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A General Method for Selective Tritylation of Primary Hydroxyl Groups in Carbohydrates and Related Compounds

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Abstract

A general and rapid procedure is developed for the selective tritylation of the primary OH-function of the four common ribonucleosides, ascorbic acid, and polyhydric compounds. Silver ion was found to have a marked effect on tritylation reactions.

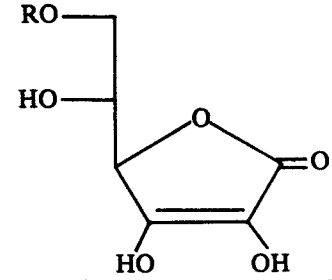
The general procedures for tritylation of ribonucleosides are based on those originally developed by the Khorana group in the deoxy area[1,2]. By this standard procedure the nucleosides and trityl chloride (Tr-Cl) are dissolved in pyridine and, after about 12 h the products are isolated by chromatography. We found that by using this procedure for tritylation of ascorbic acid, a mixture of desired product 6-OTr (5%), ditritylated (2, 6-, and 3, 6di-OTr) material and unreacted starting material was obtained and that separation of these components was time consuming.

This work shows that primary OH-groups (i.e. in ascorbic acid) may be selectively tritylated with Tr-Cl in THF/DMF (4:1 ml) by using silver nitrate as a catalyst. The addition of pyridine (5 eq.) to the system works against the progress of the reactions. Elimination of DMF from the system results in a considerable decrease in the rate of the reactions. Silver perchlorate is equally good as a catalyst, whereas $(n\text{-}Bu)_4N\ NO_3$ and $(n\text{-}Bu)_4N\ ClO_4$ are quite ineffective.

The selective protection of primary OH-groups in the presence of secondary OH-groups is an important synthetic capability. Numerous protecting groups have been evaluated in this regard, with varying degrees of success[3-12]. Specific applications have arisen in the protection of glycerol for the preparation of phospholipids[13,14], in the protection of carbohydrates[15], and in the protection of OH-groups in nucleosides[8-10]. This report describes a general method for the highly selective tritylation of primary OH-groups in the presence of secondary OH-functions. Ascorbic acid is used as a model compound.

The procedure described, arises out of our recently reported procedures for the selective 2'-O-silylation[16] or 3'-O-silylation[17,18] of ribonucleosides. We described in those reports the pronounced effect of nitrate ion on silylation. It should be noted that the same principle governs the selective O-nitration in carbohydrates[19].

Thus treatment of ascorbic acid with Tr-Cl and silver nitrate in THF/DMF (4:1 ml) gave a quantitative isolated yield of the 6-O-tritylated ascorbic acid (m.p. 68°C). These conditions were extended to uridine, cytidine, adenosine,



6-O-Tritylascorbic acid, R = Ph_3C
Ascorbic acid, R = H

and guanosine. These ribo-nucleosides were selectively tritylated at O-5' to give 5'-O-tritylated derivatives in about 40-85% yield. The results are summarized in Table 1 and the properties of protected nucleosides are collected in Table 2. The general procedure can be illustrated with the tritylation of adenosine. The nucleoside is dissolved in THF/DMF (8:2 ml) after which silver nitrate (1.2 mmol/mmol nucleoside) are added and the solution is stirred until the silver nitrate is completely dissolved (— 7 min). At this point trityl chloride (Tr-Cl, 1.3 mmol/mmol nucleoside) is added all at once and the resulting mixture is stirred at 25°C for 2 h. The mixture is then filtered and the clear solution is mixed 5% aq. $NaHCO_3$ to prevent detritylation. The product is extracted into CH_2Cl_2, dried (Na_2SO_4), and evaporated. The residue is chromatographed on silica gel and eluted with $CHCl_3$ & AcOEt to afford 5'-Tr-Ade (80%).

These results (Table 1) show very high conversion yields with remarkable selectivity in all cases except for guanosine which gave 5'-Tr-Gu in 40% yield only. It should be noted that when dimethoxytrityl chloride (DMTr-Cl) is used in place of trityl chloride (Tr-Cl), N-tritylation of exo-NH_2 function of adenine and cytidine is found to be a serious problem[18].

Compound (mmol)	Tr – Cl (mmol)	$AgNO_3$ (mmol)	Time (h)	(Yield[b]) (%)
Uridine (1)	1.3	1.2	1.5	85 (5'-OTr)
Cytidine (1)	1.3	1.2	1.5	60 (5'-OTr)
Adenosine (1)	1.3	1.2	2	80 (5'-OTr)
Adenosine (1)	2.6	2.4	2	85 (5'-OTr)
Guanosine (1)	1.3	1.2	4	40 (5'-OTr)
Uridine (1)	1.3	1.2 ($AgClO_4$)	1.5	88 (5'-OTr)
Ascorbic acid (1)	1.3	1.2	0.5	100 (6-OTr)
Ascorbic acid (1)	2.6	2.4	1	100 (6-OTr)
Ascorbic acid (1)	1.3	–	5	0
Glycol (1)	1.3	1.2	0.5	90 (1-OTr)
Glycerol (1)	2.3	2.4	1	80 (1-OTr),10(1,3di-OTr)
Glycerol (1)	4.6	4.8	5	30 (1-OTr),50(1,3di-OTr)
1,3-Propanediol (1)	1.3	1.2	1	85 (1-OTr)
1,3-Propanediol (1)	2.6	2.4	1	90 (1-OTr)
1,2-Propanediol (1)	1.3	1.2	1	87 (1-OTr)
1,4-Butanediol (1)	1.3	1.2	1	90 (1-OTr)
1,4-Butanediol (1)	2.6	2.4	1	93 (1-OTr)
2,3-Butanediol (1)	1.3	1.2	1	80 (2-OTr)
2-Butene-1,4-diol (1)	1.3	1.2	1.5	90 (1-OTr)
2-Butyne-1,4-diol (1)	1.3	1.2	1.5	80 (1-OTr)
1,4-Dihydroxybenzene (1)	1.3	1.2	2	30 (1-OTr),60(1,4di-OTr)
1,2-O-Isopropylidine-α-D-glucofuranose (1)	2.6	2.4	2	95 (6-OTr)
2-Aminoethanol (1)	1.3	1.2	1	90 (2-NTr)
2-Aminoethanol (1)	2.6	2.4	1	95 (2-NTr)
orto-Aminophenol (1)	1.3	1.2	1.5	80 (NTr)
para-Aminophenol (1)	1.3	1.2	1.5	90 (NTr)
2-Aminobenzyl alcohol (1)	1.3	1.2	1.5	85 (2-NTr)
2-Amino-5-nitro-benzyl alcohol (1)	1.3	1.2	1.5	80 (OTr)
Ethylenediamine (1)	1.3	1.2	1.5	90 (1-NTr)

a) The solvent was THF/DMF (4:1 ml) in all cases. All reactions were carried out at 25°.
b) The products were characterized by spectroscopic data (NMR., IR., UV.) and yields are based on material isolated from column chromatography or TLC.

Table 1. Silver Nitrate Catalysis of Tritylation Reaction[a])

Compound	M.P.	(EtOH) λ_{max} nm	R_f (TLC[c])
5'-TrUr.	95-97	232,264	0.78
5'-TrCy.	149-152	232,275	0.24
5'-TrAde.	130-131	234,259	0.45
5'-TrGu.	196-198	256,272 sh	0.17

a) The solvent in all cases was ether/MeOH (9:1).

Table 2. Properties of Protected Nucleosides

Having established a method for the selective tritylation of primary OH-groups in ribonucleosides and ascorbic acid, it was decided to apply this method to a series of polyhydric alcohols or amines containing OH-function to examine its generality and mildness. The results are summerized in Table 1.

This report describes a general procedure for the facile preparation of ribonucleosides, ascorbic acid, and other polyhydric alcohols including carbohydrates protected with one of the most versatile and useful blocking groups, the trityl group. This procedure incorporates the truly novel effects of silver ion and leads to the highly selective protection of a single primary OH-function. The results clearly indicate the preference of N-tritylation over O-tritylation, unless the NH_2-function is deactivated by a properly positioned electron-withdrawing group on/and or in the substrate molecules (e.g. 2-amino-5-nitrobenzyl alcohol and adenosine, Table 1).

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