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THE USE OF THE p-NITROPHENYLETHOXYCARBONYL GROUP FOR AMINO PROTECTION IN CYTIDINE AND ADENOSINE CHEMISTRY

FRANK HIMMELSBACH AND WOLFGANG PFLEIDERER*
Fakultät für Chemie, Universität Konstanz, Postfach 5560, D-7750 Konstanz/West Germany

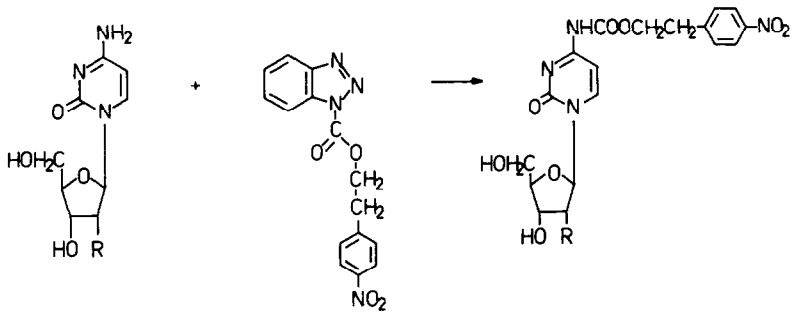
Amino protection in 2'-deoxycytidine (1) and cytidine (2) as well as in 2'-deoxyadenosine (8) and adenosine (9) respectively can be achieved by the new reagents 1-(p-nitrophenylethoxycarbonyl)-benzotriazole (3) and 1-methyl-3-(p-nitrophenylethoxycarbonyl)-imidazolium chloride (7) to form the corresponding carbamates (4, 5, 13, 14) in high yields.

Synthesis of oligonucleotides requires the development of different blocking groups for various reactive centers in nucleosides and nucleotides. A vast variety of protecting groups is in use in oligonucleotide synthesis for the 2',3'- and 5'-hydroxy as well as phosphate functions [1-7], but for exocyclic amino groups most commonly benzoyl for adenosine [8] and anisoyl for cytidines [9] have been applied, although other acyl groups were investigated [10].

More recent studies claim the introduction of the N-levulinyl group [11] and the N-phthaloyl group [12] respectively, both of which could be removed with 0.5 M hydrazine hydrate in pyridine/acetic acid at room temp. Almost simultaneously recommended Rapoport [13,14] the N-benzyloxycarbonyl group for amino protection, since removal can be achieved by phase transfer hydrogenolysis using cyclohexadiene as hydrogen source and palladium on carbon as catalyst.

Since we have recently developed the p-nitrophenylethyl group for phosphate protection [15] and have recognized a substantial improvement in nucleotide and oligonucleotide syntheses [16-19] this blocking group has now been stu-

died in its p-nitrophenylethoxycarbonyl form for amino protection in cytidine and adenosine derivatives. Based on observations of Butula [20,21] that 1-alkoxycarbonylbenzotriazoles acylate selectively amino groups in presence of hydroxy functions the 1-(p-nitrophenylethoxycarbonyl)-benzotriazole (3) has been synthesized as a new reagent from 1-chlorocarbonylbenzotriazole and p-nitrophenylethanol in dichloromethane-triethylamine at 0°C in 92 % yield. Reactions with unprotected 2'-deoxycytidine (1) and cytidine (2) proceeded smoothly in DMF at 60°C and led in 90 % to the corresponding N^4-p-nitrophenylethoxycarbonyl derivatives 4 and 5.



	R
1	H
2	OH

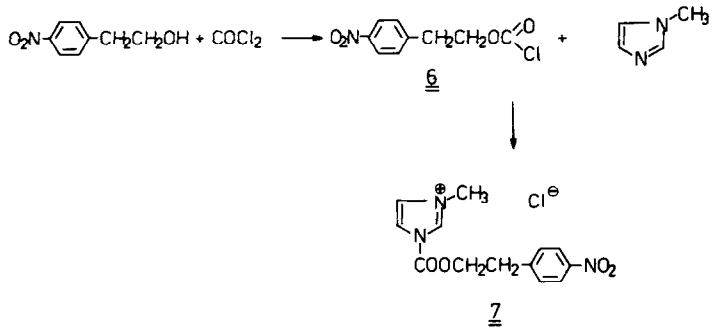
3

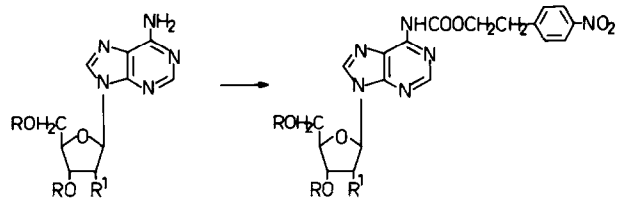
	R
4	H
5	OH

The new blocking group is stable towards ammonia and triethylamine in methanol, dioxane, and water respectively, but can be cleaved quantitatively by DBN or DBU in aprotic solvents with formation of the unprotected starting materials.

Analogous p-nitrophenylethoxycarbonylations of the 6-amino group in 2'-deoxyadenosine (8) and adenosine (9) could not be achieved directly by 3 due to a much lower nucleophilic potential of the amino function in purine nucleosides. As a more powerful reagent was then synthesized p-nitrophenylethyl chloroformate (6) from p-nitrophenylethanol and phosgene, but reaction with 3',5'-di-O-acetyl-2'-deoxyadenosine (10) and 2',3',5'-tri-O-acetyladenosine (11) always led to mixtures of the N^6-mono- and disubstituted derivatives which can fortunately be deprotected homogeneously on treatment with aqueous ammonia in methanol to N^6-p-nitrophenylethoxycarbonyl-2'-deoxyade-

nosine (13) and -adenosine (14). A more selective reagent for monoacylations was found finally in 1-methyl-3-(p-nitrophenylethoxycarbonyl)-imidazolium chloride (7), which could be obtained in high yield and pure form from 3 and 1-methylimidazole in methylene chloride. Reaction of 7 with the acetylated adenosine 10 and 11 respectively led in 85 % yield each to 3',5'-di-O-acetyl-N^6-p-nitrophenylethoxycarbonyl-2'-deoxyadenosine (15) and 2',3',5'-tri-O-acetyl-N^6-p-nitrophenylethoxycarbonyladenosine (16). Deacetylation with triethylamine in methanol can be achieved almost quantitatively to 13 and 14 respectively.





	R	R^1
8	H	H
9	H	OH
10	Ac	H
11	Ac	OAc
12	$SiMe_3$	H

	R	R^1
13	H	H
14	H	OH
15	Ac	H
16	Ac	OAc
17	$SiMe_3$	H

An even more simple one-pot reaction to 13 could be developed starting from 8, which was treated first in dichloromethane with 1-trimethylsilylimidazole to form selectively the 3',5'-bis-O-trimethylsilyl-2'-deoxyadenosine (12) [22]. Addition of 7 causes monoacylation to 3',5'-bis-O-trimethylsilyl-N^6-p-nitrophenylethoxycarbonyl-2'-deoxyadenosine (17) and subsequent work-up

in methanol with aqueous ammonia gave in 73 % overall yield 13.

Deprotection of the amino blocking group in 15 and 16 works also best in this series with DBN or DBU in pyridine to bring back the starting materials 10 and 11 in excellent yield.

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