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MW-assisted Er(OTf)$_3$-catalyzed mild cleavage of isopropylidene acetals in Tricky substrates

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Abstract

Erbium(III) trifluoromethane sulfonate is proposed as a very gentle Lewis acid catalyst in a MW-assisted chemoselective method for the cleavage of isopropylidene acetals in awkward substrates by using pure water as the solvent.

Keywords: Isopropylidene acetal; Erbium(III) triflate; MW-assisted synthesis; Water as solvent

The occurrence of diols in synthetic targets and in natural molecules (e.g., carbohydrates and nucleosides) has led to the development of a number of protective groups of varying stability. Cyclic isopropylidene acetals, also known as acetonides, have been used more frequently than any other protecting group for the protection of diols that being easily prepared and cleaved almost exclusively in protic and Lewis acids.[1] However, there are many occasions in which isopropylidene acetals are remarkably stable or there are other functional groups present, which cannot withstand drastic hydrolysis conditions. Typical examples of such kind of substrates are nucleosides and carbohydrate building blocks, where normal acidic catalysts for deprotection of acetonide can also hydrolyse acid-sensitive linkages.[1,2] For this purpose, a rapid increment in the use of mild Lewis acid catalysts has been registered[3] and some triflate derivatives were proposed as reagents in the very gentle deprotection procedures of acetals.[4] However, a mild method to deprotect stubborn isopropylidene acetals in tricky substrates was never reported.

As part of our efforts to develop new catalytic methods for valuable protection/deprotection steps of various functional groups,[5] we have already reported the use of Ce(III) and Er(III) trifluoromethane sulfonates as mild and efficient cleaving agents for acetals and ketals.[4a,b] Unfortunately, only low yield or no reaction was registered when both methods were applied to a particularly stable isopropylidene groups such as 1,2:5,6-diacetone glucofuranose **1** or problematic molecules like 2′,3′-*O*-isopropylidene nucleosides (Table 1, entries 1–4). Nevertheless, raising reaction temperature up to 60 °C permitted the quantitative isopropylidene cleavage in substrate **2** in only 45 min (Table 1, entry 5), but the application of this modified protocol still gave only partial results on different challenging substrates such as 2′,3′-*O*-isopropylideneadenosine **3**, 2,3-*O*-isopropylidene-D-ribono-1,4-lactone **4**, and 2,3-*O*-isopropylidene-D-erythronolactone **5** (Table 1, entries 6–8). In fact, only in the case of 2,3-*O*-isopropylidene-D-ribono-1,4-lactone **4**, the acetonide cleavage was completed very quickly in 30 min (Table 1, entry 7). No improvement in yield was registered when the amount of catalyst was raised up to 10 mol % (Table 1, entry 9), but some progresses were obtained when, in an attempt to improve the solubility of these substrates, the reactions were conducted

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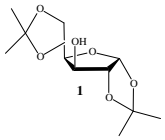
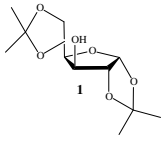
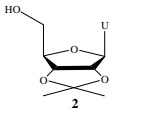
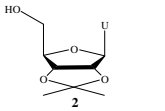
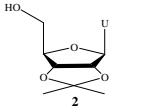
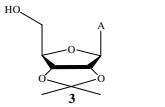
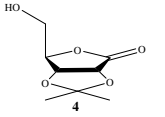
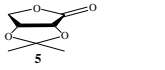
Table 1
Isopropylidene cleavage by means of Ce(III) and Er(III) triflate

Entry	Substrate	Catalyst (mol %)	Solvent	*t* (min)	Yield (%)
1		$Ce(OTf)_3$ (30)	CH_3NO_2	180	99[a]
2		$Er(OTf)_3$ (1)	CH_3NO_2	180	78[b]
3		$Ce(OTf)_3$ (30)	CH_3NO_2	180	28
4		Er(OTf) (1)	CH_3NO_2	180	48
5		Er(OTf) (1)	CH_3NO_2	45	>99[c]
6		Er(OTf) (1)	CH_3NO_2	180	15
7		Er(OTf) (1)	CH_3NO_2	30	>99
8		Er(OTf) (1)	CH_3NO_2	180	18
9	3	$Er(OTf)_3$ (10)	CH_3NO_2	180	20
10	3	$Er(OTf)_3$ (10)	CH_3CN	180	48[c]
11	5	$Er(OTf)_3$ (10)	CH_3CN	180	42[d]
12	3	$Er(OTf)_3$ (10)	H_2O	180	57
13	5	$Er(OTf)_3$ (10)	H_2O	180	53

[a] After 4 days, the 1,2-*O*-isopropylidene-D-glucopyranoside is still the only product formed.
[b] After 7 days, using 30 mol % of catalyst, only 25% of D-glucose was collected.
[c] Reaction performed at 60 °C.
[d] Higher temperatures did not improve the yield of product.

in water-saturated acetonitrile (Table 1, entries 10 and 11), and ultimately, the best conditions to accomplish the isopropylidene cleavage were experienced when the reaction was performed in simple water at 60 °C (Table 1, entries 12 and 13).

Nevertheless, on the basis of the preliminary opposite results reported in Table 1, it is evident that the traditional way to use Lewis acid catalyst will hardly be able to provide the isopropylidene cleavage under smooth conditions and in satisfactory yields, at least for the more stubborn substrates.

In last years, the use of microwave energy to heat reaction mixtures in organic synthesis is receiving increasing attention, not only since microwave heating is able to reduce chemical reaction times from hours to minutes, but also for its ability to reduce side reactions, increase yields, and improve reproducibility.[6]

Very recently, we reported a simple and efficient MW-assisted hydrolysis of acetals and ketals in simple deionized water and in extraordinarily short time.[7] Although, several different aliphatic as well as aromatic substrates were successfully treated, still some isopropylidene derivatives showed to be resistant in that experimental conditions. Nevertheless, such good preliminary results push us to test the applicability of this technique to develop an efficient and mild method for isopropylidene cleavage in resistant and/or multifunctional substrates by using the previously reported Er(III) trifluoromethanesulfonate.

First, we tested the method on diacetone glucofuranose **1** that contains in 1,2-position one of the most obstinate isopropylidene protecting group which we were not able to completely remove in our previous reports[4a,b] and is usually cleaved under very drastic conditions.[8] The double isopropylidene cleavage was first attempted in water-saturated nitromethane by using $Er(OTf)_3$ 1 mol % as well as catalyst in a teflon reaction vessel of a Synthos 3000 microwave synthesizer and stirred at 110 °C for 30 min under microwave irradiation (1000 W applying temperature control regulate irradiation intensity).

In this case a good yield of completely deprotected product was collected and almost the same result was registered performing the removal in water-saturated acetonitrile (Table 2, entry 1), but quantitative double isopropylidene cleavage was accomplished in only 15 min when the reaction was carried out in simple pure water (Table 2, entry 1). This astonishing result drove us toward adopting pure water as the solvent for the other substrates as well. So, the deprotection of 2′,3′-*O*-isopropylideneuridine **2** was completed in only 5 min (Table 2, entry 2), but for the most resistant 2′,3′-*O*-isopropylideneadenosine **3** only 70% of cleavage was registered by using 1 mol % of catalyst and satisfactory yield of deprotected adenosine was obtained by increasing up to 5 mol % the amount of $Er(OTf)_3$ (Table 2, entry 3). Noteworthy, no isopropylidene cleavage was registered performing this reaction in the same experimental conditions, but using conventional heating system [refluxing water, 5 mol % the amount of $Er(OTf)_3$] it was registered. Again, extremely fast was the complete removal of 2,3-*O*-isopropylidene-D-ribono-1,4-lactone **4** and 5,6-*O*-isopropylidene-L-ascorbic acid **6** when only 5 min were sufficient to complete the reaction (Table 1, entries 4 and 6). The use of the $Er(OTf)_3$ as Lewis acid catalyst in MW-assisted protocol showed its helpfulness in another case of obstinate acetonide removal when the complete cleavage of 2,3-*O*-isopropylidene-D-erythronolactone **5** was

Table 2
MW-assisted isopropylidene cleavage by means of Er(III) triflate in water

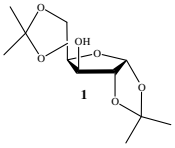
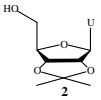
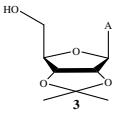
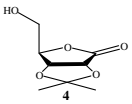
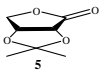
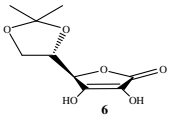
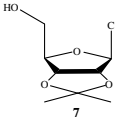
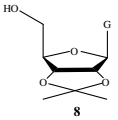
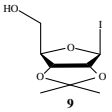
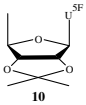
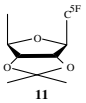
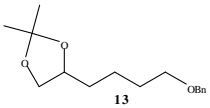
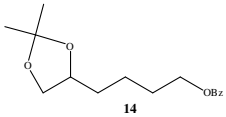
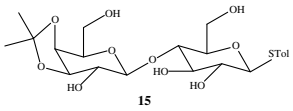
Entry	Substrate	Catalyst (mol %)	*t* (min)	Yield[a,b] (%)
1		1	30	78[c]
		1	30	80[d]
		1	15	>99
2		1	5	>99
3		1	30	70
		5	30	88
4		1	5	>99
5		5	30	>99
6		1	5	>99
7		5	30	93
8		5	30	85
9		5	30	86
10		1	5	>99
11		5	30	84
12		1	15	94
13		1	10	>99

Table 2 (*continued*)

Entry	Substrate	Catalyst (mol %)	*t* (min)	Yield[a,b] (%)
14		1	10	>99
15		5	20	88

[a] All products were purified by chromatographic column and identified by comparison of their ^{1}H and ^{13}C NMR spectral data with those of authentic compounds and the literature reported data.
[b] For hydrosoluble products the yield was determined by HPLC using the standard addition method.
[c] The reaction was performed in water saturated nitromethane.
[d] The reaction was performed in water-saturated acetonitrile.

performed in only 30 min (Table 2, entry 5), much milder than the harsh conditions previously reported for similar substrates.[9] More difficult was the cleavage of acetonide group from the three nucleosides 2′,3′-*O*-isopropylidenecytidine **7**, 2′,3′-*O*- isopropylideneguanosine **8**, and 2′,3′-*O*-isopropylideneinosine **9**, where higher amounts of catalyst were needed to collect satisfactory yields of deprotected nucleosides (Table 2, entries 7–9). Deoxynucleosides are interesting medicinal agents, since such material cannot be phosphorylated and incorporated into nucleic acids offering thus the possibility to reduce toxicity and increase specificity.[10] 5′-Deoxy-2′,3′-*O*-isopropylidene-5-fluorouridine **10**, 5′-deoxy-2′,3′-*O*-isopropylidene-5-fluorocytidine **11**, and 1-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-lyxofuranosyl)-5-fluorouridine **12** are considered strategic intermediates in some important synthetic pathways to furnish nucleoside analogues.

The present MW-assisted $Er(OTf)_3$-catalyzed mild method provided acetonide cleavage in these substrates in very efficient way, as shown in Table 2, entries 10–12. The usefulness of the present method was further explored and some other multifunctional substrates were submitted to the action of $Er(OTf)_3$ in water under MW-assistance. Recently, the selective cleavage of 1,2-*O*,-isopropylidene-6-*O*-benzylhexane-1,2,6-triol **13** and 1,2-*O*-isopropylidene-6-*O*-benzoylhexane-1,2,6-triol **14** was reported to have been accomplished in 3 h and 86% and 78% of yields, respectively, using several equivalents of $ZnBr_2$ in dichloromethane.[11] Remarkably, in our system, the same molecules reported the complete acetonide removal in only 10 min (Tabel 2 entries 13 and 14). Since the wide application of isopropylidene protecting group in the synthesis of awkward carbohydrates, we tested the present protocol in the deprotection of the acetonide system in the 3′,4′-*O,O*-isopropylidene-4-methyl phenyl (β-D-galactopyranosyl)-(1→4)-1-thio-β-D-glucopyranoside **15** which was recently reported to happen at rt, but in 17 h by means of

20 mol % vanadyl triflate as the catalyst.[12] Still surprisingly, the cleavage of the acetal accomplished in only 20 min registered a comparable yield to that reported in the above quoted reference (Table 2, entry 15).

The MW-assisted $Er(OTf)_3$ catalyzed isopropylidene cleavage protocol can be considered a tangible improvement with respect to the other existing mild methods that showed to be incapable of removing the acetonide protecting group from tricky substrates and/or very resistant position. $Er(OTf)_3$ is easy to handle and is one of the cheapest commercially available lanthanoid triflate derivatives. It is used in true catalytic amounts, all reactions run smoothly in very short time, and almost under neutral conditions; moreover, the process can really be considered 'green' since it is performed in pure water.[13]

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13. *Typical procedure*: ^1H spectra were recorded with a Bruker WM 300 instrument, at 300 MHz. Samples were dissolved in $CDCl_3$, CD_3OD, $(CD_3)CO$, or DMSO-d_6. 'Chemical shifts' are given in parts per million (ppm) from tetramethylsilane as the internal, coupling constants (J) are given in Hertz. All the chemicals were purchased from commercial sources besides the protected acetals **10–15**, synthesized according to trivial literature methods.[9–11] Compound **2** (100 mg, 0.352 mmol) was suspended in water (6.0 ml) containing 1 mol % of $Er(OTf)_3$ in the teflon reaction vessel of a Synthos 3000 microwave synthesizer and the teflon tube tapped and stirred at 120 °C for 5 min under MW irradiation (1000 W). After 5 min, the deprotection was completed and the yield was determined by HPLC using the standard addition method. The evaporation of water solution furnished the crude product, which could be purified by flash-chromatography.