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PHOSPHORYL TRIS-TRIAZOLE – A NEW PHOSPHORYLATING REAGENT

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ABSTRACT: Phosphoryl tris–triazole, a new phosphorylating reagent obtained from $POCl_3$ and 1,2,4–triazole, was found to be very useful for the preparation of nucleoside 3´–phosphotriesters bearing various alkyl phosphate protective groups.

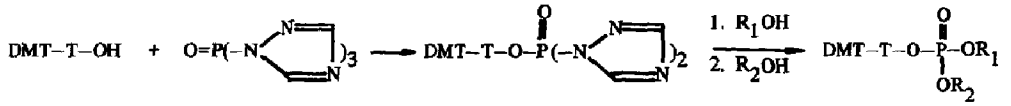
At present, aryl phosphodichloridates[1] (or diazolides[2]) and aryl alkyl phosphomonochloridates[3,4] are commonly employed as convenient reagents for the preparation of nucleoside 3´–phosphotriesters – key intermediates in oligonucleotides synthesis via triester approach.

However, up to now this kind of reagents was almost exclusively employed for the synthesis of nucleoside 3´–phosphotriesters containing aryls or aryl and alkyl groups, but there was no convenient route to the preparation of nucleoside 3´–phosphotriesters bearing two alkyl groups.

Searching for an efficient phosphorylating reagent for the synthesis of dialkyl nucleoside phosphotriesters, we tried at first to use $POCl_3$ for the phosphorylation of 5´–O–dimethoxytritylthymidine (DMT–T–OH), or alkyl phosphodichloridates prepared in situ from $POCl_3$, followed by the addition of desired alcohols. In all cases, however, we have found that although the first step i. e. phosphorylation of nucleoside I, proceeded nearly quantitatively, the yields of phosphotriester products were very low (ca 5 – 10%).

To find the explanation for these results, we studied the stability of various alkyl phosphodichloridates (2–cyanoethyl, 2,3–dibromopropyl, methyl or benzyl glycolate) in different solvents using ^1H NMR spectroscopy. We have found that all the studied alkyl phosphodichloridates underwent complete decomposition[5] in dioxane or ether (12 hrs) and in pyridine (2–3 min.), and this was probably the reason for the very low yield of phosphotriester formation during the phosphorylation reaction. It is also very likely that the same phenomenon occurred when nucleoside 3´–phosphodichloridates, obtained from nucleoside I and $POCl_3$, were treated by the appropriate alcohol.

To eliminate these undesired reactions, we replaced chlorine atoms in $POCl_3$ by triazoles and thus the resulting phosphoryl tris–trizole (II) was used for the synthesis of nucleoside dialkyl phosphotriesters (IV).



I II III IVa-f

Table 1. Synthesis of nucleoside 3´–phosphotriesters (IV) from nucleoside (I), phosphoryl tris–triazole (II) and appropriate alcohols

R_1OH	R_2OH	Products	% Yield (isolated)
$NCCH_2CH_2OH$	$NCCH_2CH_2OH$	IVa	70
$NCCH_2CH_2OH$	CH_3CH_2OH	IVb	60
$NCCH_2CH_2OH$	$PhCH_2OCOCH_2OH$	IVc	61
$NCCH_2CH_2OH$	$BrCH_2CH(Br)CH_2OH$	IVd	63
$NCCH_2CH_2OH$	Cl_3CCH_2OH	IVe	75
$PhCH_2OCOCH_2OH$	$PhCH_2OCOCH_2OH$	IVf	60

1,2,4–triazole (4.5 eqv.), $POCl_3$ (1.5 eqv) were dissolved in dioxane (5 ml for 1 mM), and under cooling (5°C), a solution of triethylamine (4.5 eqv.) in dioxane was added dropwise during 15 min. After stirring for an additional 40 min., the reaction mixture was filtered under nitrogen into the flask containing nucleoside I (1 eqv.), which had been previously evaporated with pyridine. Phosphorylation of nucleoside was completed in 15 – 20 min. and then the first alcohol (1.3 eqv.) was added. The reaction mixture was kept for 1.5 hr at room temperature, concentrated to 1/3 of the starting volume and after the second alcohol (2 eqv.) was added, the mixture left to stand overnight. Then t. l. c. on silica gel plates showed 60 – 80% of desired phosphotriesters and 20% of a trityl-containing product at the origin (probably nucleoside alkyl phosphodiester). The reaction mixture was concentrated to the gum, the residue dissolved in chloroform, and then washed with phosphate buffer (pH 7.5). After silica gel chromatography (using chloroform containing 2 – 5% of methanol as a solvent) the desired phosphotriesters IVa-f were isolated in 60 – 70% yield[6].

It is worth stressing that under the reaction conditions described above, no bis–nucleoside alkyl phosphotriesters were observed (t. l. c. analysis) although in every case symetrical nucleoside bis–alkyl phosphotriesters were present (ca 5%).

Phosphoryl tris–triazole is stable in dioxane and can be kept in this solvent as a stock solution for at least ten days although better results were obtained when this phosphorylating reagent was prepared directly before use.

In conclusion, phosphoryl tris–triazole was found to be a useful reagent for the synthesis of nucleoside 3′–phosphotriesters bearing various alkyl groups. It prevents difficulties connected with the application of $POCl_3$ or alkyl phosphodichloridates for a similar purpose, and thus may prove to be of general use in nucleoside chemistry as a convenient reagent for the introduction of a phosphoryl group.

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3. J. H. van Boom, P. M. J. Burges and P. H. van Deursen, Tetrahedron Letters, 969 (1976)
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5. In dioxane and ether, alkyl phosphodichloridates underwent decomposition into the compounds which ^1H NMR spectra were in excellent agreement with the spectra of corresponding alkyl chlorides. For example, $NCCH_2CH_2OPOCl_2$, ^1H NMR ($CDCl_3$) 4.50 (2H,m,$-CH_2OP$), 2.93(2H,t, J=6Hz, $-CH_2CN$); decomposition product – ^1H NMR ($CDCl_3$) 3.73 (2H, t, J=6Hz), 2.93 (2H, t, J=6Hz)
$PhCH_2OCOCH_2OPOCl_2$, ^1H NMR ($CDCl_3$) 7.30 (5H, s, C_6H_5), 5.13 (2H, s, $-CH_2Ph$), 4.80 (2H, d, J=12Hz, $-CH_2OP$); decomposition product – ^1H NMR ($CDCl_3$) 7.33 (5H, s, C_6H_5–), 5.16(2H, s, $-CH_2Ph$), 4.06 (2H, s).
In pyridine, however, the alternative pathway for the decoposition of this type of phosphorylating agents is also possible i. e. formation of an N–alkylpyridinium salt of dichlorophosphate, and this route is probably the main one.
See, J. Smrt and J. Catlin, Tetrahedron Letters, 5082 (1970); M. Rubinstein and A. Patchornik, Tetrahedron, 31 2107 (1975).
6. ^1H NMR spectra and chromatographic mobilities of all isolated phosphotriesters IVa-f were identical with corresponding phosphotriesters obtained from nucleoside 2–cyanoethyl phosphodiester and from appropriate alcohol in the presence of 2,4,6–triisopropylbenzenesulfonyl tetrazole as a condensing reagent.

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