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CONVERSION OF RIBONUCLEOSIDES TO PROTECTED 3'-DEOXYNUCLEOSIDES

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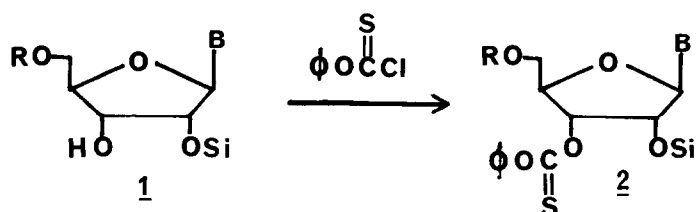
Summary - A procedure is presented for the conversion of ribonucleosides to 3'-deoxyribonucleosides and their protected derivatives.

The chemical conversion of ribonucleosides into 3'-deoxynucleosides has not been easy to accomplish. Procedures usually involve halogenation of the carbohydrate ring followed by replacement of halogen with hydrogen (1). Alternately, the desulfurization of thioanhydronucleosides leads to deoxynucleosides (2). 3'-Deoxynucleosides are of considerable interest for their biological activity with cordycepin (3'-deoxyadenosine) being the best known example (3). Recently, interest has increased in the synthesis of nucleotides from 3'-deoxynucleosides as 2'-5' linked analogues of natural DNA sequences and as possible interferon inducers (4). To date there is no general procedure for the conversion of ribonucleosides into protected 3'-deoxynucleosides. We wish to report such a procedure.

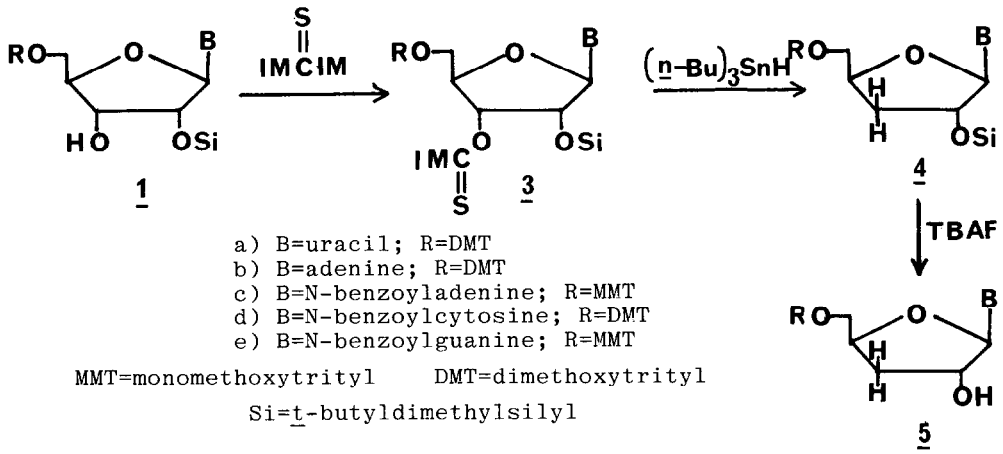
We have recently demonstrated procedures for the high yield conversion of ribonucleosides to their 2',5'-diprotected derivatives (5,6). This allows for the ready derivatization of ribonucleosides at the 3'-position. In principle, reaction of compounds of the type 1 with either phenyl chlorothionocarbonate or (thiocarbonyl)diimidazole should give products that can be readily reduced to the 3'-deoxynucleoside derivatives (7,8).

We found that phenyl chlorothionocarbonate reacted readily with the 2',5'-protected uridine (1a) and adenosine derivatives. However, with the N-protected nucleosides (1c-1e), a number of unidentified products were produced in low yield. This reagent had previously been described to react with 3',5'-protected uridine and adenosine but had not been used with N-protected nucleosides (7).



1 2

a) B=uracil
b) B=adenine
R=dimethoxytrityl; Si=t-butyldimethylsilyl



a) B=uracil; R=DMT
b) B=adenine; R=DMT
c) B=N-benzoyladenine; R=MMT
d) B=N-benzoylcytosine; R=DMT
e) B=N-benzoylguanine; R=MMT

MMT=monomethoxytrityl DMT=dimethoxytrityl

Si=t-butyldimethylsilyl

(Thiocarbonyl)diimidazole (8) reacted with both N-protected and N-unprotected nucleosides. However, in the case of the N-benzoyladenosine (1c) and N-benzoylguanosine (1e) derivatives, the reaction was very slow. The 3'-(imidazol-1-yl)thiocarbonyl derivatives 3 were reduced with $(n\text{-Bu})_3SnH$ and 2,2'-azobis (2-methylpropionitrile) in toluene to give the protected 3'-deoxynucleosides 4. Removal of the silyl group from 4 with TBAF (9) generates the 3'-deoxynucleoside derivatives 5 in high yield. Compounds 5 can be used directly in nucleotide synthesis (10).

The general procedures are described below and the results are summarized in Table 1.

Reaction with phenyl chlorothionocarbonate (7).

The protected nucleoside (1, 1 mmole) was dissolved in acetonitrile (20 ml) and 4-(dimethylamino)pyridine (6 mmole) and phenyl chlorothionocarbonate (5 mmole) were added. After stirring at room temperature for 6 h the solution was diluted with ethyl acetate (40 ml). The organic layer was washed with water (3 x), dried over $MgSO_4$, and evaporated to leave the crude product. Products were purified by silica gel chromatography. This procedure worked well only for 1a and 1b.

Reaction with (thiocarbonyl)diimidazole (8).

The protected nucleoside (1,1 mmole) was dissolved in DMF (10 ml) and (thiocarbonyl)diimidazole (3 mmole) was added. After stirring at room temperature (see Table 1 for times) the solution was diluted with ethyl acetate (100 ml) and water (50 ml). The organic layer was separated and washed with water (3 x 50 ml), dried over $MgSO_4$ and evaporated at reduced pressure. the residue was purified by silica gel chromatography.

Reactions were generally over in 4 h except for the N-benzoyladenosine and N-benzoylguanine derivatives which required 85 h and 70 h respectively. During this long reaction period, isomerization of the silyl groups occurred (11) and mixtures of the 2'- and 3'-derivatives were obtained. These mixtures were only resolved after reduction and desilylation, at which point they were readily separated.

Table 1

Compound[12]	Reaction Time (h)	Yield (%)	mp (°C)	R_f*	λ max (nm,EtoH)
2a	6	60	76-78	0.90[a]	262,233
3a	4	50	96-98	0.45[a]	263,233
4a	3	55	78-80	0.80[a]	263,232
5a	1	95	100-102	0.04[a],0.48[b]	264,232
2b	6	60	80-83	0.84[b]	260,233
3b	4	56	103-105	0.40[b]	259,235
4b	4	42	69-72	0.72[b]	259,232
5b	1	93	123-126	0.19[b]	260,234
†3c	85	40	51-60	0.48[b]	279,229
†4c	4	35	35-45	0.85[b]	279,228
‡5c	1	50	111-112	0.15[b],0.20[c]	279,229
3d	4	52	88-91	0.24[a]	303,262,235
4d	4	40	96-98	0.66[a]	304,259,234
5d	1	90	119-122	0.02[a],0.14[b]	304,260,233
†3e	70	50	42-49	0.25[b]	285,264,233
†4e	4	41	35-42	0.58[b]	286,259,232
‡5e	1	40	140-141	0.37[d]	288,259,229

*TLC, Merck Kieselgel 60 analytical plates. Solvents used were; a, ether-chloroform (1:1); b, ethyl acetate; c, chloroform-acetone (6:4); d, acetone - Et_3N (9.5:0.5).

†Mixtures of the 2'- and 3'-isomers were obtained.

‡The 3'-deoxyisomers were readily separated at this point from their 2'-deoxyisomers. The 2'-deoxyisomers of 5c and 5e had R_f's of 0.33 in c and 0.65 in d respectively.

Conversion of compounds 3 to the 3'-deoxyderivatives

A mixture of 3 (6 mmole), 2,2'-azobis(2-methylpropionitrile) (1 g) and (n-Bu)$_3$SnH (27 mmole) were heated at reflux in toluene for 3-4 h. Solvents were removed and products isolated by silica gel chromatography.

Acknowledgement

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