Erbium(III) Triflate as an Extremely Active Acylation Catalyst

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Abstract: Erbium(III) triflate is a powerful catalyst for the acylation of alcohols and phenols. The reaction works well for a large variety of simple and functionalized substrates by using different kinds of acidic anhydrides {Ac_2O, $(EtCO)_2O$, $[(CH_3)_3CO]_2O$, Bz_2O, and $(CF_3CO)_2O$} without isomerisation of chiral centres. Moreover, the catalyst can be easily recycled and reused without significant loss of activity.

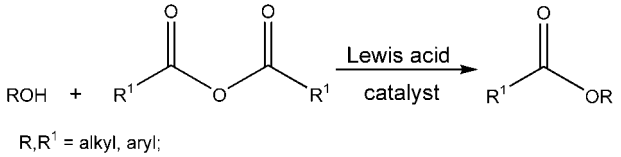
Keywords: acylation; erbium(III) triflate; homogeneous catalysis; lanthanides; Lewis acid catalysts

Introduction

The principles of green chemistry can motivate the chemists to accomplish their vital role in sustainable development by inventing, designing, and applying new chemical reagents and methods to reduce or eliminate the use and generation of hazardous substances.[1] In the last years we have directed much of our effort towards lower environmental impact chemistry, by developing new catalytic reagents for the strategic protection/deprotection steps of functional groups.[2] Acylation is one of the most important and widely used protection methods to preserve the hydroxy function during the course of multistep syntheses.[3]

Generally, acylation takes place by treatment of alcohols and phenols with acid anhydrides or acid chlorides in the presence of amines, but many other methods were proposed in the last decade.[4] More recently, metal trifluoromethanesulfonates were intensively developed as Lewis acid catalysts in the acylation protection of hydroxy groups.[2d,5]

The strong electron-withdrawing capacity of the trifluoromethanesulfonate anion enhances the Lewis acid character of the catalyst and Kobayashi et al.[6] noted a correlation between the catalytic activity and the hydrolysis constants (K_h) as well as the water-exchange rate constants (WERC) of these derivatives. In a screening test it was found that the metals which exhibit good catalytic activity had pK_h values in the range from about 4 to 10 and WERC values greater than $3.2 \times 10^6\ M^{-1}\ s^{-1}$.[6b]



Scheme 1.

The lanthanoid family possesses the interesting feature of a regular variation of these properties along the series which can be used for tuning through a proper choice of the cation. Therefore, many examples exist where rare-earth metal triflates are used as Lewis acid catalysts with efficacy varying from one reaction to another.[6c] Recently, the relative Lewis acidities of lanthanoid(III) triflates were evaluated by the use of tandem mass spectrometry, in that study erbium(III) proved to be one of the most active cations.[7] In fact its pK_h and WERC values are 7.9 and 1.4×10^8, respectively, which are perfectly in accordance with the statements of Kobayashi et al. Nevertheless, Er(III) triflate has been inexplicably neglected although some examples of its successful use in different reactions have been reported.[8]

Results and Discussion

We have already introduced the use $Er(OTf)_3$ as an efficient catalyst for the deprotection of acetals and ketals,[2f] we now report a simple and efficient method for the acylation of alcohols and phenols with different acid anhydrides catalyzed by Er(III) triflate (Scheme 1). First, we tested the catalytic activity of $Er(OTf)_3$ in the acetylation reaction of 1-octanol at room temperature in different solvents and with different mol % of catalyst using 1.5 equivalents of acetic anhydride. On the basis of our preliminary results, which are shown in Table 1,

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Table 1. Attempted acetylation of 1-octanol in various solvents.

Entry	Solvent	$Er(OTf)_3$ [mol %]	Time [min]	Yield [%]
1	CH_3CN	0.1	20	>95
2	CH_3CN	0.05	40	80
3	CH_3CN	0	90	20
4	CH_3NO_2	0.1	45	>95
5	ethylic ether	0.1	90	30
6	THF	0.1	–	35
7	CH_2Cl_2	0.1	–	40
8	$CHCl_3$	0.1	–	45
9	toluene	0.1	–	85
10	CH_3CN (not dry)	0.1	–	35
11	CH_3NO_2 (not dry)	0.1	–	30

$Er(OTf)_3$ acts more efficiently in dry polar aprotic solvents such as CH_3CN and CH_3NO_2 (entries 1 and 4, Table 1), while less satisfactory results were obtained in dry diethyl ether, THF, CH_2Cl_2, $CHCl_3$ and toluene (entries 5–9, Table 1).

The absence of water seems to be essential and only low yields of acetylated product was obtained when not-dry CH_3CN and CH_3NO_2 were used as solvents (entries 10 and 11, Table 1). $Er(OTf)_3$ was still extremely active when only 0.05 mol % of catalyst was used in the same conditions, but with less satisfactory results (entry 2, Table 1), meanwhile only 20% of acetylated product was obtained in absence of catalyst (entry 3, Table 1). 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[9] as a pale pink solid (85–90% recovered), which can be reused after drying overnight over P_2O_5. The recovered catalyst was used five times in the acetylation reaction of the 1-octanol maintaining 0.1 mol % of catalyst and the registered yields were always higher than 90%.

In order to explore the generality and the scope of erbium(III) triflate as a Lewis acid catalyst in acylation protections, the reaction was carried out on a variety of substrates using different acid anhydrides.

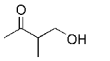
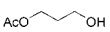
Based on the results reported in Table 1, we generally adopted a simple experimental procedure that involves stirring the solution of substrate containing the hydroxy function and acid anhydride in dry CH_3CN in the presence of only 0.1 mol % of $Er(OTf)_3$.

As shown in Table 2, not only primary (entries 1 and 22), but also secondary and tertiary alcohols and phenols underwent smooth acetylation with almost quantitative yields. No competitive dehydration was registered in the acetylation of secondary and tertiary substrates (entries 7, 27, and 31, Table 2), and only in the case of the heavy sterically hindered 2-phenylisopropanol, were a lower reaction temperature ($-10\,^{\circ}C$) and the use of acetic anhydride as solvent necessary to suppress the competitive elimination reaction (entries 28–30, Table 2).

The Ac_2O-$Er(OTf)_3$ acetylating system tolerates the presence of other functionalities on the substrates such as carbonyl and acetyl groups (entries 20 and 21, Table 2), no rearrangement took place with allylic and propargyl substrates (entries 12 and 16, Table 2), and also optically active substrates were efficiently acetylated without any loss of optical purity (entries 7 and 31, Table 2) demonstrating the mildness of this method. No selective acetylation was observed when the present method was applied for the acetylation of α-D-glucose and only less than 20% of peracetylated sugar was obtained; but an almost quantitative yield of this product (entry 33, Table 2) was collected in the presence of 0.5 mol % of catalyst when acetic anhydride was used as solvent. In spite of the fact that a 0.1 M solution of $Er(OTf)_3$ in water is only weakly acidic (pH ≈ 5.9), and the aqueous layer from the work-up in the present method was also less acidic (pH ≈ 6.6), the acid sensitive *t*-butyldimethylsilyl (TBDMS) and tetrahydropyranyl (THP) protective groups did not survive during the acetylation under these conditions and both the functions were replaced by the acetyl group to furnish the corresponding diacetate (entries 48 and 49, Table 2). The present protocol was tested also in the acetylation reaction of phenols (entries 34, 35, 39 and 44, Table 2). In all the cases nearly quantitative yields were obtained, even for a phenol as highly crowded as the 2,6-di-*t*-butyl-*p*-cresol (BHT) which required simply in increase of the percentage of catalyst up to 0.5 mol % (entry 34, Table 2), and no substantial differences in reactivity were registered on changing the electron requirements on the aromatic moiety (entries 35, 39 and 44, Table 2). Furthermore, no by-products arising from Fries rearrangement were obtained from any phenols submitted to this acetylating procedure even after prolonged reaction times.

In our previous work, we proposed the use of $Ce(OTf)_3$ as a mild Lewis acid catalyst in acetylation reactions,[2d] but we could not realize other kinds of acylation and also in the successfully reported acetylations 1.0 mol % of catalyst was necessary, while only 0.1 mol % of $Er(OTf)_3$ was sufficient to replicate these

Table 2. Acylation of alcohols using $Er(OTf)_3$ as catalyst.

Entry	Substrate	Acid anhydride (equivs.)	$Er(OTf)_3$ [mol %]	T [°C]	Time [min]	Yield [%][a, b]
1	1-octanol	Ac_2O (1.5)	0.1	r.t	20	> 95
2	”	$(EtCO)_2O$ (1.5)	”	”	120	”
3	”	$(EtCO)_2O$ (1.5)	0.5	”	15	”
4	”	(t-BuCO)$_2$O (1.5)	”	”	25	”
5	”	Bz_2O (3.0)	”	50	30	”
6	”	$(CF_3CO)_2O$ (1.5)	”	r.t.	150	”
7	”	Ac_2O (1.5)	0.1	”	50	”
8	(+)-menthol	$(EtCO)_2O$ (1.5)	0.5	r.t.	30	”
9	”	(t-BuCO)$_2$O (1.5)	”	”	35	”
10	”	Bz_2O (3.0)	”	50	100	”
11	”	$(CF_3CO)_2O$ (1.5)	”	r.t.	180	”
12	$CH_3CH{=}{=}CHCH_2OH$	Ac_2O (1.5)	0.1	”	30	”
13	”	$(EtCO)_2O$ (1.5)	0.5	”	40	”
14	”	(t-BuCO)$_2$O (1.5)	”	”	60	”
15	”	Bz_2O (3.0)	”	50	120	”
16	$HC{\equiv}CCH_2OH$	Ac_2O (1.5)	0.1	r.t	30	”
17	”	$(EtCO)_2O$ (1.5)	0.5	”	25	”
18	”	(t-BuCO)$_2$O (1.5)	”	”	35	”
19	”	Bz_2O (3.0)	”	50	”	”
20		Ac_2O (1.5)	”	r.t.	25	”
21		Ac_2O (1.5)	”	”	20	”
22	$PhCH_2OH$	Ac_2O (1.5)	0.1	”	25	”
23	”	$(EtCO)_2O$ (1.5)	0.5	”	15	”
24	”	(t-BuCO)$_2$O (1.5)	”	”	25	”
25	”	Bz_2O (3.0)	”	50	50	”
26	”	$(CF_3CO)_2O$ (1.5)	”	r.t.	10	”
27	t-BuOH	Ac_2O (1.5)	0.1	”	30	”
28	$Ph{-}{-}C(CH_3)_2OH$	Ac_2O (1.5)	0.5	”	120	0[c]
29	”	”	–	– 10	”	”[c]
30	”	Ac_2O as solvent	–	”	”	> 95
31	cholesterol	Ac_2O (1.5)	0.1	r.t	”	”
32	”	$(CF_3CO)_2O$ (1.5)	0.5	”	240	”
33	α-D-glucose	Ac_2O as solvent	”	r.t	100	”[d]
34	BHT	Ac_2O (1.5)	”	50	60	”
35	4-MeO-C_6H_4-OH	”	0.1	r.t	20	”
36	”	$(EtCO)_2O$ (1.5)	0.5	”	15	”
37	”	(t-BuCO)$_2$O (1.5)	”	”	20	”
38	”	Bz_2O (3.0)	”	50	30	”
39	4-Me-C_6H_4-OH	Ac_2O (1.5)	0.1	r.t.	25	”
40	”	$(EtCO)_2O$ (1.5)	0.5	”	20	”
41	”	(t-BuCO)$_2$O (1.5)	”	”	25	”
42	”	Bz_2O (3.0)	”	50	30	”
43	”	$(CF_3CO)_2O$ (1.5)	”	r.t.	480	”
44	4-NO_2-C_6H_4-OH	Ac_2O (1.5)	0.1	”	25	”
45	”	$(EtCO)_2O$ (1.5)	0.5	”	10	”
46	”	(t-BuCO)$_2$O (1.5)	”	”	15	”
47	”	Bz_2O (3.0)	”	50	”	”
48	$HO(CH_2)_4OTBDMS$	Ac_2O (1.5)	0.1	r.t.	20	”[d]
49	$HO(CH_2)_4OTHP$	”	”	”	30	”[d]

[a] Unless otherwise specified, all products were identified by comparison of their EI-MS and ^{1}H NMR data with those of authentic compounds and data reported in the literature.[10]

[b] Unless otherwise specified, isolated yield by flash column chromatography on silica gel is reported.

[c] 1,4-Butandiol diacetate was the only product obtained.

[d] Only peracetate derivatives were obtained.

results. In view of this much higher activity, we decided to explore the application of the $Er(OTf)_3$-acid anhydride protocol to other acylations. When 1-octanol in dry CH_3CN was treated with 1.5 equivs. of propionic anhydride in the presence of 0.1 mol % of erbium(III) trifluoromethanesulfonate the acylation proceeded smoothly within 3 h with almost quantitative yield (entry 2, Table 2), but the reaction was completed in only 15 minutes when the amount of catalyst was raised to 0.5 mol % (entry 3, Table 2).

Surprisingly, the same result was reached when this modified protocol was applied to introduce the pivalate function, which is one of the most stubborn ester protecting groups due to its steric hindrance, and a quantitative yield of 1-octyl pivalate was obtained in only 25 minutes (entry 4, Table 2).

To explore the generality of the method, structurally different alcohols and phenols were submitted to the action of the Er(III) triflate at 0.5 mol % in 1.5 equivalents of propionic or pivaloyl anhydrides in dry acetonitrile. No evident differences of reactivity were registered between primary (entries 3, 4, 21, and 22, Table 2) and secondary alcohols (entries 8, and 9, Table 2), or even between the two aliphatic anhydrides, and, again, no rearrangement took place for allylic and propargyl substrates (entries 13, 14, 17 and 18, Table 2).

In order to extend the scope of this catalyst further, the benzoylation of alcohols and phenols with the less reactive benzoic anhydride was also investigated. The benzoylation of 1-octanol was relatively slow in comparison with the acylation using other aliphatic carboxylic anhydrides, and only a 38% yield was obtained also after prolonged reaction time when the usual experimental protocol was applied. Better results were reached when the reaction temperature was raised to 50 °C and 3.0 equivalents of benzoic anhydride were used in the presence of 0.5 mol % of $Er(OTf)_3$ (entry 5, Table 2). The present modified method permitted to easily obtain benzoylated derivatives in almost quantitative yields, not only from primary substrates (entries 5 and 25, Table 2), but also from secondary ones (entry 10, Table 2). Furthermore, also in the case of benzoylation, no rearrangements were noted for allylic and propargyl substrates (entries 15 and 19, Table 2).

The $Er(OTf)_3$-benzoyl anhydride protocol was applied with the same successful results in the benzoylation reaction of substituted phenols and the 4-methoxy-, 4-methyl-, and 4-nitrophenol benzoylated derivatives were all obtained in excellent yields without evident differences in reactivity (entries 38, 42, and 47, Table 2). Notably, the reported methods to form acyl esters by using Lewis acid catalysts fail to mention the formation of trifluoroacetate derivatives and some of them explicitly declare failures in this attempt.[4y] Thus, we finally extended the $Er(OTf)_3$-anhydride protocol to preparation of trifluoroacetate esters of alcohols and phenols. Both primary and secondary alcohols (entries 6, 11, 26 and 32, Table 2) as well as *p*-cresol (entry 43, Table 2) were trifluoroacetylated in almost quantitative yields at room temperature in very short reaction times by using 1.5 equivalents of trifluoroacetic anhydride in dry acetonitrile in the presence of 0.5 mol % of $Er(OTf)_3$.

Conclusion

The erbium(III) trifluoromethanesulfonate/acyl anhydrides protocol can be considered a tangible improvement with respect to the other existing methods which involve the use of triflate derivatives as catalysts in the preparation of acyl esters of alcohols and phenols, especially with respect to our cerium(III) triflate method.[2d]

In fact, $Sc(OTf)_3$, which is much more expensive,[10] gave results quite similar to $Er(OTf)_3$,[5c] but by using higher mol % of catalyst for acylations different from acetylation and mixed anhydrides for propionic, pivalic and trifluoroacetyl derivatives.

$Er(OTf)_3$ is easy to handle and is one of the cheapest commercially available lanthanoid triflate derivatives. It is used in really catalytic amounts in the presence of a very low excess of acyl anhydride. All acylation reactions run smoothly at room temperature, except for the most demanding benzoylation, and almost under neutral conditions. Moreover, it is possible to recover the catalyst almost quantitatively and without a significant loss of activity. Finally, to the best of our knowledge $Er(OTf)_3$ is the first triflate derivative proposed as a Lewis acid catalyst in acylation reactions that shows such a wide applicability.

Experimental Section

Typical Procedures

In a model reaction 1-octanol (500 mg, 3.85 mmol) was added to 1.0 mL of a solution of Ac_2O (0.590 g, 5.78 mmol) and $Er(OTf)_3$ (2.37 mg, 0.00385 mmol) in 5.0 mL of dry acetonitrile, the acetylation was complete in 20 min under these conditions at room temperature affording a 98% yield.

Acylations with propionic and pivalic anhydrides were still conducted at room temperature but using 0.5 mol %.

Acylation with benzoic anhydride was carried out at 50 °C by using 0.5 mol % of $Er(OTf)_3$ and 3.0 equivalents of Bz_2O.

Especially after pivalation and benzoylation the purification of products requires a tedious work-up to separate the esters from the remaining acyl anhydride. Therefore, methanol was added at the end of the acylation reaction in order to convert the remaining acyl anhydride to the corresponding methyl ester and after that, the product was obtained in sufficient purity by simple filtration through a thin pad of silica gel with petroleum ether (60–80 °C).

All known products were identified by comparison of their EI-MS and ^1H NMR data with those of authentic compounds,

when commercially available, and data reported in the literature.[11]

EI-MS and ^{1}H-NMR data of unknown compounds are listed below.

Table 2, Entry 11: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.68 (m, 1H, *J* = 10.86, 4.38 Hz), 1.94–2.03 (m, 1H), 1.80–1.93 (m, 1H), 1.59–1.70 (m, 2H), 1.31–1.42 (m, 2H), 1.01–1.10 (m, 2H), 0.88–0.97 (m, 6H), 0.76 (d, 3H, *J* = 6.96 Hz);GC-MS: *m/z* = 183 $[M-CF_3]^+$ (1), 138 [alcohol]$^+$ (64), 95 $[M-(CH_3)_2CH-CH_3-CF_3CO_2H]^+$ (100), 69 $[CF_3]^+$ (15); anal. calcd. for $C_{12}H_{19}F_3O_2$: C 57.13, H 7.59, F 22.59, O 12,69; found: C 57.20, H 7.60.

Table 2, Entry 18: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.63 (d, 2H, *J* = 2.28 Hz), 2.40 (t, 1H), 1.18 (s, 9H); GC-MS: *m/z* = 85 $[(CH_3)_3CCO]^+$ (16), 57 $[(CH_3)_3C]^+$ (100), 55 $[M-(CH_3)_3CCO]^+$ (5); anal. calcd. for $C_7H_{12}O_2$: C 65.60, H 9.44, O 24.96; found: C 65.55, H 9.45.

Table 2, Entry 32: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.43 (m, 1H), 4.823 (m, 1H), 2.36–2.50 (m, 2H, CH_2), 2.01–2.05 (m, 2H, CH_2), 1.80–1.95 (m, 6H, $3CH_2$), 1.65–1.74 (m, 2H CH_2), 1.40–1.60 (m, 8H, $3CH_2$ and 2CH), 1.06–1.25 (m, 8H, $2CH_2$ and 4CH), 1.04 (s, 3H, CH_3), 0.916 (d, 3H, *J* = 6.531 Hz, CH_3), 0.876 (d, 3H, *J* = 1.35 Hz, CH_3), 0.854 (d, 3H, *J* = 1.357 Hz, CH_3), 0.68 (s, 3H, CH_3); GC-MS: *m/z* = 368 $[M-CF_3COO]^+$ (100), 255 $[M-CF_3CO_2H-(CH_3)_2CH(CH_2)_3CHCH_3]^+$ (43), 69 $[CF_3]^+$ (41); anal. calcd. for $C_{29}H_{45}F_3O_2$: C 72.17, H 9.40, F 11.80, O 6.63; found: C 72.10, H 9.40.

Table 2, Entry 42: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10–8.40 (m, 2H, Ar), 7.45–7.65 (m, 3H, Ar), 7.05–7.25 (m, 3H, Ar), 2.37 (s, 3H, *J* = 0.21 Hz, CH_3); GC-MS: *m/z* = 212 $[M]^+$ (9), 105 $[PhCO]^+$ (100), 77 $[C_6H_5]^+$ (40); anal. calcd. for $C_{14}H_{12}O_2$: C 79.23, H 5.70, O 15.07; found: C 79.30, H 5.65.

Table 2, Entry 45: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.23–8.32 (m, 2H, Ar), 7.24–7.33 (m, 2H, Ar), 2.65 (q, 2H, *J* = 7.51 Hz, CH_2), 1.29 (t, 3H, *J* = 7.51 Hz, CH_3); GC-MS: *m/z* = 195 $[M]^+$ (3), 139 [alcohol]$^+$ (2), 57 $[CH_3CH_2CO]^+$ (100); anal. calcd. for $C_9H_9NO_4$: C 55.38, H 4.65, N 7.18, O 32.79; found: C 55.30, H 4.65, N 7.20.

Table 2, Entry 46: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.22–8.30 (m, 2H, Ar), 7.21–7.28 (m, 2H, Ar), 1.37 [s, 9H, $(CH_3)_3C$], GC-MS: *m/z* = 223 $[M]^+$ (1), 85 $[(CH_3)_3CCO]^+$ (24), 57 $[(CH_3)_3C]^+$ (100); anal. calcd. for $C_{11}H_{13}NO_4$: C 59.19, H 5.83, N 6.28, O 28.70; found: C 59.12, H 5.80, N 6.24.

Table 2, Entry 47: ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.34 (d, 2H, *J* = 8.15 Hz, $H_{B1}+H_{B1'}$), 8.21 (d, 2H, *J* = 8.15 Hz, $H_A+H_{A'}$), 7.69 (t, 2H, *J* = 7.52 Hz, $H_{A1}+H_{A1'}$), 7.55 (t, 2H, *J* = 7.52 Hz, $H_{B2}+H_{B2'}$) 7.43 (d, 2H, *J* = 7.52 Hz, H_{C2}); GC-MS: *m/z* = 243 $[M]^+$ (0.1), 105 $[M-PhCO]^+$ (100), 77 (31); anal. calcd. for $C_{13}H_9NO_4$: C 64.20, H 3.73, N 5.76, O 26.31; found: C 64.15, H 3.70, N 5.80.

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