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Short communication

A facile and efficient synthesis of β-amino alcohols using 2,2,2-trifluoroethanol as a metal-free and reusable medium

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ABSTRACT

Trifluoroethanol was used as a reusable catalyst and medium for the ring opening of epoxides using aliphatic and aromatic amines as nucleophile under mild conditions to give the corresponding β-amino alcohols in high yields and regioselectivity.

1. Introduction

Due to their ease of formation and high reactivity, epoxides are important and useful synthetic intermediates in organic synthesis. The strain of their three-membered ring together with the polarization of the C–O bonds makes epoxides susceptible to reaction with a large variety of reagents such as nucleophiles, electrophiles, acids, bases, reducing agents and some of the oxidizing reagents [1]. Epoxides are efficiently converted into functionalized alcohols, as a handle for further manipulations, by employing various nucleophilic ring-opening reactions. This method provides a suitable route for the formation of C–C, C–N, C–O, C–P, C–S, C–N_3, C–X (X = halogen) 6-bonds [2]. This reaction, which is usually carried out with a large excess of nucleophiles at elevated temperature with long reaction times and drastic conditions, often fails when the nucleophile or the epoxides is sterically too bulky or the nucleophile having poor nucleophilicity or low boiling point is used. Unless there is a structural or a stereochemical bias, generally multiple products are obtained due to the lack of regioselectivity in the ring opening step [3]. These are some significant limitations on the general utility of nucleophilic ring-opening reactions.

β-Amino alcohols are of interest as structural units with wide utility for the synthesis of various biologically active natural products, unnatural amino acids, β-blockers, insecticidal agents, chiral auxiliaries and as synthons for the synthesis of heterocyclic compounds [4–13]. Despite the potential importance of β-amino alcohols, comparatively few methods for their preparations have been reported. Classical method for the synthesis of β-amino alcohols involves the heating of epoxide with an excess of amines at elevated temperature, which is not only unfavorable to certain functional groups, but also to the control of regioselectivities [14,15]. Several Lewis acids or Bronsted acids as a useful activator have been reported. That is, high to excellent regioselectivity of aminolysis of epoxides has been observed with $Sn(OTf)_2$ [16], $Cu(OTf)_2$ [16], $Sm(OTf)_3$ [17], $Al(OTf)_3$ [18], $Er(OTf)_3$ [19], $InCl_3$ [20], $BiCl_3$ [21], $SbCl_3$ [22], $ZnCl_2$ [23], $InBr_3$ [24], $CoCl_2$ [25], $Cu(BF_4)_2$ [26], Al_2O_3 [27], ionic liquids [28], silica [29–30], sulfated zirconia [31] and $Y(NO_3)_3{\cdot}6H_2O$ [32]. In general, efficient separation of the amino alcohol product from the Lewis acid catalyst used is often troublesome due to the emulsion formation under basic conditions at the aqueous work-up step. Furthermore, with many Lewis acids, amines fail to open up epoxides, because the strong affinity of many Lewis acids for amino groups does not allow regeneration of the Lewis acids in the reaction. Moreover, the main disadvantage of almost all existing methods is that the catalysts are destroyed in the work-up procedure and cannot be recovered or reused. A major drawback associated with metal amides Mg, Li, Pb, Sn, Si is that epoxides bearing α-hydrogens, frequently undergo rearrangement

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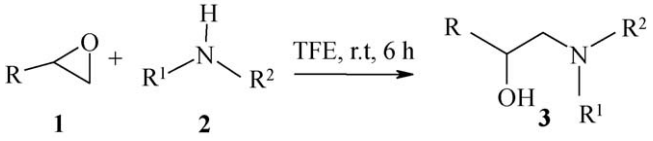
to produce allyl alcohols as the major products and primary amines show no regioselectivity [33]. Aliphatic amines do not react under the $CoCl_2$ catalyzed opening of epoxides. Hence, there is a need for new versatile methods.

Fluorinated alcohols are well-known as a polar solvent [34,35] of high ionizing power [36], low nucleophilicity [37–41] and have been the subject of considerable interest since their introduction as "green" solvents for reactions. Besides their usefulness as powerful reaction media, fluorinated alcohols have been well recognized as efficient catalysts and successfully applied in many organic reactions [42–60]. The most commonly used and cheapest fluorinated alcohols are trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP), which are available on a commercial scale.

2. Results and discussion

In 2000 Bégué et al. introduced the use of TFE and HFIP to catalyze the ring opening of epoxide with amines [52]. They reported that no reaction was observed between cyclohexene oxide and aniline in TFE at room temperature and even at reflux temperature. Much to our surprise, when we carried out the reaction between 2,3-epoxy-propylphenyl ether and aniline in TFE, the corresponding amino alcohol derivative (Scheme 1) **3aa** was obtained in high yield (86%) at ambient temperature. The scope of the reaction was explored by using a variety of epoxides **1a–e** and



1 **2** **3**

Scheme 1. Ring opening of epoxides with amines.

amines **2a–g** of diverse structures could be used with the results collected in Table 1.

These data indicate that the reaction is highly efficient for all types of substrates. In a similar manner epoxides (**1a–d**) reacted smoothly with aromatic and aliphatic amines to afford the corresponding β-amino alcohols in very good yields with high regioselectivity. In these cases (**1a–c**), the epoxide opening took place in regioselective manner preferentially by terminal attack of the nucleophile. Furthermore, the cyclic aliphatic amines such as morpholine and piperadine reacted with opxides **1a–c** to afford the corresponding β-amino alcohols in excellent yields (Scheme 1, entries **3aa–cc**). We have clearly observed the ^{1}H NMR spectra of crude products showing the formation of only one regioisomer in each case and any other products could not be detected. An interesting feature of this aminolysis (Scheme 1) is that the reaction of aniline derivatives and aliphatic amines with styrene oxide gives the corresponding β-amino alcohols in high yield and

Table 1
Ring opening of epoxides with various amines at room temperature in TFE.

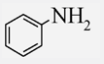
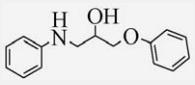
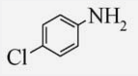
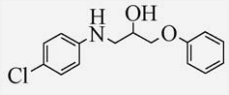
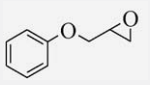
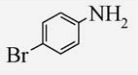
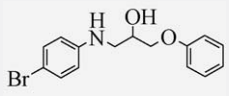
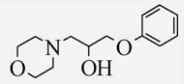
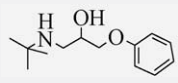
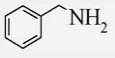
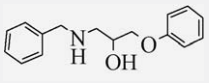
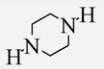
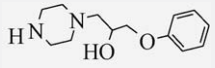
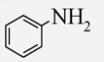
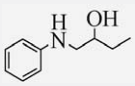
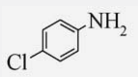
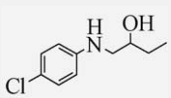
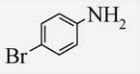
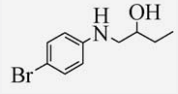
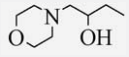
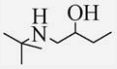
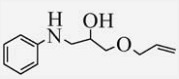
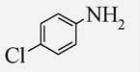
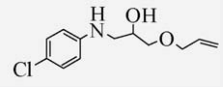
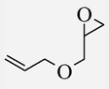
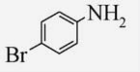
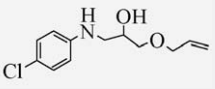
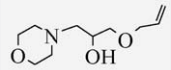
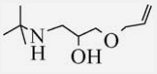
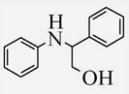
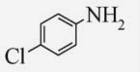
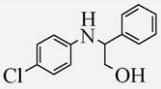
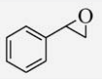
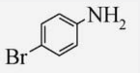
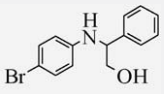
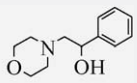
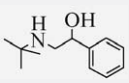
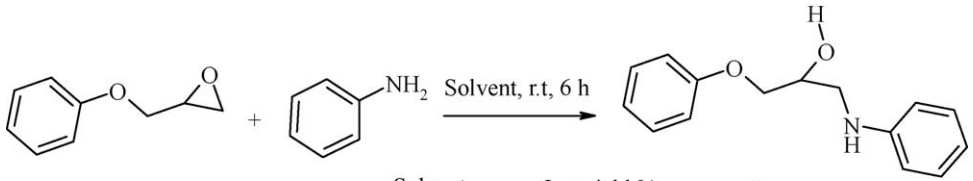
Entry	Epoxide	Amine	Product	% **3** [Ref.]
1				86 [26]
2				90 [18]
3				92 [18]
4				100 [18]
5				100 [18]
6				85 [18]
7				100 [18]
9				92 [26]
10				90 [18]

Table 1 (*Continued*)

Entry	Epoxide	Amine	Product	% **3** [Ref.]
11				92 [18]
12				100 [31]
13				70 [31]
13				100 [18]
14				80 [18]
15				90 [18]
16				100 [18]
17				90 [18]
18				92 [26]
19				90 [26]
20				92 [26]
21				90 [26]
22				70 [26]
23			No reaction	

in a different regioselectivity. In the case of aniline and low reactive aniline derivatives, preferential attack occurs at the benzylic carbon (α), however, reactive aliphatic amines attack preferentially at the terminal carbon (β) of styrene oxide. We propose hydrogen bonding interaction and amine reactivity are the main factors that influence the regioselectivity of the process. This regioselectivity was observed previously in the literature [61]. When we carried out the reaction between cyclohexene oxide and aniline in TFE at room temperature, the result was similar to Bégué's study [52]. After the reaction, TFE can be easily separated from the product and reused without any decrease in its activity. For example, the reaction of 2,3-epoxy-propylphenyl ether (**1a**) and morpholine (**2d**) afforded the corresponding β-amino alcohol (**3ad**) in 100%, 95%, and 95% isolated yield over three cycles.

We focused our attention on the study of scope and limitations of title reaction with respect to the solvents. Thus,



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

Solvent	**3aa** yield %
H_2O	0
CH_2Cl_2	0
$C_2H_4Cl_2$	0
MeOH	30
EtOH	20
DMF	0
CH_3CO_2H	0
HCOOH	0
tert-Butanol	5
TFE	86
HFIP	80

Scheme 2. The reaction of 2,3-epoxyallyl phenyl ether and aniline in different solvents.

we examined the reaction of 2,3-epoxyallyl phenyl ether and aniline in different solvents. The results are summarized in Scheme 2, and show that, high conversions were obtained with TFE and HFIP. Although there is no solid evidence to support the catalytic mechanism of TFE in the reaction, it is surely reasonable to propose that the high polarity and the hydrogen bonding interaction of TFE with epoxides may be responsible for the promotion of the reaction.

3. Conclusions

In summary, we have described herein an efficient methodology for the synthesis of β-amino alcohols using several epoxides and amines in good to excellent isolated yields. In contrast to the existing methods using potentially hazardous catalysts/additives, the present method offers the following competitive advantages: (i) avoiding the use of any base, metal or Lewis acid catalyst, (ii) short reaction time, (iii) ease of product isolation/purification by non-aqueous work-up, (iv) high regioselectivity, (v) no side reaction, and (vi) low costs and simplicity in process and handling. The recovered TFE can be reusable.

4. Experimental

General procedure: To a solution containing epoxide (1 mmol), in TFE (2 mL) was added to the amine (1 mmol) and the mixture was vigorously stirred at r.t. for 6 h. The products were isolated after selective evaporation of TFE and were purified by silica gel column chromatography eluted by AcOEt and hexane (1:1) to afford the corresponding pure β-amino alcohols in very good yields. The physical data (m.p., NMR, IR) of known compounds were found to be identical with those reported in the literature. Spectroscopic data for selected examples are shown below.

1-Phenoxy-3-phenylamino-propan-2-ol (**3aa**): ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.22–3.26 (m, 1H), 3.38–3.42 (m, 1H), 3.60–3.65 (m, 2H), 3.98–4.05 (m, 2H), 4.25 (br s, 1H), 6.64–6.68 (m, 2H), 6.70–6.75 (m, 2H), 6.88–6.91 (m, 2H), 7.05–7.25 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 46.8, 69.7, 70.2, 113.8, 115.8, 117.8, 118.1, 121.3, 129.4, 148.8, 156.6.

1-Benzylamino-3-phenoxy-propan-2-ol (**3af**): ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.75–2.85 (m, 1H), 2.95 (br s, 1H), 3.80 (d, 2H, J = 2.0 Hz), 3.95 (d, 2H, J = 5.0 Hz), 4.05–4.15 (m, 1H), 6.85–6.95 (m, 3H), 7.30–7.40 (m, 7H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 53.8, 55.3, 68.2, 70.5, 114.7, 121.1, 128.1, 128.3, 128.5, 129.2, 140.1, 158.8.

1-Phenoxy-3-piperazin-1-yl-propan-2-ol (**3ag**): ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.44–1.62 (m, 6H), 2.37–2.61 (m, 6H), 3.95–4.09 (m, 3H), 6.92–6.96 (m, 2H), 7.26–7.29 (m, 3H) ^{13}C NMR ($CDCl_3$, 125 MHz): δ 24.2, 26.1, 54.7, 61.2, 65.3, 70.4, 76.8, 114.6, 120.8, 129.4, 129.6, 158.8.

2-Phenyl-2-phenylamino-ethanol (**3da**): ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.78 (dd, 1H, J = 5.0, 10.5 Hz), 3.90 (dd, 1H, J = 4.0, 10.5 Hz), 4.55 (dd, 1H, J = 6.5, 10.8 Hz), 6.40 (d, 2H, J = 7.5 Hz), 6.80 (t, 1H, J = 7.8 Hz), 6.95 (d, 2H, J = 8.0 Hz), 7.30–7.45 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 57.8, 68.5, 112.1, 117.8, 126.4, 127.43, 128.5, 129.7, 136.1, 146.8.

1-Allyloxy-3-morpholin-4-yl-propan-2-ol (**3cd**): ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.1–2.3 (m, 6H), 3.2 (dd, 2H, J = 4.5, 11.2 Hz), 3.45–4.1 (m, 8H), 4.9–5.1 (m, 2H), 5.6–5.7 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): $\underline{\delta}$ 53.6, 61.2, 66.2, 66.5, 72.5, 116.6, 134.4.

1-Allyloxy-3-(4-chloro-phenylamino)-propan-2-ol (**3cc**): ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.1–3.5 (m, 5H), 4.0–4.1 (m, 3H), 5.23 (dd, 2H, J = 5, 18 Hz, 2H), 5.91–5.94 (m, 1H), 6.5 (d, 2H, J = 8 Hz), 7.1 (d, 2H, J = 8 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 46.7, 68.8, 72.3, 72.4, 114.2, 117.6, 122.3, 129.1, 134.3, 146.8.

1-Morpholin-4-yl-butan-2-ol (**3bd**): ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.76 (t, 3H, J = 7.4 Hz), 1.21–1.26 (m, 2H), 2.04–2.18 (m, 7H), 3.4–3.5 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 9.62, 27.5, 46.1, 53.6, 64.4, 66.7, 67.2, 67.8.

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