Tetrahedron Letters No. 33, pp 2865 - 2868, 1974. Pergamon Press. Printed in Great Britain.

Selective Protection of Hydroxyl Groups in Deoxynucleosides Using Alkylsilyl Reagents.

Kelvin K. Ogilvie*, Elaine A. Thompson, Michael A. Quilliam, & John B. Westmore,

Department of Chemistry,

University of Manitoba,

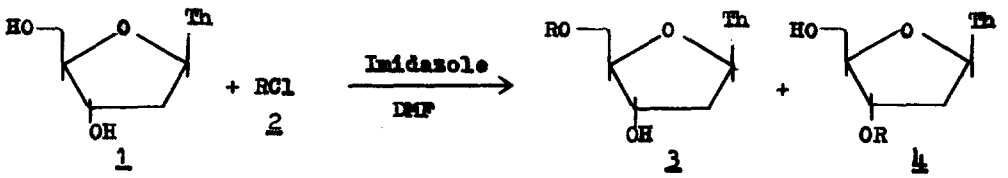
WINNIPEG, Manitoba,

Canada, R3T 2N2.

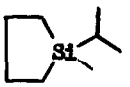
(Received in USA 22 May 1974; received in UK for publication 1 July 1974)

The chemical synthesis of oligonucleotides requires the availability of versatile reagents for protecting the hydroxyl and amino groups of nucleosides. We have recently described (1) the tert-butyldimethylsilyl (TBDMS) group as an exceedingly useful group for protecting the hydroxyl functions of nucleosides. This report describes a series of silyl groups which (a) provide a range of selectivity toward the 5'-hydroxyl group in deoxynucleosides; (b) provide a range of stabilities toward acid and base hydrolysis and which (c) all show different rates of acid hydrolysis for 5'versus 3' substitution. This allows perhaps for the first time a rapid and

Scheme 1

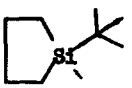


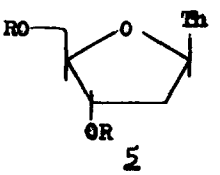
(i) R = $(C_6H_5)_2Si(CH_3)-$ MDIPSi

(ii) R =  TMIPSi

(iii) R = $(CH_3)_2Si(CH_3)-$ TBDMS

(iv) R = $(C_6H_5)_3Si-$ TIPSi

(v) R =  TMTBS



convenient synthesis of either 5' or 3' monosubstituted nucleosides from the same protecting group. Further (d) we have found silylating agents which are very nearly specific for the 5'-hydroxyl of nucleosides.

Scheme 1 and Table 1 illustrate points (a) and (b) above. All of the reactions shown in Scheme 1 were carried out at room temperature by mixing the reagents in DMF (1 ml/mmole of nucleoside) and using two equivalents of imidazole per mmole of silyl chloride. The ratio of silyl chloride to nucleoside was 1.1 in each case.

TABLE 1

Reactions of Silyl Chlorides (2) With Deoxythymidine*

	% Yields		
R-Cl	3	4	5
2i	59	5	28
2ii	35	6	46
2iii†	73	1	15
2iv	82	2	4
2v	82	1	3

*all new compounds have been fully characterized

†included only for comparison.

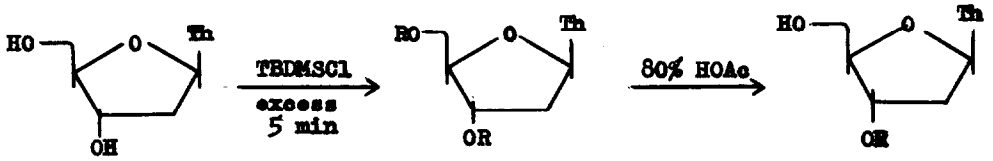
Table 1 shows that TMIPSi-Cl is the least selective reagent toward the 5'-hydroxyl group. The stability of the groups toward acid hydrolysis is roughly in the same direction as their selectivities (Table 2) with a wide range of stability being provided. Further as can be seen from Table 2 there is a considerable difference in rates of acid hydrolysis between 5' and 3' isomeric derivatives. The 3'-isomers are considerably more stable in all cases.

TABLE 2

Compound	Conditions	Time to 100% Hydrolysis
5'-DIPSi-dT	80% HOAc, RT	1 1/2 hr
3'-DIPSi-dT	80% HOAc, RT	6 hr
5'-TMIPSi-dT	80% HOAc, RT	2 hr
3'-TMIPSi-dT	80% HOAc, RT	6 hr
5'-TBDMS-dT	80% HOAc, RT	5 hr
3'-TBDMS-dT	80% HOAc, RT	25 hr
5'-TIPSi-dT	*0.01NHCl, steam bath	15 min
3'-TIPSi-dT	*0.01NHCl, steam bath	80 min
5'-TMTBS-dT	*0.01NHCl, steam bath	35 min
3'-TMTBS-dT	*0.01NHCl, steam bath	120 min

* in 50% EtOH-H_2O.

The difference in reactivity between 3' and 5'-silylated nucleosides leads to the remarkably useful feature that the 3'-isomers (4) can be rapidly obtained from the parent nucleoside. For example, thymidine can be quantitatively disilylated with TBDMS-Cl in 5 min. Removal of solvent followed by treatment with 80% acetic acid at room temperature for 12 hr or on a steam bath for 10 min leads to a 52% or 50% yield of 4iii respectively.



1 5iii 4iii

Because of this wide range of stabilities toward 80% acetic acid, the silyl groups themselves provide a nearly complete hydroxyl protecting group system. For example 5'-TBDMS-3'-TIPSi- thymidine is quantitatively converted to 3'-TIPSi-dT in 10 min on a steam bath with 80% HOAc. Similarly 5'-TMTBS- 3'-TMIPSi is converted to 5'TMTBS-dT in 25 min. These reactions clearly demonstrate the compatability of the silyl groups in protecting both the growing and stable end of a synthetic nucleotide chain.

Finally we wish to report that the TBDMS-imidazole and Bis-TBDMS-acetamide reagents are

nearly specific toward the 5'-hydroxyl group of deoxynucleosides. This introduces a remarkably convenient system for the large scale synthesis of the 5'-isomers. When thymidine is treated with an excess of either reagent in pyridine for 24 hr and the solution poured into ice-water, the product 3iii precipitates out as a white solid. Crystallization of the product from ether-hexane gave a 91% yield of pure 5'-TBDMS-dT in each case.

All of these silyl groups are cleanly removed by treating the protected nucleoside with (n-butyl)$_4$NF in tetrahydrofuran for 0.5 hr at room temperature, these conditions do not affect other acid and base labile protecting groups (1).

All of the 3' and 5' isomeric pairs (3 and 4) of thymidine derivatives described above show major differences in fragmentation in the mass spectrometer, are separable by gas chromatography, are amenable to GC-mass spec analysis, and are soluble in organic solvents such as ether and hexane. This latter feature greatly enhances the TLC separation and purification of these derivatives.

Because of the versatility of the silyl groups described in this report they are of major importance in the nucleoside and nucleotide field.

ACKNOWLEDGEMENT

We wish to acknowledge generous financial support from the National Research Council of Canada.

REFERENCES

1. K. K. Ogilvie, Can. J. Chem., 51, 3799 (1973).