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TETRA-t-BUTOXYDISILOXANE-1,3-DIYL, A NEW TYPE OF BIFUNCTIONAL SILYL PROTECTIVE GROUP

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SUMMARY: Tetra-t-butoxydisiloxane-1,3-diyl (TBDSi) group is introduced into nucleoside chemistry as an analogue of tetraisopropyldisiloxane-1,3-diyl (TIPDSi) and an example of a new type of bifunctional silyl protective group.

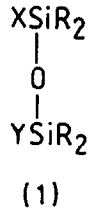
We have introduced a bifunctional silyl reagent, 1,3-dichlorotetraisopropyldisiloxane (1a, X=Y=Cl), into nucleoside chemistry[1,2] and the tetraisopropyldisiloxane-1,3-diyl group (TIPDSi) has become widely used for protection of hydroxylic functions due to its mode of introduction, compatibility with many types of other protective groups and its properties of partial cleavage and ring transformation[1-3].

However, some of the TIPDSi properties for example the 3'-end hydrolytic cleavage (3a⟶4a, X=OH) under alkaline conditions[2-4] or 3',5'- to 2',3'-O--TIPDSi ring transformation (3a⟶5a) under acidic conditions[3,5,6] might cause it to be inconvenient for certain synthetic applications.

Introduction of alkoxy substituents onto the silicon instead of alkyl groups should enlarge the range of factors influencing the properties of a protective group. The removal of these alkoxy substituents during a deprotection process might ease and finally result in a cleavage of an ether bond between silicon and a protected hydroxyl function. Thus, the approach we propose should allow for yet another way to control properties of the derived silyl protections[7].

From a consideration of the stability towards hydrolysis[8,9] of tetraalkoxysilanes containing at least two bulky alkoxy substituents and the steric hindrance at silicon with such substituents it was decided to replace isopropyl groups in 1a by t-butoxy groups to give a disiloxane derived bifunctional protecting reagent (1b).

Thus, 1,1,3,3-tetra-t-butoxydisiloxane[10] (1b, X=Y=H) was obtained by reaction of trichlorosilane and t-butanol (2 molar equivalents) in diethyl ether[10] in the presence of pyridine at low temperature, followed by addition of water. 1b (X=Y=H) was isolated after vacuum distillation in ca 50% yield[11]. 1b (X=Y=H) was chlorinated in pyridine with chlorine solution in carbon tetrachloride and after removal of carbon tetrachloride under vacuum compound 1b (X=Y=Cl) formed in situ,was reacted overnight at room temp. with uridine (2, B=uracil-1-yl)[12]. The main product, isolated in ca 48% yield after work-up with aqueous sodium bicarbonate and silica gel chromatography in chloroform-



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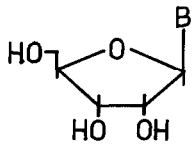

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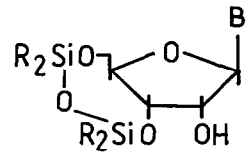

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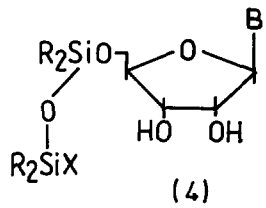

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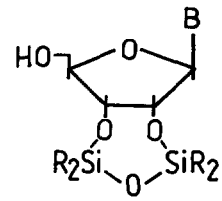

(5)

B=pyrimidine or purine residue

(a) R=i-Pr (b) R=t-BuO

-methanol, was identified as 3',5'-O- tetra-t-butoxydisiloxane-1,3-diyl uridine (3b, B=uracil-1-yl)[13]. When the chlorination of 1b was incomplete 4b(X=H) was isolated as a main product[11]. This shows the high selectivity of the silylating reagent for the primary 5'-hydroxyl groups. In our opinion this corroborates indirectly the previously proposed mechanism of the introduction of the TIPDSi group and its application to the TBDSi group introduction.

Pure 1,3-dichloro-1,1,3,3-tetra-t-butoxydisiloxane[14] 1b (X=Y=Cl) could be obtained after a chlorination of 1b (X=Y=H) in cyclohexane with chlorine in carbon tetrachloride in the presence of pyridine (4 molar equivalents) followed by vacuum distillation.

Four common ribonucleosides - uridine, cytidine, adenosine and guanosine[15] - were then silylated with pure 1b (X=Y=Cl) (1.25 molar equivalent) in pyridine (2 ml/mmole of 2) at room temperature to give 3',5'-O-TBDSi derivatives 3b. Tlc analysis showed the reactions were complete in ca 3 h. and that the main products 3b were present to an extent of over 90%. The products could be isolated after the silica gel column chromatography in yields of 83, 80, 77 and ca 50% respectively[11,16].

The TBDSi group properties were studied for the uridine derivative in comparison[1-5] to the TIPDSi analogue 3a. The TBDSi group in 3b was found to be more stable to hydrolytic conditions than the TIPDSi group. Hydrolysis under alkaline conditions (0.2 M NaOH in aq. 1,4-dioxan) leads to 4b (X=OH, B=uracil-1-yl)[11] but cleavage occurs ca 25 times slower ($t_{1/2}$ ca 3.5 h) than for TIPDSi derivatives 3a ($t_{1/2}$ 8 min)[4]. 3b was found to be stable overnight under acidic conditions (0.2 M HCl in aq. 1,4-dioxan) under which conditions 3a are completely cleaved at the 5'-end in 2.5 h[2-4]. The TBDSi group of 3b is easily removed with tetra-n-butylammonium fluoride[17] in THF in less than 2 min. It is

however much less reactive towards triethylammonium fluoride[3,4] contrary to the TIPDSi group.

The remarkable stability of the TBDSi group under acidic conditions indicates that this group, contrary to the TIPDSi group, should not undergo the transformation reaction[5,6] 3b⟶5b. It should be also useful in the alkylation of nucleoside derivatives.

Thus preliminary data on the properties of the new bifunctional silyl protecting group indicate that it might find useful application in the chemistry of nucleosides. Further studies are in progress[7].

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10. 1,1,3,3-tetra-t-butoxydisiloxare (1b, X=Y=H), b.p. 118-120°C (at 12 mm), ^{1}H NMR ($CDCl_3$, int. TMS): δ 1.340 (s, 12xCH_3CO), 4.484 (s, 2xHSi); colourless liquid; IR (neat): ν_{SiH} 2200 cm^{-1}. Other aprotic solvents can be used (cyclohexane, chloroform, dichloromethane, toluene, THF) however the highest yield till now was obtained with diethyl ether.
11. Structures of all described compounds were corroborated by their ^{1}H and ^{13}C NMR spectra and elemental analyses.
12. The silylation procedure with 1b obtained in situ (X=Y=Cl) leads to the formation of some coloured impurities.
13. 3b (B=uracil-1-yl) m.p. 206-209°C; anal. $C_{25}H_{46}O_{11}N_2Si_2$: calc. C 49.48, H 7.64, N 4.62, found C 49.17, H 7.81, N 4.65; ^{1}H NMR ($CDCl_3$): δ 1.34 (s, 12xCH_3CO), 4.1 (m, H 2',3',4',5'), 5.72 (d, $J_{5,6}$ 8 Hz, H 5), 5.76 (s, H 1'), 7.60 (d, $J_{6,5}$ 8 Hz, H 6); ^{13}C NMR ($CDCl_3$) δ 163.6 (C 4), 150.3 (C 2), 140.1 (C 6), 102.2 (C 5), 91.1 (C 1'), 81.9 (C 4'), 74.9 (C 3'), 70.4 (C 2'),

61.5 (C 5'), 74.9, 74.1, 73.8, 73.6 (TBDSi), 31.3 (CH_3 TBDSi); 2'-O-acetyl derivative of 3b (B=uracil-1-yl) ^{1}H NMR ($CDCl_3$): δ 1.32 (3s, 12xCH_3CO), 2.14 (s, 2'-O-Ac), 4.15 (m, H 4',5'), 4.42 (m, H 3'), 5.40 (d, $J_{2',3'}$ 5Hz, H 2'), 5.70 (d, $J_{5,6}$ 8 Hz, H 5), 5.84 (s, H 1'), 7.62 (d, $J_{6,5}$ 8.3 Hz,H6).

14. 1b (X=Y=Cl), colourless liquid stable under exclusion of moisture, b.p. 95°C (at 0.3 mm); yield ca 50%.
15. In the case of guanosine 2 (B=guanin-9-yl) pyridine-DMF mixture was used as a solvent and reaction was carried overnight.
16. In the case of adenosine, cytidine and guanosine derivatives only m.p., el.anal. and ^{1}H NMR ($CDCl_3$, δ, int. TMS) data are given: 3b (B=adenin-9-yl 88-91°C; anal. $C_{26}H_{47}O_9N_5Si_2$: calc. C 49.58, H 7.52, N 11.12, found C 49.61, H 7.79, N 10.87; 8.30 and 7.95 (2xs, H 2 and 8), 6.1 (s, NH_2), 5.98 (d, $J_{1',2'}$ 1.7 Hz, H 1'), 5.06 (t, J 7 Hz, H 3'), 4.66 (dd, J 1.7 and 7 Hz, H 2'), 4.1 (m, H 4' and 5'), 1.37, 1.34 and 1.33 (3xs, 12xCH_3CO); 3b (B=cytosin-1-yl) 230°C dec. ; anal. $C_{25}H_{47}O_{10}N_3Si_2$: calc. C 49.58, H 7.82, N 6.93, found C 49.10, H 7.95, N 6.62; 7.60 (d, $J_{6,5}$ 7.2 Hz, H 6), 5.88 (d, $J_{5,6}$ 7.3 Hz, H 5), 5.77 (s, H 1'), 4.2 (m, H 2',3',4',5'), 1.34 and 1.28 (2xs, 12xCH_3CO); 3b (B=guanin-9-yl) 130°C (dec.); anal. $C_{26}H_{47}O_{10}N_5Si_2$: calc. C 48.35, H 7.34, N 10.84, found C 48.90, H 7.59, N 11.02; 7.80 (s, H 8), 6.8 (s, NH_2), 4.7 (m, H 3'), 4.5 (m, H 2'), 4.2 (m, H 4', 5'), 1.35 and 1.32 (2xs, 12xCH_3CO).
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