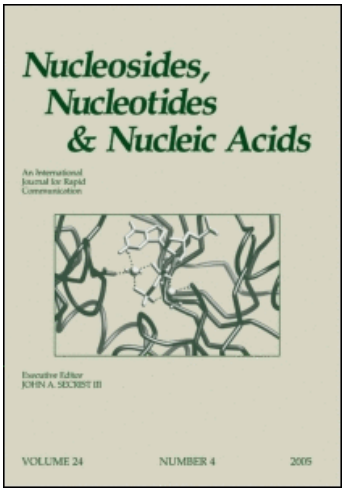

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Base Labile Protecting Groups for Hydroxyl Functions in Ribonucleosides and Deoxyribonucleosides

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BASE LABILE PROTECTING GROUPS FOR HYDROXYL FUNCTIONS IN RIBONUCLEOSIDES AND DEOXYRIBONUCLEOSIDES

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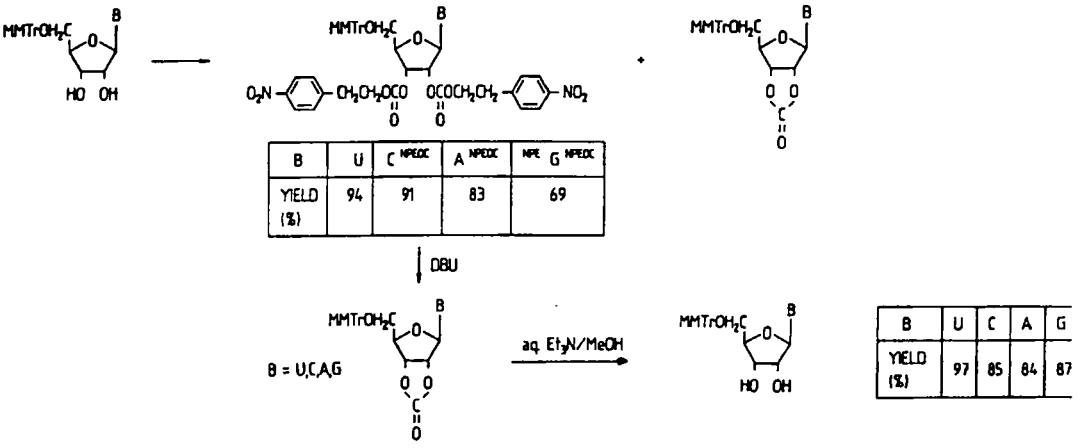
Summary: The use of the base labile 2-(p-nitrophenyl)-ethoxycarbonyl (NPEOC), 2-(2,4-dinitrophenyl)-ethoxycarbonyl (DNPEOC) and 2-cyanoethoxycarbonyl (CEOC) group for hydroxyl protection of the sugar moiety in ribonucleosides and deoxyribonucleosides are described and discussed.

The protection of sugar hydroxyl functions represents an important step in designing a strategy for a multistep chemical synthesis of oligonucleotides (1). The striking features of the p-nitrophenylethyl (NPE) and 2-(p-nitrophenyl)-ethoxycarbonyl (NPEOC) protecting group for various functions (2,3,4) prompted us to use the latter base labile group for blocking the hydroxyl groups in ribo- and deoxyribonucleosides respectively.

Treatment of 5'-O-MMTr-ribonucleosides proceeds in high yields with 1-methyl-3-p-nitrophenylethoxycarbonylimidazolium chloride in presence of 4-dimethylaminopyridine in dry CH_2Cl_2 within 2 h to the corresponding 2',3'-di-O-carbonates and formation of little 2',3'-cyclic carbonate derivatives (Scheme 1).

The NPEOC groups as wellas the 2-(2,4-dinitrophenyl)-ethoxycarbonyl (DNPEOC) group are also suitable for selective protection of the 5'-hydroxy position in deoxyribonucleosides. Dropwise addition of the 2-(4-nitrophenyl)-ethyl chloroformate and 2-(2,4-dinitrophenyl)-ethyl chloroformate respectively to the deoxyribonucleosides in dry pyridine at $-10^{o}C$ resulted after few hours in high yields of the corresponding 5'-O-protected deoxyribonucleoside derivatives (Schemes 2,3).

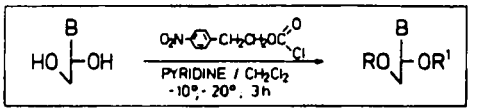
The NPEOC group is removable quantitatively at $20^{o}C$ by action of 0.5 M DBU in dry pyridine whereas the DNPEOC group can be cleaved under relatively mild reaction conditions by

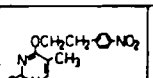
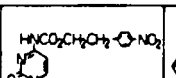
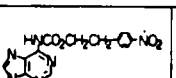
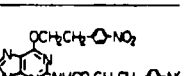
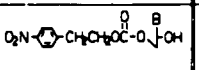
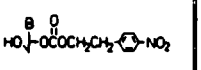
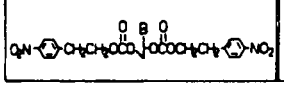


B	U	C NPEOC	A NPEOC	G NPE NPEOC
YIELD (%)	94	91	83	69

B	U	C	A	G
YIELD (%)	97	85	84	87

SCHEME 1



					
	70%	73%	65%	69%	78%
	-	8%	8%	-	-
	29%	15%	11%	22%	14%

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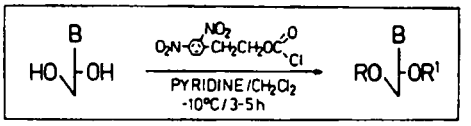
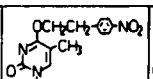
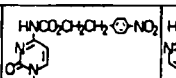
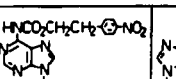
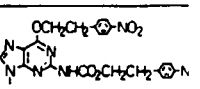
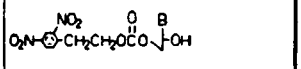
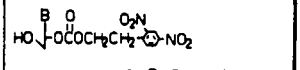
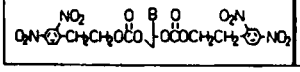
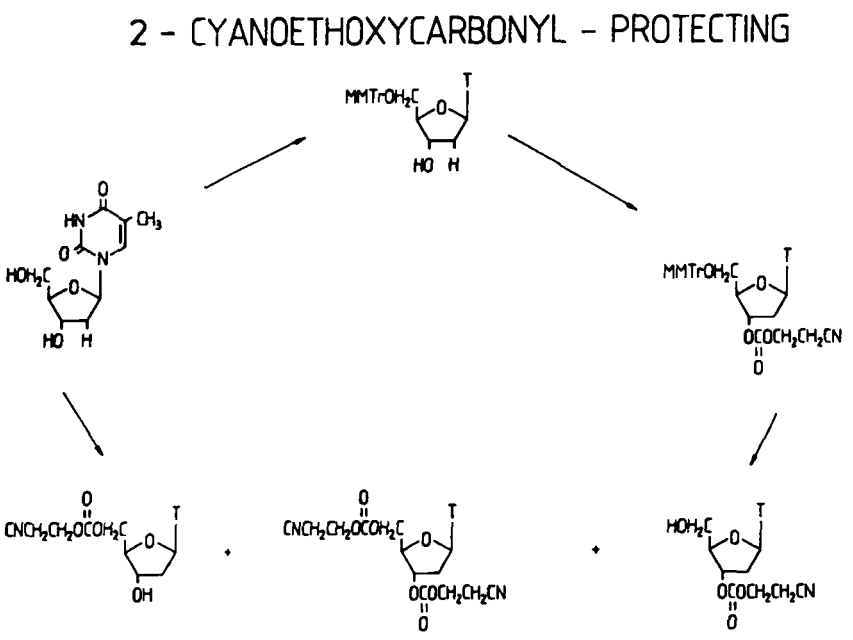


					
	75%	70%	71%	80%	81%
	6%	6%	3%	3%	2%
	1%	7%	3%	7%	1%

SCHEME 3



SCHEME 4

triethylamine to unmask the 5'-OH function (5). The experimental details will be published soon.

Another easily accessible reagent, the 2-cyanoethyl chloroformate (6) can also conveniently be used for the protection of hydroxy functions at the sugar moiety of ribo- and deoxyribonucleosides respectively (Scheme 4).

For instance, the reaction of thymidine with CEOCOCl leads to the desired 5'-O-cyanoethoxycarbonyl-thymidine in satisfactory yield and the selective cleavage was possible by treatment with aqueous triethylamine within few minutes.

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