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NITRATE ION AS CATALYST FOR SELECTIVE SILYLATIONS OF NUCLEOSIDES

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Summary - Nitrate ion has been found to have a remarkable effect on the selectivity of silylation of ribonucleosides using the t-butyldimethylsilyl group.

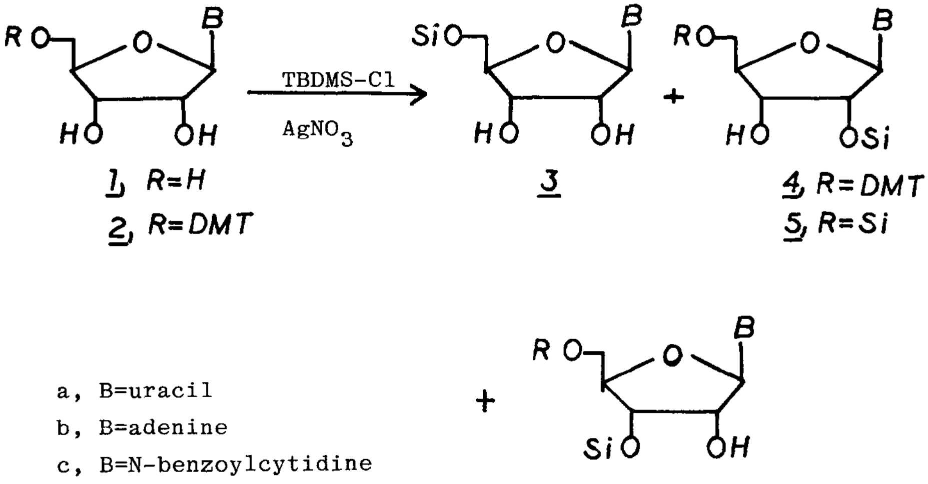
During our recent development of a total procedure for the synthesis of oligoribonucleotides (1-5), the use of the t-butyldimethylsilyl (TBDMS) group in protecting the 2'-hydroxyl position has been an essential ingredient (6,7). The use of this protecting group has greatly reduced the time, effort and number of steps in arriving at a 2',5'-protected ribonucleoside. However, while the total yield of 2',5'-and 3',5'-protected derivatives is generally high (5,7), the two sets of isomers 4,6 and 5,7 are produced in nearly equal amounts. We have been searching for a method to give higher selectivity of the compounds 4 and 5.

Several general procedures have been suggested (8-10) to improve either total yields or selectivity in silylation reactions. We have found that these procedures offer very little advantage in the selective silylation of ribonucleosides. In this report we wish to describe the effect of nitrate ion in providing remarkable selectivity in the silylation of ribonucleosides.

The reactions are outlined in Scheme 1 and results are collected in Table 1. The general procedure can be illustrated with the silylation of 5'-dimethoxytrityl-N-benzoylcytidine (2c). The nucleoside 2c is dissolved in THF after which pyridine (3.7 mmole/mmole of $AgNO_3$) and silver nitrate (1.2 mmole/mmole 2c) are added and the solution is stirred until the silver nitrate is completely dissolved (∿5 min). At this point t-butyldimethylsilyl chloride (TBDMS-Cl, 1.3 mmole/mmole 2c) is added all at once and the resulting mixture is stirred at room temperature. After 1.5 h the mixture is filtered into 5% aqueous $NaHCO_3$ to prevent detritylation during work-up. The product is extracted into methylene chloride which is dried and concentrated and the residue applied to a short silica gel column (Merck silica gel 60,10g/g of product, column 5 cm is diameter). The column was eluted using ether-hexane (3:1) and excellent separation of the products 4c (68%) and 6c (20%) was obtained. Table 1 shows the yields for all compounds studied.

When the unprotected nucleosides 1 were used in this procedure excellent yields of the 2',5'-diprotected compounds 5 were obtained (eg. 5a in 90% yield). An interesting contrast exists between guanosine (1d) and N-benzoylguanosine (1e). In the former case very good selectivity was obtained (60% 5d and 35% 7d) while in the latter case there was very little selectivity (48% 5e vs 40% 7e). This seems to reflect the steric influence of the N^2-benzoyl group on the 2'-hydroxyl region.

Scheme 1



1, R=H
2, R=DMT

3

4, R=DMT
5, R=Si

a, B=uracil
b, B=adenine
c, B=N-benzoylcytidine
d, B=guanine
e, B=N-benzoylguanine

6, R=DMT
7, R=Si

DMT=dimethoxytrityl
Si=t-butyldimethylsilyl

A base such as pyridine is essential for the disilylation. In the absence of pyridine virtual quantitative yields of the 5'TBDMS derivatives 3 were obtained, regardless of the amount of TBDMS-Cl and $AgNO_3$ used. On the other hand, the nitrate ion is essential both for the speed and selectivity of the reaction. Silver trifluoroacetate has no effect on the reaction while tetrabutylammonium nitrate gives the same results as silver nitrate.

In a separate experiment TBDMS-nitrate was prepared by mixing TBDMS-Cl and $AgNO_3$ in THF. After filtering from AgCl the THF was removed at reduced pressure and TBDMS-NO_3 distilled at 140-142°C (1 atm). TBDMS-NO_3 was found to react with nucleosides in the presence or absence of pyridine to give exactly the results described for the general procedures and listed in Table 1.

The results described in this report clearly indicate a novel effect of nitrate ion in silylation reactions. This has resulted in a highly selective silylation of ribonucleosides.

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TABLE 1

Nitrate Catalysis of Silylation Reactions+

Nucleoside	TBDMS-Cl (mmole)	$AgNO_3$ (mmole)	Pyridine (mmole)	Time (h)	Product(%)		
					5'	2',5'	3',5'
DMT-U (2a)	1.3	1.2	3.7	1.5	-	70	15
DMT-A (2b)	1.3	1.2	3.7	5	-	65	21
DMT-C^{BZ} (2c)	1.3	1.2	3.7	1.5	-	68	20
DMT-G^{BZ} (2e)	1.7	1.5	5	5	-	45	40
U (1a)	2.2	2.2	5	1	-	90	5
U (1a)	2.2	-	5	5	<10	-	-
U (1a)	4	4	-	3	98	-	-
U (1a)	2.2	2.2	-	3	95	-	-
A (1b)	2.2	2.2	5	1	-	68	22
A (1b)	2.2	2.2	-	3	95	-	-
C^{BZ} (1c)	2.2	2.2	5	1	-	82	13
C^{BZ} (1c)	2.2	2.2	-	3	95	-	-
*G (1d)	2.2	2.2	5	2	-	60	35
G (1d)	2.2	2.2	-	3	95	-	-
*G^{BZ} (1e)	2.2	2.2	5	2	-	48	40
G^{BZ} (1e)	2.2	2.2	-	4	97	-	-
U (1a)	2	$(nBu)_4NSO_3H$(2)[11]	5	2	90	-	-
U (1a)	2	$(nBu)_4NI$(2)[11]	5	2	-	-	-
A (1b)	2	$(nBu)_4NNO_3$(2)[11]	5	1	-	67	23

+The solvent was THF in all cases except for * where THF-DMF (1:1) was used. Yields are bas on material isolated from short column chromatography or TLC.

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11. Numerous soluble silver and tetrabutylammonium salts were tested. Only nitrate salts had any effect on disilylation. Other salts showed no effect on silylation at all except for tetrabutylammonium sulfate where a good yield of monosilyl derivative (3) was obtained.

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