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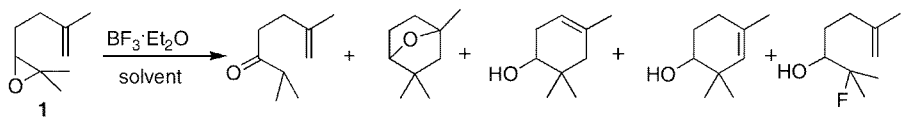
A Study of Epoxyolefin Cyclizations Catalyzed by Bismuth Trifluoromethanesulfonate and Other Metal Triflates

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Abstract—Epoxyolefin cyclizations have attracted considerable interest due to their importance in biosynthetic pathways. Bismuth trifluoromethanesulfonate as well as several other metal triflates are shown to be highly effective (0.1 mol %) catalysts for the cyclization of geraniolene oxide. The product composition is found to be more dependent on solvent and substrate concentration than on the nature of the metal triflate. Cyclization products are favored in CH_2Cl_2 and under high dilution conditions. Ether solvents favored acyclic products.

The cyclization of epoxyolefins has been the subject of intense study ever since the discovery that these reactions are involved in the biosynthesis of many terpenes, including cholesterol. An early example is the cyclization of geraniolene oxide **1** using $BF_3{\cdot}Et_2O$ to give a mixture of acyclic and cyclic products (Scheme 1).[1]

A classic example of such a cyclization was first reported by van Tamelen who demonstrated that squalene 2,3-epoxide is an intermediate in the enzymatic cyclization of squalene to lanosterol and cholesterol.[2] Several non-enzymatic conditions have been reported to effect epoxyolefin cyclizations. The non-enzymatic cyclizations of (±)-10,11-oxidofarnesyl acetate, methyl farnesate, methyl (±)-10,11-oxidofarnesate, and 14,15-geranylgeranyl acetate have been studied using several catalysts such as BF_3, H_3PO_4, and $SnCl_4$.[3] Johnson and co-workers have elegantly demonstrated epoxide-initiated olefin cyclizations.[4] The Lewis acid induced cyclization of vinyl ether-epoxides has also been studied.[5] Lewis acid mediated epoxy alcohol rearrangements have been shown to be directed by the hydroxy group.[6] The potential of the epoxy furan cyclization for the formation of six- and seven-membered rings has been well demonstrated.[7] The Friedel–Crafts cyclic alkylations of several epoxides have been studied using $AlCl_3$ and $SnCl_4$.[8] The utility of epoxyolefin cyclizations in the construction of carbocycles has been used to advantage in the synthesis of natural products such as *d*,*l*-malabaracanediol,[9a] (±)-martimol,[9b] (±)-karahana ether,[9c] and (+)-aphidicolin.[9d] The cyclization of epoxy-silanes has been investigated using $TiCl_4$.[10] Epoxyolefin cyclizations have also been initiated by $MeAlCl_2$[1b] and bis(4-bromo-2,6-di-*tert*-butylphenoxide).[11] However, most of the catalysts that have been used for epoxyolefin cyclizations are highly corrosive, toxic, and difficult to handle.[12] In addition, few of them have been employed under highly catalytic conditions (ca. 0.1 mol % catalyst). An added



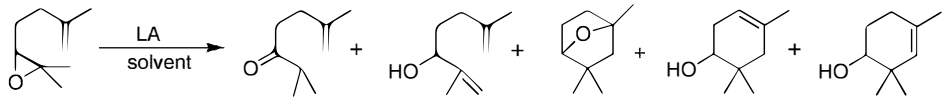
Scheme 1.

problem with Lewis acids containing a nucleophilic anion is that products can arise from attack by the anion on the epoxide. For example, when geraniolene oxide **1** is treated with $BF_3{\cdot}Et_2O$, a significant amount of the fluorohydrin (Scheme 1) is obtained.[1a] In spite of their demonstrated versatility, metal triflates have not been used as catalysts for epoxyolefin cyclizations. Our continued interest in bismuth compounds, due primarily to their remarkably low toxicity, ease of handling, and low cost prompted us to study epoxyolefin cyclizations catalyzed by bismuth triflate.[13,14] Herein we report a study of the reactions of geraniolene oxide **1** in the presence of a variety of metal triflates, including bismuth triflate, under highly catalytic conditions (0.1 mol % catalyst). To the best of our knowledge, this is the first example of a metal triflate catalyzed cyclization of an epoxyolefin.[15]

Geraniolene oxide **1** was treated with $Bi(OTf)_3{\cdot}xH_2O$ (0.1 mol %) in a variety of solvents including CH_2Cl_2, DME, dioxane, pentane, THF, and toluene. These results are compared with those obtained with other metal triflates such as $Ga(OTf)_3$, $In(OTf)_3$, KOTf, $La(OTf)_3$, LiOTf, $Sc(OTf)_3$, and $Yb(OTf)_3{\cdot}xH_2O$. In addition, the cyclization of **1** was carried out with CF_3SO_3H in CH_2Cl_2 and TMSOTf in an ionic liquid, [bmim][OTf]. These results are summarized in Table 1. Metal triflates derived from Bi(III), Ga(III), In(III), and Sc(III) were the most effective catalysts (0.1 mol %) while La(III) triflate (entry 12), Yb(III) triflate (entries 15 and 16) as well as the alkali metal triflates (entries 11 and 13) proved less efficient. Due to its low cost, ease of handling, and relative insensitivity to moisture, $Bi(OTf)_3{\cdot}xH_2O$ was found to be the metal triflate of choice for the reaction. We initially carried out the reactions of geraniolene oxide **1** at ca. 0.36 M concentrations (typically 0.20 g of the epoxide was dissolved in 4.0 mL of the solvent). Under these conditions, in addition to the cyclization products **4**, **5a**, and **5b**, two acyclic products, **2** and **3** were also formed in significant amounts.[16]

The reaction was also catalyzed by 0.10 mol % triflic acid (entry 17) and the ratio of products was essentially

Table 1. Results of the reaction of geraniolene oxide **1** with various metal triflates[a]



1 **2** **3** **4** **5a** **5b**

Entry	Catalyst	Mol %	Solvent	t[b]	Ratio of products[c,d]				Yield[e]
					2[21]	**3**[22]	**4**[1a]	(**5a**[23]+**5b**[24])	
1	$Bi(OTf)_3{\cdot}xH_2O$	0.10	CH_2Cl_2	5 min	22	29	13	36 (82:18)	95
2	$Bi(OTf)_3{\cdot}xH_2O$, Proton sponge®	0.10 1.0	CH_2Cl_2	24 h	NR				—
3	$Bi(OTf)_3{\cdot}xH_2O$, K_2CO_3	0.10 40	CH_2Cl_2	5 min	19	31	11	39	95
4	$Bi(OTf)_3{\cdot}xH_2O$	1.0	Pentane	10 min	57	20	6.0	17	—
5	$Bi(OTf)_3{\cdot}xH_2O$	0.10	Toluene	45 min	25	50	9.0	16	—
6	$Bi(OTf)_3{\cdot}xH_2O$	1.0	THF	10 min	55	39	0	6.0	72
7	$Bi(OTf)_3{\cdot}xH_2O$	0.10	Dioxane	10 min	49	43	2.0	6.0	—
8	$Bi(OTf)_3{\cdot}xH_2O$	0.10	DME	20 min	59	36	1.0	4.0	—
9	$Ga(OTf)_3$	0.10	CH_2Cl_2	10 min	22	32	11	35	85
10	$In(OTf)_3$	0.10	CH_2Cl_2	40 min	20	37	10	33	90
11	KOTf	5.0	CH_2Cl_2	17 h	23	31	10	36	79
12	$La(OTf)_3$	5.0	CH_2Cl_2	5.5 h	22	31	11	36	94
13	LiOTf	5.0	CH_2Cl_2	5.5 h	NR				—
14	$Sc(OTf)_3$	0.10	CH_2Cl_2	35 min	20	31	10	39	80
15	$Yb(OTf)_3{\cdot}xH_2O$	1.0	CH_2Cl_2	17 h	11	22	8.0	59	79
16	$Yb(OTf)_3{\cdot}xH_2O$	1.0	THF (dry)	18 h	41	54	0	5.0	80
17	CF_3SO_3H	0.10	CH_2Cl_2	20 min	21	33	10	36	88
18	CF_3SO_3H, K_2CO_3	0.10 40	CH_2Cl_2	16 h	NR				—
19	TMSOTf	3.0	[bmim][OTf]	30 min	74	15	0	11	75

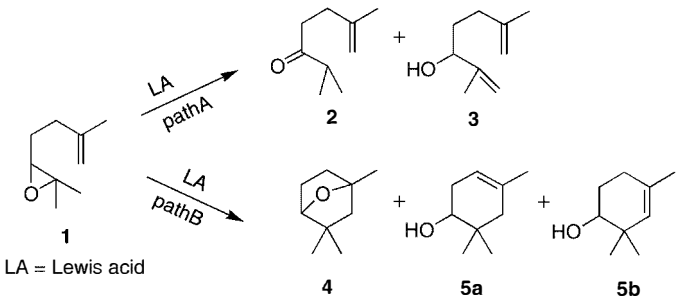
[a] All reactions were carried out in reagent grade solvents at room temperature unless otherwise mentioned. The ionic liquid was dried at 70 °C under vacuum (0.1 mmHg) for 12 h prior to use.

[b] Reaction progress was followed by GC.

[c] Ratios are normalized to 100% and were determined by GC analysis of the crude reaction product mixture. The average of 2–6 runs is reported for each entry. Ratios obtained by GC analysis agree closely with those obtained by integration of appropriate peaks in the ^1H NMR spectrum. The relative ratio of **5a** and **5b** was obtained by ^1H NMR spectroscopy. The ratio of **5a**:**5b** was the same with all the metal triflates.

[d] Superscript against product refers to literature reference for the compound.

[e] Refers to isolated yield of crude product mixture. The products shown typically comprised 85–90% of the crude mixture. Isolated yields of purified products were low due to the laborious chromatography required to separate products with similar R_f values. Products were characterized by IR and NMR spectroscopy as well as by comparison of their spectral data with those reported in the literature.



Scheme 2.

Table 2. Effect of epoxide **1** concentration (M) on product composition using $Bi(OTf)_3 \cdot xH_2O$ as the catalyst

Entry	Mol % $Bi(OTf)_3 \cdot xH_2O$	Epoxide **1** concentration (M)	Solvent	Ratio of products[a]		Yield[b]
				2+**3** path A	**4**+**5a/b** path B	
1	0.10	0.357	CH_2Cl_2, rt	51	49	95
2	1.0	0.357	CH_2Cl_2, −78 °C	40	60	83
3	1.0	0.0713	CH_2Cl_2, rt	26	74	70
4	1.0	0.0285	CH_2Cl_2, rt	15	85	79
5	1.0	0.00713	CH_2Cl_2, rt	8	92	79

[a] Ratios are normalized to 100% and were determined by GC analysis of the crude reaction product mixture.
[b] Refers to isolated yield of crude product mixture. The products shown typically comprised 85–90% of the crude mixture.

the same as that obtained with the metal triflates. This observation raised the possibility that the reactions in the presence of metal triflates are actually catalyzed by triflic acid, released in situ by hydrolysis of the metal triflates by any water present in the solvent, especially since anhydrous solvents were not used. In order to test this hypothesis, the $Bi(OTf)_3 \cdot xH_2O$ catalyzed reaction of geraniolene oxide was carried out in the presence of solid K_2CO_3 as well as proton-sponge® (*N*,*N*,*N*′,*N*′-tetramethyl-1,8-naphthalenediamine)®.[17] It was found that no reaction occurred even after 24 h (Table 1, entry 2) in the presence of proton sponge® while the addition of K_2CO_3 had no effect on the reaction (Table 1, entry 3). In order to test the efficacy of K_2CO_3 in neutralizing any triflic acid generated in situ, geraniolene oxide **1** was treated with 0.1 mol % CF_3SO_3H in the presence of K_2CO_3 (entry 18). In this case, no reaction was observed and the starting material was recovered. These observations suggest that bismuth triflate is indeed acting as a Lewis acid and presumably initiates the reaction by complexing with the epoxide oxygen.[18] The inactivity of bismuth triflate in the presence of proton sponge® is due likely to the complexation of bismuth to the amine nitrogens.

In Scheme 2, two possible pathways to the products obtained from the reaction of geraniolene oxide **1** are outlined. Presumably, products **2** and **3** arise via some very short-lived intermediate or via a concerted pathway (Scheme 2, path A). The acid-catalyzed cyclization of geraniolene oxide **1** has been studied in $ClCH_2COOH$, and it has been proposed that the cyclization products formed via a pathway in which the epoxide C–O bond formation and C–C bond formation are concerted (Scheme 2, path B).[19] We found that the product composition was much more sensitive to the solvent than the Lewis acid.

As can be seen from the results in Table 1, the overall ratio of acyclic products to cyclization products (**2**+**3**):(**4**+**5a/b**) remained unchanged with the nature of the metal triflate for a given solvent. With metal triflates, the greatest amounts of cyclized products were obtained in CH_2Cl_2 as the solvent and the least amounts were formed in ether solvents such as THF, dioxane, and DME as well as in the ionic liquid, [bmim][OTf].[20] We next examined the effect of temperature and substrate concentration on product composition. With $Bi(OTf)_3 \cdot xH_2O$ as the Lewis acid, it was found that the amount of cyclization product was concentration dependant (Table 2). When the reaction is carried out under high dilution conditions, greater percentages of cyclized products **4** and **5a/b** are obtained (Table 2, entries 3–5). A lower reaction temperature (Table 2, entry 2) however, only marginally favors the cyclization products.

In summary, the utility of metal triflates in catalyzing epoxyolefin cyclizations has been demonstrated. Product composition is influenced more by the nature of the solvent and substrate concentration than by the choice of metal triflate. Bismuth triflate is an especially attractive catalyst for these reactions due to the low toxicity, ease of handling, and low cost of bismuth(III) compounds.

Acknowledgments

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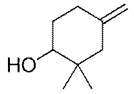
(University of Maryland Baltimore County) for useful discussions.

Supplementary data

General experimental section, representative procedures, isolation, and characterization of all reaction products. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.10.013.

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5c

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