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Efficient and catalytic deprotection of triphenylmethyl ethers with $Ce(OTf)_4$

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Abstract—A very simple and efficient method is described for deprotection of trityl, mono and dimethoxytrityl ethers using catalytic amount of ceric triflate in acetonitrile under mild reaction conditions. High reactivity was observed for detritylation of saturated and benzylic ethers and also for structurally different nucleosides. © 2001 Published by Elsevier Science Ltd.

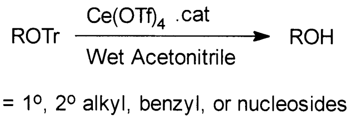
Ether cleavage is a versatile transformation in organic chemistry and its importance for the deprotection of the hydroxyl group especially in pharmaceuticals, drugs and other fine chemicals has attracted the attention of synthetic chemists. The triphenylmethyl (trityl) group, as a protecting group for the 5′-OH function of the nucleoside moiety is a most desirable protecting group due to its stability in slightly acidic, basic and other reaction conditions as is widely used in oligodeoxynucleoside synthesis.[1] However, this desirable protecting group has not been applied frequently for the protection of the 5′-OH of nucleosides due to very severe acidic reaction conditions required for their deprotection (e.g. the use of protic acids such as hydrogen chloride, hydrogen bromide, acetic acid, trifluoroacetic acid, or basic conditions such as use of sodium in liquid ammonia).[2] Thus, its removal from nucleosides would cause a cleavage, which is accompanied by depurination (glycosidic cleavage).

Previously, $ZnBr_2$ in dichloromethane or nitromethane,[3] and dialkylaluminum chloride in a homogeneous phase under nonpolar and completely aprotic conditions,[4] have been used for detritylation. Recently, the trityl and monomethoxytrityl groups were removed from protected nucleosides or nucleotides by the use of ceric ammonium nitrate (CAN) in wet acetonitrile under neutral conditions.[5] However these methods encounter some drawbacks. For example detritylation under acidic conditions may cause acyl migration for ester containing compounds[6] and cleavage of glycosidic bond in nucleosides and nucleotides,[7] and also reactions take place in a long time, with low yields of the products and tedious work-up of the reaction mixture. Recently we have reported that $SnCl_2$ is an efficient reagent for removal of the dimethoxytrityl group from protected nucleosides.[8]

Ceric triflate $[Ce(OTf)_4]$[9] is neutral in comparison with wet CAN and is also readily soluble in organic solvents.[10,11] Here, we report that ceric triflate is a convenient catalyst for deprotection of trityl ethers to their corresponding hydroxyl compounds (Scheme 1).

The choice of solvent in deprotection of trityl ethers with $Ce(OTf)_4$ is important. On the basis of our results which are shown in Table 1, $Ce(OTf)_4$ acts more efficiently in polar solvents such as CH_3CN.

Examination of the results shows that primary and secondary, aliphatic and benzylic trityl and dimethoxytrityl ethers are converted to their corresponding hydroxyl compounds very easily with a catalytic amount of $Ce(OTf)_4$ in CH_3CN in high yields (Table 2).



$$\text{ROTr} \xrightarrow[\text{Wet Acetonitrile}]{Ce(OTf)_4\ .\text{cat}} \text{ROH}$$

R = 1°, 2° alkyl, benzyl, or nucleosides

Scheme 1.

Table 1. Effect of different solvents on deprotection of di(*p*-methoxyphenyl)phenylmethylbenzyl ether with catalytic amount of $Ce(OTf)_4$ at room temperature

Solvent	Time	Yield[a] (%)
CH_2Cl_2	24 h	10
THF	18 h	30
CH_3CN	5 min	95
CH_3NO_2	5 min	93

[a] Isolated yield after column chromatography.

Keywords: deprotection; trityl ethers; ceric triflate; catalytic amount; nucleoside.

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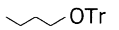
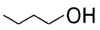
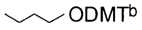
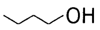
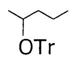
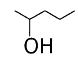
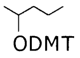
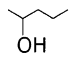
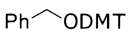
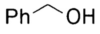
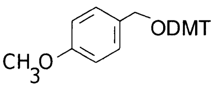
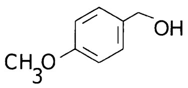
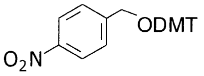
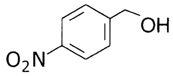
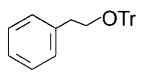
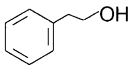
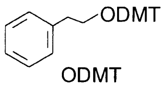
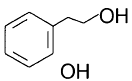
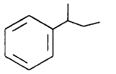
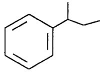
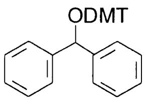
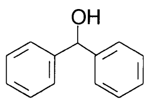
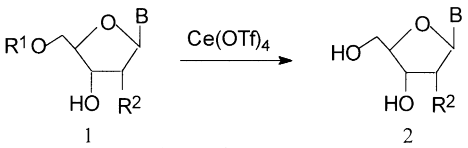
Table 2. Deprotection of trityl and dimethoxytrityl ethers with $Ce(OTf)_4$ (0.1 equiv.) in CH_3CN at room temperature

Entry	Substrate	Product	Time (min.)	Yield[a] (%)
1)			120	87
2)			30	93
3)			170	82
4)			75	88
5)			5	95
6)			Immediately	95
7)			50	87
8)			120	89
9)			30	92
10)			90	80
11)			120	81
12)	(-) Menthol- ODMT	(-) Menthol	135	78

[a] Isolated yield after column chromatography.

[b] DMT=Di(p-methoxyphenyl)phenylmethyl: $(p\text{-}MeC_6H_4)_2PhC–$.

Trityl ethers are more stable than dimethoxytrityl (DMT) ethers and in all cases in our studies their less reactivity, longer reaction times, and mostly lower yields have been observed (Table 2, entries 1,2). Primary benzylic and saturated trityl ethers are more reactive than secondary aliphatic and benzylic trityl ethers (Table2, entries 5,10-2,4).



a): R^1= Tr, R^2= OH, B=Adenine
b): R^1= DMT, R^2= OH, B= Adenine
c): R^1= Tr, R^2= H, B= Thimine
d): R^1= MMTr, R^2= H, B= Thymine
e): R^1= DMT, R^2= H, B= Thymine
f): R^1= Tr, R^2= OH, B= Uracil
g): R^1=DMT, R^2= OH, Uracil

Scheme 2.

Table 3. Deprotection of 5′-tritylated nucleosides with $Ce(OTf)_4$ (0.1 equiv.) in CH_3CN at room temperature

Substrate	Product[a]	Time (min)	Yield[b] (%)
1a	**2a**	1.5 h	88[5]
1b	**2b**	45 min	95[8]
1c	**2c**	1 h	90[5]
1d	**2d**	30 min	92[13]
1e	**2e**	10 min	96[13]
1f	**2f**	1 h	89[5]
1g	**2g**	30 min	93[8]

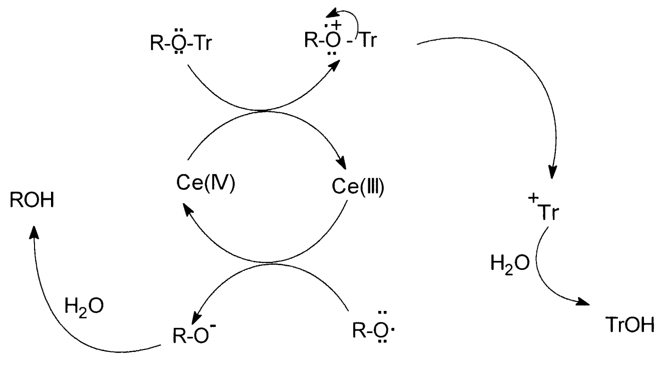
[a] The products were isolated and identified by comparison with authentic samples.

[b] Isolated yields after column chromatography.

Substituted groups on the benzene ring affect the reactivity of the substrates against the deprotection reaction. Electron-donating groups such as $–OCH_3$, increase (Table 2, entry 6), and electron-withdrawing groups such as $–NO_2$, decrease the activity of trityl ethers in deprotection reactions (Table 2, entry 7).

An interesting feature of this procedure is the conversion of 5′-tritylated nucleosides to the corresponding nucleosides with a catalytic amount of $Ce(OTf)_4$ (Scheme 2, Table 3).

Our results show that the rate of detritylation is much faster than those reported by CAN. Moreover, no depurination and any side reactions were observed. We found that the feasibility of deprotection by use of $Ce(OTf)_4$ depends upon the stability of the resultant carbocation. At the same temperature, deprotection of 5′-*O*-dimethoxytrityladenosine (**1a**, Table 3) is faster than deprotection of 5′-*O*-trityladenosine (**2b**, Table 3). This is because the dimethoxytrityl cation is more stable than trityl cation.



Scheme 3.

A detritylation mechanism is proposed by using tritylated alcohols (Scheme 3). An essential step involves oxidation of trityl ether $ROCPh_3$ to the corresponding cation radical while reduction of Ce(IV) to Ce(III) takes place.[12]

$Ce(OTf)_4$ seems to be a more reliable and more efficient reagent than protic acids and other reagents previously used for the deprotection of trityl ethers.

1. Experimental

Chemicals were either prepared in our laboratories or were purchased from Fluka, Merck, and Aldrich Chemical Companies. Products were characterized by comparison of their physical data with those of authentic samples. All yields refer to isolated products. The purity determination of the substrates and the reaction monitoring were accomplished by TLC on silica gel polygram SILG/UV 254 plates or GLC on a Shimadzu GC-14A instrument. All yields refer to the isolated products.

1.1. General procedure for deprotection of trityl, and dimethoxytrityl ethers with a catalytic amount of $Ce(OTf)_4$

Trityl ether (1 mmol) in wet acetonitrile (10 mL) was treated with a catalytic amount of $Ce(OTf)_4$ (73.6 mg, 0.1 mmol) at 25°C. The TLC indicated the completion of the reaction. The solvent was removed under reduced pressure and the residue purified by column chromatography using silica gel.

1.2. Deprotection of dimethoxytritylbenzyl ether as a typical procedure

Dimethoxytritylbenzyl ether (0.41 g, 1 mmol) in wet acetonitrile (10 mL) was treated with a catalytic amount of $Ce(OTf)_4$ (73.6 mg, 0.1 mmol) at 25°C for 5 min. The solvent was removed under reduced pressure and the residue purified on silica column, using dichloromethane to give the benzyl alcohol in 95% yield. All the products are known compounds and were identified by comparison of their physical and spectral data with those reported in CRC.[13]

1.3. General procedure for removal of trityl, monomethoxytrityl, and dimethoxytrityl group from protected nucleosides

The protected nucleoside (1 mmol) in wet acetonitrile (30 ml) was treated with a catalytic amount of $Ce(OTf)_4$ (73.6 mg, 0.1 mmol) at 25°C for 10–90 min. the solvent was removed under reduce pressure and the residue purified on silica column, first washed with ether to removed triphenylmethanol, then eluting with ethyl acetate–methanol (1:1) to give the product. The product were isolated and identified by comparison with authentic samples.[5,8,14]

Acknowledgements

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