

Er(OTf)₃ as a Mild Cleaving Agents for Acetals and Ketals

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Received 17 December 2003

Abstract: Er(OTf)₃ is proposed as a very gentle Lewis acid catalyst in a chemoselective method for the cleavage of alkyl and cyclic acetals and ketals at room temperature in wet nitromethane is presented.

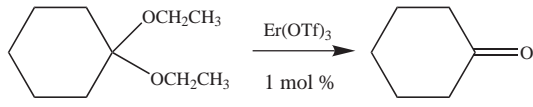
Key words: erbium(III) triflate, Lewis acid catalyst, acetals, ketals

The principles of green chemistry can guide the chemists to waste minimization in fine chemical processes through the substitution of classical organic syntheses employing stoichiometric amounts of inorganic reagents with cleaner, catalytic alternatives.¹ An important part of our efforts toward more environmentally friendly chemistry is aimed at developing new catalytic reagents for valuable protection/deprotection steps of functional groups.² Acetals and ketals are frequently used to protect carbonyl function during complex synthetic pathways,³ and a wide variety of methods using Lewis acids have been developed for their deprotection in mild conditions. In recent years the use of mild Lewis acid catalysis has increased very quickly⁴ and some lanthanide derivatives were proposed as catalysts in the very gentle deprotection procedures of acetals and ketals.^{2c,5} It is worth noting that many lanthanide triflates were efficient for this purpose, showing a regular variation of their properties along the series which can be tuned through a proper choice of the cation. Kobayashi et al.⁶ suggested a correlation between the catalytic activity of a metal cation and two kinds of constants: hydrolysis constants (K_h) and exchange rate constants for substitution of inner sphere water ligand (WERC). The metals, which exhibited good catalytic activity in screening experiments had pK_h values in the range 4–10 and WERC values greater than $3.2 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$. More recently, the relative Lewis acidity of rare earth metal triflates was evaluated based on their competitive ligand dissociation from complexes using tandem mass spectrometry.⁷ In this last study Er(III) resulted in one of the most active lanthanoid (III) derivatives, and in addition, its K_h and WERC values are respectively 7.9 and 1.4×10^8 perfectly in accordance with Kobayashi findings. Nevertheless, erbium(III) triflate has been inexplicably neglected despite the fact that it was used with satisfactory results as Lewis acid catalyst in several reactions.^{3,8} Thus, we decided to

explore the activity of Er(OTf)₃ as a Lewis acid catalyst in the deprotection reaction of ketals and acetals.

We preliminarily tested the catalytic activity of Er(OTf)₃ in the deprotection of 1,1-diethoxy cyclohexane as reference substrate using Er(OTf)₃ in 1 mol% at room temperature in different solvents. Er(OTf)₃ acts more efficiently in polar solvents such as CH₃NO₂ and CH₃CN saturated with water. Less satisfactory results were obtained in wet THF, diethyl ether, chloroform, and dichloromethane (Table 1). Furthermore, only 80% of deprotected substrate was recovered after an hour of reaction in wet CH₃NO₂ using only 0.1 mol% of catalyst. The water seems to be an essential element in the reaction pathway, and only very low yields of deprotected product were obtained when dry solvents were used (Table 1).

Table 1 Deprotection of 1,1-Diethoxy Cyclohexanone by Using Er(OTf)₃ in Various Wet or Dry solvents



Solvent	Time	Yield (%)
CH ₂ Cl ₂	1 d	64
CHCl ₃	1 d	60
Et ₂ O	90 min	37
THF	90 min	30
CH ₃ CN	1 d	38
CH ₃ CN wet	240 min	>99
CH ₃ NO ₂	1 d	45
CH ₃ NO ₂ wet	30 min	>99

Based on results reported in Table 1, we adopted a simple experimental procedure that involves stirring the solution of acetal or ketal substrates in nitromethane saturated with water in the presence of Er(OTf)₃.⁹

Dialkyl acetals and ketals derived from aromatic as well as aliphatic carbonyl compounds underwent smooth deprotection at room temperature without significant differences (entries 1–6 and 11, Table 2). No substantial differences in reactivity between dimethyl and diethyl ketals were registered, and cyclohexanone dimethyl and diethyl

ketals were both removed very quickly (entries 1 and 2, Table 2).

Cyclic acetals and ketals required prolonged reaction times to be quantitatively deprotected. So 2-phenyl-1,3-dioxolane is deprotected in 12 hours, meanwhile its parent derivative, benzaldehyde dimethylacetal gave the corresponding aldehyde in only 1 hour (entries 3 and 7, Table 2). The current method is compatible with the presence of other functional groups on the substrates such as triple bond, hydroxyl and carbonyl groups (entries 4, 6, and 16; Table 2). In the case of heptanal dimethyl acetal (entry 5, Table 2), it was noted that after a prolonged reaction time the yield of deprotected product fell to only 60%.

The cleavage of cyclic acetals and ketals of aromatic carbonyl compounds was showed to be strongly dependent on the presence of electron-withdrawing groups on the aromatic ring. In fact, it was possible to obtain quantitative deprotection of 2-(chlorophenyl)1,3-dioxolane (entry 8, Table 2), by raising the amount of Er(OTf)₃ to 5 mol%. Also no cleavage was observed for 2-(4-nitrophenyl)-1,3-dioxolane even after a very long reaction time and using a higher amount of catalyst (entry 9, Table 2). However, 2-(4-nitrophenyl)-2-methyl-1,3-dioxolane (entry 13, Table 2) was completely deprotected using 30 mol% of catalyst after 4 days, confirming the trend in which the aromatic cyclic ketals are more labile than the corresponding acetals (entries 7–9 and 10, 12, 13; Table 2). Er(OTf)₃ showed its extraordinary activity also in the case of diacetone D-glucose. Diacetone-D-glucose was converted exclusively to 1,2-isopropylidene-D-glucose with good yield after 3 hours using only 1 mol% of catalyst meanwhile, 25% of D-glucose was obtained after prolonged reaction time using higher percentage of Er(OTf)₃ (entry 14, Table 2).

Moreover, this method may be proposed to selectively deprotect acetals and ketals in presence of some other protecting groups (Ac, Bn, *p*-MeOBn, TBDMS) such as is shown for differently protected 2,2-dimethoxycyclohexanol (entries 16–19, Table 2).

Table 2 Deprotection of Acetals and Ketals in Wet CH₃NO₂ Using Er(OTf)₃

Entry	Substrate	Er(OTf) ₃ mol (%)	Time (h)	Yield (%)
1		1	0.3	>99
2		1	0.4	>99
3		1	0.5	>99
4		1	1.5	>99

Table 2 Deprotection of Acetals and Ketals in Wet CH₃NO₂ Using Er(OTf)₃ (continued)

Entry	Substrate	Er(OTf) ₃ mol (%)	Time (h)	Yield (%)
5		1	1	90
6		1	6	95
7		1	12	95
8		1 5	20 8	76 97
9		5 30	148 148	<1 <1
10		1	1	93
11		1	5	>99
12		1	120	95
13		5 30	148 96	43 94
14		1 30	3 168	78 ^a 68 ^b
15		1	0.5	>99
16		1 5	27 4	94 >99
17		1	2	>99
18		1	2.5	>99
19		1	3	>99

^a The 1,2-*O*-isopropylidene-D-glucopyranoside is the only product formed.

^b 25% of D-glucose was also collected.

Er(OTf)₃ can be used several times without significant loss of activity. After work-up, the aqueous phase can be evaporated under reduced pressure to furnish Er(III) salt which can be reused after drying overnight over P₂O₅.

Er(OTf)₃ has been proven to be a very versatile agent for deprotection of acetals and ketals under almost neutral conditions; a 0.1 M solution of Er(OTf)₃ in water is only weakly acidic (pH ca. 5.9), and the aqueous layer from workup was less acidic (pH ca. 6.6). Furthermore, the use of Er(OTf)₃ as a Lewis acid catalyst in the deprotection of acetals and ketals is, also an improvement with respect to the use of Ce(OTf)₃ that we recently reported.^{2c} Er(OTf)₃ is much more active than analogous cerium (III) derivative and amounts 6–50 times smaller are sufficient to hydrolyse the same substrates. Finally, Er(OTf)₃ is non toxic and commercially available at a lower price than other active lanthanide triflates;¹⁰ it presents still some other advantages in terms of many green chemistry principles: it is of general use in the cleavage of dialkyl as well as cyclic acetals and ketals giving very high yields of carbonyl compounds with good selectivity and very smooth reaction conditions, only catalytic amounts of promoter are required, the reactions are conducted at room temperature, and it is easy to recover and reuse the catalyst.

Deprotection with Er(OTf)₃; Typical Procedure

A solution of 1,1-diethoxycyclohexane (172.3 mg, 1.0 mmol) and Er(OTf)₃ (6.14 mg, 0.01 mmol) in CH₃NO₂ saturated with water (20 mL) was stirred at r.t. After 30 min, the solvent was removed under reduced pressure and the residue was extracted with Et₂O. The organic layer was washed with water and dried over anhyd. Na₂SO₄. The yield of cyclohexanone was determined by GC-MS using the standard addition method (>99%). All compounds reported in Table 2 were isolated by flash chromatography and their full NMR and IR data were compared with those of a pure sample.

References

- (1) (a) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford Science Publications: Oxford, **1998**. (b) Collins, T. C. *Green Chemistry: Frontiers in Chemical Synthesis and Processes*; Oxford University Press: Oxford, **1998**. (c) Tundo, P.; Anastas, P.; St Clair Black, D.; Breen, J.; Collins, T.; Memoli, S.; Miyamoto, J.; Polyakoff, M.; Tumas, W. *Pure Appl. Chem.* **2000**, *72*, 1207.
- (2) (a) Bartoli, G.; Cupone, G.; Dalpozzo, R.; De Nino, A.; Maiuolo, L.; Marcantoni, E.; Procopio, A. *Synlett* **2001**, 1897. (b) Bartoli, G.; Cupone, G.; Dalpozzo, R.; De Nino, A.; Maiuolo, L.; Procopio, A.; Sambri, L.; Tagarelli, A. *Tetrahedron Lett.* **2002**, *43*, 5945. (c) Dalpozzo, R.; De Nino, A.; Maiuolo, L.; Procopio, A.; Tagarelli, A.; Sindona, G.; Bartoli, G. *J. Org. Chem.* **2002**, *67*, 9093. (d) Dalpozzo, R.; De Nino, A.; Maiuolo, L.; Procopio, A.; Nardi, M.; Bartoli, G.; Romeo, R. *Tetrahedron Lett.* **2003**, *44*, 5621.
- (3) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd Ed.; John Wiley and Sons: New York, **1999**. (b) Kocienski, P. J. *Protecting Groups*, 1st Ed.; Georg Thieme Verlag: Stuttgart, **1994**.
- (4) (a) Steel, P. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2727. (b) Kobayashi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209. (c) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem Rev.* **2002**, *102*, 2227.
- (5) (a) Marcantoni, E.; Nobili, F.; Bartoli, G.; Bosco, M.; Sambri, L. *J. Org. Chem.* **1997**, *62*, 4183. (b) Carrigan, M. D.; Sarapa, D.; Smith, R. C.; Wieland, L. C.; Mohan, R. S. *J. Org. Chem.* **2002**, *67*, 1027.
- (6) Kobayashi, S.; Nagayama, S.; Busujima, T. *J. Am. Chem. Soc.* **1998**, *120*, 8287.
- (7) Tsuruta, H.; Yamaguchi, K.; Imamoto, T. *Chem. Commun.* **1999**, 1703.
- (8) Castell, P.; Galia, M.; Serra, A.; Salla, J. M.; Ramis, X. *Polymer* **2000**, *41*, 8465.
- (9) All the chemicals were purchased from commercial sources besides the protected ketals **16–19** in Table 2, which were synthesized according to the trivial literature methods.^{2c}
- (10) Er(OTf)₃ can be purchased from Aldrich €41.00 for 5 g (0.008 mol) meanwhile, the prices of Sc(OTf)₃ and Yb(OTf)₃ sold by Aldrich are €206.4 for 5 g (0.01 mol) and €79 for 5 g (0.008 mol), respectively.