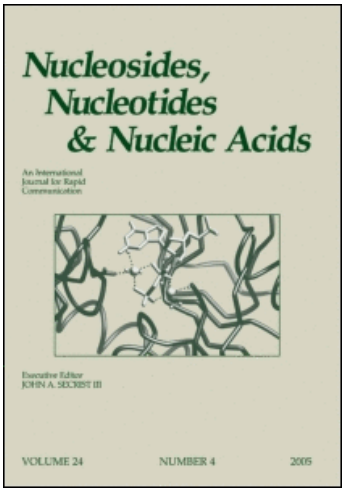

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Amide Protection in Oligodeoxynucleotide Synthesis

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AMIDE PROTECTION IN OLIGODEOXYNUCLEOTIDE SYNTHESIS

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Summary: Several O^6-protected deoxyguanosine- as well as O^4-protected thymidine-phosphoramidites were prepared according to the Mitsunobu reaction and Michael addition and were tested in a solid-phase automated DNA synthesizer.

During the last ten years some possible side reactions of the amide function of thymidine and deoxyguanosine, especially the phosphorylation by activated nucleotides, have been reported. In order to look into this problem we prepared several derivatives which can be cleaved by ß-elimination. The nucleosides 2a-f were tried to synthesize via a Mitsunobu reaction, using the procedure developed by Pfleiderer et al. <1>, applying additionally the transient protection method of Jones et al. <2>. But only the

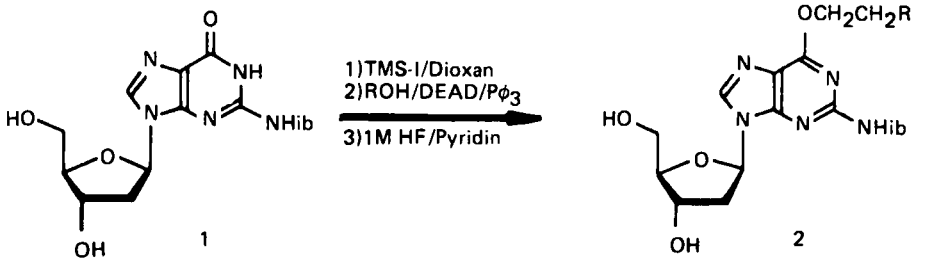

Fig.1 2a R= $-C_6H_4NO_2$, (NPE), 80%; 2b R= $-S-C_6H_4NO_2$, (NPTE), 40%; 2c R= $-S-C_6H_5$, 0%; 2d R= $-SO_2-C_6H_4NO_2$, 0%; 2e R= $-SO_2-C_6H_5$, 0%; 2f R= $-CN$, 0%

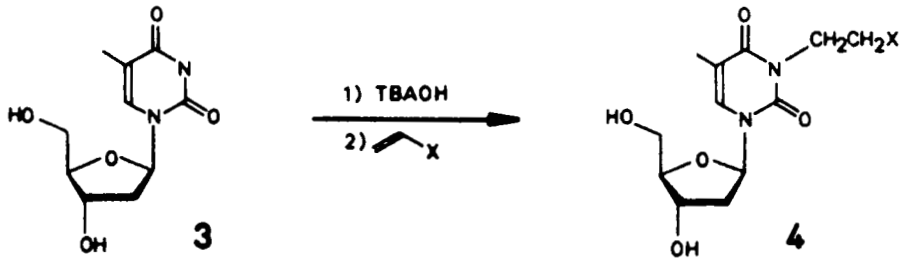

FIG.2 4a R= $-SO_2-C_6H_4NO_2$, 84%; 4b R= $-SO_2-C_6H_5$, 80%; 4c R= $-SO_2-CH_3$, 0%; 4d R= -CN, 45%

Fig.3

compounds 2a-b were obtained by using this transient protection/Mitsunobu alkylation sequence.

The NPE group can be cleaved by DBU in aprotic solvents while we had to oxidise the NPTE group to the sulfoxide before the cleavage by ammonia could be accomplished.

The appropriatly protected thymidines were obtained by adding the Michael acceptors to a pyridine solution of dT in the presence of tetrabutyl ammonium hydroxyde (TBAOH) <3>.

Structure assignments of 4a-c for N- or O-alkylation were done by 2-D-NMR in the COLOC-experiment <4> ^{13}C-shift as well as ^{3}J-coupling support the above assignment of N-alkylation.

The protected 2a and 4a were subsequently tritylated and converted to the phosphoramidites. These monomers were used for the syntheses of the sequences(Fig.3) with a ABI 380A DNA-synthesizer. After ammonia deprotection the crude mixtures were directly loaded on a 1mm 12%/7M urea polyacrylamide gel and visualized by uv-shadowing.

Conclusion: When using a long cycle (Ogilvie et al., <5>, coupling time 360s) O-6 protection seems to be advantageous, wheras shorter addition times (20s) do not seem to justify additional amide protection in this system.

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