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Bismuth(III) Trifluoromethanesulfonate and Trifluoroacetate as Convenient and Efficient Catalysts for Regio- and Chemoselective Ring Opening of Epoxides in Reactions with Anilines*

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Abstract—Bismuth(III) trifluoromethanesulfonate and trifluoroacetate are highly efficient and practical catalysts for oxirane ring opening in reactions of epoxides with substituted anilines. The reactions are characterized by high chemoselectivity and good to excellent yields of the products.

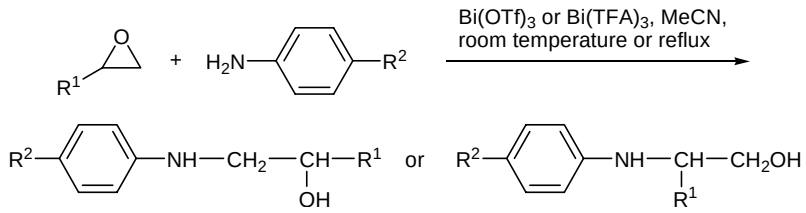
β-Amino alcohols are universal synthons which are widely used in organic chemistry. Some β-amino alcohols are starting compounds for the synthesis of dihydrooxazoles which were proposed as protecting groups [1]. β-Amino alcohols exhibit insecticide properties and are used as chiral ligands in asymmetric syntheses [2–4]. In addition, the β-amino alcohol fragment is a very important functional group in some physiologically active natural compounds, e.g., *Sphingosine*, which is an intracellular secondary messenger [5]. Therefore, elaboration of simple and ecologically clean procedures for the synthesis of β-amino alcohols constitutes a field of extensive research in organic synthesis.

Despite diverse pharmacological activity and synthetic applications, little attention was given to methods of synthesis of β-amino alcohols. The most important procedures are based on opening of epoxy derivatives with amines in the presence of Lewis acids [6–14] or ionic liquids [15]. These procedures often require the use of expensive reagents, long reaction time, and severe conditions; they are characterized by poor yields (especially in reactions with aliphatic epoxides) and are accompanied by side processes involving polymerization and rearrangements of initial oxiranes. Acid-catalyzed opening of the oxirane ring in epoxy compounds has received a limited application, and careful control of the acidity of the medium is necessary to prevent side reactions. Therefore, development of new efficient procedures for the above transformations remains an important problem.

In a series of recent publications it was noted that the use of bismuth compounds in organic reactions is ecologically friendly [16–19]. Moreover, bismuth derivatives are widely used in medicine [20–23]. A number of bismuth salts are commercially available, cheap, easy to handle with, and relatively stable in air in the presence of a small amount of moisture [24–26].

Taking into account our interest in bismuth(III) salts [27–30] as ecologically clean reagents for organic

Scheme 1.



R = Ar, Alk; R' =H, Me, Br.

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Table 1. Reactions of epoxy derivatives with aromatic amines in the presence of $Bi(TFA)_3$ and $Bi(OTf)_3$

Run no.	Product[a]	Catalyst $Bi(OTf)_3$			Catalyst $Bi(TFA)_3$		
		yield,[b] %	amount of catalyst, mmol	reaction time, min	yield,[b] %	amount of catalyst, mmol	reaction time, min
1	*trans*-2-Phenylaminocyclohexanol	96	0.02	30[c]	90	0.04	35[c]
2	*trans*-2-*p*-Tolylaminocyclohexanol	90	0.01	30	93	0.03	60
3	*trans*-2-*p*-Bromophenylaminocyclohexanol	99	0.03	45[c]	90	0.07	45[c]
4	$PhNHCH(Ph)CH_2OH$	93	0.02	15[c]	89	0.04	25[c]
5	$p\text{-}MeC_6H_4NHCH(Ph)CH_2OH$	90	0.01	15[c]	88	0.03	15[c]
6	$p\text{-}BrC_6H_4NHCH(Ph)CH_2OH$	92	0.02	15[c]	82	0.04	15[c]
7	$PhNHCH_2CH(OH)CH_2OPh$	95	0.02	30	86	0.04	30
8	$p\text{-}MeC_6H_4NHCH_2CH(OH)CH_2OPh$	94	0.01	30	78	0.03	40
9	$p\text{-}BrC_6H_4NHCH_2CH(OH)CH_2OPh$	90	0.03	60	83	0.07	30
10	$PhNHCH_2CH(OH)CH_2OCH_2CH{=}CH_2$	89	0.02	40	70	0.04	45
11	$p\text{-}MeC_6H_4NHCH_2CH(OH)CH_2OCH_2CH{=}CH_2$	85	0.01	45	72	0.03	60
12	$p\text{-}BrC_6H_4NHCH_2CH(OH)CH_2OCH_2CH{=}CH_2$	88	0.03	85	70	0.07	75
13	$PhNHCH_2CH(OH)(CH_2)_5CH_3$	83	0.02	20	72	0.04	35
14	$p\text{-}MeC_6H_4NHCH_2CH(OH)(CH_2)_5CH_3$	95	0.01	40	79	0.03	60
15	$p\text{-}BrC_6H_4NHCH_2CH(OH)(CH_2)_5CH_3$	98	0.03	90	70	0.07	65
16	$PhNHCH_2CH(OH)CH_2O(CH_2)_3CH_3$	85	0.02	60	73	0.04	80
17	$p\text{-}MeC_6H_4NHCH_2CH(OH)CH_2O(CH_2)_3CH_3$	92	0.02	60	85	0.04	70
18	$p\text{-}BrC_6H_4NHCH_2CH(OH)CH_2O(CH_2)_3CH_3$	89	0.03	90	80	0.04	100
19	$PhNHCH_2CH(OH)CH_2Cl$	88	0.02	75	70	0.04	60
20	$p\text{-}MeC_6H_4NHCH_2CH(OH)CH_2Cl$	85	0.02	70	75	0.04	85
21	$p\text{-}BrC_6H_4NHCH_2CH(OH)CH_2Cl$	92	0.03	75	80	0.1	85

[a] All compounds were characterized by the IR, ^1H and ^{13}C NMR, and mass spectra.
[b] Yield of the isolated product.
[c] At room temperature.

synthesis, we have already reported that bismuth(III) trifluoroacetate $Bi(TFA)_3$ and trifluoromethanesulfonate $Bi(OTf)_3$ are very effective catalysts for the transformation of epoxides into thiiranes [31] and 1,3-dioxolanes [32]. In continuation of our studies on the application of bismuth(III) salts in organic synthesis, the present communication describes a mild and efficient procedure of oxirane ring opening in epoxy compounds by the action of aromatic amines in acetonitrile in the presence of $Bi(TFA)_3$ and $Bi(OTf)_3$ (Scheme 1). The catalytic nature and wide potential of these reagents makes the proposed procedure an attractive alternative to the existing methods of preparation of β-amino alcohols.

Various epoxides containing both activated and inactivated groups were brought into reaction with aniline, *p*-toluidine, and *p*-bromoaniline in the presence of a catalytic amount of Bi(III) salts. The reactions were carried out at room temperature or at the boiling point of the mixture, and the corresponding β-amino alcohols were isolated in good yields. The results are summarized in Table 1. The observed high reactivity and selectivity are analogous to those reported for the reactions in the presence of strong Lewis acids [6–14]. Epoxycyclohexane (as model compound) readily reacted with aromatic amines in the presence of $Bi(TFA)_3$ and $Bi(OTf)_3$ within a short time (15–100 min) and with excellent yields (Table 1, run nos. 1–3). Unlike the other oxiranes, 1,2-epoxy-1-phenylethane reacted with aromatic amines (Table 1, run nos. 4–6) to afford the corresponding β-amino alcohols as a result of attack on the α-carbon atom with high yield and regioselectivity. The data in Table 1 show that opening of the oxirane ring in epoxides by

the action of aromatic amines in the presence of $Bi(OTf)_3$ is faster than in the presence of $Bi(TFA)_3$; therefore, the process requires a shorter time. It should be noted that we failed to obtain the corresponding β-amino alcohols by reactions with *p*-nitroaniline, *o*-phenylenediamine, and aliphatic amines under similar conditions. A probable reason is the reduced nucleophilicity of *p*-nitroaniline or strong basicity and complexing power of the above amines with respect to the catalyst. An analogous pattern was observed previously [13] in reactions with metal trifluoromethanesulfonates as catalysts.

In order to estimate intermolecular chemoselectivity of the catalysts, we performed competing reactions. The results are given in Table 2. No such selectivity was observed previously, and this fact can be regarded as an additional advantage of the proposed procedure.

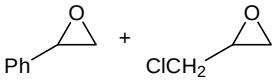
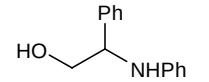
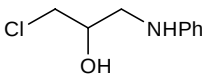
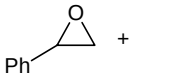
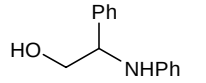
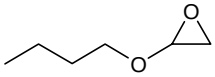
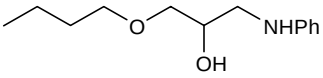
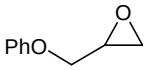
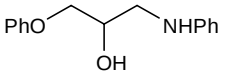
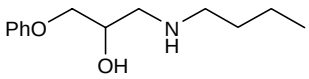
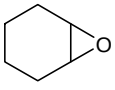
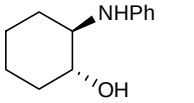
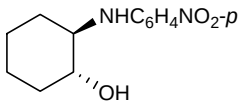
Thus, the described method is an attractive alternative ensuring regio- and chemoselective opening of the oxirane ring in epoxy derivatives in reactions with aromatic amines. It is advantageous due to mild reaction conditions, high selectivity, improved yields of the products, high rate, and experimental simplicity; in addition, it utilizes stable and nontoxic catalysts.

EXPERIMENTAL

The products were identified by comparing their spectral parameters (^{1}H NMR and IR) with those reported in the literature. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance spectrometer (200 MHz). The IR spectra were measured on a Shimadzu 470 spectrophotometer. GLC analysis was performed on a Shimadzu Gc-8A chromatograph equipped with a flame ionization detector. Bismuth(III) trifluoroacetate and trifluoromethanesulfonate were prepared by the procedures described in [33, 34].

Reaction of epoxy derivatives with anilines in the presence of $Bi(TFA)_3$ and $Bi(OTf)_3$ (*general*

Table 2. Competing opening of the oxirane ring with aromatic amines in the presence of $Bi(TFA)_3$ and $Bi(OTf)_3$

Run no.	Substrate	Amine	Product	Yield, % (reaction time, min)	
				$Bi(OTf)_3$[a]	$Bi(TFA)_3$[b]
1		$PhNH_2$		85 (25)	80 (25)
				0	0
2		$PhNH_2$		87 (20)	79 (30)
				8	5
3		$PhNH_2$ + $C_4H_9NH_2$		93 (45)[c]	82 (45)[c]
				0	0
4		$PhNH_2$ + p-$O_2NC_6H_4NH_2$		95 (30)	88 (45)
				0	0

[a] 0.02 mmol.

[b] 0.04 mmol.

[c] At the boiling point.

procedure). A 0.03–0.1-mol portion of $Bi(TFA)_3$ or a 0.01–0.04-mol portion of $Bi(OTf)_3$ was added to a solution of 1 mol of the corresponding epoxy derivative and 1 mmol of aniline in 2 ml of acetonitrile. The mixture was stirred at room temperature or at the boiling point over a period specified in Table 1. The progress of the reaction was monitored by GLC or TLC. When the reaction was complete, the solvent was evaporated, the residue was washed with 25 ml of 0.5 N hydrochloric acid and extracted with methylene chloride (3×10 ml), the organic phase was dried over Na_2SO_4, the solvent was evaporated, and the crude product was purified by column or thin-layer chromatography on silica gel. The yields of pure β-amino alcohols were 70–99%. Spectral parameters of some β-amino alcohols are listed below.

***trans*-2-(4-Bromophenylamino)cyclohexanol** (Table 1, run no. 3). Yellow crystals, mp 126–128°C; published data: mp 125–127°C. IR spectrum, ν, cm^{-1}: 3497–3286 (NH, OH), 1580, 1506, 1063. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.09 m (1H), 1.38 m (3H), 1.72 m (2H), 1.92–2.23 m (2H), 2.94–3.2 d.d.d (1H, *J* = 10.9, 9.4, 3.8 Hz), 3.22–3.42 d.d.d (1H, *J* = 10.1, 10.1, 4.3 Hz), 3.51–4.07 br.s (2H), 6.49 d (2H, *J* = 10.3 Hz), 7.22 d (2H, *J* = 10.3 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 24.6, 25.3, 31.8, 33.7, 60.9, 74.8, 110.6, 116.5, 132.5, 146.9.

1-Allyloxy-3-phenylamino-2-propanol (Table 1, run no. 10). Viscous liquid. IR spectrum (NaCl), ν, cm^{-1}: 3510–3115 (NH, OH), 3009, 1598, 1500, 1068. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.15 d.d (2H, *J* = 9.9, 10 Hz), 3.26 d.d (2H, *J* = 5, 7 Hz), 3.52 m (2H), 3.81 br.s (1H), 4.08 d (2H, *J* = 9 Hz), 5.23 d (2H, *J* = 12 Hz), 5.98 m (1H), 6.62 d (2H, *J* = 10 Hz), 7.15 d (2H, *J* = 10 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 47.4, 69.4, 72.8, 73.9, 113.9, 117.9, 118.5, 129.7, 134.7, 142.7. Found, %: C 69.30; H 8.39; N 6.68. $C_{12}H_{17}NO_2$. Calculated, %: C 69.54; H 8.27; N 6.76.

1-Phenylamino-2-octanol (Table 1, run no. 13). Viscous liquid. IR spectrum (NaCl), ν, cm^{-1}: 3598–3100 (NH, OH), 1592, 1495. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.92 t (3H, *J* = 7 Hz), 1.24–1.86 m (10H), 3.21 d.d (2H, *J* = 10, 10 Hz), 3.32 d.d (1H, *J* = 8, 4 Hz), 3.91 m (1H), 6.68–7.35 m (5H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.5, 23.0, 26.0, 29.8, 32.2, 35.5, 51.0, 70.7, 114.0, 118.7, 129.7, 151.6. Found, %: C 75.71; H 10.66; N 6.48. $C_{14}H_{23}NO$. Calculated, %: C 75.97; H 10.47; N 6.33.

3-Chloro-1-phenylamino-2-propanol (Table 1, run no. 19). Viscous liquid. IR spectrum (NaCl), ν, cm^{-1}: 3504–3100 (NH, OH), 1594, 1497, 1090. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.24 m (2H), 3.45 d.d (1H, *J* = 10.1, 4.8 Hz), 3.72 d (2H, *J* = 8 Hz), 4.12 m (1H), 6.74 m (3H), 7.19 m (2H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 47.7, 48.1, 70.2, 113.9, 118.9, 129.9, 148.0. Found, %: C 58.02; H 6.68; N 7.69. $C_9H_{12}ClNO$. Calculated, %: C 58.23; H 6.51; N 7.54.

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