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SILYLATIONS OF RIBONUCLEOSIDES USING DIBUTYLTIN OXIDE

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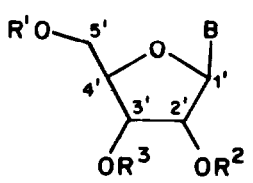
Abstract : Ribonucleosides 4 on silylation in presence of dibutyltin oxide yield selectively 5'-O-silyl derivatives 6.

Regiospecific alkylsilylations of 2'-hydroxyl group of ribonucleosides has assumed significance recently due to its successful use in RNA synthesis[1]. Current methods for this involve silylations of 5'-O-dimethoxytrityl ribonucleosides 1 followed by a very tedious chromatographic separation of the resulting 2',3'-O-silyl isomeric mixtures 2,3[2a,b]. Selective derivatisation (only alkylations, acylations and tosylation) of the *cis*-diol system of ribonucleosides 4 in preference to the primary hydroxyl or the base amino groups in the presence of dibutyltin oxide (DBTO) have been reported[3]. The DBTO mediated 2',3'-O derivatisation of ribonucleosides has been attributed to the formation of a cyclic 2',3'-O-dibutylstannylene intermediate 5 in which Sn-O bonds are activated, leading to selectivity at C2'/C3' hydroxyls[3].

Our interest in obtaining selective 2'-O-silyl ribonucleosides for RNA synthesis prompted us to explore the selectivity of DBTO assisted silylations of ribonucleosides 4, hitherto unknown[4]. Interestingly this lead to exclusive 5'-O-silyl derivatives 6. Alkylsilylations of ribonucleosides with *t*-butyldimethylsilyl chloride (TBDMSC) have been reported in the presence of different solvents (pyridine, DMF, THF), bases (pyridine, imidazole) and catalysts ($AgClO_4$, $AgNO_3$)[2b-d]. In all these cases predominant 5'-O-silyl derivatives were obtained only under stringent stoichiometric conditions, slight departures from this yielding mixtures of products.

In the method reported here, silylations of ribonucleosides in DMF/dioxane, in the presence of DBTO, gave exclusive 5'-O-silyl derivatives 6. Even with excess reagents no 2',3'-O-silylations were observed. The reactions were also fast (30-40min. as compared to 3-4hr. in previous methods) and gave good yields (Table-1).



1 R^1 = DMT, R^2 = R^3 = H; B = U, A^{Bz}, C^{Bz}, G^{Bz}
2 R^1 = DMT, R^2 = TBDMS, R^3 = H; B as in 1
3 R^1 = DMT, R^2 = H, R^3 = TBDMS; B as in 1
4 R^1 = R^2 = R^3 = H; B = U, A, C
5 R^1 = H, R^2, R^3 = Bu_2Sn; B = U, A, C
6 R^1 = TBDMS, R^2 = R^3 = H; B = U, A, C
7 R^1 = DMT, R^2, R^3 = Bu_2Sn; B = U, A^{Bz}, C^{Bz}
8 R^1 = TBDMS, R^2, R^3 = Bu_2Sn; B = U, A, C

Table-1

Entry	Nucleoside	TBDMSC (mmol eqiv.)	Reaction[+] solvent	Time (min.)	Product, 6[a] (yield %)[b]
i.	5U	1.0	A	30	91
ii.	5A	1.0	A	40	80
iii.	5C	1.0	A	40	82
iv.	5U	1.0	B	40	20[c]
v.	5U	2.0	A	40	78
vi.	7U,A,C	1.0	A	18 hr.	-
vii.	7U or 8U[d]	1.0	A	18 hr.	-

[+] A: DMF\Dioxane(dry)1:4(5ml);B: DMF or Dioxane. a. Characterised by comparison with authentic sample[2] b. After chromatography. c. Starting material recovered. d. +Bu_4NBr, RTto110°C

From the data presented in Table-1, it can be seen that (a) under the above experimental conditions, 5'-O silyl derivatives are always the major products (Entry i-iii). (b) the ideal solvent composition was found to be DMF/dioxane (1:4) and in either of the pure solvents, the progress was poor (Entry iv). (c) addition of excess silylating reagent (Entry v) does not lead to any 2' or 3'-O silylations. The slightly lower yield observed in this case is due to decomposition by the acid produced and (d) no silylations were observed in 5'-O-substituted nucleosides 7,8 even after prolonged reaction periods. Change of solvents (MeCN, DMF, Dioxane, THF), higher temperatures (RT to 110°C) and addition of catalyst (Bu_4NBr)[5] also failed to bring about further silylations (Entry vi, vii).

Our present observation that silylations under above conditions result in exclusive 5'-O-products can only be explained by steric interference of the postulated cyclic stannylidene intermediate[6] with the bulky TBDMS group. It is possible that DBTO may act as a mild base in these reactions. The enhanced rate of DBTO assisted silylations over reactions in pyridine or DMF/imidazole, absence of disilylated products and good yields make this method rapid, convenient and efficient for 5'-O silylations of ribonucleosides. Applications of this simple procedure for selective protection of polyhydroxy compounds is in progress.

Experimental Procedure: Nucleoside (1mM) was refluxed in methanol (30ml) with DBTO (1mM), until homogeneous. Methanol was removed to obtain a solid which after drying was treated with TBDMSC(1Mm) in DMF/dioxane (1:4, 5ml). Reactions were monitored by tlc and products purified by short silica gel chromatography. Products were characterized by (i) Benzidene spray test for cis-diol systems[7] and (ii) p.m.r. spectroscopy[2b-d].

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