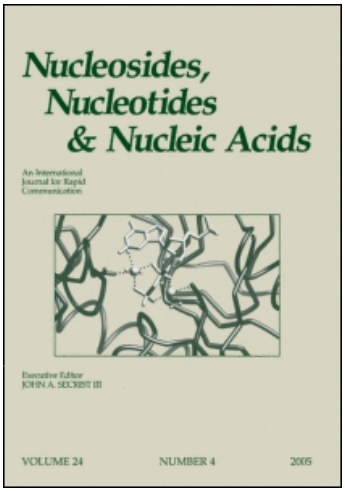

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Simultaneous Protection of 3'- and 5'-Hydroxyls of Ribonucleosides with Di-t-Butoxydichlorosilane

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SIMULTANEOUS PROTECTION OF 3'- AND 5'-HYDROXYLS OF RIBONUCLEOSIDES WITH DI-T-BUTOXYDICHLOROSILANE¶

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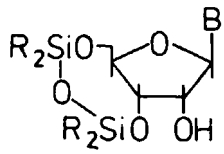
ABSTRACT. Di-t-butoxydichlorosilane was found to protect simultaneously 3'- and 5'-hydroxyls of uridine. The preliminary results on the dialkoxysilanediyl group introduction, properties and applications are presented.

A simultaneous protection of 3'- and 5'-hydroxyl groups of ribonucleosides is possible with bifunctional reagents containing two silicon atoms bearing either isopropyl (TIPDSi)[1,2] (1a) or t-butoxyl (TBDSi)[3,4] (1b) substituents at silicon atoms. The reactivity of bifunctional monosilyl reagents towards ribonucleosides has not been described yet.

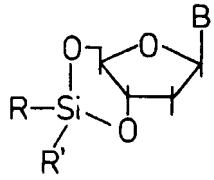
However, dimethyldichlorosilane was used for transient protection of hydroxyls during the synthesis of N-protected 2'-deoxynucleosides[5]. The formation of 3',5'-O-dialkyl or -alkylarylsilanediyl derivatives of 2'-deoxynucleosides (2a-e) was proved for dialkyl- and arylalkylsilyl reagents[6]. Di-t-butyldichlorosilane was non-reactive towards thymidine in pyridine and it was necessary to use imidazole in N,N-dimethylformamide to obtain compound 2b (B=thymine-1-yl)[6].

In the recent papers we focused on the study of alkoxysilyl protective groups[3,4]. In this paper the preliminary results of our studies on the reactivity of bifunctional monosilyl reagent, namely di-t-butoxydichlorosilane[7] ($DBSiCl_2$) towards ribonucleosides are presented.

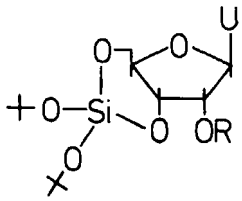
¶This paper is dedicated to Professor Maciej Wiewiórowski on the occasion of his 70th birthday in August 1988.



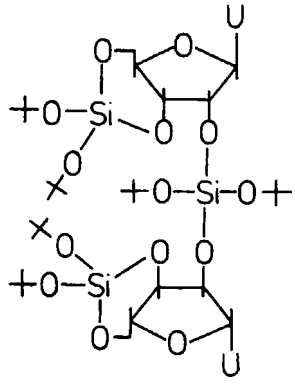
1a R = i-Pr
b R = t-BuO



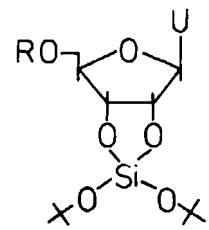
2a R = R' = Me
b R = R' = t-Bu
c R = R' = i-Pr
d R = Ph R' = Me
e R = Ph R' = t-Bu



3a R = H
b R = Ac
c R = 



4



5a R = H
b R = DMT

B = pyrimidine or purine residue
U = uracil-1-yl ; +O = t-BuO

Thus, $DBSiCl_2$ (1.1 molar equivalents) was added slowly to the stirred 0.25 M solution of uridine in anhydrous pyridine at ca -30°C. The tlc analysis[8] showed that the reaction went to completion in ca 30 minutes[9]. The reaction mixture was worked-up with aq. $NaHCO_3$ and chloroform extraction. The main product was isolated (silica gel column chromatography, ca 43% yield) and found to be 3',5'-O-di-t--butoxysilanediyluridine (3a)[10]. Its structure was proved by the formation of a 2'-O-acetyl derivative (3b)[1,2,11].

The silylation of uridine with a greater excess of $DBSiCl_2$ (2 molar equivalents) at room temperature overnight gave 4 as the main product[12]. 4 can be regarded as a dialkoxysilyl 2',2'-linked analogue of oligonucleotides and further investigations of alkoxysilyl internucleoside linkages could be interesting as well[13].

Attempts to obtain a 2',3'-O-DBSi isomer (5) both from uridine or 5'-O-dimethoxytrityluridine and $DBSiCl_2$ have so

far been unsuccessful which is rather unexpected when compared to the disiloxane-1,3-diyl group (TIPDSi)[1,2] and a orthocarbonate analogue[14] of DBSi.

The DBSi group properties were studied in order to establish its usefulness in nucleoside chemistry. Thus, the DBSi group of 3a can be very easily removed with tetra-n--butylammonium fluoride[15] (in less than 2 min.) or triethylammonium fluoride[2,16] (TEAHF) (ca 20 min). Hydrolysis under acidic conditions (0.2 M HCl in aq. 1,4-dioxan) leads to uridine in ca 10 min. The DBSi group of 3a is unstable ($t_{1/2}$ 1 min) under alkaline conditions (0.2 M NaOH in aq. 1,4-dioxan)[17]. However, the DBSi group is stable overnight under anhydrous acidic conditions (0.02 M p-toluenesulfonic acid in 1,4-dioxan). Thus, the reaction of 3a with 2,3-dihydropyran ($CHCl_3$-p-TsOH)[16] gave 3c which was then desilylated with TEAHF[16] to 2'-O-tetrahydropyranyluridine identical with the authentic sample.

The above results indicate that the DBSi group might be useful in the chemistry of nucleosides especially after improvement of the yields of 3. Furhter studies on the DBSi group properties, the mechanism of its introduction, the reactivity of $DBSiCl_2$ towards other ribonucleosides as well as their analogues are in progress.

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8. Reactions were monitored with the tlc analysis on E.Merck (a) silica gel (chloroform-MeOH, 2:1, v/v) and (b) silanized silica gel plates (acetone-water, 7:3, v/v).
9. Reaction conditions were not optimized.
10. 3a (R=H) R_F(a) 0.44, R_F(b) 0.65; ^{1}H NMR ($CDCl_3$,TMS): δ 9.85 (s, NH), 7.28 (d, $J_{6,5}$ 8.3 Hz, H 6), 5.77 (d, $J_{5,6}$ 8.1 Hz, H 5), 5.70 (s, H 1'), 4.40 (m, H 2'), 4.15 (m, H 3',4',5'), 1.34 (s, 6xCH_3CO); ^{13}C NMR ($CDCl_3$,TMS): δ 163.5 (C 4), 149.9 (C 2), 140.9 (C 6), 102.7 (C 5), 95.0 (C 1'), 76.2 (C 4'), 74.6 and 74.1 (CH_3CO of DBSi), 74.3 (C 3'), 73.2 (C 2'), 65.7 (C 5'), 31.3 (CH_3 of DBSi).
11. 3b (R=Ac) ^{1}H NMR ($CDCl_3$,TMS): δ 5.77 (d, $J_{5,6}$ 8.0 Hz, H 5), 5.72 (s, H 1'), 5.43 (dd, $J_{2',3'}$ 5.4 Hz, H 2'), 4.36 (m, H 3'), 2.15 (s, 2'-O-Ac), 1.33 (s, 6xCH_3CO).
12. 4, R_F(a) 0.59, R_F(b) 0.32; ^{1}H NMR ($CDCl_3$,TMS): δ 6.27 (d, $J_{6,5}$ 8.3 Hz, 2xH 6), 5.76 (d, $J_{5,6}$ 8.3 Hz, 2x H 5), 5.75 (s, 2xH 1'), 4.0-4.6 (m, 2xH 2',3',4',5'), 1.33 (s, 18xCH_3CO).
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17. The hydrolysis giving uridine and monosilyl derivative(s) is studied in detail now.