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THE SYNTHESIS OF S-PHENYL NUCLEOSIDE PHOSPHOROTHIOATES

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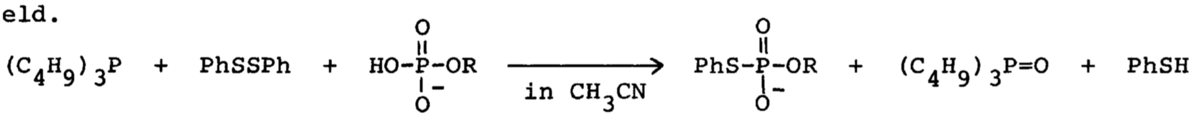
A convenient method for the synthesis of S-phenyl nucleoside phosphorothioates by the reaction of nucleotides with diphenyl disulfide in the presence of tri-n-butylphosphine is described.

Ethylthio group described by Nussbaum[1)] in 1965 has proved particularly valuable for the protection of phosphate esters in oligonucleotide synthesis.[2)] This group can be introduced by the reaction of protected nucleosides with S-ethyl phosphorothioate by the use of dicyclohexylcarbodiimide as a condensing agent, but this method does not appear to be general bacause of the instability of S-ethyl phosphorothioate.[2b)] It is therefore necessary to find a useful method for the synthesis of S-alkyl or S-aryl nucleoside phosphorothioate starting from nucleotides. A possibility for the preparation of S-aryl nucleoside phosphorothioate is suggested by Mukaiyama and Hashimoto.[3)] They showed that S-(2-pyridyl)nucleoside phosphorothioate was detected when the nucleotide was treated with 2,2'-dipyridyl disulfide and triphenylphosphine.

In this paper, we wish to report a convenient method for the synthesis of S-phenyl nucleoside phosphorothioates starting from the corresponding nucleotide by the use of diphenyl disulfide and tri-n-butylphosphine. An important feature of the present method is that it doesn't involve the use of S-alkyl phosphorothioate and protected nucleosides, which are sometimes difficultly accessible in the nucleotide field.



$$(C_4H_9)_3P \;+\; PhSSPh \;+\; HO\text{-}\underset{O^-}{\overset{O}{\overset{\|}{P}}}\text{-}OR \xrightarrow[\text{in } CH_3CN]{} PhS\text{-}\underset{O^-}{\overset{O}{\overset{\|}{P}}}\text{-}OR \;+\; (C_4H_9)_3P{=}O \;+\; PhSH$$

R =nucleoside residue

When a mixture of one equiv. of pyridinium salt of 3'-O-acetylthymidine 5'-phosphate and 10 equiv. of diphenyl disulfide in dry acetonitrile was treated with 10 equiv. of tri-n-butylphosphine at room temperature for 30 min, S-phenyl 3'-O-acetylthymidine 5'-phosphorothioate [$\lambda_{max}^{H_2O}$ 267 (ε=10,100), 243 nm; $\lambda_{min}^{H_2O}$ 250, 236 nm] was obtained in 96% yield. When thymidine 5'-phosphate was employed in place of 3'-O-acetylthymidine 5'-phosphate, S-phenyl thymidine 5'-phosphorothioate was obtained in 91% yield. In this case, no coupling reaction between phosphate and 3'-hydroxyl group on sugar moiety was observed.

In a similar manner, S-phenyl N^6-benzoyladenosine 5'-phosphorothioate [$\lambda_{max}^{H_2O}$ 283 (ε=18,500), 238 nm; $\lambda_{min}^{H_2O}$ 262, 230 nm], and S-phenyl N^4-anisoylcytidine 5'-phosphorothioate [$\lambda_{max}^{H_2O}$ 303 (ε=22,450), 244 nm; $\lambda_{min}^{H_2O}$ 254, 237 nm] were obtained in 80% and 71% yields respectively.

In the above reactions, it is noted that tri-n-butylphosphine is remarkably effective for the synthesis of S-phenyl nucleoside phosphorothioates. When triphenylphosphine was used in place of tri-n-butylphosphine, the symmetrical dinucleoside pyrophosphate was formed as a main product.

While the phenylthio group on phosphate end is quite stable to concentrated ammonium hydroxide at room temperature overnight or to 80% aqueous acetic acid at 100° for 10 min, it can be easily removed by iodine or silver acetate in aqueous pyridine at room temperature.

References

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