ARTICLE

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Mild and efficient method for the cleavage of benzylidene acetals by using erbium (III) triflate

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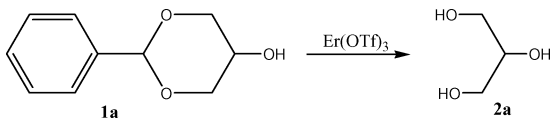
$Er(OTf)_3$ is proposed as new efficient Lewis acid catalyst in a mild deprotection protocol of benzylidene derivatives. In a modified procedure, where acetic anhydride is used as the reaction solvent, the simultaneous cleavage of the benzylidene acetal and the peracetylation of the substrates is obtained in quantitative yields and very short reaction times.

Introduction

Chemoselective transformation of multifunctional organic compounds still presents a severe challenge for the organic chemists and the success of a multi-step synthesis very often depends on efficient manipulation of the functional groups involved. The selective protection–deprotection of polyhydroxylated substrates is a key step in the chemical synthesis of complex molecules. Numerous methods and reagents exist for this purpose, particularly for carbohydrate and natural products chemistry,[1] but considerable efforts are still directed towards developing efficient, selective, mild and environmentally-friendly systems for both the introduction and cleavage of many existing protective groups.

Benzylidene acetals, commonly used to protect 1,2- and 1,3-diols, have the obvious advantage that they can be used to simultaneously protect two hydroxyl groups and be removed under neutral conditions by hydrogenolysis or by strong acid hydrolysis.[1,2] Moreover, the benzylidene acetals possess the useful property that one of the two C–O bonds can be selectively cleaved, with the direction of cleavage depending upon steric and electronic factors and the nature of the cleavage.[2,3] For this peculiar versatility the benzylidene acetals find wide applicability in the synthesis of carbohydrates and natural products.[4] Nevertheless, the complete cleavage of benzylidene acetal suffers limiting drawbacks, since very strong acidic media [H_2SO_4, $Zn(OTf)_2$, $FeCl_3$, BCl_3; $SnCl_2$;[5] CSA[6]] or demanding conditions [H_2/Pd–C, AcOH;[5,7] electrolysis; Pd–C, hydrazine; $Pd(OH)_2$, cyclohexane; EtSH; $NaHCO_3$; Na/NH_3; I_2[5]] are required, so some more acid-labile alternatives have been proposed (anisylidene,[8] methoxybenzylidene,[2] and 9-anthraldehyde acetal[9]).

In recent years, we have spent many efforts developing new catalytic reagents for several strategic steps of organic synthesis with the aim to lower the environmental impact of the chemistry.[10] During our work on epoxide manipulation by means of $Er(OTf)_3$,[10i] we observed the cleavage of the benzylidene group in methyl 2,3-anhydropyranosides and this result pushed us to explore the use of erbium(III) trifluoromethanesulfonate as Lewis acid catalyst in the cleavage of benzylidene acetals. First, we tested the catalytic activity of $Er(OTf)_3$ in the deprotection reaction of *cis*-1,3-*O*-benzylidene glycerol **1a** at rt in different solvents and with different mol% of catalyst (Scheme 1).



Scheme 1

The developing of the reaction was monitored by TLC and HPLC. No cleavage or only very low yields of deprotected glycerol were obtained in apolar solvents such as dichloromethane, diethyl ether, chloroform, tetrahydrofuran and toluene (entries 1–5 in Table 1).

Nevertheless, the catalyst showed to be active in aprotic polar solvents such as acetonitrile and nitromethane (entries 6 and 11 in Table 1), but efficient cleavage was registered only by improving the amount of catalyst up to 5.0 mol% (entries 7 and 10 in Table 1) indicating acetonitrile and 5.0 mol% of $Er(OTf)_3$ at rt as the best reaction conditions. In fact, prolonged reaction times did not significantly improve the reaction yield (entry 8 in Table 1), while higher reaction temperature seemed to produce an equilibrium when only 45% of glycerol is present (entry 9 in Table 1).

Table 1 Deprotection of *cis*-1,3-*O*-benzylidene glycerol (**1a**) at rt in different solvents and with different mol% of catalyst

Entry	$Er(OTf)_3$ (mol%)	Solvent	Time/min	Yield[a] (%)
1	1.0	CH_2Cl_2	30	10
2	1.0	Et_2O	30	0
3	1.0	$CHCl_3$	30	20
4	1.0	THF	30	28
5	1.0	Toluene	30	5
6	1.0	CH_3CN	30	63
7	5.0		30	90
8	5.0		120	93
9	5.0		30	45[b]
10	1.0	CH_3NO_2	30	52
11	5.0		30	73
12	5.0	CH_3CN (wet)	30	15
13	5.0	CH_3NO_2 (wet)	30	8
14	5.0	CH_3CN (dry)	30	91
15	5.0	CH_3NO_2 (dry)	30	70

[a] Yield determined by HPLC. [b] Reaction conducted under reflux.

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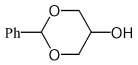
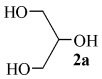
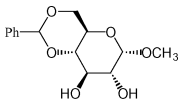
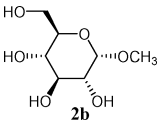
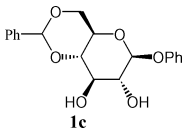
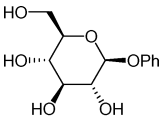
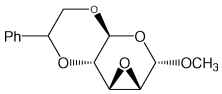
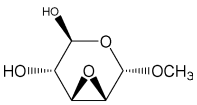
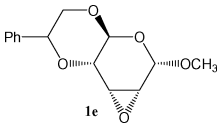
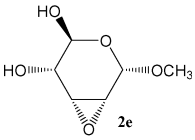
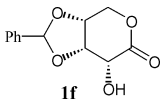
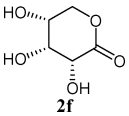
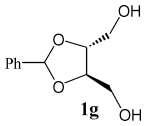
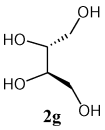
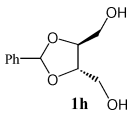
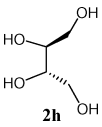
Table 2 Cleavage of benzylidene acetals using 1–5 mol% of $Er(OTf)_3$ in CH_3CN at rt

Entry	Substrate	Product	Time/h	Yield (%)[a,b]
1	 **1a**	 **2a**	2	93[c]
2	 **1b**	 **2b**	2.5	95
3	 **1c**	 **2c**	5	78
4	 **1d**	 **2d**	2[d]	81
5	 **1e**	 **2e**	2[d]	90
6	 **1f**	 **2f**	24[c,e,f]	14
7	 **1g**	 **2g**	24[c]	55
8	 **1h**	 **2h**	24[c]	60

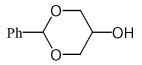
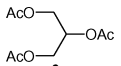
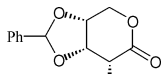
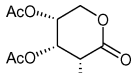
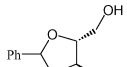
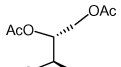
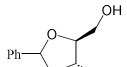
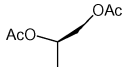
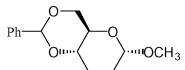
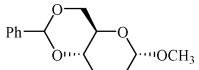
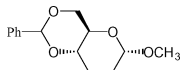
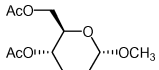
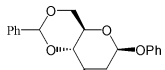
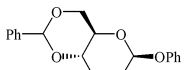
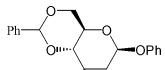
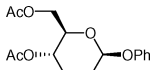
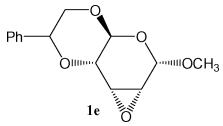
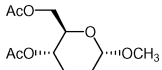
[a] Unless otherwise specified, isolated yield by flash column chromatography on silica gel was reported. [b] Unless otherwise specified, all products were identified by comparison of their EI-MS and ^{1}H-NMR spectral data with those of authentic compounds and literature reported data.[11] [c] Yield was determined by HPLC using the standard addition method. [d] Only 1 mol% of catalyst was required. [e] CH_3NO_2 was a better solvent for this substrate. [f] Reaction conducted under reflux.

Finally, when dry acetonitrile or nitromethane were used, no significant improvment of the yields was registered (entries 14 and 15 in Table 1) meanwhile, by adding small amounts of water, lower yields of product were obtained (entries 12 and 13 in Table 1).

Based on the results reported in Table 1, in order to explore the generality and the scope of erbium (III) triflate as a Lewis acid catalyst in the cleavage of benzylidene acetal, the reaction was carried out on different substrates such as (+)-(4,6-*O*-benzylidene)methyl-α-D-glucopyranoside (**1b**), (−)-(4,6-*O*-benzylidene)phenyl-β-D-glucopyranoside (**1c**), methyl 2,3-anhydro-4,6-*O*-benzyliden-α-D-mannopyranoside (**1d**), methyl 2,3-anhydro-4,6-*O*-benzyliden-α-D-allopyranoside (**1e**), 3,4-*O*-benzylidene-D-ribonic-δ-lactone (**1f**), (−)-2,3-*O*-benzylidene-L-threitol (**1g**), (+)-2,3-*O*-benzylidene-D-threitol (**1h**). We generally adopted a simple experimental procedure that involved stirring the solution of benzylidene protected substrate and 1–5 mol% of $Er(OTf)_3$ in commercial CH_3CN. The reactions carried out on substrates reported in Table 2 proceed quickly and with high yields, and only the 3,4-*O*-benzylidene-D-ribonic-δ-lactone **1f** furnished a very scarce yield of deprotected product (in another reaction solvent and at a higher reaction temperature—entry 6 in Table 2). This suggests that an equilibrium between protected–deprotected products is established where probably insoluble deprotected sugars are subtracted to this equilibrium.

To take advantage from this observation, and in the light of our previous reports on the use of $Er(OTf)_3$ as an acylation catalyst,[9h] the original experimental cleavage protocol was modified by using acetic anhydride as solvent with the aim to straightforwardly collect the peracetylated products in high yield and very short reaction times by shifting the cleavage equilibrium reaction of the benzylidene substrates. In a very simple experimental procedure, a solution of benzylidene protected substrate and 5 mol% $Er(OTf)_3$ in acetic ahydride was stirred at rt and followed by TLC and GC-MS until the disappearance of the starting material.

Table 3 One-pot deprotection–acetylation of benzylidene acetals using 5 mol% of $Er(OTf)_3$ in Ac_2O at rt

Entry	Substrate	Product	Time	Yield (%)[a,b]
1	 **1a**	 **3a**	40 min	94
2	 **1f**	 **3f**	2 h	96
3	 **1g**	 **3g**	15 min	94
4	 **1h**	 **3h**	20 min	95
5	 **1b**	 **3b'**	15 min	97
6	 **1b**	 **3b**	10 h	95
7	 **1c**	 **3c'**	15 min	96
8	 **1c**	 **3c**	10 h	95
9	 **1e**	 **3b**	8 h[c]	98

[a] Unless otherwise specified, the product was obtained pure enough without any other purification steps. [b] Unless otherwise specified, all products were identified by comparison of their EI-MS and ^{1}H-NMR spectral data with those of authentic compounds and literature reported data.[13] [c] After 15 min the only product obtained was **3b'**.

In every case, the exchange reaction between the benzylidene and acetyl protecting group took place in very short reaction times with quantitative yields, still using 5 mol% of Er(III) triflate as catalyst and without further purification (Table 3).

It is reasonable to retain the simultaneous acetylation of the former benzylidene product as the key step in shifting the equilibrium reaction between protected-deprotected substrate. Notably, (+)-(4,6-*O*-benzylidene)methyl-α-D-glucopyranoside **1b** and (−)-(4,6-*O*-benzylidene)phenyl-β-D-glucopyranoside **1c** gave the 2′,3′-acetylated derivatives in very short times and only in much more prolonged times the completely peracetylated products are collected (entries 5–8 in Table 3).

The oxirane ring does not stand the reaction conditions, being more labile than the benzylidene group; in fact in the case of the methyl 2,3-anhydro-4,6-*O*-benzyliden-α-D-allopyranoside **1e** the **3b'** was the only product collected after only 15 min of reaction, whilst after 8 h the whole reagent was transformed in the peracetylated methyl-α-D glucose **3b** (entry 9 in Table 3) as confirmed by coupling constant $J_{H1-H2} = 3.71$ in the ^{1}H-NMR spectrum (3.60 was the value find in the ^{1}H-NMR spectrum of reference peracetylated methyl-α-D glucose).

Furthermore, the catalyst can be reused several times without significant loss of activity. After work-up, the aqueous phase can be evaporated under reduced pressure to furnish the Er(III) salt[12] as a pale pink solid (85–90% recovered), which can be recycled after drying overnight over P_2O_5. The recovered catalyst was used five times in the simultaneous acylation reaction of the *cis*-1,3-*O*-benzylidene glycerol (**1a**) maintaining 5.0 mol% of catalyst and the registered yields were always higher than 90%.

Conclusions

$Er(OTf)_3$ is one of the cheapest commercially available triflate lanthanoid derivative, easy to handle and used in true catalytic

amounts; furthermore, this catalyst can be reused several times without significant loss of activity. All cleavage reactions are performed smoothly at rt and almost in neutral conditions, the solution 0.1 M of $Er(OTf)_3$ in water is only weakly acidic (pH *ca.* 5.9). Moreover, the present method fulfils most of the 12 Principles of Green Chemistry.[14] In fact, erbium is not toxic, it is used in true catalytic amounts at rt, and can be recovered and reused after reaction without significant loss of activity. Finally, the presented protocol permits the simultaneous transformation of acid-labile protected substrates into base-labile acetate derivatives in quantitative yields by using an easily-recoverable non-toxic catalyst, and without further purification steps, showing very versatile applicability and tangible improvement with respect to the other existing methods.

Experimental

All reactants, catalyst and solvents are commercially available and were used without purification, except methyl 2,3-anhydro-4,6-*O*-benzyliden-α-D-mannopyranoside (**1d**) and methyl 2,3-anhydro-4,6-*O*-benzyliden-α-D-allopyranoside (**1e**) which were synthesized following reported procedures.[15] ^{1}H- and ^{13}C-NMR spectra were recorded with a Brucker WM 300 instrument at 300 MHz and 75 MHz respectively. Samples were dissolved in $CDCl_3$. Chemical shifts are given in parts per million (ppm) from tetramethylsilane as internal standard for ^{1}H- and ^{13}C-NMR. Coupling constants (J) are given in Hz. The reactions have been monitored by TLC when possible or with a GC-MS Shimadzu workstation, constituted by a GC 2010 (provided of a 30 m-QUADREX 007–5MS capillary column, operating in "splitless" mode, 1 ml min^{-1} flow of He as carrier gas) and a 2010 quadrupole mass-detector or by HPLC analysis [HP 1100, Phenomenex Luna NH_2, 250 × 4.6 mm, 5 μm, RI detector, 1.0 ml min^{-1}, H_2O, 50 °C].

General procedure for benzylidene cleavage

$Er(OTf)_3$ (50 μmol, 5 mol%) was added at rt to a magnetically stirred solution of benzylidene derivative **1a**–**h** (1.0 mmol) in CH_3CN (4.0 mL). The reaction course was followed by TLC or HPLC analysis until disappearance of the starting material or to invariance of starting material : product ratio. Crude reaction mixture was poured into water and extracted with organic solvent. This organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. Unless otherwise specified, all products were identified by comparison of their EI-MS and ^{1}H NMR spectral data with those of authentic compounds and literature reported data.[14]

Methyl 2,3-anhydro-α-D-mannopyranoside (2d). ^{1}H-NMR ($CDCl_3$): $\delta = 4.89$ (s, 1H, H_1); $\delta = 3.86$ (d, 1H, H_4, $J_{H4\text{–}H5} = 9.19$); $\delta = 3.78$ (dd, 2H, H_6, $J_{H6\text{–}H6'} = 3.98$; $J_{H_6\,H_5} = 3.43$); $\delta = 3.51$ (m, 1H, H_5); $\delta = 3.46$ (s, 3H, OMe); $\delta = 3.32$ (d, 1H, H_2, $J_{H2\text{–}H3} = 3.70$); $\delta = 3.13$ (d, 1H, H_3, $J_{H3\text{–}H2} = 3.70$).

Anal. calcd for $C_7H_{12}O_5$: C 47.73; H 6.82; found: C 47.70; H 6.87.

General procedure for simultaneous peracetylation

$Er(OTf)_3$ (50 μmol, 5 mol%) was added at rt to a magnetically stirred solution of benzylidene derivative **1a**–**h** (1.0 mmol) in acetic anhydride (1.0 mL). The reaction course was followed by TLC or HPLC analysis until disappearance of the starting material or to invariance of starting material : product ratio. Crude reaction mixture was poured into water and extracted with organic solvent. This organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure giving the product pure enough without any other purification steps. Unless otherwise specified, all products were identified by comparison of their EI-MS and ^{1}H NMR spectral data with those of authentic compounds and literature reported data.[15]

Methyl 2,3,4,6-tetraacetyl-α-D-glucopyranoside (3b). ^{1}H-NMR ($CDCl_3$): $\delta = 1.57$ (s, 3H, OAc); $\delta = 1.75$ (s, 3H, OAc); $\delta = 1.99$ (s, 3H, OAc); $\delta = 2.45$ (s, 3H, OAc); $\delta = 3.38$ (s, 3H, OMe); $\delta = 3.95$ (ddd, 1H, H_5, $J_{H5\text{–}H4} = 10.29$; $J_{H5\text{–}H6} = 4.50$; $J_{H5\text{–}H6'} = 2.20$); $\delta = 4.05$ (dd, 1H, $H_{6'}$, $J_{H6'\text{-}H6} = 12.30$; $J_{H6'\text{–}H5} = 2.20$); $\delta = 4.25$ (dd, 1H, H_6, $J_{H6\text{–}H6''} = 12.30$; $J_{H6\text{–}H5} = 4.50$); $\delta = 4.47$ (dd, 1H, H_2, $J_{H2\text{–}H1} = 3.71$; $J_{H2\text{–}H3} = 10.02$); $\delta = 4.87$ (d, 1H, H_1, $J_{H1\text{–}H2} = 3.71$); $\delta = 5.43$ (t, 1H, H_3).

Anal. calcd for $C_{15}H_{22}O_{10}$: C 49.72; H 6.08; found: C 49.70; H 6.07.

Methyl-4,6-*O*-benzylidene-2,3,-diacetyl-α-D-glucopyranoside (3b′). ^{1}H-NMR ($CDCl_3$): $\delta = 1.80$ (s, 3H, OAc); $\delta = 2.o5$ (s, 3H, OAc); $\delta = 3.37$ (s, 3H, OAc); $\delta = 3.56$ (t, 1H, H_4); $\delta = 3.73$ (1H, t, H_6, $J_{H6\text{–}H6'} = J_{H6\text{–}H5}$ 10.29); $\delta = 3.90$ (dt, 1H, H_5, $J_{H5\text{–}H6'} = 4.80$); $\delta = 4.30$ (dd, 1H, H_6, $J_{H6\text{–}H6'} = 10.15$; $J_{H6'\text{–}H5} = 4.80$); $\delta = 4.55$ (dd, 1H, H_2 $J_{H2\text{–}H3} = 9.74$; $J_{H2\text{–}H1} = 3.57$); $\delta = 4.85$ (d, 1H, H_1); $\delta = 5.45$ (d, 1H, H_7); $\delta = 5.55$ (t, 1H, H_3); $\delta = 7.25$–7.45 (m, 3H, Ar); $\delta = 7.80$ (d, 2H, Ar).

Anal. calcd for $C_{18}H_{22}O_8$: C 59.02; H 6.01; found: C 59.07; H 6.07.

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