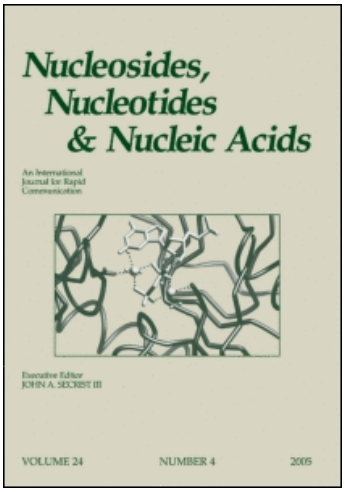

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A New Protecting Group Strategy for Amino Groups in Oligonucleotide Chemistry: CEOC Group

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A NEW PROTECTING GROUP STRATEGY FOR AMINO GROUPS IN OLIGONUCLEOTIDE CHEMISTRY: CEOC GROUP

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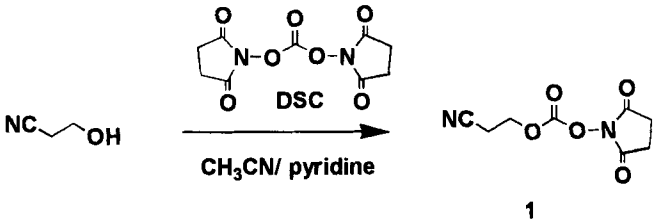
SUMMARY: A new protecting group, 2-cyanoethyloxycarbonyl, or CEOC, has been developed for amino groups and utilized in synthesizing modified oligonucleotides. (CEOC)-oxy-succinimide reagent has been synthesized to introduce this protecting group. The protecting group is removed by standard oligonucleotide deprotection protocols. Using this approach, oligonucleotides have been synthesized with various types of alkylamine substituents.

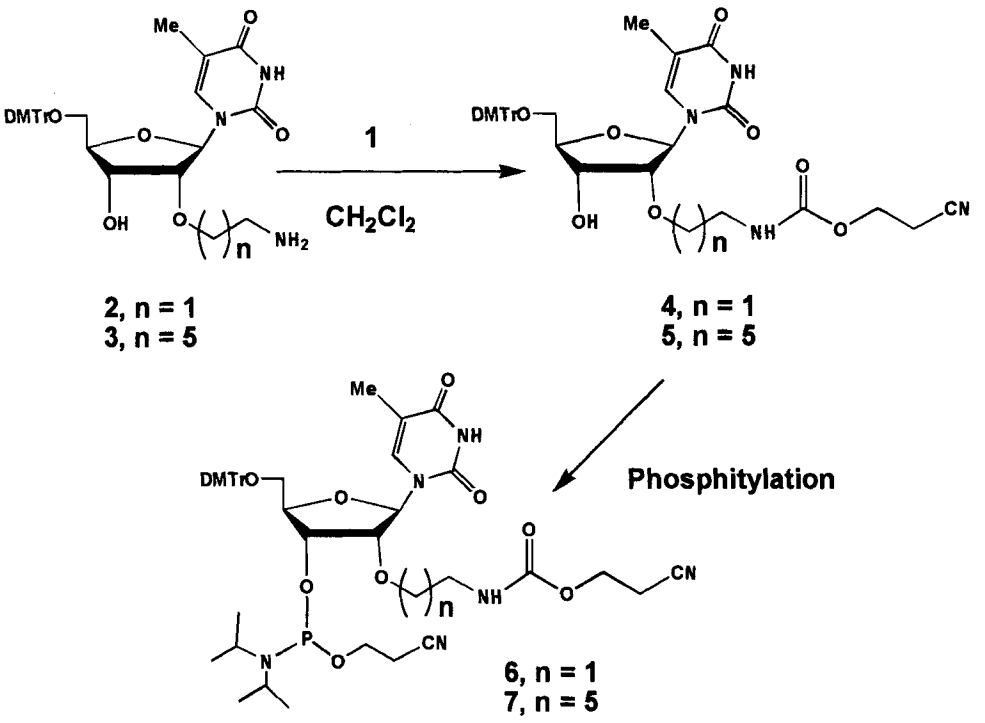
During oligonucleotide synthesis, convenient amino group protection methodology is important not only for exocyclic amines but also useful for side chain amino groups ("aminolinkers" or "aminotethers"). Conjugation of different ligands to improve the properties of oligonucleotides requires placement of protected amino groups with appropriate tethers in the appropriate building blocks and synthesizing oligonucleotides.

Our goal to make a convenient reagent for cyanoethyloxycarbonylation reagent resulted in cyanoethyloxycarbonyloxy succinimide (CEOC succinimide), a stable crystalline compound that can be synthesized from readily available commercial chemicals. In addition to the potential applications in the nucleic acid field, this reagent can also be of general use for amino groups in all classes of compounds. CEOC succinimide **1** was generated from reacting 2-cyanoethanol with disuccinimidyl carbonate (DSC) [1-3] in acetonitrile in the presence of pyridine to yield CEOC succinimide (**Scheme 1**).

Scheme 1



Scheme 2



The CEOC group was used in protecting amino groups in nucleosides building blocks according to **Scheme 2.** The phosphoramidites **6** and 7 were used in standard oligonucleotide synthesis; subsequently, standard deprotection conditions (concentrated ammonium hydroxide, 12 hrs) were used to deprotect the oligomers. The CEOC groups were removed without any side products in oligomers having all four nucleobases. In summary, a convenient solid reagent to protect aminolinkers (CEOC-oxy-sucicnimide) has

been developed and used to protect nucleoside-based 2'-amino linkers and non-nucleosidic aminolinkers. After oligonucleotide synthesiscon containing these aminolinkers, standard NH_4OH treatment removes the CEOC group by ß-elimination.The resultant oligonucleotides with 2'-*O*-alkylamines stabilize antisense oligomers toward RNA binding. The aminolinkers generated by this new method are also useful for conjugation chemistry.

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