

STANNOUS CHLORIDE: A REAGENT FOR REMOVAL OF DIMETHOXYTRITYL GROUP FROM 5'-DIMETHOXYTRITYL NUCLEOSIDES

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ABSTRACT: *Detritylation of 5'-dimethoxytrityl nucleosides have been quantitatively achieved in minutes at room temperature under aprotic neutral conditions by using stannous chloride. Of additional practical consideration and in contrast to protic acids, no depurination was observed with this reagent.*

KEY WORDS: *Deprotection, 5'-Dimethoxytrityl group, Nucleosides.*

INTRODUCTION

Nucleoside analogues have received increasing importance through their biological activity, particularly as antiviral and anticancer compounds [1]. The triphenylmethyl (trityl) group, as a protecting group for 5'-OH of the nucleoside moiety is most desirable, as trityl ethers are stable in slightly acidic, basic and other reaction conditions in use for oligodeoxynucleotide synthesis [2]. However, this desirable group has not been applied frequently as the deprotection needs use of protic acids [3] which is accompanied by depurination (glycosidic cleavage). Previously, zinc bromide in methylene chloride or nitromethane [4-5] and dialkylaluminium chlorides in a homogeneous phase under nonpolar and completely aprotic conditions [6] have been used for detritylation. Recently, the trityl and monomethoxytrityl groups were removed from protected nucleoside or nucleotide by the use of ceric ammonium nitrate (CAN) in wet acetonitril and DMF under neutral conditions [7]. However, the above mentioned pro-

cedures have disadvantages. Zinc bromide as a Lewis acid has low solubility in nonpolar aprotic solvents and, more important, the deprotection is accompanied by depurination. Dialkylaluminium chloride results in a relatively low yield and also some side reactions occur. In the case of CAN, the reaction time is too long.

EXPERIMENTAL

General procedure

The protected nucleoside (1 mmol) was dissolved in CH_3NO_2 (10 mL), which is cooled to 0°C and added to a stirred slurry of SnCl_2 (0.38 g, 2 mmol) in CH_3NO_2 (10 mL) at the same temperature. After 15 minutes the solvents was removed under vacuum. The residue was washed with ether to remove dimethoxytritylchloromethane and was then dissolved in EtOAc and extracted with 5% NaHCO_3 . After drying (Na_2SO_4) and evaporation in vacuo the detritylated product was obtained.

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RESULTS AND DISCUSSIONS

In our current experiments, deprotection was done in the presence of mild Lewis acid SnCl_2 in various solvents. The results showed high reaction yields without any considerable depurination (Table 1). As it seen from Table 1, nitromethane is superior among different solvents tested, since detritylation was complete within one minute.

Table 1: The Rate of detritylation of 5'-dimethoxytrityladenosine in a SnCl_2 saturated solution at room temperature.

Solvent	%Detritylation	Time
CH_2Cl_2	20 ^a	24 h
THF	40 ^a	24 h
DMF	100 ^b	15 min
CH_3CN	100 ^b	5 min
CH_3NO_2	100 ^b	1 min

a) Yields were on the basis of products isolated from column chromatography.

b) Complete detritylation has been demonstrated by TLC on silica gel.

The rate of removal of dimethoxytrityl group and depurination of 5'-dimethoxytrityladenosine was measured and the results are summarized in Table 2. As it is seen, the depurination is too low all though after a long reaction time.

Table 2: The rate of detritylation and depurination of 5'-dimethoxytrityladenosine using various conditions.

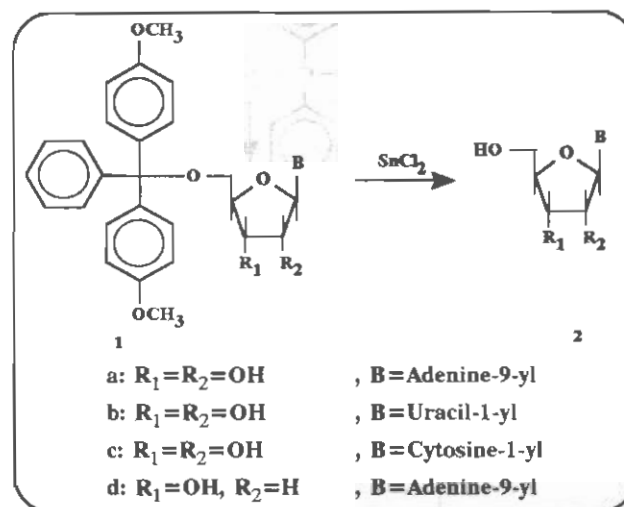
Solution	Detritylation ^a			Depurination ^b	
	Temp. (C°)	Time (min)	%	Time (h)	%
Satd. $\text{SnCl}_2/\text{CH}_3\text{NO}_2$ (dry) ^c	25	1	100	24	15
Satd. $\text{SnCl}_2/\text{CH}_3\text{NO}_2$ (dry)	0	15	100	24	<5

a) Yields are based on TLC.

b) Complete detritylation has been demonstrated by TLC on silica gel.

c) A nitromethane saturated with SnCl_2 is approximately 0.1 M in SnCl_2 .

Some other nucleosides (Scheme 1) were also tested by measuring the rate of deprotection. The results are summarized in Table 3.



Scheme 1

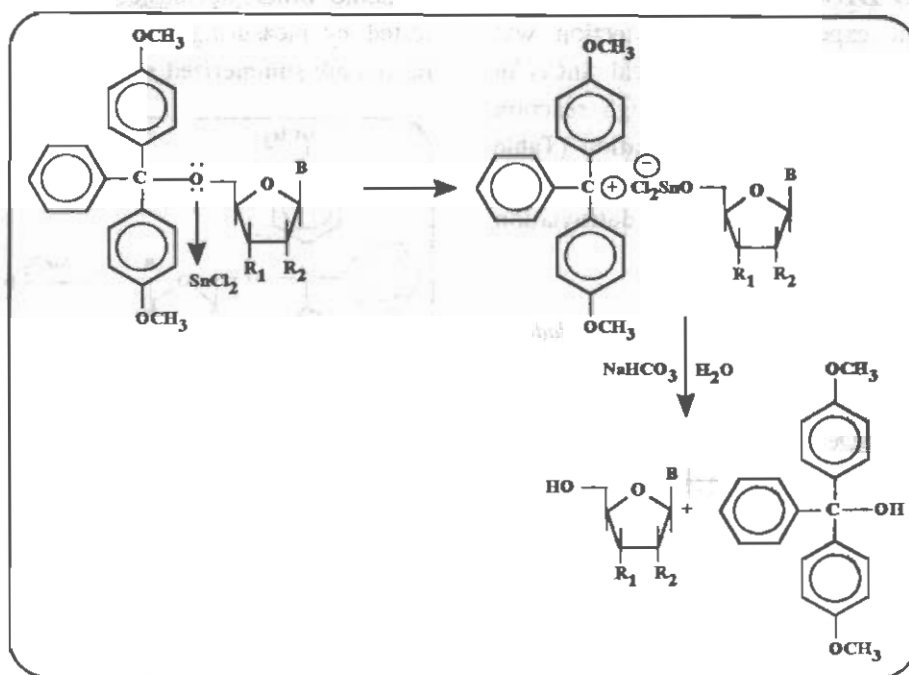
Table 3: Removal of dimethoxytrityl of protected Nucleosides by use of $\text{SnCl}_2/\text{CH}_3\text{NO}_2$.

Starting material	Temp. (C°)	Time (min)	Product ^a	Yield%
1a	0	15	2a	100
1a	25	1	2a	100
1b	0	15	2b	95
1b	25	1	2b	85
1c	0	15	2c	85
1c	25	1	2c	77
1d	0	15	2d	92
1d	25	1	2d	80

a) The products were isolated and identified by comparison with authentic samples.

The possible mechanism of detritylation is suggested in Scheme 2. It is interesting to note that, the inherent stability of the trityl carbonium ion as observed by concomitant colouration of the reaction mixture acts as a driving force for the detritylation (Scheme 2).

The presence of trace amounts of water in the starting reactants or solvents can react with SnCl_2 and liberate HCl which in turn enhances the depuri-



Scheme 2

nation rate.

In other experiments using a one to one ratio of ZnBr_2 and 5'-dimethoxytrityl-adenosine shows a depurination rate of 10% after 10 hours, where under the same conditions, SnCl_2 results in no measurable depurination (Table 4).

Table 4: The Rate of detritylation and depurination of 5'-dimethoxytrityl-adenosine in nitromethane by using various reagents at room temperature.

Solution	Detritylation ^a		Depurination ^b	
	Temp. (min)	%	Time (h)	%
$\text{ZnBr}_2/5'$ -dimethoxytrityl-adenosine(1:1)	15	80	10	10
$\text{SnCl}_2/5'$ -dimethoxytrityl-adenosine(1:1)	15	75	10	0

a) Yields were on the basis of products isolated from column chromatography.

b) Complete detritylation has been demonstrated by TLC on silica gel.

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