1,2-Diacetates by epoxide ring opening promoted by erbium(III) triflate

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Dedicated to Professor Giuseppe Bartoli on his 65th birthday

Abstract
Erbium triflate is able to afford *vic*-diacetates in better yields, lower catalyst amounts and shorter times than most of the reported methods. Therefore, the present procedure represents a valuable, general and environmentally benign procedure to prepare these compounds.

Keywords: Epoxide, erbium(III) triflate, nucleophile, ring opening, Lewis acid, catalysis

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Introduction

Epoxides have been recognized among the most versatile intermediates in organic synthesis. They can be easily prepared and, due to their ring strain, which enhances their reactivity, they react with nucleophiles to highly regioselectively lead to ring-opened products.[1] Among reactions involving epoxides three are worth noting: 1,2-diol preparation, which is one of the most useful reactions and the acetylation of alcohols, which is a fundamental process, providing a cheap and efficient means for protecting hydroxy frameworks;[2] β-hydroxy ethers synthesis, since they are important precursors for the preparation of α-alkoxy ketones and acids; [3] β-amino alcohols preparation, because they are an important class of organic compounds being versatile intermediate for a vast range of biologically active natural products.[4]

Notwithstanding a wide choice of activators or promoters available for each of the above-cited transformations, many are associated with one or more drawbacks. They include the use of anhydrous solvents, moisture sensitive catalysts, expensive and/or hazardous reagents, strongly acidic conditions, extended reaction times, unsatisfactorily yields etc. Therefore, the development of simple and easily handling reagents, which are efficient and provide convenient procedures with high yields, is needed.

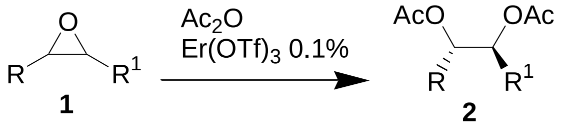
Among the reactions mentioned above, direct transformation of epoxides into 1,2-diacetates is a very important, but scarcely studied, reaction. In fact, if a plethora of methods are reported for the synthesis of β-hydroxy ethers and β-amino alcohols, only few methods lead to 1,2-diacetates from epoxides involving the use of acetic anhydride with aluminosilicate,[5] phosphorus[6] and boron[7] compounds or sulfuric acid,[8] and only two reports have a general value,[5b,6a] being the others limited in scope.

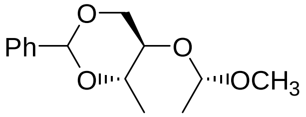
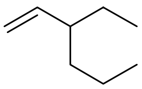
In the last years, the ongoing work in our laboratory was on the use of erbium(III) triflate as useful and environmentally friendly catalyst for many acid-catalyzed reactions.[9] It should be noted that, among lanthanide triflates, erbium salt was the most neglected, notwithstanding it appears in good agreement with Kobayashi's relationship among catalytic activity / K_h / WERC, having $pK_h = 7.9$ and WERC = 1.4×10^8.[10]

We were interested, among others, in Lewis acid catalyzed reactions of epoxides,[11] and acetylation reactions,[9a] therefore it seemed obvious to investigate the use of this reagent for the efficient conversion of epoxide into 1,2-diacetates.

Results and Discussion

Table 1. Synthesis of *vic*-diacetates from epoxides and acetic anhydride in the presence of erbium(III) triflate (0.1% mol)



Entry	Substrate	R and R^1	Time (h)	Product	Yield(%)[a]
1	**1a**		0.25	**2a**[b]	97
2	**1b**	-(CH_2)$_4$-	3	**2b**	93
3	**1c**	Bu, H	1	**2c**	>99
4	**1d**	CH_2OH, H	5	**2d**[c]	60
5	**1e**	CH_2OCH_3, H	1	**2e**	>99
6	**1f**	$(CH_2)_2CH{=}CH_2$, H	1	**2f**	91
7	**1g**		6	**2g**	73

[a] Isolated yields based on epoxides.

[b] See ref. 9c.

[c] Peracetylated product was obtained

The reactions were carried out in the presence of 0.1% mol of erbium(III) triflate as catalyst, by mixing together the epoxide and acetic anhydride. Since the only by-product is acetic acid from the excess of anhydride, these conditions are also environmentally benign. A control experiment showed that no reaction occurred in the absence of triflate. The results are collected in Table 1.

All reactions proceeded in good- to very high- yields, with the formation of only one diastereoisomer with the two acetoxy groups *anti* each other, in agreement with literature.[5-8] The stereochemistry was demonstrated by prolonging the reaction time to remove the benzylidene protection in methyl 2,3-anhydro-4,6-*O*-benzyliden-α-**D**-allopyranoside (**1a**), which was then quantitatively converted into peracetylated methyl-α-**D**-glucose. In fact, we measured a coupling constant J_{H1-H2} = 3.71 in good agreement with the value found in the ^{1}H-NMR spectrum of true peracetylated methyl α-**D** glucose.

Aromatic epoxides cannot be converted into 1,2-diacetoxy derivatives. The reaction of styrene oxide in acetic anhydride afforded a 1:1 mixture of 1,2- and 2,2-diacetoxy-1-phenylethanes, owing to the competitive epoxide rearrangement to aldehyde catalyzed by erbium triflate,[11b] followed by diacetoxy protection of the aldehyde.[12] Attempts to avoid rearrangement were unsuccessful. The reaction was carried out either in dichloromethane or with cerium(III) triflate as catalyst, leading to 13/65 and 45/56 1,2 *vs.* 2,2-diacetoxy-1-phenylethane ratios, respectively.

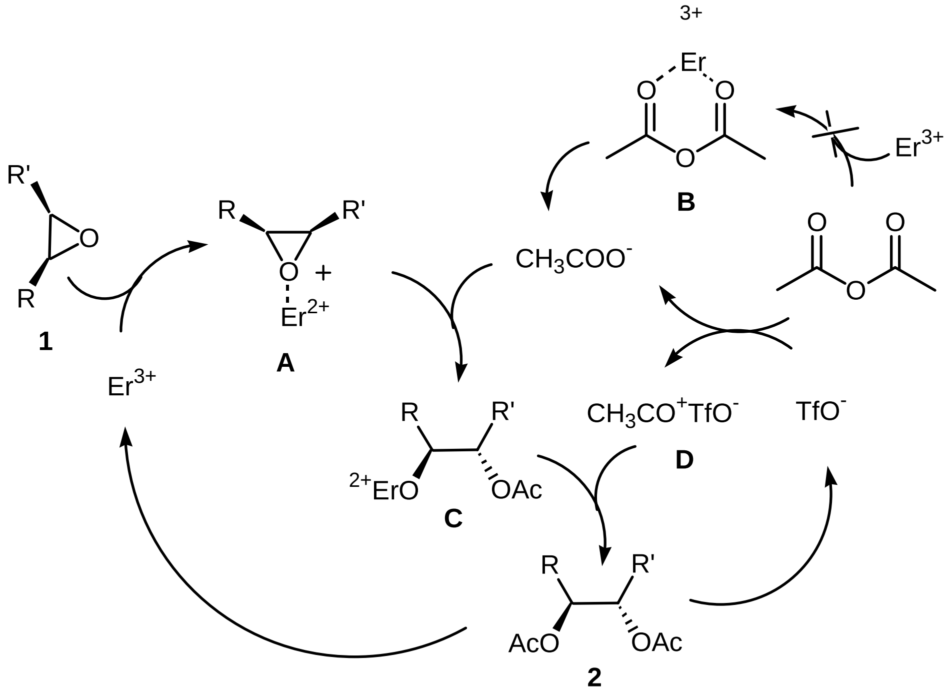
In order to show the merit of present work, the results from cyclohexene oxide (**1b**) and 1-hexene oxide (**1c**) can be compared with the catalyst amount, the reaction time, and the yields reported in the other two general protocols.[5b,6a] Table 2 shows that erbium triflate is able to afford *vic*-diacetates in better yields, lower catalyst amounts, and shorter times than the most efficient reported method.

Table 2. Comparison of the of the effect of catalyst for *vic*-diacetate synthesis

Product	Catalyst	Amount	Time	Yield (%)	Ref.
1b	$Er(OTf)_3$	0.1 %	3	93	-
	PBu_3	10%	24[a]	92	6a
	Zeolite HY	0.5 g per 10 mmol	10	85	5b
1c	$Er(OTf)_3$	0.1 %	1	>99	-
	PBu_3	10%	24[a]	96	6a
	Zeolite HY	0.5 g per 10 mmol	9.5	95	5b

[a] Reaction time is not reported. One day is the requested time for *N*-tosylaziridine ring opening

Although we never conducted a complete mechanistic investigation on the reaction, a tentative explanation is depicted in Scheme 1.



Scheme 1. Tentative mechanism for the reaction.

There are, in principle, two coordination sites for the erbium ion: the epoxide oxygen atom or the carbonyl groups of acetic anhydride, giving rise to complexes **A** and **B** respectively (Scheme 1). Both can give a catalytic loop able to reach the products. In our previous works we had evidences of coordination to both compounds.[9a,11] However, since, in aryl epoxides, the rearrangement is independent of the presence of acetic anhydride, and it occurs at a rate comparable to the ring-opening, it allows us to think that **A**, rather than **B**, is the first intermediate of the reaction. The activated epoxide ring (**A**) is then opened from the opposite side by acetate ion, which acts as a nucleophile, giving intermediate **C**. Acetate ion is released by interaction between the anhydride and triflate ion. Formation of a mixed anhydride such as **D**, which releases carboxylate salt, has already been invoked in the reaction of triflates and anhydrides.[13] Moreover, tributylphosphine is reported to activate acetic anhydride to form a salt which attacks epoxide to give the ring opened product.[6a] Finally, coupling between **C** and **D** leads to catalyst re-generation and product formation.

In a fashion of a preferential coordination to epoxide oxygen, ring opening must occur with any nucleophile. In order to confirm this hypothesis, we performed epoxide ring opening with an alcohol and an amine. Methanol and aniline were chosen as typical examples of these classes of compounds.

Actually, methanol opened cyclohexene oxide faster than acetic anhydride (1h *vs.* 3h), leading to *trans*-2-methoxycyclohexanol in almost quantitative yields. Ring opening with methanol is so fast that rearrangement of styrene oxide is prevented and also 2-phenyl-2-methoxyethanol is recovered in almost quantitative yield. Formation of this product rather than its regioisomer 1-phenyl-2-methoxyethanol, however, is not conclusive evidence of an acid-catalyzed reaction, which would prove a metal-epoxide interaction. In fact, it is known that anion can attack styrene oxide at the more substituted carbon terminus.[14] On the other hand, these findings demonstrate that anhydride cleavage is the rate-determining step of the reaction.

Finally, a further reaction between styrene oxide and aniline was performed and the expected 2-(*N*-phenylamino)-2-phenylethanol was obtained in 95% yield.

Conclusions

Erbium(III) triflate provides the first really general method of direct conversion of epoxides into 1,2-diacetates, providing a cheap, efficient, general and environmentally benign mean for protecting diol frameworks. It is able to afford *vic*-diacetates in better yields, with lower catalyst amounts and shorter times than most of the reported methods.[5-8] The present procedure does not need sophisticated equipment, and uses a non-toxic[15] and non-explosive catalyst. The catalyst can be easily and consistently recovered, and therefore there is negligible release into the environment.[16]

Finally, studies are in progress in our laboratory to extend this reaction to other nucleophiles, prompted by the preliminary results reported here with methanol and aniline.

Experimental Section

General Procedures. ^{1}H- NMR and ^{13}C-NMR spectra were recorded with a Bruker WM300 instrument, at 300 MHz and 75 MHz respectively. Reactions were monitored by a GC-MS Hewlett-Packard workstation, formed by a GC-HP 6890 (30-m HPS capillary column, 1 mL/min He as carrier gas) and by an HP 5973 mass detector. Commercial products (Aldrich or Fluka) were used without further purification.

General procedure for epoxide ring opening with acetic anhydride. A solution of epoxide (**1a-h**) (5 mmol) in acetic anhydride (1 mL) was stirred and Er(OTf)$_3$ (3 mg, 0.005 mmol, 0.1 mol.%) was added at room temperature. The reaction progress was monitored by TLC. After the appropriate time (Table 1) a 10% solution of Na2CO3 was added and the mixture was extracted with ether (2x2mL). The combined organic layers were dried (Na$_2$SO$_4$). The solvents were removed on a rotary evaporator to give the corresponding *vic*-diacetates (**2**). 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: **2a**,[9c] **2b**, **2c**, **2d,**[5b] **2e**,[17] **2f**, **2g**[18]

Reaction of cyclohexene oxide (1b) and styrene oxide with methanol. A solution of **1b** (0.98 g, 10 mmol) in methanol (2 mL) was stirred and Er(OTf)$_3$ (6 mg, 0.001 mmol, 0.1 mol.%) was added at room temperature. The reaction progress was monitored by TLC. After 1 h, a 10% solution of Na2CO3 was added and the mixture was extracted with ether (2x2mL). The combined organic layers were dried (Na_2SO_4). The solvents were removed on a rotary evaporator to give *trans*-2-methoxycyclohexanol in almost quantitative yield, which was recognized by comparison of its spectroscopic data with the literature.[19]

The reaction of styrene oxide (1.20 g, 10 mmol) was carried out under the same reaction conditions. After 0.5 h, a 10% solution of Na2CO3 was added and the mixture was extracted with ether (2x2mL). The combined organic layers were dried (Na_2SO_4). The solvents were removed on a rotary evaporator to give 2-phenyl-2-methoxyethanol in almost quantitative yield, which was recognized by comparison of its spectroscopic data with literature.[20]

Reaction of styrene oxide with aniline. The reaction of styrene oxide (1.20 g, 10 mmol) and aniline (1 mL) was stirred and $Er(OTf)_3$ (6 mg, 0.001 mmol, 0.1 mol.%) was added at room temperature. After 0.5 h, a 10% solution of Na_2CO_3 was added and the mixture was extracted with ether (2x2mL). The combined organic layers were dried (Na_2SO_4). The solvents were removed on a rotary evaporator to give 2-(*N*-phenylamino)-2-phenylethanol in 95% yield, which was recognized by comparison of its spectroscopic data with the literature.[21]

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15. LD_{50} of erbium salts is 4417 mg/Kg against 4000 mg/Kg of NaCl.
16. Scaling-up the reaction, catalyst is very likely recovered in higher yields with respect our experiments, where it is recovered more than 90%. To recover the catalyst, the work-up aqueous phase can be evaporated under reduced pressure to furnish the Er(III) salt as a pale pink solid, which can be reused after drying overnight over P_2O_5. The purity of recovered $Er(OTf)_3$ was confirmed by comparison with the IR spectrum of commercial product.
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