Synthesis of Acetonides from Epoxides Catalyzed by Erbium(III) Triflate

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Abstract: Epoxides dissolved in acetone can be converted almost quantitatively in acetonides in the presence of catalytic amounts of erbium(III) triflate. The procedure can be usefully applied to other substrates and can be extended to other ketones.

Keywords: acetonides; dioxolanes; epoxides; erbium(III) triflate; Lewis acid catalyst

Introduction

1,3-Dioxolanes are among the most commonly used protecting groups for carbonyl compounds.[1] They are generally prepared by acid-catalyzed reactions between diols and carbonyl compounds at high temperature, making them unsuitable for the protection of sensitive compounds.

On the other hand, the 2,2-dimethyl-1,3-dioxolane (acetonide) group is perhaps the most widely used protecting group for vicinal diols, particularly for carbohydrates and steroids. Preparation of acetonides usually involves reaction of the diol with acetone, 2,2-dimethoxypropane, or 2-methoxypropene under acidic conditions.[2]

A quite different approach to both targets is the acid-catalyzed addition of an epoxide to a ketone. Since the 1930s, oxiranes were demonstrated to react with carbonyl compounds to give dioxolanes in low to moderate yields,[3] but only recently has this reaction received increased interest among organic chemists. BF_3 is the most successfully employed catalyst for this reaction,[4] however, $SnCl_4$,[3,5] $TiCl_4$,[6] $TiCl_3(OTf)$ and $TiO(TFA)_2$,[7] tetracyanoethylene,[8] $CuSO_4$,[9] zeolites,[10] CH_3ReO_3,[11] K10-montmorillonite,[12] $[Cp^*Ir(NCMe)_3]^{2+}$,[13] $RuCl_3$,[14] bismuth(III) salts,[15] 2,4,4,6-tetrabromo-2,5-cyclohexadienone,[16] tin(IV) tetraphenylporphyrin perchlorate,[17] $K_5CoW_{12}O_{40}\cdot 3\,H_2O$,[18] and $SnCl_2$,[19] have also been used with varying degrees of success pertaining to yield and selectivity. However, many of these catalysts are rather strong Lewis acids and are incompatible with other functional or protecting groups.

In the course of our research program on Lewis acid-catalyzed reactions, we found that erbium triflate is a very useful, environmentally-friendly catalyst for several acid-catalyzed reactions.[20] Moreover, erbium(III) triflate works in almost neutral conditions,[21] therefore it is tolerant towards many organic functions. In particular, erbium triflate has proved to be a highly efficient and regioselective catalyst for the rearrangement of epoxides to carbonyl compounds.[22]

The capability of erbium to coordinate the oxygen atom of the three-membered epoxy ring prompted us to explore other reactions involving epoxides, which can be catalyzed by erbium(III) triflate. In this communication we present the direct conversion of epoxides to acetonides catalyzed by this mild and environmentally-friendly Lewis acid catalyst, in order to obtain a one-step stereoselective procedure to convert epoxides into protected diols. The reaction was then extended to other ketones, in order to test its generality.

Results and Discussion

When erbium triflate is added to a solution of epoxide **1** in acetone acetonides **2** are easily recovered from the reaction mixture in very good yields. The catalyst amount is critical for every epoxide: aromatic epoxides, such as styrene oxide (**1a**), needed only 0.1% mol (Table 1, entry 1) since, with higher catalyst percents, considerable amounts of phenylacetaldehyde (the rearranged product) are recovered.[22] In the case of aliphatic epoxides, where the rearrangement process is slower,[22] the reac-

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tion is better performed with 1 mol % of catalyst. Higher amounts of catalyst did not influence the reaction rate significantly. For example, the reaction of cyclohexene oxide (**1c**) was performed with 10 mol % catalyst without substantial modifications of product distribution (about 77% yields after 48 h, Table 1, entry 4,).

It should be noted that the presence of benzyloxy, phenyloxy and propargyloxy groups on the epoxide ring, drastically decreased the reaction rate. In fact, benzyl, phenyl and propargyl glycidols (**1f**–**h**) are converted into the corresponding dioxolanes in 44, 29 and 30% yields, respectively, after two days, whereas glycidol **1d** and methyl glycidol **1e** give the products almost quantitatively (Table 1, entries 5 and 6). Besides, when the same reactions for **1c** and **1g** were performed at higher temperature (50 °C) no improvement in yields and reaction rate was registered.

Many reported mechanisms for this kind of reaction hypothesize the activation of the epoxide ring through the coordination of a metal cation to the oxygen.[9,11,13] For the present method, we proposed the mechanism reported in the Scheme 1, as supported by some experimental evidence and in agreement with several proposed mechanisms.

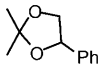
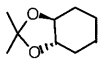
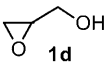
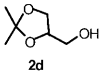
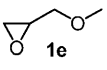
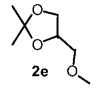
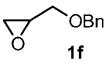
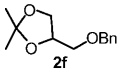
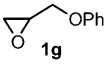
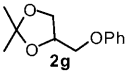
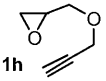
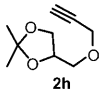
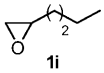
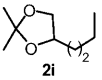
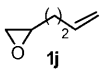
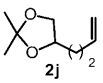
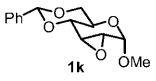
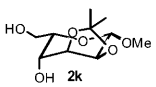
The coordination of Er(III) on the epoxide **3** rather than on the carbonyl oxygen atom is demonstrated by the slow reaction of the methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside (**1k**), which is converted into the corresponding deprotected dioxolane **2k**, with only 30% conversion after two days, the most part of the remainder is starting material. The structure of **2k** was established by ^{1}H-NMR analysis,[28] and presumes the stereochemical inversion at C-2 during the reaction as is confirmed by the identification of α-D-methyl mannopyranoside as the only hydrolysis product.

Moreover, the isomer, methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside (**1l**, Scheme 2), whose epoxide oxygen is crowded by the benzylidene protection, is unreactive at all and the epoxy sugar **7** [24] was the only recovered product.

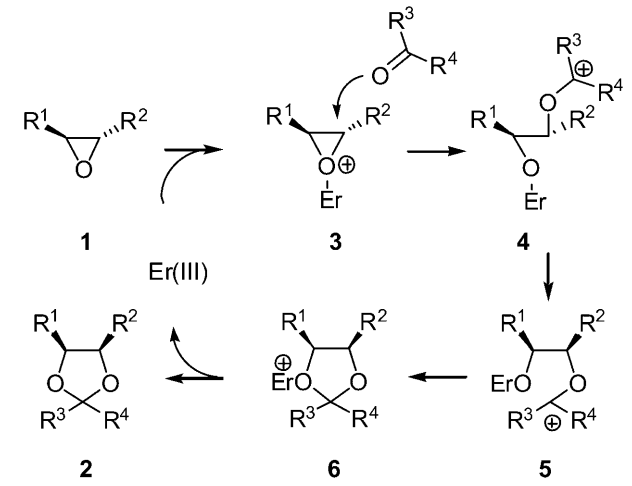
The torsion of the carbon-oxygen bond to face the carbocation with the coordinated oxygen atom (step **4** → **5**, Scheme 1) is supported by the slow reaction of cyclohexene oxide, where the strain of the cycle opposes rotation and also, when using different percentages of catalyst (0.1, 1.0, and 10.0), the only observed change was the formation of rearrangement products. Finally, the reactions of the stereochemically-defined butene2-oxides **1b** (Table 1, entries 2 and 3) confirm the occurrence of stereochemical inversion at the carbon atom at the C–O bond cleavage site in the epoxide, such as depicted in the mechanism in Scheme 1.

Finally, in order to test the generality of the reaction we then extended the present method to other ketones. 1-Hexene oxide (**1i**) was allowed to react

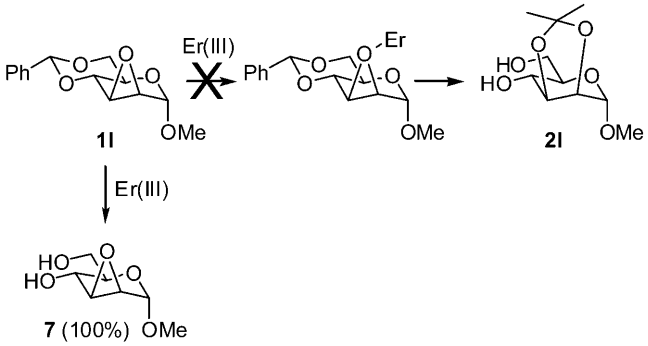
Table 1. Formation of acetonides in the presence of $Er(OTf)_3$ at room temperature.

entry	epoxide	Product	$Er(OTf)_3$ [mol %]	t [h]	yield [%][a]
1	 **1a**	 **2a**	0.1	0.5	>99
2	 ***cis*-1b**	 ***trans*-2b**	1	0.5	>99
3	 ***trans*-1b**	 ***cis*-2b**	1	0.5	>99
4	 **1c**	 **2c**	1 10	48 48	75 77
5	 **1d**	 **2d**	1	48	>99
6	 **1e**	 **2e**	1	0.5	>99
7	 **1f**	 **2f**	1	48	44
8	 **1g**	 **2g**	1	48	29
9	 **1h**	 **2h**	1	48	30
10	 **1i**	 **2i**	1	1	>99
11	 **1j**	 **2j**	1	2	>99
12	 **1k**	 **2k**	1	48	30

[a] All compounds were identified by MS-EI and ^{1}H-NMR giving satisfactory microanalyses and ^{1}H-NMR identical to those reported in literature: **2a**,[24] *trans*-**2b**, *cis*-**2b**,[25] **2c**,[24] **2d**,[26] **2e**,[23] **2f**,[27] **2g**,[24] **2h**,[23] **2i**,[28] **2j**,[29] **2k**.[30]



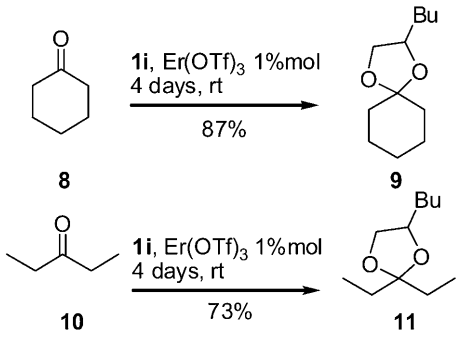
Scheme 1. Proposed mechanism for the reaction.



Scheme 2.

with cyclohexenone (**8**) and 3-pentanone (**10**) under the same reaction conditions. The reactions were considerably slower and the corresponding dioxolanes (**9** and **11**) were recovered in 87% and 73% yields, respectively, after 4 days (Scheme 3).[23]

A lower amount of catalyst (0.1 mol %) results in poor yield of product and after prolonged reaction time only rearranged products were obtained.



Scheme 3.

Conclusion

In conclusion, erbium triflate is a very useful and general catalyst to perform both direct transformation of epoxides in diols protected as acetonides or protection of ketones as dioxolane using epoxides. The present procedure affords comparable yields, ratios, catalyst percentage with the best reported methods. The reaction mechanism is similar to that with iridium catalysis.[13] Finally, this is a good example of chemistry with low environmental impact, since there is atom economy (the unreacted ketone used as solvent is completely recoverable after distillation), no purification process requirement, and use of an easily recoverable, non-toxic catalyst.

Experimental Section

^{1}H NMR spectra were recorded with a Bruker WM 300 instrument, at 300 MHz. Samples were dissolved in $CDCl_3$. Chemical shifts are given in parts per million (ppm) from tetramethylsilane as internal, coupling constants (J) are given in Hertz.

General Procedure

$Er(OTf)_3$ (0.01 mmol) was added to a solution of epoxide (1 mmol) in acetone (2 mL), under magnetic stirring at room temperature The reaction was followed by GC-MS analysis up to disappearance of the epoxide. Then, the organic solution was washed with saturated aqueous $NaHCO_3$ and then with water The organic layer, after being dried over $MgSO_4$, was evaporated under reduced pressure and the residue was submitted to ^{1}H NMR analysis showing the exclusive presence of dioxolanes (see Table 1), and **2c**, **2f**, **2g**, **2k** and **7** were the only products purified by flash chromatography on a silica gel column (eluent: chloroform/methanol, 9/1), while the compounds **2b** were recovered by distillation at atmospheric pressure.

4-(Methoxymethyl)-2,2-dimethyl-1,3-dioxolane (2e)

^{1}H NMR ($CDCl_3$): $\delta = 1.45$ (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 3.40 (s, 3H, OCH_3), 3.68–3.47 (m, 2H, $H_cH_{c'}$), 4.04 (dd, 1H, $H_{a'}$, $J_{Ha,Ha'} = 6.28$ Hz, $J_{Ha',Hb} = 8.50$ Hz), 4.27 (dd, 1H, H_a, $J_{Ha,Hb} = 11.50$ Hz, $J_{Ha,Ha'} = 6.28$); EI-MS: m/z (%) = 146 [M^+] (0), 131 (97), 101 (76), 71 (88), 43 (100); anal. calcd. for $C_7H_{14}O_3$: C 57.53, H 9.59; found: C 57.91, H 9.43.

4-(Prop-2-yn-1-yloxymethyl)-2,2-dimethyl-1,3-dioxolane (2h)

^{1}H NMR ($CDCl_3$): $\delta = 1.36$ (s, 3H, $CH_{3'}$), 1.43 (s, 3H, CH_3), 2.45–2.48 (m, 1H, CH_e=), 3.56–3.63 (m, 2H, H_c, $H_{c'}$), 3.72–3.75 (m, 1H, H_b), 4.06 (dd, 1H, $H_{a'}$, $J_{Ha',Ha} = 6.45$ Hz, $J_{Ha',Hb} = 8.23$ Hz), 4.21–4.22 (m, 2H, H_e), 4.27–4.31 (m, 1H, H_a); EI-MS: m/z (%) = 156 [M^+] (5), 155 (62), 101 (66), 67 (26), 43

(100); anal. calcd. for $C_9H_{14}O_3$: C 63.53, H 8.23; found: C 63.29, H 8.33.

Spiro[5,4]7,10-dioxa-8-butyldecane (9)

^{1}H NMR ($CDCl_3$): $\delta = 0.90$ (t, 3H, CH_3, $J = 6.86$ Hz), 1.30–1.40 (m, 2H), 1.57–1.64 (m, 2H), 1.67–1.78 (m, 8H), 1.82–1.92 (m, 4H), 3.49 (t, 1H, $H_{a'}$, $J = 6.88$ Hz), 4.10–4.00 (m, 2H, H_aH_b); anal. calcd for $C_{12}H_{22}O_2$: C 72.73, H 11.11; found: C 72.66, H 10.98.

Methyl 2,3-Anhydro-α-D-mannopyranoside (7)

^{1}H NMR ($CDCl_3$): $\delta = 3.13$ (d, 1H, H-3, $J_{H_3,H_2} = 3.70$ Hz), 3.32 (d, 1H, H-2, $J_{H_2,H_3} = 3.70$ Hz), 3.46 (s, 3H, OCH_3), 3.50–3.65 (m, 1H, H-5), 3.78 (t, 2H, H-6, $J_{H_6,H_5} = 3.98$ Hz), 3.87 (d, 1H, H-4, $J_{H_4,H_3} = 9.19$ Hz), 4.89 (s, 1H, H-1); anal. calcd. for $C_7H_{12}O_5$: C 47.73, H 6.82; found: C 47.51, H 6.69.

References and Notes

[1] T. W. Greene, P. G. M. Wuts, *Protecting Groups in Organic Synthesis,* 2nd edn., John Wiley & Sons, New York, **1991**, pp 188–195.

[2] T. W.Greene, P. G. M. Wuts, *Protecting Groups in Organic Synthesis,* 2nd edn., John Wiley & Sons, New York, **1991**, pp 123–125.

[3] M. T. Bogert, R. O. Roblin Jr., *J. Am. Chem. Soc.* **1933**, *55*, 3741–3745; b) T. Bersin, G. Willfang, *Ber. dtsch. chem. Ges.* **1937**, *70*, 2167–2173; c) G. Willfang, *Ber. dtsch. chem. Ges.* **1941**, *74*, 145–153.

[4] D. Torok, J. Figueroa, W. Scott, *J. Org. Chem.* **1993**, *58*, 7274–7276.

[5] V. C. Dryuk, V. I. Avramenko, V. N. Yandovskii, *J. Chem. Soc. Perkin Trans. 2* **1977**, 1526–1528.

[6] T. Nagata, T. Takai, T. Yamada, K. Imagawa, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2614–2616.

[7] N. Iranpoor, B. Zeynizadeh, *J. Chem. Res. (S)* **1998**, 466–467.

[8] Y. Masaki, T. Miura, M. Ochiai, *Chem. Lett.* **1993**, 17–20.

[9] R. Hanzlik, J. Leinwetter, *J. Org. Chem.* **1978**, *43*, 438–440.

[10] L. W. Zatorski, P. T. Wierzchowski, *Catal. Lett.* **1991**, *10*, 211–214.

[11] Z. Zhu, J. Espenson, *Organometallics* **1997**, *16*, 3658–3663.

[12] I. Busci, A. Meleg, A. Molnar, M. Bartok, *J. Mol. Catal.* **2001**, *168*, 47–52.

[13] R. D. Adams, T. S. Barnard, K. Brosius, *J. Organomet. Chem.* **1999**,*582*, 358–361.

[14] N. Iranpoor, F. Kazemi, *Synth. Commun.* **1998**, *28*, 3189–3193.

[15] I. Mohammadpoor-Baltork, A. Khosropour, H. Aliyan, *Synth. Commun.* **2001**, *31*, 3411–3416.

[16] H. Firouzabadi, N. Iranpoor, H. Shaterian, *Bull. Chem. Soc. Jpn.* **2002**, *75,* 2195–2205.

[17] S. Tangestaninejad, M. Habibi, V. Mirkhani, M. Moghadam, *J. Chem. Res. S* **2001**, 365–367.

[18] M. Habibi, S. Tangestaninejad, V. Mirkhani, B. Yadollahi, *Catal. Lett.* **1975**, *3–4*, 205–207.

[19] J. R. Vyvyan, J. A. Meyer, K. D. Meyer, *J. Org. Chem.* **2003**, *68*, 9144–9147.

[20] a) R. Dalpozzo, A. De Nino, L. Maiuolo, M. Nardi, A. Procopio, A. Tagarelli, *Synthesis* **2004**, 496–498; b) A. Procopio, R. Dalpozzo, A. De Nino, L. Maiuolo, B. Russo, G. Sindona, *Adv. Synth. Catal.* **2004**, 346, 1465–1470.

[21] A 0.1 M water solution of $Er(OTf)_3$ is only weakly acidic (pH *ca.* 5.9), and the aqueous layer from work-up is even less acidic (pH *ca.* 6.6).

[22] A. Procopio, R. Dalpozzo, A. De Nino, M. Nardi, G. Sindona, A. Tagarelli, *Synlett* **2004**, 2633–2635.

[23] a) E. Marcantoni, F. Nobili, G. Bartoli, M. Bosco, L. Sembri, *J. Org. Chem*. **1997**, *62*, 4183–4184; b) B. Bartels, R. Hunter, *J. Org. Chem*. **1993**, *58*, 6756–6765.

[24] G. Tangestaninejad, *J Chem. Res.* **2001**, *9*, 365–367.

[25] a) F. A. L. Anet, *J. Am. Chem. Soc,* **1962**, *84*, 747–752; b) W. J. Richter, *J. Org. Chem.* **1981**, *46*, 5119–5124; c) M. K. Akkapeddi, H. K. Reimschuessel, *Macromolecules.* **1979**, *12*, 827–831.

[26] K. Danielmeier, E. Steckhan, *Tetrahedron: Asymmetry* **1995**, *6*, 1181–1190.

[27] G. Xiang, L. Mc Laughlin, *Tetrahedron* **1998**, *54*, 375–392.

[28] F. Wittko, F. Schoeder, W. Felix, V. Sinwell, H. Baumann, M. Kaib, *Ann. Org. Bioorg. Chem.* **1995**, *6*, 965–978.

[29] J. S. Bradshaw, P. Huszthy, W. C. McDaniel, C. Y. Zhu, N. K. Dalley, R. M. Izatt, S. Lifson, *J. Org. Chem*. **1990**, *55*, 3129–3137.

[30] a) S. H. Khan, K. J. Rackesh, L. M. Kheushi, *Carbohydrate Res.* **1990**, *207*, 57–69; b) R. Eby, K. T. Webster, C. Shuerch, *Carbohydrate Res.* **1984**, *129*, 111–120.

