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SYNTHESIS OF O^4-p-NITROPHENYLETHYL THYMIDINE AND URIDINE DERIVATIVES

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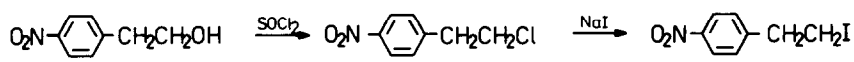
O^4-Protection in thymidine and uridine derivatives has been achieved by the p-nitrophenylethyl group in a silver-ion catalysed alkylation reaction to form valuable building blocks for oligonucleotides syntheses.

In the present oligonucleotide syntheses via the phosphotriester approach the most serious problems concern various side reactions resulting from the reactive sites of base residues involving especially amide functions. The problem of O^6-protection of guanosine derivatives was studied by different groups, including the 6-O-(2-nitrophenyl) group by Reese [1], various 6-O-substituted silyl, sulfonyl, phosphoryl, and phosphinothioyl derivatives [2] as well as a new type of protection mode for the guanine moiety in using the 1,2-diisobutyryloxyethylene group by Hata [3] and also various properly ß-substituted ethyl groups prone to ß-elimination cleavage reactions by Jones [4]. Our own contribution finally has climaxed in the introduction of the p-nitrophenylethyl group onto O^6 of acylated guanosine derivatives by the Mitsunobu reaction [5].

Efforts to protect also O^4 in thymidines and uridines result from observations [6] involving an amide modification especially during the second phosphorylation step of the phosphotriester approach, when 1-(mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazole [7,8] or the corresponding tetrazole derivative (MST) [9] as used as the condensing agent. It was subsequently found that the use of o-chlorophenyl phosphorodi-(1,2,4-triazolide) [10] in the first phosphorylating step of the phosphotriester approach can also lead

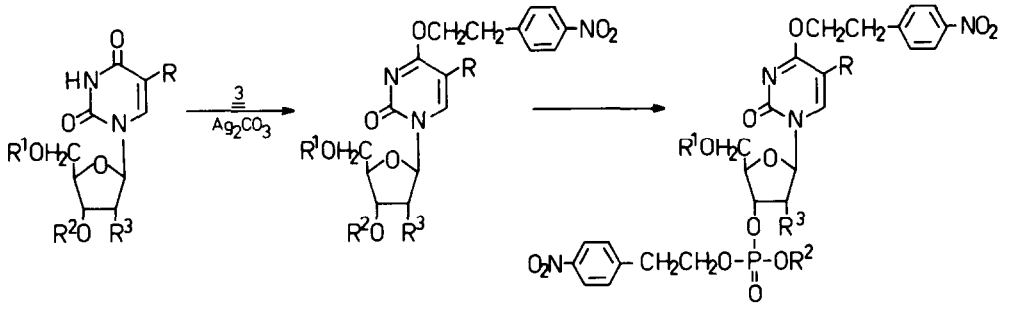
[11] to related side-reactions. Simultaneously, studies of phosphorylation of nucleosides indicated that p-chlorophenyl phosphorodichloridate and 1,2,4-triazole are capable of similar modification [11]. Even thymidine, which seems to be less susceptible to the modification by MST [6], has been successfully converted to the 4-(1,2,4-triazolyl)-pyrimidinone derivative [11]. This type of compounds is then prone to nucleophilic displacement reactions forming cytidine derivatives with ammonia and amines respectively [11-13].

A first successful attempt for amide protection at O^4 in uridine has recently been achieved by phenol and 2,4-dimethylphenol in a four-step procedure [1]. Both blocking groups can be cleaved simultaneously with the subst. aryl phosphotriester functions in the oximate process.
Our own efforts in this connection have been directed towards the introduction of the p-nitrophenylethyl group onto O^4. Since the Mitsunobu reaction does not afford O^4 but N-3 substitution the silver-catalysed S_N1-type alkylation with p-nitrophenylethyl iodide (3) in benzene was investigated. The new reagent was prepared from 2-(p-nitrophenyl)-ethanol (1) on treatment with thionyl chloride in the presence of catalytic amounts of pyridine and 2 hours refluxing to give first p-nitrophenylethyl chloride (2) [14] in 90 % yield followed by a Finkelstein reaction with sodium iodide in ethylmethylketone to form crystalline 3, which has recently also been reported in literature by Jencks [15].



1 2 3

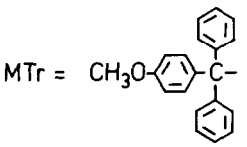
3',5'-Di-O-acetyl-(4) and 3'-O-benzoyl-5'-O-monomethoxytritylthymidine (5) react with 3 in presence of silver carbonate in benzene at 50°C for 3 days to give 3',5'-di-O-acetyl-O^4-p-nitrophenylethylthymidine (8) and 3'-O-benzoyl-5'-O-monomethoxytrityl-O^4-p-nitrophenylethylthymidine (9) in 80 and 65 % yield respectively. Treatment with absol. methanolic ammonia at room temp. cleaves off the acyl groups to form 10 and 11 respectively.

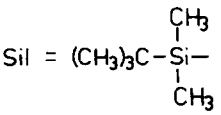


	R	R^1	R^2	R^3
4	CH_3	Ac	Ac	H
5	CH_3	MTr	Bz	H
6	H	MTr	Bz	OBz
7	H	MTr	Ac	OAc

	R	R^1	R^2	R^3
8	CH_3	Ac	Ac	H
9	CH_3	MTr	Bz	H
10	CH_3	H	H	H
11	CH	MTr	H	H
12	H	MTr	Bz	OBz
13	H	MTr	Ac	OAc
14	H	MTr	H	OH
15	H	MTr	H	OSil

	R	R^1	R^2	R^3
16	CH_3	MTr	$Cl_2C_6H_3$(2.5)	H
17	CH_3	MTr	$HNEt_3$	H
18	CH_3	H	$Cl_2C_6H_3$(2.5)	H
19	H	MTr	$Cl_2C_6H_3$(2.5)	OSil
20	H	MTr	$HNEt_3$	OSil
21	H	H	$Cl_2C_6H_3$(2.5)	OSil





In order to find out the stability of the O^4-p-nitrophenylethyl blocking group in oligonucleotide synthesis the corresponding phosphotriester 16 was synthesized from 11 with 2,5-dichlorophenyl phosphorodichloridate in presence of 1,2,4-triazole and subsequent treatment with p-nitrophenylethanol in 82 % yield. Oximate cleavage [16] leads to the triethylammonium 5'-O-monomethoxytritylthymidine-3'-p-nitrophenylethyl phosphate (17) in 85 % yield and detritylation of 16 to 18 with p-toluenesulfonic acid in methylene chloride-methanol proceeded with 91 % yield.

The corresponding uridine derivatives showed expectedly a similar behaviour. 2',3'-Di-O-benzoyl-(6) and 2',3'-di-O-acetyl-5'-O-monomethoxytrityluridine (7) gave on O^4-alkylation 12 and 13 respectively in 60-70 % yield. Ammonia treatment afforded deacylation to 14, which gave on silylation with tert-

butyldimethylsilyl chloride/imidazole in pyridine a mixture of the two isomeric 2'-(15) and 3'-O-tert-butyldimethylsilyl derivatives in 38 and 28 % yield respectively. 15 was phosphorylated in the usual manner to 19, which was further modified by the oximate procedure to 20 and by p-toluenesulfonic acid to 21 respectively.

The removal of the O^4-p-nitrophenylethyl protecting group can be achieved selectively by 0.5 M DBU in absol. pyridine not harming any of the various other blocking groups in the different thymidine and uridine derivatives.

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