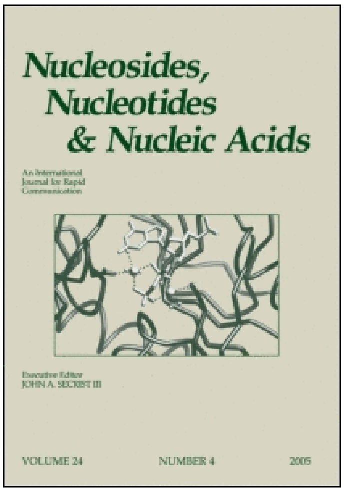

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# The Prooligonucleotide Approach: Synthesis of Mixed SATE-Phosphotriester Phosphodiester Oligonucleotides

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# THE PROOLIGONUCLEOTIDE APPROACH: SYNTHESIS OF MIXED SATE-PHOSPHOTRIESTER PHOSPHODIESTER OLIGONUCLEOTIDES

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**ABSTRACT:** Synthesis of mixed SATE phosphotriester-phosphodiester prooligos was done following two ways. Phosphodiesters were generated by selective β-elimination of cyanoethyl using DBU or were introduced with H-phosphonate chemistry.

We have already shown that prooligonucleotides (prooligos) could be synthesized on solid support with either methyl or tert-butyl S-AcylThioEthyl (SATE) groups (1). However, demasking by carboxyesterases of these prooligos was not efficient for the most lipophilic ones. This prompted us to reintroduce some charges in prooligos to modulate their lipophilicity and to increase their solubility.

The first synthetic way to obtain mixed SATE-phosphotriester and phosphodiester (PO/PS) uses thymidine phosphoramidite building blocks bearing a tBuSATE group. The phosphodiester linkages were generated by a selective removal of standard cyanoethyl (CNE) groups through a β-elimination mechanism using the non-nucleophilic base DBU in anhydrous THF (2) (**FIG. 1**):

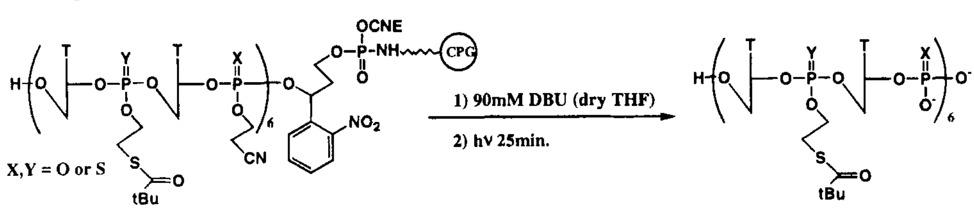

**FIG.1**: β-elimination of CNE groups

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However, this synthetic way does not allow the preparation of MeSATE prooligos. A second synthetic way using both phosphoramidite and H-phosphonatechemistries has been therefore set up. The phosphodiester linkages ($PO^-/PS^-$) were now generated by a post-synthetic oxydation of H-phosphonate linkages (**Fig.2**), prooligos were then cleaved from the solid support by photolysis (3).

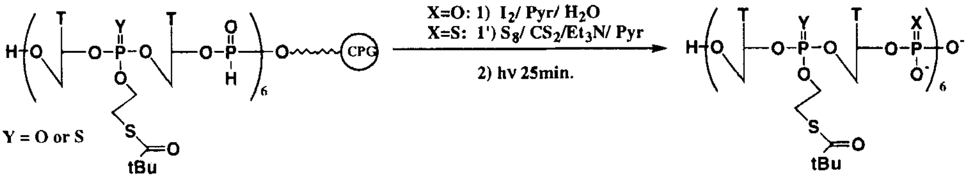

**FIG.2**: post-synthetic oxydation of H-phosphonate internucleosidic linkages

This method allows the synthesis of various mixed prooligos (Me- or tBuSATE, PO/PS diester or triester linkages) on a wide range of lipophilicity.

The substrate capacity of several prooligos series (alternated, gap or fully protected) was studied in presence of pig liver esterase (PLE) and in total CEM cell extract (TCE). These results showed a strong influence of the global lipophilicity as well as the hydrophobicity surrounding the SATE group. The esterase activities of PLE seems to be very sensitive to adjacent charges of SATE groups. Moreover, similar substrate capacities were observed in TCE for prooligos with closed lipophilicity: an alternated prooligo was hydrolysed slower than its gap analog. For each type of structure, the higher lipophilicity of the compound, the lower the rate of hydrolysis for the first SATE group.

## REFERENCES and NOTE

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2. Tosquellas, G.; Bologna, J. C.; Morvan, F.; Rayner, B.; Imbach, J. L. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2913-2918.
3. A 3'-desulfurization and dimerization for prooligos bearing a 3'-phosphorothioate monoester occurred during the release of the prooligo from the solid support due to the formation of a nitroso function during the photolysis. This side reaction could be avoid by addition of DTT.