Tetrahedron Letters 51 (2010) 5150–5153

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Efficient ring opening of epoxides with trimethylsilyl azide and cyanide catalyzed by erbium(III) triflate

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ARTICLE INFO

Article history:
Received 19 May 2010
Revised 19 July 2010
Accepted 21 July 2010
Available online 29 July 2010

Keywords:
Erbium(III) triflate
Epoxide ring-opening
Cyanohydrins
Azido alcohols

ABSTRACT

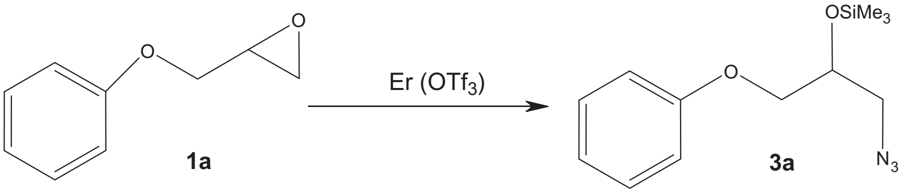
Epoxides can be opened under neutral conditions with $TMSN_3$ and TMSCN in the presence of catalytic amounts of Lewis acid, affording the corresponding ring-opened compounds in high yields.

Epoxides are recognized among the most versatile intermediates in organic synthesis. They can be easily prepared and due to their ring strain they react with different nucleophiles with high regioselectivity, leading to ring-opened products.[1]

In the past, we have found that erbium(III) triflate [$Er(OTf)_3$] is a very useful and environmentally friendly functional group, and tolerant catalyst for several acid-catalyzed reactions.[2] Owing to its unique qualities,[3] erbium triflate has already proven to be a highly efficient and regioselective catalyst for many reactions involving epoxides; such as the rearrangement to carbonyl compounds,[4] the synthesis of acetonides,[5] the conversion into 1,2-diacetates,[6] the synthesis of β-amino alcohols,[7] and the preparation β-hydroxy sulfides.[8]

As a consequence of the necessity of milder and environmentally friendly reaction conditions, and in continuation of our interest on the application of erbium triflate into organic transformations; in this Letter, we aim to report that $Er(OTf)_3$ can act as a mild and efficient Lewis acid catalyst for another regio- and stereoselective epoxide ring opening with trimethylsilylazide ($TMSN_3$) and trimethylsilylcyanide (TMSCN) (Scheme 1).

α-Azido alcohols are important precursors for alternative syntheses of β-aminoalcohols;[9] some of them appeared in the structures of pharmaceutical, useful chiral auxiliaries, or intermediates for the synthesis of amino sugars. The classical reagents for azidohydrin synthesis are the combined use of NaN_3,[10] $TMSN_3$,[11] or other azide sources[12] in the presence of a Lewis acid or a transition metal complex. The oldest reported epoxide ring-opening reactions with NaN_3 suffer from high temperatures, long reaction times or side isomerization, epimerization, and rearrangement reactions. Recently, a large variety of activators or promoters have been



Scheme 1. Epoxide ring-opening with ($TMSN_3$) and (TMSCN).

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doi:10.1016/j.tetlet.2010.07.123

Table 1
Reaction of 3-phenyloxy-1,2-epoxypropane (**a**) with $TMSN_3$ catalyzed by $Er(OTf_3)$

Entry	Er (OTf_3) (mol %)	$TMSN_3$ (equiv)	*T* (°C)[a]	Conversion (%)	Yield[b] (%)
1	5	2	25	100	83 (5)[c]
2	5	1.1	0→25	100	67 (21)
3	5	1.5	0→25	95	81 (4)
4	5	1.5	25	95	69 (16)
5	3	1.5	0→25	64	30 (26)
6	1	1.5	0→25	9	14 (9)

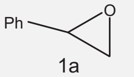
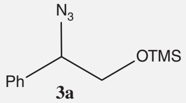
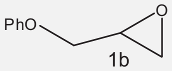
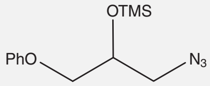
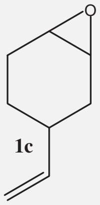
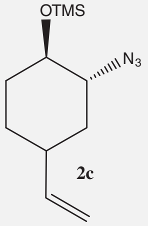
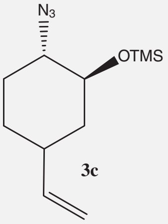
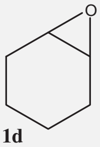
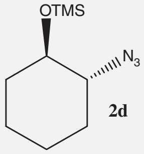
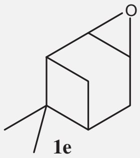
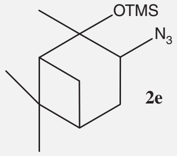
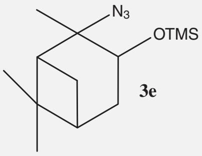
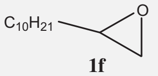
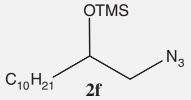
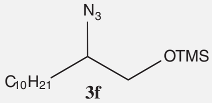
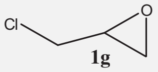
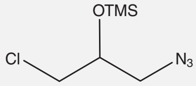
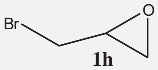
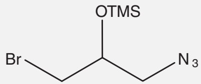
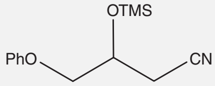
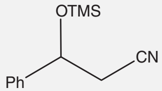
[a] Reaction was monitored up to 400 min.
[b] Determined by GC/MS.
[c] % of hydrolyzed product determined by GC/MS.

reported to promote epoxide ring-opening reactions with azides under milder reaction conditions.[10–12]

Moreover, β-hydroxynitriles are useful synthetic intermediates in organic synthesis owing to their versatile hydroxy and cyano moieties. The reaction of epoxides with different cyanide sources; such as hydrogen cyanide,[13] cyanids,[14] TMSCN,[15] or cyanide formed upon treatment of acetone cyanohydrins with bases;[16]are among the most direct methods for the preparation of these compounds. However, some of them usually require long reaction times and harmful solvents.

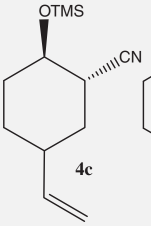
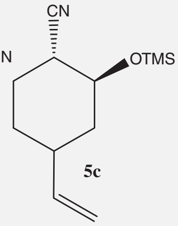
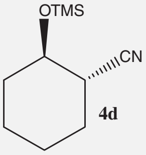
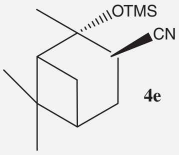
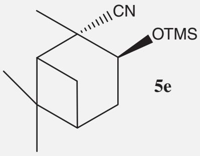
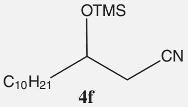
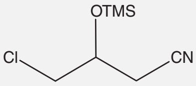
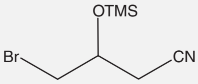
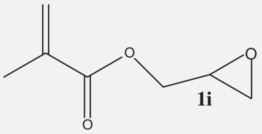
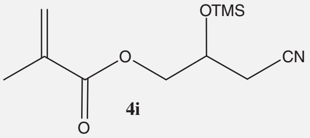
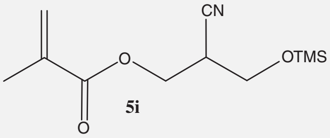
In order to find the best experimental conditions, we tested the catalytic activity of $Er(OTf)_3$ in the epoxide ring opening of the sub-

Table 2
Reaction of epoxides with $TMSN_3$ (1.5 equiv) and TMSCN (2.0 equiv) in the presence of $Er(OTf_3)$ (5 mol %)

Entry	Epoxide	Product[b]	Time (min)	Yield (%)	Ratio
1	 1a	 **3a**	30	86	0:100
2	 1b	 **2b**	400	86	100:0
3	 **1c**	 **2c**  **3c**	30	100	51:49
4	 **1d**	 **2d**	30	74	–
5	 **1e**	 **2e**  **3e**	30	93[a]	83:17
6	 **1f**	 **2f**  **3f**	400	83	65:35
7	 **1g**	 **2g**	120	81	100:0
8	 **1h**	 **2h**	300	80	100:0
9	**1a**	 **4a**	240	89	100:0
10	**1b**	 **4b**	30	57	0:100

(*continued on next page*)

Table 2 (*continued*)

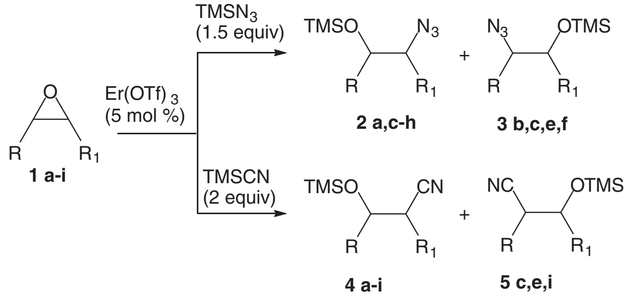
Entry	Epoxide	Product[b]	Time (min)	Yield (%)	Ratio
11	**1c**	 **4c**  **5c**	10	95	47:53
12	**1d**	 **4d**	20	91	–
13	**1e**	 **4e**  **5e**	10	96[a]	82:18
14	**1f**	 **4f**	60	94	100:0
15	**1g**	 **4g**	10	100	100:0
16	**1h**	 **4h**	240	82	100:0
17	 **1i**	 **4i**  **5i**	60	97	62:38

[a] All four diastereomers were detected.

[b] Compounds **2a, 3b, 2d,**[10h] **2c, 3c,**[18] **2g,**[19] **2h,**[11d] **4a, 4b, 4d, 4g,** and **4h**[15c] are known products and were characterized by the comparison of their spectra with the literature data. Spectroscopic data for unknown products supplied in Supplementary data. The minor isomers **3e** and **3f** were detected by the EI-MS spectra only.

strate model 3-phenyloxy-1,2-epoxypropane (**a**) with $TMSN_3$ (Scheme 1). After a series of preliminary experiments, the best conversion was observed when a slightly defective silyl derivative was added to the epoxide at 0 °C in the presence of 5 mol % of the catalyst and then allowed to warm to room temperature (Table 1).[16] This is surprising, since in all the reported procedures the limiting reagent is always the epoxide.

All the reactions proceeded smoothly under these conditions and, after the appropriate reaction time (Table 2), afforded the desired products in excellent yields and high purity. The product can be separated with simple and mild work-up and only a partial desilylation was observed in some cases, but without rearrangements to isonitriles (see Scheme 2).[15d]



Scheme 2.

Experiments conducted with both *cis* and *trans*-stilbene lead to the complex mixtures of products, both with $TMSN_3$ and TMSCN.[17] A GC/MS analysis of the reaction-product distribution allowed significant amounts of elimination products; namely, non-hydrolyzed (1,2-diphenylvinyloxy)trimethylsilane and hydrolyzed 1,2-diphenylethanone; to be recognized together with some additional products. TMSCN was more reactive than $TMSN_3$, as its reaction times are significantly lower (Table 2, cf. entries 1–9, 2–10, etc.). The higher reactivity of the TMSCN also affected regioselectivity. In fact, addition to 1-dodecene oxide (**1f**) was completely selective in the case of TMSCN, but not when using TMSN$_3$ where significant amounts of the isomer **3f** were recovered (Table 2, entry 6). Conversely, the closely related cerium(III) chloride is completely selective with 1-hexene oxide, when charged in 50 mol %.[11b] Moreover, addition to styrene oxide (**1b**) was completely α-selective with TMSN$_3$ and β-selective TMSCN. Other addition of azides[10–12] always led to mixtures with prevalence of one or the other isomer, whereas nitrile was already reported to give prevalence of **4b**.[15] Finally, complete selectivity for nucleophilic attack at the less-hindered carbon of glycidyl phenyl ether and epihalohydrins was always observed.

In order to include the present results into our proposed mechanism,[8] where Er(OTf)$_3$ serves as Lewis acid by coordination to the oxygen atom; we envisaged that in an asymmetrical epoxide, the higher nucleophilic CN$^-$ added at an early transition state in which epoxide was still intact and crowded, the positions highly influenced the attack. On the other hand, the less nucleophilic N$_3^-$ added at a late transition state where ring opening proceeded in a manner that C–O bond cleavage gave the best stabilization of the developing positive charge. Thus, the β- and benzylic positions were the favored sites for the nucleophilic attack for CN$^-$ and N$_3^-$, respectively. However, highly encumbered substrates such as **1e** led to mixtures, since crowding inhibits to charge-stabilization (Table 2[**], entries 5 and 13). In summary, we have developed an economical and green method for the synthesis of a wide range of β-hydroxynitriles and α-azido alcohols by using readily available reagents under neutral conditions. This method is yield- and selectivity-competitive with the previously reported methods, even the most recent ones. Moreover, these results have allowed better clarification of the mechanisms involved in the erbium(III) triflate-catalyzed epoxide ring opening, by expanding the perspective of its interaction with other nucleophiles. Further studies in this direction are in progress in our laboratory.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.123.

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17. *General procedure:* TMSN$_3$ (1.5 equiv) or TMSCN (2.0 equiv) was added to a mixture of 2.5 mmol of epoxide and Er(OTf)$_3$ (5 mol %) in a test tube. The mixture was stirred at 0 °C for a few minutes, and then at room temperature for 30–400 (TMSN$_3$) or 10–240 min (TMSCN). The reaction was monitored by TLC or GC/MS. The mixture was subsequently diluted with ether, and three samples were extracted using water. The catalyst was recovered from the aqueous phases by evaporation under vacuum. The collected organic phases were dried on Na$_2$SO$_4$, filtered, and then evaporated under vacuum. The desired pure product was separated from tars by flash chromatography on a short silica gel column. Samples containing the products were collected, whereby the yields and the diastereoisomeric ratios are calculated on the entire set. A more careful chromatographic separation was performed in order to obtain pure samples of unknown products to be characterized (see Supplementary data).
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