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HIGH YIELD SELECTIVE 3'-SILYLATION OF RIBONUCLEOSIDES

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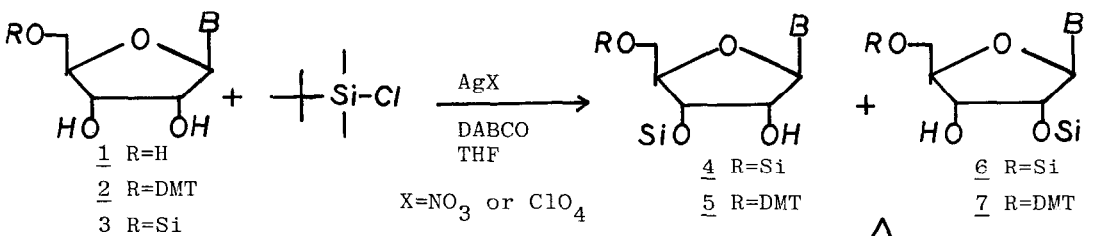
Summary - Procedures have been developed which permit the highly selective silylation of the 3'-hydroxyl of ribonucleosides to produce 3',5'-diprotected derivatives in high yields.

The manipulation of ribonucleosides whether for coupling to form ribonucleotides or for the selective chemical modification of the carbohydrate portion of the structure, requires the availability of versatile hydroxyl protecting groups. It is usually desirable to be able to protect the 2'- and 5'- positions or the 3'- and 5'- positions. We have been developing the alkylsilyl groups in ribonucleoside chemistry (1,2) and have recently reported a procedure for highly selective silylations at the 2'- position (3).

It is equally important to have procedures available for the selective protection of the 3'-position. This however has been a more difficult task. Markiewicz (4) has described the preparation of a bifunctional silylating agent, 1,3-dichloro-1,1,3,3-tetraisopropyl disiloxane, which simultaneously protects the 5'- and 3'- positions. Procedures have also been described which



1 R=H
2 R=DMT
3 R=Si

a)B=N-benzoylcytidine
b)B=uracil
c)B=adenine
d)B=N-benzoylguanine

4 R=Si
5 R=DMT

6 R=Si
7 R=DMT

DABCO= 

Si=t-butyldimethylsilyl
DMT=dimethoxytrityl

permit the isolation of 3'-acyl derivatives in good yields (5). To date no procedure has been reported for the direct and selective derivatization of the 3'- position of ribonucleosides using a monofunctional silylating agent. We wish to describe in this report a procedure for the rapid and selective silylation of the 3'- position of 5'-protected ribonucleosides in greater than 90% yields.

We have found that the silylation of ribonucleosides in the presence of silver salts and 1,4-diazabicyclo [2.2.2] octane (DABCO) leads to the formation of 3',5'-disilylated derivatives in high yields.

Table 1

DABCO Catalyzed Silylation of Ribonucleosides*

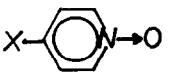
Entry	Nucleoside	TBDMS-Cl (mmole)	Salt (mmole)	Time (h)	Product (%) 5'	3',5'	2',5'
1	C^{BZ} (1a)	2.4	$AgClO_4$(2.3)	3	-	4a,92	6a,3
2	C^{BZ} (1a)	2.4	$AgNO_3$(2.3)	3	-	4a,90	6a,5
3	U (1b)	2.3	$AgClO_4$(2.2)	3	-	4b,90	6b,5
4	U (1b)	2.3	$AgNO_3$(2.2)	3	-	4b,94	6b,3
5	U (1b)	2.3	$AgO\overset{O}{\overset{\|}{C}}CF_3$(2.2)	3	-	4b,90	6b,5
6	U (1b)	2.3	$(nBu)_4NClO_4$(2.2)	10	3b,65	4b,18	6b,2
7	U (1b)	2.3	$(nBu)_4NNO_3$(2.2)	10	3b,60	4b,25	6b,1
8	U (1b)	2.3	---	10	3b,85	4b,2	-
9	A (1c)	2.4	$AgClO_4$(2.3)	4	-	4c,70	6c,25
10	A (1c)	2.4	$AgNO_3$(2.3)	4	-	4c,70	6c,20
11	A (1c)	2.4	$AgO\overset{O}{\overset{\|}{C}}CF_3$(2.3)	4	-	4c,66	6c,30
12	A (1c)	2.4	---	12	3c,90	4c,3	-
13	G^{BZ} (1d)	2.6	$AgClO_4$(2.5)	6	-	4d,60	6d,30
14	G^{BZ} (1d)	2.6	$AgNO_3$(2.5)	6	-	4d,60	6d,35
15	DMT C^{BZ} (2a)	1.3	$AgClO_4$(1.2)	3	-	5a,90	7a,5
16	DMT C^{BZ} (2a)	1.3	$AgNO_3$(1.2)	3	-	5a,93	7a,3
17	DMT U (2b)	1.3	$AgClO_4$(1.2)	2	-	5b,91	7b,5
18	DMT A (2c)	1.3	$AgClO_4$(1.2)	4	-	5c,70	7c,25
19	DMT G^{BZ} (2d)	1.5	$AgNO_3$(1.5)	5	-	5d,30	7d,60
20	Si U (3b)	1.3	$AgClO_4$(1.2)	3	-	4b,90	6b,5
+21	U (1b)	2.8	$AgNO_3$(2.7)	10	3b,98	-	-
+22	U (1b)	2.2	$AgClO_4$(2.2)	2	3b,90	4b,3	6b,3

*Reactions carried out in THF as described in the text using 6 mmole of DABCO/mmole of nucleoside.

+DABCO was ommitted from these experiments.

Table 2

Effect of Pyridine N-Oxides on Silylation of Ribonucleosides*



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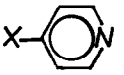

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a, X=NO_2 c, X=CH_3
b, X=H d, X=Ac

Nucleoside	Salt (mmole)	Catalyst (mmole)	Time (h)	Product (%) 5'	3',5'	2',5'
C^{BZ}, 1a	$AgClO_4$(2.2)	8a (2.3)	2	-	4a,90	6a,8
C^{BZ}, 1a	$AgNO_3$(2.2)	8a (2.3)	12	3a,90	-	-
C^{BZ}, 1a	$(nBu)_4NClO_4$(2.2)	8a (2.3)	5	-	-	-
C^{BZ}, 1a	$AgClO_4$ (2.2)	pyridine (5)	2	-	4a,5	6a,90
C^{BZ}, 1a	$AgClO_4$ (2.2)	----	2	3a,98	-	-
C^{BZ}, 1a	----	pyridine (5)	5	-	-	-
C^{BZ}, 1a	$AgClO_4$(2.2)	8b (2.3)	2	-	4a,40	6a,40
C^{BZ}, 1a	$AgClO_4$(2.2)	8c (2.3)	2	-	4a,40	6a,40
C^{BZ}, 1a	$AgClO_4$(3.7)	8d (3.5)	60	3a,40	4a,25	6a,18
U , 1b	$AgClO_4$(2.2)	8a (2.3)	1.5	-	4b,50	6b,40
A , 1c	$AgClO_4$(2.2)	8a (2.3)	2	-	4c,89	6c,5
C^{BZ}, 1d	$AgClO_4$(2.5)	8a (2.6)	2.5	-	4d,98	6d,-
C^{BZ}, 1a	$AgClO_4$(2.7)	9a (4)	15	3a,15	4a,70	6a,5
C^{BZ}, 1a	$AgClO_4$(2.7)	9d (4)	10	3a,20	4a,5	6a,70

*Reactions were carried out in THF (25 ml/mmole of nucleoside) using TBDMS-Cl (2.2 mmole/mmole 1). Dimethoxytritylated compounds 2 undergo rapid detritylation under these conditions.

The procedure can be illustrated by the silylation of N-benzoylcytidine (1b). DABCO (0.67g, 6 mmole) was dissolved in dry THF (25 ml). Silver nitrate (0.37 g, 2.2 mmole) was added and the solution was stirred at 20°C. After 5 min, t-butyldimethylsilyl chloride (TBDMS-Cl, 0.35 g, 2.3 mmole) was added and after an additional 5 min N-benzoylcytidine (1a, 0.35 g, 1 mmole) was added. Stirring was continued for 3 h. The solution was collected by filtration, diluted with 50 ml of water, and extracted with chloroform (80 ml). The organic layer was dried and concentrated. The products were separated by short column chromatography (7 g silica gel) using chloroform: methanol (9.7:0.3, 200 ml). The 2',5'-disilylderivative (6a, mp.67-71°C) was obtained in 3% yield while the 3',5'-disilylisomer (4a, mp. 147-151°C) was obtained in 92% yield.

The results summarized in Table 1 show a remarkable degree of selectivity for the 3'- position. The nature of the cation seems to be important in this reaction while the anion is of little importance. DABCO is necessary to ensure silylation at the 3'- position (compare entries 21 and 22).

During the course of these investigations we found that 4-nitropyridine N-oxide was also capable of catalyzing selective silylation at the 3'- position. These results are summarized in Table 2. It is clear from the results listed in Table 2 that of the pyridine N-oxides tested, only 4-nitropyridine N-oxide had the desired effect. 4-Nitropyridine produced a similar result in a slower reaction. It must also be noted that the 4-nitropyridine N-oxide conditions result in rapid loss of dimethoxytrityl groups (eg. from 2).

The results described in this report offer a new and efficient procedure for the 3',5'- protection of ribonucleosides.

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