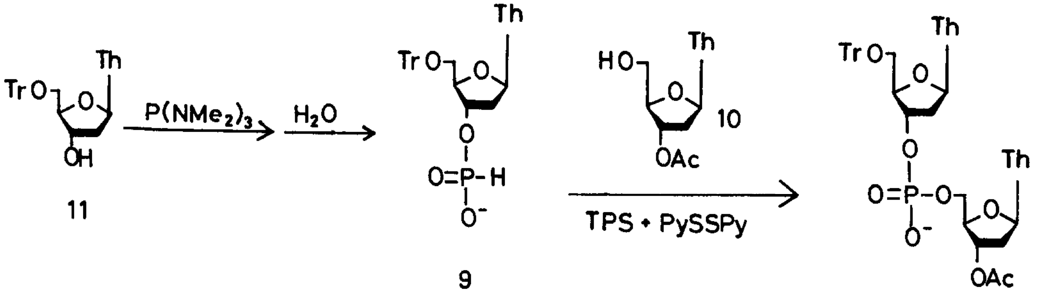
5'-O-Tritylthymidine 3'-phosphonate (9) was prepared simply by the following modification of Burgada's reaction$^{7)}$. Tris(dimethylamino)phosphine or tris(diethylamino)phosphine could be used as a reagent for introduction of phosphonyl group into nucleoside hydroxyl groups. For example, when 5'-O-tritylthymidine (11) was treated with tris(dimethylamino)phosphine (8 equiv.) in pyridine at r.t. for 24 h and then the mixture was hydrolyzed by addition of water, 5'-O-tritylthymidine 3'-phosphonate was obtained in nearly quantitative yield without any phosphate derivatives. This method was quite useful but limited to the preparation of alkali-stable nucleoside phosphonates since one equimolar dialkylamine, which was accumulated as the reaction proceeded, caused acyl protecting groups taken off.



The oxidative coupling reaction between 9 (0.1 mmol) and 10 (0.1 mmol) by use of TPS (0.4 mmol) in the presence of 2,2'-dipyridyl disulfide (0.1 mmol) at r.t. for 24 h gave TpT in 57 % yield after removal of all protecting groups. When the coupling reaction was carried out in the absence of 2,2'-dipyridyl disulfide, the yield of TpT decreased to 31 %. A better yield (80 %) of TpT was obtained when two equiv. of 9 was used. In the above reactions, the use of arenesulfonyl azolides such as p-toluenesulfonyl imidazolide, p-toluenesulfonyl triazolide, p-chlorobenzenesulfonyl triazolide, and p-nitrobenzenesulfonyl triazolide in place of TPS gave poorer yields of TpT.

It is concluded that the present reactions described here provide a new type of oxidative phosphorylation in which unreactive phosphonate functions of nucleoside phosphonates were activated by condensing agents through highly reactive phosphite-type intermediates.

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