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The Use of Silyl Groups in Protecting the Hydroxyl Functions of Ribonucleosides

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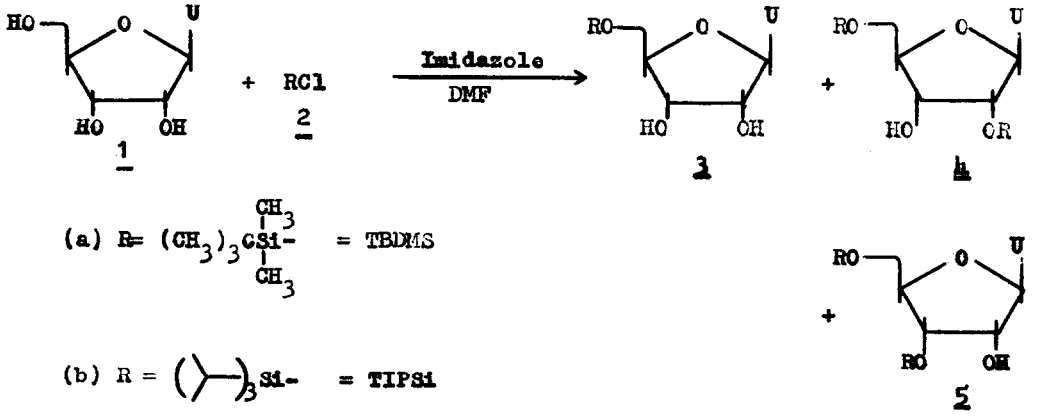
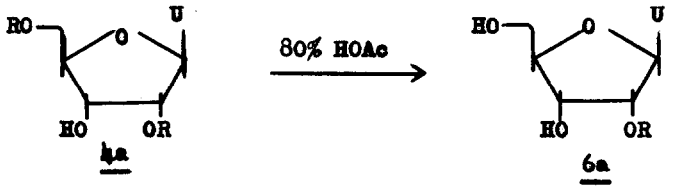
One of the most serious problems in the chemical synthesis of oligoribonucleotides involves the preparation of nucleosides bearing suitable protecting groups on the 2'-hydroxyl. Reese (1) and Smrt (2) have outlined in detail the problems of protecting groups in the ribonucleotide area. We wish to describe in this report the use of alkylsilyl groups for the protection of 2'- and 2',5'-positions in ribonucleosides. These derivatives are readily prepared, are nicely crystalline, and overcome most of the problems associated with currently used protecting groups.

The two reagents that we have initially found to be most useful are the tert-butyldimethylsilyl (TBDMS) group and the tri-isopropylsilyl (TIPSi) group.



All reactions are carried out in DMF (1 ml/mmole of nucleoside) using two equivalents of imidazole per mmole of silyl chloride. Uridine reacts under these conditions with 1.2 equivalents of 2a to produce 3a (mp 136-139°C) in 73% yield. 4a (mp 121-123°C) and 5a (mp 137-139°C) are obtained in 11% and 7% yields respectively. Increasing the ratio of 2a:1 to 2.5:1 gives a 46% yield of 4a and 32% yield of 5a. The tri-isopropylsilyl chloride (2b) is more selective. Thus using 2b:1 in the ratio of 1.2:1 gives a 76% yield of 3b (mp 126-127°C) while a ratio of 2.5:1 produces 4b (mp 146-147°C) and 5b (mp 121-122°C) in 61% and 20% yields respectively. The isomeric compounds 4 and 5 separate cleanly on silica gel thick layer plates using ether or ether-hexane (1:1) as solvent.

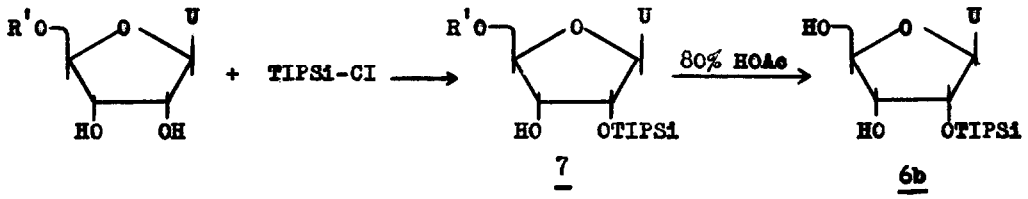
We have also noted a large difference in rates of acid hydrolysis between a 2'(or 3') substituent and a 5'-substituent. This leads to a rapid and convenient preparation of 2'-mono-silylated nucleosides. Thus heating 4a with 80% HOAc for 20 min. on a steam bath gives 6a



4a 6a

(mp 189-191°C) in 64% yield. We have not detected any isomerization of 4 and 5 under these acid conditions.

An excellent method for obtaining 2'-TIPSi-Uridine (6b) is shown below. When 5'-Trityl-



7 6b

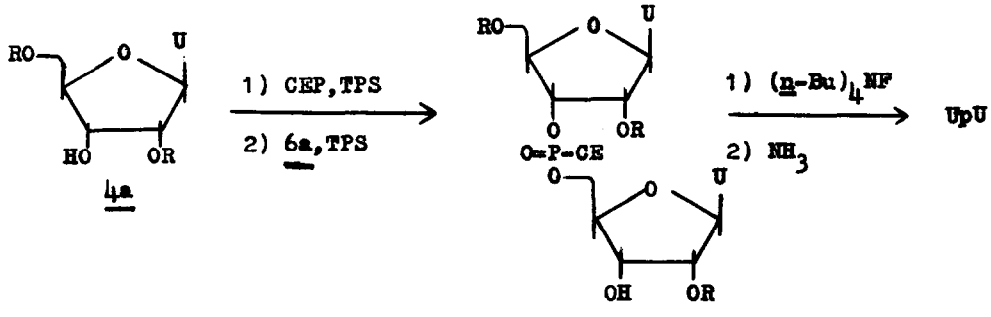
(a) R' = Trityl

(b) R' = TBDMS (3a)

uridine is treated with 1.2 equivalents of TIPSi-Cl under the usual conditions 7a (mp 125-126°C) is obtained in 70% yield. A 25% yield of the 3'-isomer (mp 80-82°C) is also obtained.

Treatment of 7a with 80% HOAc on a steam bath gives 6b (mp 154-155°C) in 98% yield. If one starts with 5'-TBDMS-uridine under the same conditions a 70% yield of 7b (mp 180-181°C) is obtained (12% of the 3'-isomer mp 106-107°C). Again acetic acid on a steam bath for 20 min quantitatively converts 7a to 6b. Thus compounds 6 and 7 are readily available and are clearly desirable derivatives for the present methods of nucleotide synthesis (1, 2).

We have synthesized a dinucleotide of uridine using the silyl protecting groups. Thus 4a was phosphorylated with β-cyanoethyl phosphate and condensed with 6a in the usual manner (3).



4a

9

Compound 9 was isolated on thick layer plates using ether as developing solvent. The silyl groups were removed with (n-butyl)$_4$NF in THF while the cyanoethyl group was removed with ammonia (3). The resulting nucleotide uridylyl-(3'-5')-uridine (UpU) was completely degraded by both snake venom and spleen phosphodiesterases.

We will shortly describe the synthesis of important oligoribonucleotides sequences using only silyl groups for the protection of the hydroxyl functions.

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