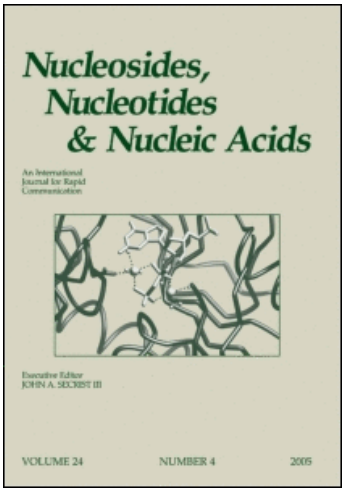

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Use of Photolabile Amino-Protecting Groups in the Synthesis of Base-Sensitive DNA SATE-Phosphotriesters

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USE OF PHOTOLABILE AMINO-PROTECTING GROUPS IN THE SYNTHESIS OF BASE-SENSITIVE DNA SATE-PHOSPHOTRIESTERS

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ABSTRACT: The first solid phase syntheses of prooligonucleotide heteropolymers carrying base-sensitive SATE phosphotriester linkages have been performed using the photolabile protecting groups 6-Nitroveratryloxycarbonyl (NVOC) and 2,2'-Di-(2-nitrophenyl)ethyloxycarbonyl) (diNPEOC) and a modified phosphoramidite approach.

In relation with our prooligonucleotide[1] strategy, we recently reported the solid-phase synthesis of dodecathymidine SATE-phosphotriesters using a photolabile solid support[2] and thymidine S-acylthioethyl (SATE) phosphoramidites[3].

We have evaluated here, the use of the photolabile NVOC and diNPEOC groups for nucleobase protection in the synthesis of heteropolymers. To our knowledge, the use of photolabile protecting groups was never reported for the protection of exocyclic amino functions of the natural nucleobases.

At the nucleoside level, the removal of the protecting groups was performed by photolysis (hv, λ>280nm), in dioxane/water/acetic acid (3/2/0.25, v/v/v) at 0.1mM. The diNPEOC protected nucleosides had photolysis rates approximately 5-fold greater than the corresponding NVOC derivatives (6min for diNPEOC instead of 40min for NVOC).

Synthesis of d($^{5'}$TpXpTpTpTp$^{3'}$) (X=A,C) tBuSATE phosphotriester pentamers was performed using apppropriate phosphoramidites (**FIG.**). Photolysis showed complete conversion into unprotected oligonucleotides in 45min at 0.05mM for NVOC oligomers and in 10min at 0.1mM for diNPEOC ones. However, an heteropolymer

bearing 4 NVOC was not fully deprotected after 5 hours at 0.05mM. In comparison, diNPEOC protected oligomers d($^{5'}$TpXpXpXpTp$^{3'}$) (X=A,C,G) were successfully deprotected in 20min at 1mM.

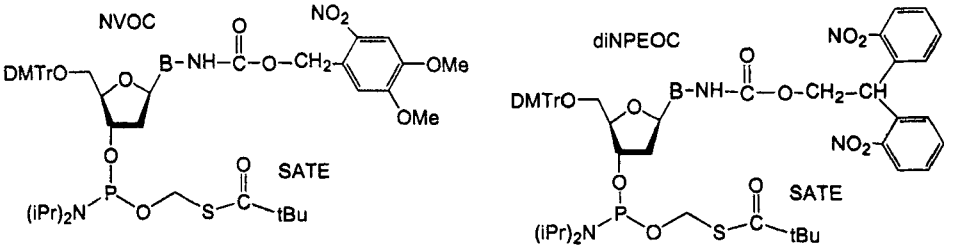

FIG. *N*-NVOC and *N*-diNPEOC tBuSATE phosphoramidite synthons.

Finally, the syntheses of SATE-phosphotriester dodecamers d($^{5'}$ApCpApCpCpCpApApTpTpCpTp$^{3'}$) and d($^{5'}$ApGpApApTpTpGpGpGpTpGpTp$^{3'}$) were carried out using diNPEOC protection. Standard Ac_2O/NMI capping reagent, wich induced acetylation of dA and dG amino functions, was replaced by N-N-diisopropyl phosphoramidite+ tetrazole treatment[4]. The removal of the protecting groups and the cleavage of the prooligonucleotides from the solid support[2] was accomplished in a single procedure upon UV irradiation.

It appears from this study that the diNPEOC was appropriate to obtain SATE-prooligonucleotides whereas the NVOC was not.

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