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# An efficient method for regioselective ring opening of epoxides by amines under microwave irradiation using Bi(NO<sub>3</sub>)<sub>3</sub>.5H<sub>2</sub>O as a catalyst<sup>†</sup>

Bismuth(III)nitrate pentahydrate, a highly efficient environmentally benign catalyst, is used for the nucleophilic

ring opening of epichlorohydrin and styrene oxide with aromatic, aliphatic and heteroaromatic amines under solvent free microwave conditions reducing the reaction time drastically to afford the corresponding β-amino

alcohols in good to excellent yields with high regioselectivity. The products obtained were directly purified

by column chromatography and characterised by  ${}^{1}H \oplus {}^{13}C$  NMR, FTIR and mass spectroscopy.

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### Introduction

β-Amino alcohol has attracted a large number of researchers in the synthesis of a good amount of biologically active natural and synthetic products<sup>1,2</sup> including chiral auxiliaries.<sup>3a</sup> These play an increasingly vital role in medicinal chemistry, pharmaceuticals and organic synthesis. β-Blockers are used in the treatment of a wide variety of human disorders, like hypertension, sympathetic nervous system disorders, heart failure, and cardiac arrhythmias<sup>3b</sup> and also as insecticidal agents.<sup>3c</sup> The ring opening of epoxides with amines represents one of the most important and straightforward methods of preparing these compounds.<sup>4</sup> Various Lewis acid, viz. Y(NO<sub>3</sub>)<sub>3</sub>·6H<sub>2</sub>O,<sup>5</sup> ZrCl<sub>4</sub>,<sup>6</sup> Sc(OTf)<sub>3</sub>,<sup>7</sup> SmI<sub>2</sub>,<sup>8</sup> RuCl<sub>3</sub>,<sup>9</sup> and NbCl<sub>5</sub><sup>10</sup> catalysed reactions have been examined for this class of reactions. The classical synthesis of β-amino alcohol involves heating of epoxides with amines in excess at elevated temperatures<sup>11</sup> but high temperature may not be the standard condition for molecules having sensitive functional groups. Therefore a milder and improved procedure has been developed using alumina,<sup>12</sup> metal amides,<sup>13</sup> metal alkoxides,<sup>14</sup> metal halides,<sup>15</sup> and silica perchloric acid.<sup>16</sup> Due to the toxicity of metals, a better catalyst is still desirable for the nucleophilic ring opening of epoxides by various amines to afford the corresponding β-amino alcohols. A literature survey also reveals that epoxide ring opening reaction can be conducted under microwave irradiation.<sup>17-20</sup> Bismuth(m)chloride<sup>21</sup> has also been tried earlier for the ring opening of epoxides but it required a longer reaction time.

It is evident from the literature survey that bismuth(m)nitrate pentahydrate has been used for functional group transformation,<sup>22</sup> Michael addition,<sup>23</sup> synthesis of coumarins<sup>24</sup> and nitration.<sup>25</sup> The low toxicity,<sup>26</sup> lower cost and versatile nature of bismuth(m)nitrate pentahydrate as an efficient catalyst prompted us to investigate its activity for epoxide ring opening. Here the present report describes a highly regioselective and efficient protocol for the aminolysis of aliphatic and aromatic epoxides with a variety of amines under solvent free microwave conditions.

## Results and discussion

In our initial efforts to optimise the finest reaction conditions for aminolysis of styrene oxide, aniline and bismuth(m)nitrate pentahydrate as catalysts were mixed and placed in a microwave for the appropriate time intervals as a model reaction. Monitoring of the reaction was done by TLC and the completion of the reaction was confirmed by the complete disappearance of the starting materials. To our delight the reaction was completed in much less time with a single isomer. The reaction mixture was treated with dichloromethane; the crude product thus obtained was purified by column chromatography to get the regioselective 2-phenyl-2-phenylaminoethanol in an appreciably good amount (Scheme 1).

To study the effect of catalyst loading and the wattage of the microwave on the ring opening of epoxides with amines, we next examined the model reaction in the presence and absence of the catalyst under varied microwave conditions (Table 1). The results in Table 1 depict that in the absence of a catalyst, the reaction did not proceed at all (Table 1, entry 1), while the desired product was isolated in 85% yield under optimized conditions (Table 1, entry 5). Reaction at a higher wattage of

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Scheme 1 Synthesis of  $\beta$ -amino alcohol under optimized conditions.

 
 Table 1
 Optimal conditions of catalyst loading and wattage used for microwave irradiation

Entry	Watt	Catalyst loading <sup>a</sup> (mol%)	Yields <sup><math>b</math></sup> (%)
1	100	No catalyst	NR
2	100	1	60
3	100	3	60
4	100	5	70
5	100	10	85
6	300	10	83
7	900	10	82

<sup>*a*</sup> Reaction conditions: epoxide (1 mmol), amine (1 mmol), solvent free microwave irradiation. <sup>*b*</sup> Isolated yield.

900 W did not show any remarkable change in the yield of the product.

We also examined the model reaction in various solvents in the presence of 10 mol% of catalyst (Table 2). The reaction did not proceed even with longer irradiation times when toluene was taken as a solvent (Table 2, entry 1) while other polar solvents gave similar regioselectivity, but required a longer reaction time with low yield of the product as compared to our optimized solvent free microwave assisted reaction conditions (Table 2, entries 2–6). We examined the above model reaction under neat conditions at 50 °C, 100 °C and 150 °C also. But under all these conditions the products were isolated in poor yields (Table 2, entries 7–9).

On comparison of the developed method with the state of the art protocols, the results obtained by our newly developed methodology were very much exciting and inspiring in terms of being solvent free and less time consuming, and yielding the products in appreciably good amounts (Table 3).

The versatility of this protocol was studied by using various substituted amines and epoxides under optimized reaction conditions (Scheme 2, Table 4). The desired product was obtained in good to very good yields and also in a shorter reaction time. Solvent free conditions are found to be the best as the effective

Table 2 Screening of the solvent and thermal conditions for the ring opening of styrene oxide with aniline using  $Bi(NO_3)_3$ - $SH_2O$  (10 mol%)

Entry	Solvent	Time (s)	Yields <sup>d</sup> (%)
1	PhMe	7200	NR
2	H <sub>2</sub> O	2400	25
3	THF	7200	20
4	DCM	3600	70
5	MeCN	1500	80
6	Microwave 100 W solvent free	150	85
Thermal o	conditions		
7	_	$3600^{a}$	20
8	_	$3600^{b}$	23
9	_	3600 <sup>c</sup>	24

 $^a$  Solvent free thermal conditions at 50 °C.  $^b$  100 °C.  $^c$  150 °C.  $^d$  Isolated yield.

Table 3 A table of comparison with state of the art protocols

Entry	Catalyst	Amount	Time (min)	Yields <sup>a</sup> (%)	Ref.
1	Y(NO <sub>3</sub> ) <sub>3</sub> ·6H <sub>2</sub> O	1 mol%	180-420	81-92	5
2	ZrCl <sub>3</sub>	5 mol%	15	92-98	6
3	Sc(OTf) <sub>3</sub>	5 mol%	120-300	82-95	7
4	Montmorillonite	0.2 gm	1	25-85	19
5	BiCl <sub>3</sub>	15 mol%	60-270	71-92	21
6	$Bi(NO_3)_3 \cdot 5H_2O$	10	0.2-4	75 <b>-92</b>	Our work
a					

Reported yields



Scheme 2 Aminolysis of epoxides with aromatic and aliphatic amines.

 Table 4
 Microwave assisted ring opening of epoxides with various amines

 in the presence of a catalyst
 Image: Comparison of the presence of the pr

Entry	$R_1$	R <sub>2</sub>	R <sub>3</sub>	Product <sup>a</sup>	Time (s)	Yields <sup>b</sup> (%)
1	Ph	Ph	Н	А	150	85
2	Ph	N-Methyl pip	erazine	Α	30	85
3	Ph	Piperadine		Α	50	85
4	Ph	4-Methyl pipe	erazine	Α	27	92
5	Ph	Isopropyl	Isopropyl	Α	110	87
6	Ph	n-Propyl	<i>n</i> -Propyl	Α	160	88
7	Ph	α-Naphthyl	н	Α	55	90
8	Ph	$2-CH_3C_6H_4$	Н	Α	150	86
9	Ph	<i>n</i> -Butyl	Ме	Α	56	84
10	-CH <sub>2</sub> Cl	Ph	Н	В	150	76
11	-CH <sub>2</sub> Cl	$4-CH_3C_6H_4$	Н	В	180	82
12	-CH <sub>2</sub> Cl	$2-CH_3C_6H_4$	Н	В	240	92
13	-CH <sub>2</sub> Cl	α-Naphthyl	Н	В	50	92
14	-CH <sub>2</sub> Cl	<i>n</i> -Propyl	<i>n</i> -Propyl	В	120	78
15	-CH <sub>2</sub> Cl	Piperadine	10	В	60	80
16	-CH <sub>2</sub> Cl	N-Methyl pip	erazine	В	30	75
17	-CH <sub>2</sub> Cl	$2,4,6-BrC_6H_2$	Н	NR	>2 h	
18	Ph	2,4,6-BrC <sub>6</sub> H <sub>2</sub>	Н	NR	>2 h	

<sup>*a*</sup> Purity of isolated regioisomers was determined by HPLC. <sup>*b*</sup> Isolated yield.

concentrations of the reagents are always maximum under solvent free conditions. The results also indicate the effect of both steric and electronic factors on the regioselectivity of the reaction.

The reaction of styrene oxide with both aromatic and aliphatic amines afforded a high ratio of regioisomer A by nucleophilic attack at the benzylic carbon (Table 4, entries 1–9), which could be due to the localized positive charge on the more highly substituted benzylic carbon, and yields the major product.<sup>27</sup> While the regioselectivity was reversed when an aliphatic epoxide like epichlorohydrin was treated with aromatic and aliphatic amines to afford the regioisomer B (Table 4, entries 10–16). This behaviour may be due to steric factors predominating over electronic factors. Aniline having electron withdrawing groups at the *ortho* and *para* positions did not yield any product even in trace amounts (Table 4, entries 17 and 18).

All the products were produced in very good yields despite the lower reactivity of aromatic primary amines, while cyclic secondary amines took much less time for the completion of the reaction yielding the product in excellent yield (Table 4, entries 7–9 and 15–16). Aromatic amines bearing electron withdrawing groups did not react to give the desired product even after prolonged exposure to microwave irradiation (Table 4, entries 17 and 18). Aminolysis of epoxides afforded  $\beta$ -amino alcohol with high regioselectivity with a single isomer only. The <sup>1</sup>H NMR spectrum of all the products is pure enough to confirm the presence of a single isomer which is also supported by HPLC data.

Inspired by the above result, we next examined the ring opening of epoxides with heteroaromatic amines like imidazole. The literature survey of such reports suggests the requirement of high temperature<sup>28</sup> and high pressure<sup>29</sup> to obtain this pharmaceutically important entity and thus milder conditions for the synthesis of such hetero-amino alcohols are required. Therefore we studied the ring opening of styrene oxide and epichlorohydrin with imidazole to afford heteroamino alcohols in excellent yield in much less time (Scheme 3).

The actual mechanism of these reactions is not clear at this stage. The possible mechanism for the ring opening of epoxides with bismuth(m)nitrate pentahydrate as the catalyst under microwave irradiation conditions occurred through a weak interaction between the catalyst and epoxide. In order to understand the role of the nitrate ion in the reaction we here performed the following sets of reactions under our optimized reaction conditions, and the results are summarised in Table 5.

These observations indicate that both nitrate and  $Bi^{3+}$  play an active role in the transition state to initiate the reaction (Table 5, entry 4). In our preliminary mechanistic investigation the secondary effect of the nitrate anion may be attributed to the unusual catalytic behaviour of the bismuth metal ion (Scheme 4). The regioselectivity of products A and B depends upon both



Scheme 3 Synthesis of heteroamino alcohols.

Table 5	Table analysing	the role of	nitrate ions in	catalysing th	ne reaction
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Entry	Catalyst <sup>a</sup>	Result
1	Bi(OH) <sub>3</sub>	No reaction
2	$Al(NO_3)_3 \cdot 9H_2O$	No reaction
3	Fe(NO <sub>3</sub> ) <sub>3</sub> ·6H <sub>2</sub> O	No reaction
4	$Bi(OH)_3$ and $KNO_3$	Effective reaction

 $^a$  Reaction conditions: epoxide (1 mmol), amine (1 mmol), catalyst (10 mol%), solvent free microwave irradiation.



**Scheme 4** Plausible mechanism for the regioselective ring opening of epoxide by amines as a nucleophile.

steric and electronic factors.

To our curiosity we also studied the role of water of crystallisation of bismuth nitrate pentahydrate in the formation of  $\beta$ -amino alcohol, by replacing the water molecule with a DMF molecule.<sup>30</sup> It is very interesting to report that the reaction did not proceed at all indicating that water of crystallization is also playing a notable role in proton exchange at the transition state to form  $\beta$ -amino alcohol by the ring opening of epoxides with both aliphatic, aromatic and heteroaromatic amines.

### Experimental

#### Materials and methods

All the solvents and reagents were used as supplied by commercial sources. The recorded melting points are uncorrected. IR spectra were recorded in KBr on a Schimadzu FTIR 8401 spectrometer and Perkin Elmer version 10.03.06 for the liquid samples. <sup>1</sup>H and <sup>13</sup>C spectra were recorded on a Bruker DRX 300 spectrometer operating at 300 MHz for <sup>1</sup>H NMR and 75 MHz for <sup>13</sup>C NMR as solutions in  $CDCl_3$  and  $DMSO-d_6$ . The ESI mass spectra were measured on a Waters UPLC-TQD spectrometer. TLC was performed on a silica coated glass plate, spots were developed in an I2 Chamber or visualized in a UV chamber. A CEM Discover microwave was used for irradiation purposes. A HPLC system (Cyberlab, 20, Salo Terrace, Milbury, MA 01527, USA) was used with a HISEIDO C18 column, MG 5  $\mu$ m, size – 4.6 mm ID  $\times$  250 mm, and an injection system, 7725i (Rheodyne) made in USA, with an injection volume of 20 µL, and a flow rate of 0.5 µL. Pure HPLC grade methanol was used as an eluent.

#### General procedure for the synthesis of β-amino alcohols

An epoxide (1 mmol), amine (1 mmol) and catalyst (10 mmol%) were mixed thoroughly at room temperature and afterwards the mixture was intermittently irradiated in a microwave for the appropriate time period. The reaction was monitored by TLC; after the completion of the reaction, the obtained crude product was purified by column chromatography to afford the corresponding  $\beta$ -amino alcohols. All synthesized compounds were fully characterized by FTIR, <sup>1</sup>H & <sup>13</sup>C NMR and mass spectroscopy (ESI†).

### Conclusions

Bi(NO<sub>3</sub>)<sub>3</sub>·5H<sub>2</sub>O, an environmentally benign and cheaper catalyst, effectively prompts the ring opening of epoxides under solvent

free microwave conditions. The nature of the catalytic reaction shows the secondary effect of the nitrate group. The milder reaction conditions, shorter reaction times, excellent regioselectivity, reasonably higher yields, and applicability to aromatic, aliphatic and heteroaromatic amines are the main advantages of the protocol developed.

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- 30  $Bi(NO_3)_3 \cdot 5H_2O$  was heated in anhydrous DMF for 4 hours. DMF was removed under vacuum until dryness, the residue obtained was analysed with the help of FTIR to check the replacement of the water molecule with the DMF molecule. See the ESI<sup>†</sup>.