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Microwave-enhanced bismuth triflate-catalyzed epoxide opening with aliphatic amines

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Abstract

In the presence of a catalytic amount of $Bi(OTf)_3{\cdot}4H_2O$ and under microwave irradiation, neat mixtures of epoxides and amines afforded smoothly the corresponding 2-amino alcohols. A wide variety of aliphatic amines were reacted with cycloalkene oxide, styrene oxide, and stilbene oxide. The reaction proceeded rapidly and afforded the 2-amino alcohols in high up to quantitative yields. All products could be obtained without aqueous work-up by simple filtration.

Keywords: Bismuth; Bismuth(III) triflate; Epoxide; Aliphatic amine; 2-Amino alcohol

1. Introduction

Nucleophilic opening of epoxide by amines is an important reaction for synthetic, organic and medicinal chemists, as the resultant 2-amino alcohols represent a broad range of intermediates widely present in biologically active natural and synthetic products.[1] The classical approach for the synthesis of 2-amino alcohols from epoxides involves the treatment of an epoxide with an amine under heating. However, this procedure has drawbacks such as the need of excess of amines and elevated temperature.[2] Moreover, poorly nucleophilic and sterically hindered amines do not always lead to good yields of the expected amino alcohols. Thus, there has been a lot of effort to develop methodologies for epoxide opening by amines as evidenced by numerous recent reports.[3] Still, some of these methods could not overcome the requirement for long reaction times, moisture/air sensitive, and costly catalysts. More importantly, most of the above described methods could not avoid the use of solvents (for both the reaction and the extraction process) and toxic catalysts, and generate large amounts of waste.

As a part of our ongoing interest in bismuth(III)-catalyzed epoxide opening,[4] we report herein our results in the microwave-assisted bismuth(III) triflate-catalyzed epoxide opening. In the last few years, bismuth compounds have attracted attention due to their low toxicity, low cost, and good stability.[5] Bismuth salts have been reported as catalysts for Mukaiyama-aldol reactions,[6] Mannich-type reactions,[7] imine allylation,[8] formation and deprotection of acetals,[9] Friedel–Crafts acylations,[10] Diels–Alder reactions,[11] Fries rearrangement,[12] and Claisen rearrangement.[13] $Bi(OTf)_3$ is particularly attractive because it is commercially available or can be easily prepared from readily available starting materials.[14] The BiX_3-catalyzed epoxide opening has already been reported with various alkene oxides and various nucleophiles.[15] In particular, the $BiCl_3$-catalyzed cyclohexene and cyclopentene oxide opening has been disclosed by our group with various substituted anilines.[4a] $Bi(OTf)_3$ was then reported to be efficient for the epoxide opening in aqueous conditions.[4b] Recently, a very elegant asymmetric version of a $Bi(OTf)_3$ catalyzed epoxide opening has been reported by Kobayashi using a chiral bipyridine diol in aqueous conditions.[15a]

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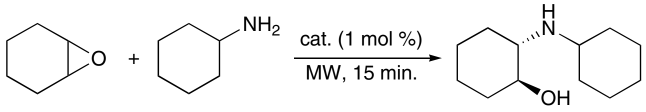
Microwave-assisted organic synthesis is currently gaining importance in synthetic chemistry largely due to the advancement in the technology that provides precision controlled microwave equipments.[16] Previous studies have shown that epoxide opening reactions can be conducted under microwave irradiation.[15d,17] These methods usually report the opening of aryloxymethyl epoxides with anilines and sometimes involve the use of conventional kitchen microwave ovens, often leading to modest and irreproducible yields. We wish to disclose our results in this area, that is, the development of an efficient, microwave-assisted bismuth-catalyzed epoxide opening with aliphatic amines that takes advantage of very mild reaction conditions. The reaction is indeed run neat, with a catalyst loading as low as 1 mol %, and is completed within a few minutes under microwave assistance.

2. Results and discussion

Initial investigations in the epoxide opening with aliphatic amines involved the opening of cyclohexene oxide with cyclohexylamine as a model reaction (Scheme 1, Table 1). These results were promising, as the corresponding 2-amino alcohol could be obtained in excellent yield with 1 mol % of $Bi(OTf)_3 \cdot 4H_2O$ as the catalyst (Table 1, entry 4). A lower loading of $Bi(OTf)_3 \cdot 4H_2O$ (0.1 mol %) led to a decreased yield (52% of **3a**). While $BiCl_3$ gave almost no conversion (Table 1, entry 2), $BiBr_3$ provided the product in only moderate yield (Table 1, entry 3). Other metal triflate catalysts, for example, $Sc(OTf)_3$, $Ga(OTf)_3$, and $Zn(OTf)_2$, appeared to be as efficient as $Bi(OTf)_3 \cdot 4H_2O$ (Table 1, entries 5–7). Triflic acid led to the expected product in almost quantitative yield (Table 1, entry 8).



1 **2a** **3a**

Scheme 1.

Table 1
Microwave-enhanced catalyzed opening of cyclohexene oxide by cyclohexylamine[a]

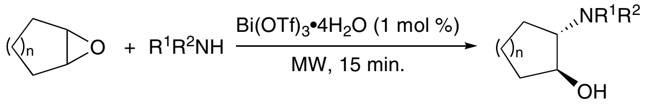
Entry	Catalyst	Yield **3a** (%)
1	—	<5
2	$BiCl_3$	5
3	$BiBr_3$	47
4	$Bi(OTf)_3 \cdot 4H_2O$	96
5	$Sc(OTf)_3$	97
6	$Ga(OTf)_3$	94
7	$Zn(OTf)_2$	95
8	HOTf	99

[a] Conditions: cyclohexene oxide **1** (1 mmol), cyclohexylamine **2a** (1.1 mmol), catalyst (1 mol %), microwaves, 15 min.

With $Bi(OTf)_3 \cdot 4H_2O$ identified as an effective catalyst for the epoxide opening, cyclohexene oxide was treated with various aliphatic amines (Scheme 2, $n = 2$). The reaction gave the corresponding 2-amino alcohols in high yields with all amines tested (Table 2, entries 1–5 and entry 7) except with dipropylamine (Table 2, entry 6). The procedure for these reactions is very simple as the pure product is obtained without aqueous work-up and without purification. In addition, the reaction could be substantially scaled up without decreasing the yield (conditions: cyclohexene oxide 30 mmol, morpholine 33 mmol, $Bi(OTf)_3 \cdot 4H_2O$ 0.3 mmol, microwaves, 15 min, 99% yield of 2-morpholinocyclohexanol).

The same method was also effective for the opening reaction of cyclopentene oxide with the same amines giving the corresponding 2-amino alcohols **5** (Scheme 2, Table 2, $n = 1$). Cyclohexylamine, piperidine, morpholine, pyrrolidine, and *n*-hexylamine afforded the expected product in high yields (Table 2, entries 1–5). Only dipropylamine produced the corresponding 2-amino alcohol in moderate yield (Table 2, entry 6).

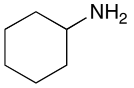
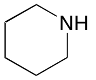
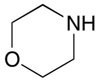
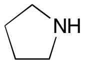
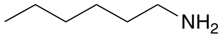
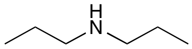
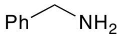
On the other hand, treatment of styrene oxide with different aliphatic amines gave a mixture of two regioisomers: **7a** and **7b** in high yields (Scheme 3, Table 3). Aminolysis of



1 (n = 2)
4 (n = 1)
2
3 (n = 2)
5 (n = 1)

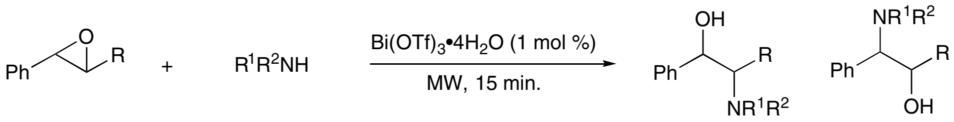
Scheme 2.

Table 2
Microwave-enhanced $Bi(OTf)_3 \cdot 4H_2O$-catalyzed opening of cyclohexene and cyclopentene oxide with various aliphatic amines[a]

Entry	Amine **2**	Yield **3** (%) ($n = 2$)	Yield **5** (%) ($n = 1$)
1	 NH2	96	90
2	 NH	92	100
3	 NH O	93	97
4	 NH	96	100
5	 NH2	93	96
6	 H N	48	48
7	 Ph NH2	100[b]	—

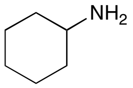
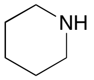
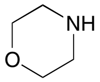
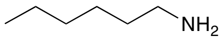
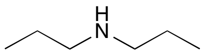
[a] Conditions: cyclohexene or cyclopentene oxide **1** or **4** (1 mmol), amine **2** (1.1 mmol), $Bi(OTf)_3 \cdot 4H_2O$ (1 mol %), microwaves, 15 min.

[b] Epoxide/amine ratio = 1.1:1.



Scheme 3.

Table 3
Microwave-enhanced $Bi(OTf)_3 \cdot 4H_2O$-catalyzed opening of styrene oxide with various aliphatic amines[a]

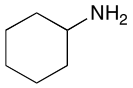
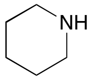
Entry	Amine **2**	Ratio **7a/7b**[b]	Yield **7** (%)
1		68/32	96[c]
2		59/41	100
3		37/63	100
4		66/34	84[c]
5		60/40	100

[a] Conditions: styrene oxide **6** (1 mmol), amine **2** (1.1 mmol), $Bi(OTf)_3 \cdot 4H_2O$ (1 mol %), microwaves, 15 min.

[b] Determined by ^1H NMR.

[c] Traces (<10%) of the corresponding amino diol were also detected.

Table 4
Microwave-enhanced $Bi(OTf)_3 \cdot 4H_2O$-catalyzed opening of *trans*-stilbene oxide with cyclohexylamine and piperidine[a]

Entry	Amine **2**	Yield **9** (%)
1		99
2		100

[a] Conditions: *trans*-stilbene oxide **8** (1 mmol), amine **2** (1.1 mmol), $Bi(OTf)_3 \cdot 4H_2O$ (1 mol %), microwaves, 15 min.

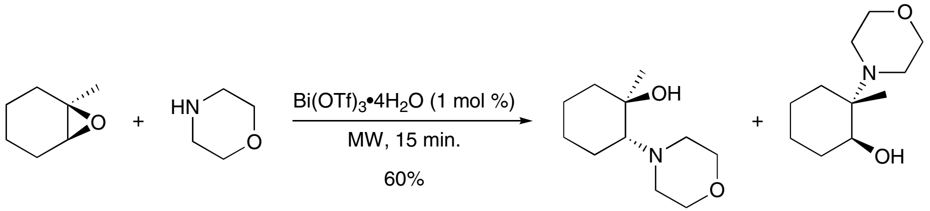
styrene oxide with cyclohexylamine, piperidine, and *n*-hexylamine afforded **7a** as the major regioisomer, by nucleophilic attack at the terminal carbon (Table 3, entries 1, 2, and 4). In the case of morpholine, preferential attack occurred at the benzylic position (Table 3, entry 3). The opening of styrene oxide by *n*-hexylamine led to the corresponding 2-amino alcohol in good yield (Table 3, entry 4). In this particular case and in the case of cyclohexylamine, traces of diol arising from the reaction of the amine with 2 equiv of styrene oxide were also detected (<10%) (Table 3, entries 1 and 4). Compared to the modest yields obtained for the opening of cyclohexene and cyclopentene oxides with dipropylamine (Table 2, entry 6), a quantitative yield was obtained for the opening of styrene oxide with dipropylamine (Table 3, entry 5).

In addition, the opening of *trans*-stilbene oxide **8** was studied with both cyclohexylamine and piperidine (Scheme 3, Table 4). In both cases, the pure 2-amino alcohol **9** was isolated in a quantitative yield using our standard conditions (Table 4, entries 1 and 2). Finally, the opening of the trisubstituted epoxide **10** with morpholine proceeded smoothly with good regioselectivity and moderate yield (Scheme 4).

Interestingly, for all these experiments, no side reaction such as epoxide rearrangement was observed under these conditions.[18] Indeed, when cyclohexene oxide was heated under microwave irradiation in the presence of $Bi(OTf)_3 \cdot 4H_2O$ and in the absence of amine, only trace amount of the rearranged aldehyde was observed, the major pathway being decomposition of starting material.

3. Conclusion

As an improvement over other catalyst systems, $Bi(OTf)_3 \cdot 4H_2O$ is a versatile catalyst for the epoxide opening with amines. The reaction affords up to quantitative yields in 2-amino alcohols in very short reaction times



Scheme 4.

(15 min), and using only 1 mol % of the catalyst under microwave assistance.[19] This method offers several advantages including mild reaction conditions, highly catalytic process, and no formation of by-products. The conditions are suitable for a variety of aliphatic amines. Also, the practical use of $Bi(OTf)_3 \cdot 4H_2O$ is highly valuable as an environmentally benign Lewis acid. Moreover, our protocol does not require any solvent for the reaction to proceed. The reaction is run neat. No aqueous work-up is needed for the reaction: the 2-amino alcohol is directly obtained after quick filtration of the catalyst. Because of its numerous benefits, this method for the green and straightforward synthesis of 2-amino alcohols using $Bi(OTf)_3 \cdot 4H_2O$ catalysis should find utility in the synthesis of biologically active compounds.

Acknowledgments

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Supplementary data

Experimental procedure and spectral data for all new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.12.100.

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19. All reactions were performed using a 400 W Biotage Initiator™ microwave synthesis instrument. *General procedure for the microwave-enhanced bismuth triflate-catalyzed epoxide opening*: In a capped microwave reactor, the epoxide (1 mmol), the amine (1.1 mmol), and $Bi(OTf)_3 \cdot 4H_2O$ (0.01 mmol) were mixed together, then brought to 160 °C for 15 min under microwave irradiation. 1 mL of diethyl ether

was added to the residue and the mixture was stirred, then filtered on a short Celite pad, washed with 1 mL of diethyl ether, and concentrated under vacuum. Ethyl acetate was used instead of diethyl ether to dissolve and wash when the crude mixture was not soluble in diethyl ether. Pure 2-amino alcohol was obtained as shown by ^{1}H NMR. Spectral data for **3**, **5**, **7**, **9**, and **11** agree with those previously reported in the literature.[17g,20]

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