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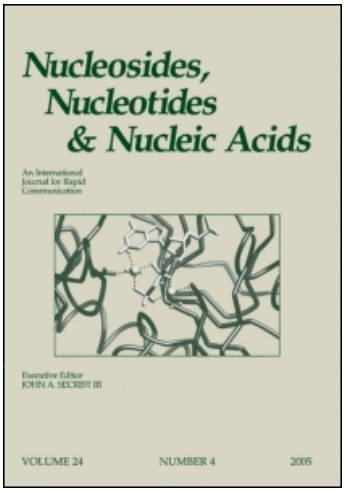

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To cite this Article Markiewicz, Wojciech T. and Adrych-Rozek, Katarzyna(1991) 'Properties of Trialkoxysilyl Grows', Nucleosides, Nucleotides and Nucleic Acids, 10: 1, 415 — 418
To link to this Article: DOI: 10.1080/07328319108046492
URL: http://dx.doi.org/10.1080/07328319108046492

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NUCLEOSIDES & NUCLEOTIDES, 10(1-3), 415-418 (1991)

PROPERTIES OF TRIALKOXYSILYL GROUPS[¶]

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Abstract: Two monofunctional silyl protecting groups with alkoxy substituents (triisopropoxy- and tri-t-butoxysilyl) were introduced to nucleosides and their properties such as stability under hydrolytic conditions are described.

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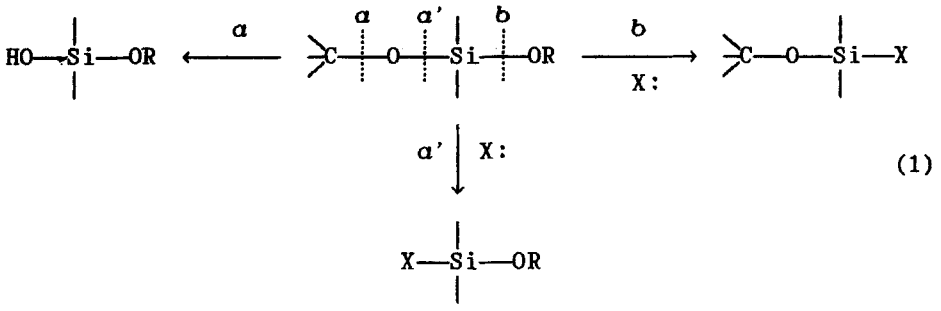
Recently we proposed a new type of protecting groups which contain alkoxy substituents instead of alkyl or aryl functions present in commonly used silyl protecting groups.[1,2] The groups described so far were bifunctional (tetra-t-butoxydisiloxane-1,3-diyl[1], TBDSi, 1 and di-t-butoxysilylene[2], DBSi, 2) and allowed the simultaneous protection of two hydroxy functions of nucleosides. These groups differ remarkably in their stability under hydrolytic conditions (Table).

Introduction of alkoxy substituents to the silicon should allow for a flexible control of properties of derived silyl groups[1] according to equation (1). In other words, during the removal of an alkoxysilyl



(1)

[¶]This paper is dedicated to Professor Colin B. Reese on the occasion of his 60th Birthday in July 1990.

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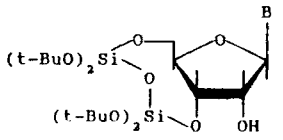
protecting group might occur the cleavage of a silyl ether bond either with a protected alcoholic residue (route b) or the alkoxy substituent (route a or a'). (In alkylsilyl protecting groups the cleavage may occur on a route b only.)

Monofunctional alkoxysilyl reagents might be obtained easily from trichlorosilane acc. to equation (2). Thus, 3 and 4 were obtained[3] in good yields using pyridine as a base in both steps.

$$ROH + HSiCl_3 \xrightarrow{:B} (RO)_3SiH \xrightarrow[:B]{Cl_2} (RO)_3SiCl \qquad (2)$$

3 R=i-Pr; 4 R=t-Bu

3 (1.2 molar equivalents) was reacted with ribonucleosides in pyridine at -30°C to give 5'-O-derivatives 5 as main products which were isolated in moderate yields.[4,5] The triisopropoxysilyl group in 5 was found to be relatively easily cleaved in acidic and stable under alkaline conditions (Table). Then the reaction of 3 with 2'-O-tetrahydropyranyluridine[6] was studied and the formation of monosilyl derivative 6 was accompanied by the bissilyl compound 7. This difference in the selectivity of silylation results, in our opinion, rather from the instability of 2'(3')-O-trialkoxysilylribonucleosides bearing free 3'(2')-OH function,[7] than actual relative reactivity of 3 towards 1° and 2° OH groups.



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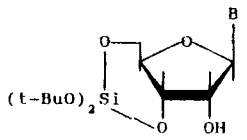

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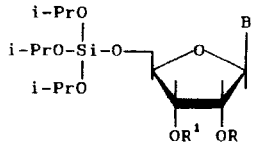
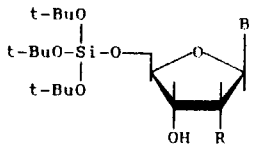


5 R, R^1 = H
6 R = thp, R^1 = H
7 R = thp, R^1 = $(i\text{-PrO})_3Si$



8 R = OH
9 R = H, B = Thy

Abbreviations: t-Bu, t-butyl; i-Pr, isopropyl; thp, tetradropyranyl; B, purine or pyrimidine residue; Thy, thymine-1-yl.

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TABLE. PROPERTIES OF SILYL GROUPS IN 5'-O-TRIALKOXYSILYL (5, 8 AND 9), 3',5'-O-TBDSi (1) AND 3',5'-O-DBSi (2) NUCLEOSIDES.

CONDITIONS	$(i\text{-PrO})_3Si$	$(t\text{-BuO})_3Si$	TBDSi	DBSi
1 M TBAF/THF	rem. 2 min.	$t_{1/2}$ 24 h	rem. 2 h	rem. 2 min
1 M TEAHF/THF	n.d.	n.d.	stable	several min.
0.2 N HCl aq diox.	$t_{1/2}$ 2 min.	$t_{1/2}$ 1 week	stable	rem. 10 min.
4 M HF aq dioxane	n.d.	rem. 48 h	n.d.	n.d.
1 N HCl aq diox.	n.d.	rem. 48 h	n.d.	n.d.
1 N HF aq dioxane	n.d.	stable	n.d.	n.d.
0.2 N NaOH aq diox.	stable	stable	3', 20 h	rem. 10 min.
0.02 M TsOH/diox.	n.d.	n.d.	stable	stable

Abbreviations: TBDSi - tetra-t-butoxydisiloxane-1,3-diyl, DBSi - di-t-butoxysilylene, TBAF - tetra-n-butylammonium fluoride, THF - tetrahydrofurane, TEAHF - triethylamine hydrofluoride,aq diox. - 1,4-dioxane/water, 4/1, by vol., TsOH - p-toluenesulphonic acid, rem. - removal, stable - stable overnight with only traces of removal, 3' - 3'-end cleavage, n.d. - not determined.

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Then the reactivity of 4 bearing bulky t-butoxy substituents was studied. The silylation reaction was relatively slow (overnight, at room temp.) but led with high selectivity to 5'-O-monosilylated nucleosides 8 and 9.[5,8] The studies of stability of the silyl group in 8 and 9 (Table) indicate that tri-t-butoxysilyl is remarkably stable under both acidic and alkaline conditions. It is quite resistant towards TBAF and can be cleaved completely with strong acids only. Significantly, 1 N HCl removes tri-t-butoxysilyl group as quickly as 4 N HF and moreover 1 N HF is not able to promote the silyl group cleavage. In our opinion this indicates that the hydrolysis of this group takes place rather on route *a* (t-butyl carbocation) and not *b*.

Thus, we have shown that one can control to the great extent the properties of silyl groups by choosing different alkoxy substituents.

Acknowledgement: We thank Mrs. B. Nowakowska for the technical assistance. Financial support from the Polish Academy of Sciences (project CPBR 3.13.4.1.2) is gratefully acknowledged.

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3. 3 and 4 were obtained from trichlorisilane, appropriate alcohol in diethyl ether in the presence of pyridine. The resultant trialkoxysilanes were chlorinated with Cl_2/CCl_4 in pyridyne as a solvent and distilled under vacuum. $(i\text{-}PrO)_3SiH$: ^1H NMR: 4.34 (s, 1, SiH), 4.26 (sep, 3, J 6.1Hz, CH-i-Pr), 1.23 (d, 18, J 6.1Hz, CH_3-i-Pr); b.p. 53°C/8 mm Hg. 3: ^1H NMR: 4.15 (sep, 3, J 6.1Hz, CH-i-Pr), 1.12 (d, 18, J 6.1Hz, CH_3-i-Pr); ^{13}C NMR: 67.37 (C-α-i-Pr), 25.00 (C-β-i-Pr); b.p. 80°C/8 mm Hg. $(t\text{-}BuO)_3SiH$: ^1H NMR: 4.48 (s, 1, SiH), 1.33 (s, 27, t-Bu); b.p. 75°C/8 mm Hg. 4: ^1H NMR: 1.28 (s, t-Bu); ^{13}C NMR: 74.93 (OC), 31.21 (CH_3); b.p. 58°C/0.4 mm Hg.
4. 5 were isolated by silica gel chromatography in yields: 77%, B=Ura; 44%, B=Cyt; 36%, B=Ade; 25%, B=Gua (DMF/ pyridine as solvent).
5. Structures of all described compounds were corroborated by their ^1H, ^{13}C NMR spectra and C,H,N analyses. All NMR spectra were recorded in $CDCl_3$ and δ (ppm) data are given with TMS as the reference. Some NMR data are presented: 5 (B=Ura): ^1H NMR: 10.28 (s, 1, NH), 8.03 (d, 1, $J_{6,5}$ 8.1Hz, H-6), 5.94 (d, 1, $J_{1',2'}$ 1Hz, H-1'), 5.71 (d, 1, $J_{5,6}$ 8.1Hz, H-5), 3.8-4.4 (m, 5, H-2',3',4',5'), 4.23 (sep, 3, J 6.1Hz, CH-i-Pr), 1.20 (d, 18, J 6.1Hz, CH_3-i-Pr);
   acetyl derivative of 5 (B=Ura): ^1H NMR: 9.0 (s, 1, NH), 7.86 (d, 1, $J_{6,5}$ 8.1Hz, H-6), 6.21 (d, 1, $J_{1',2'}$ 6.8Hz, H-1'), 5.69 (d, 1, $J_{5,6}$ 8.3Hz, H-5), 5.3-5.45 (m, 2, H-2',3'), 4.18 (sep, 3, J 6.1Hz, CH-i-Pr), 4.0-4.2 (m, 3, H-4',5'), 2.01 (s, 6, 2',3'-OAc), 1.14 (d, 18, J 6.1Hz, CH_3-i-Pr).
   8 (B=Ura): ^1H NMR: 10.2 (s, 1, NH), 8.00 (d, 1, $J_{6,5}$ 8Hz, H-6), 5.93 (s, 1, H-1'), 5.69 (d, 1, $J_{5,6}$ 7.5Hz, H-5), 3.8-4.3 (m, 5, H-2',3',4',5'), 1.31 (s, 27, t-Bu); ^{13}C NMR: 163.73 (C-4), 151.32 (C-2), 140.54 (C-6), 102.35 (C-5), 90.53 (C-1'), 85.17 (C-4'), 75.85 (C-2'), 73.25 (C-α-i-Pr), 70.16 (C-3'), 62.14 (C-5'), 31.48 (C-β-i-Pr);
   acetyl derivative of 8 (B=Ura): ^1H NMR: 9.56 (s, 1, NH), 7.90 (d, 1, $J_{6,5}$ 8.0Hz, H-6), 6.29 (d, 1, $J_{1',2'}$ 6.6Hz, H-1'), 5.75 (d, 1, $J_{5,6}$ 8.0Hz, H-5), 5.25-5.55 (m, 2, H-2',3'), 4.20 (m, 1, H-4'), 3.95 (m, 2, H-5'), 2.06, 2.15 (2xs, 2',3'-OAc), 1.33 (s, 27, t-Bu).
6. W.T. Markiewicz, E. Biała, R. Kierzek, Bull. Pol. Ac.: Chem., **32**, 433 - 451 (1984)
7. The presented rationalization is in agreement with the observation that 2',3'-O-DBSi ribonucleosides could not be obtained.[1]
8. 5'-O-monosilyl 8 and 9 were sole products formed which were then isolated chromatographically in good yields: 8: 77%, B=Ura; 68%, B=Cyt; 75%, B=Ade; 65%, B=Gua; 9, 72%.