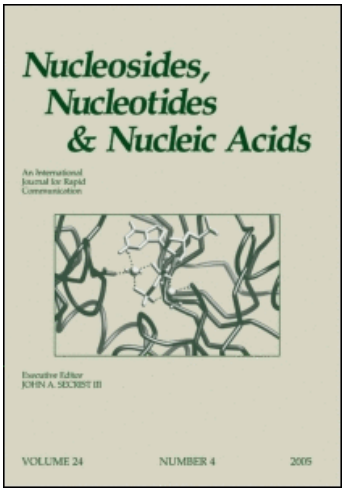

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A Mild Procedure for O-Deacylation of the Fully Acylated Sugar Moiety of Nucleosides in the Presence of Cyanide

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A MILD PROCEDURE FOR O-DEACYLATION OF THE FULLY ACYLATED SUGAR MOIETY OF NUCLEOSIDES IN THE PRESENCE OF CYANIDE

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Abstract

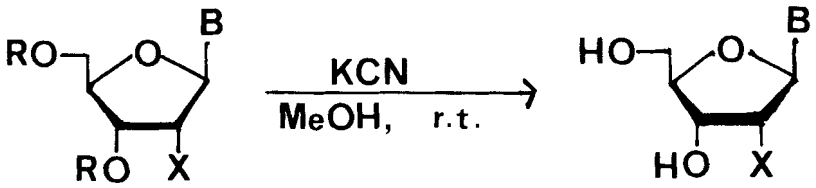
The solvolytic O-deacylation of the fully acylated sugar moiety of uridine and thymidine was found to take place readily in the presence of KCN in methanol at room temperature.

Protection or deprotection of hydroxyl groups is one of the most important procedures in the field of sugar, nucleoside, and nucleotide chemistry. In general acetylation and benzoylation are most often used for protecting hydroxyl groups or amino groups in mono- and oligosaccharides syntheses, as well as in nucleoside and nucleotide syntheses. Acyl groups of protected esters have generally been removed by treatment with alcoholic ammonia or strong bases such as metal hydroxides or alkoxides. However, when strong bases are used, the protected ester groups in sugar moieties sometimes migrate, or other protected groups are untimely removed.[1] In this point of view, the development of deprotection reaction under neutral condition is necessary in nucleic acid related chemistry.

Birch et al.[2] found that the reaction of methyl esters of cyclohexenone derivatives with KCN in 95% ethanol gave the corresponding ethyl esters, perhaps through the formation of acyl cyanide intermediates. This finding was later applied by Mori et al. for transesterification[3] of methyl trans, trans-farnesoate and deacylation[4] in the synthesis of a tricyclic pheromone. The deacylation of a carbohydrate

derivative[5] and galactosides[6] have also been successfully carried out using KCN.

We found that uridine and thymidine fully acylated on the sugar hydroxyl groups were deacylated in the presence of KCN as a catalyst in methanol at room temperature. We now wish to report these results. Quite recently, Nudelman and co-workers[7] have reported that a catalytic amount of KCN is effective for deestrification of polyacylated sugar in methanol.



1

a R=Ac, X=OAc, B=U
b R=Bz, X=OBz, B=U
c R=Ac, X=H, B=T
d R=Bz, X=H, B=T

2

X=OH or H
B=U or T

The deacylation reaction was performed as follows: To a solution of KCN (10 mg, 0.15 mmol) in methanol (7 mL) was added the fully O-acylated nucleoside 1[8] (100-170 mg, 0.27-0.31 mmol), and the mixture (solution or suspension) was stirred at room temperature. After complete deacylation was shown by TLC, the KCN was removed by treating with an equimolar amount of H^+ (Dowex 50) and OH^- (Dowex 1) form ion exchange resin mixture. After the mixture was stirred for 1 h, the resin was filtered off, and the methanol was evaporated under the reduced pressure. The residue was recrystallized to give the pure deacylated nucleoside 2.

As shown in Table 1, the deacylated products were obtained in good yields. Analytical data (400-MHz ^1H NMR, UV-spectral, elemental analyses, and melting points) on these products agreed with the commercially available authentic samples.

The reaction of 1d with KCN in methanol was heterogeneous at the begining of the reaction, but became homogeneous after several hours

Table 1. O-Deacylation of fully acylated sugar of uridine and thymidine in the presence of KCN.[a)]

Compound 1	KCN eq. mol.	Time h	Product[b)] 2	Yield[c)] %
a	0.5	7	A	82
	4.5	2	A	80
b	0.5	38	A	83
	4.5	6	A	79
c	0.5	8	B	88
	4.5	3	B	86
d	0.5	45 (43[d)])	B	90 (87[d)])
	4.5	12	B	82

a) Reaction was carried out in methanol at room temperature.
b) A=Uridine, B=Thymidine. c) Purified yield. d) Chloroform (3 mL) was added in the reaction mixture

passed. Addition of chloroform to the reaction mixture made the system homogeneous, but no difference in the reaction rate was observed from the reaction carried out in methanol. Cleavage of acetates proceeded more readily than the corresponding benzoates. Similar results have been reported.[7]

Rate studies of the reactions monitored by TLC revealed that the uridine derivatives are more reactive than the thymidine derivatives. It has been reported that the reactivity toward base of an acyl group on the acylated sugar in a nucleoside, in general, increases in order of 2' >3'>5'-position.[9] In the reaction of acylated uridines, one would expect that the first attack of the nucleophile takes place at the 2'-position to form the 2'-hydroxyl compound. The hydroxyl group initially formed may form a hydrogen-bond with the adjacent 3'-acyl group. This will accelerate the attack of nucleophile on the 3'-acyl group.[7, 9] On the other hand, the reactivity was lower for thymidine which does not have a hydroxyl group at the 2'-position. This lack of 2'-neighboring group partcipation may explain the decreased reactivity of the acylated thymidines. Deacylation reaction by KCN in methanol proceeds in good yields, under mild and nuetral conditions.

This procedure may be generally useful for deacylation of acylated sugar hydroxyl groups of nucleosides having acid- or base-labile groups.

Further investigations on this line are now conducted in our laboratories.

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