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Short communication

An efficient protocol for regioselective ring opening of epoxides using samarium triflate: Synthesis of propranolol, atenolol and RO363

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Abstract

The oxiranes undergo rapid ring opening reaction with amines catalyzed by samarium triflate under mild reaction conditions. The reactions were carried out at below room temperature to afford the corresponding β-amino alcohols in excellent yields and high regioselectivity. This protocol has been applied for the synthesis of various β-blockers.

Keywords: Epoxides; Amines; Samarium triflate; 2-amino alcohols; β-blockers

1. Introduction

2-Amino alcohols are versatile intermediates for the synthesis of various biologically active natural products, unnatural amino acids, β-blockers, insecticidal agents, chiral auxiliaries and oxazolines [1]. One of the most straightforward synthetic approaches for the preparation of β-amino alcohols involves the heating of an epoxide with an excess of amines at elevated temperature [2]. Since some functional groups are sensitive to high temperature, a variety of activators, such as alkali metal halides [3], metal perchlorates [4], metal triflates [5], Bu_3P, ionic liquids and hexafluoro-2-propanol [6] have been developed for this conversion.

However, many of these methods involve the use of expensive and stoichiometric amounts of reagents, suffer from poor regioselectivity and also require extended reaction times. Therefore, the development of a new and efficient protocol for this transformation under mild and more convenient conditions is still needed. $Sm(OTf)_3$ (samarium triflate) is a mild, water-tolerant and efficient Lewis acid catalyst for various organic transformations [7].

2. Results and discussions

As part of our ongoing program towards the development of new synthetic methodologies [8], we report herein our results on regioselective ring opening of various oxiranes with a variety of amines using catalytic amount (10 mol%) of samarium triflate under mild reaction conditions (Scheme 1).

In a typical experiment, styrene oxide (2 mmol) and aniline (2 mmol) were stirred in presence of samarium triflate (0.2 mmol) at room temperature in dichloromethane to obtain the corresponding β-amino alcohol in 96% yield (entry **a**). The reaction was completed within 1 h and the epoxide opening took place in a regioselective manner with the attack of nucleophile at benzylic position. Only a single product was obtained from the reaction of styrene oxide with aromatic and benzyl amines (entry **a**, **d**, **j**). The structure of the products was confirmed by their ^{1}H NMR spectrum. The mass spectrum of these compounds showed a fragment of M^+-31 due to the loss of CH_2OH. In case of sterically hindered alicyclic amine, such as *N*-phenyl piperazine (entry **g**), the product was obtained as a mixture of regioisomers in a ratio of 3:2, arised from the attack of nucleophile at benzylic as well as at terminal position. However, in case of isopropyl amine and styrene oxide, the product was obtained as a single isomer resulting from the terminal attack of the nucleophile (entry **m**). The product thus obtained was identified by its ^{1}H NMR spectrum that showed a doublet of doublet at δ 4.80 for benzylic proton. In a similar manner, glycidyl aryl ethers

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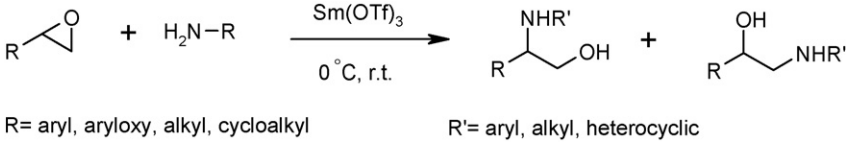
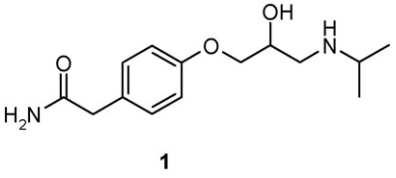
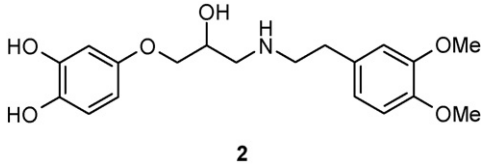


Scheme 1.



1

Fig. 1. Atenolol.



2

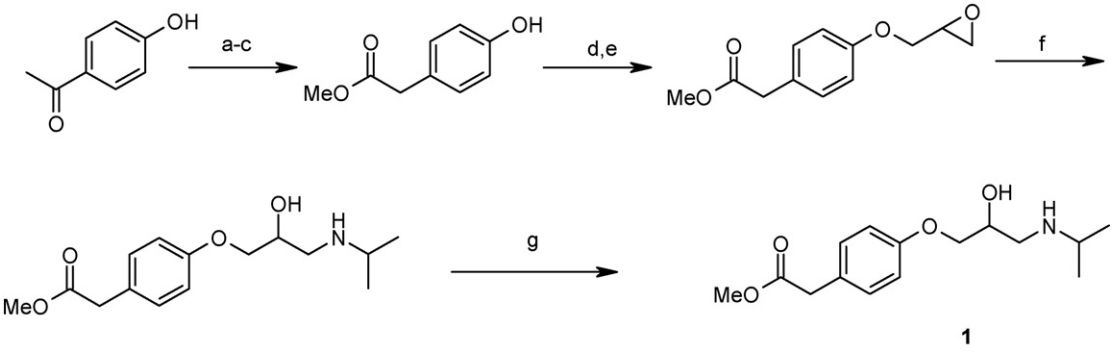
Fig. 2. RO363.

(entry **p**, **q**, **r**, **s**, **t**, **u**) and aliphatic alkyl oxiranes (entry **c**, **f**, **i**, **l**, **o**) reacted smoothly with aromatic, aliphatic and alicyclic amines to afford the corresponding β-amino alcohols in very good yields with high regioselectivity. In these cases, the epoxide opening took place in regioselective manner preferentially by terminal attack of the nucleophile. In these reactions also, the product was obtained as a single isomer and the structure of which was confirmed by their ^{1}H NMR spectrum. Furthermore, cycloalkyl epoxide, such as cyclohexene oxide reacted smoothly in a S_N2 fashion with different substituted aromatic, benzylic and aliphatic amines to afford the corresponding β-amino alcohols (entry **b**, **e**, **h**, **k**, **n**) in excellent yields. The stereochemistry of the ring opening products was found to be *trans* from the coupling constants of the ring protons in ^{1}H NMR spectrum. All the reactions were carried out at room temperature using a 10 mol% of samarium triflate in methylene dichloride. This methodology was applied for the synthesis of various β-blockers, such as propranolol (entry **p**), atenolol (Fig. 1) and RO363 (Fig. 2). Atenolol is one of the top five best-selling drugs in the world today for the treatment of hypertention, angina pectoris and in the treatment of post myocardial infarction. The atenolol intermediate was synthesized from commercially available 4-hydroxy acetophenone. By using Willgerodt reaction, 4-hydroxy acetophenone was converted to the corresponding 4-hydroxy phenyl acetic acid [1c].

The product thus obtained was esterified and then treated with allyl bromide to afford *O*-allyl derivative. The allylic group was treated with *meta*-chloroperbenzoic acid (*m*-CPBA) to give desired epoxide. This epoxy ester was further treated with isopropyl amine in presence of samarium triflate to afford β-amino alcohol in very good yield. β-Amino alcohol thus obtained was treated with liquid ammonia at low temperature to furnish the target molecule atenolol **1** in very good yield (Scheme 2).

In a similar manner, another β-adrenoceptor agonist RO363 was synthesized successfully by applying this protocol. The synthetic route started from well-known compounds veratraldehyde and vanillin. Accordingly, vanillin was treated with aqueous HBr in acetic acid to hydrolyze the methyl ether. 3,4-Dihydroxy benzaldehyde thus obtained was treated with benzyl bromide in presence of base to protect both phenolic groups. The dibenzyloxy aldehyde was treated with *meta*-chloroperbenzoic acid followed by base to afford 3, 4-dibenzyloxy phenol. The phenol was reacted with epichlorohydrin to give the desired epoxide. Another fragment was synthesized by the reaction of veratraldehyde with nitromethane in presence of base followed by reduction with Pd/C in ethylacetate under hydrogen atmosphere.

Thus, obtained 3′,4′-dimethoxyphenylethyl amine and the above epoxide were treated in presence of samarium triflate



Scheme 2.

Table 1
Samarium triflate catalyzed regioselective ring opening of epoxides

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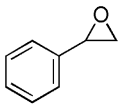
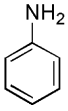
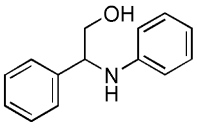
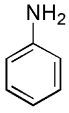
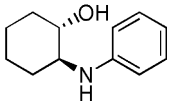
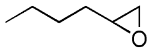
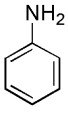
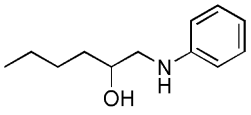
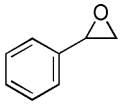
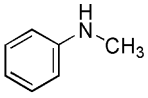
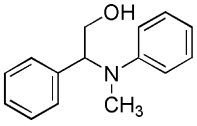
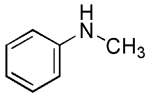
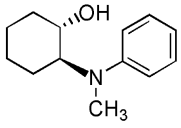
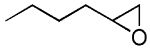
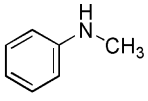
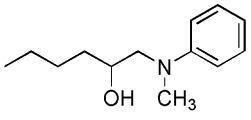
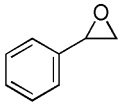
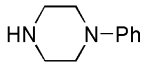
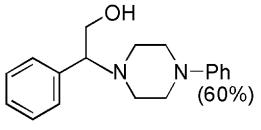
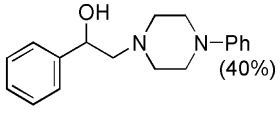
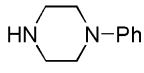
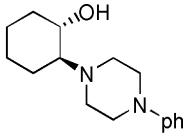
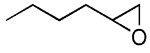
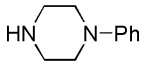
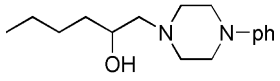
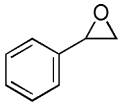
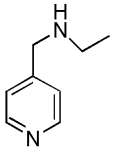
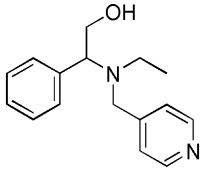
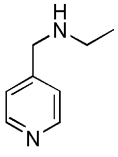
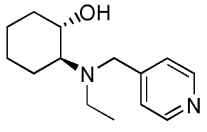
a.				1.0	96
b.				2.5	93
c.				3.0	90
d.				1.5	93
e.				2.0	90
f.				3.0	88
g.				2.0	92
					
h.				2.5	89
i.				3.0	89
j.				2.0	91
k.				2.5	89

Table 1 (*Continued*)

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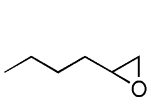
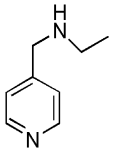
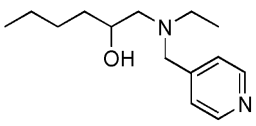
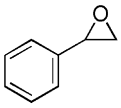
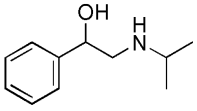
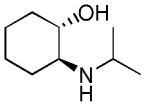
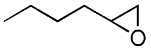
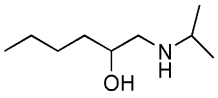
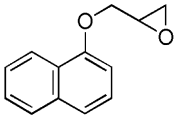
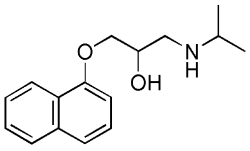
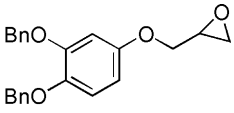
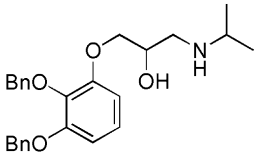
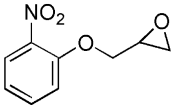
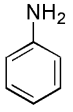
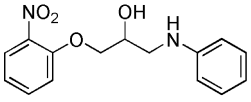
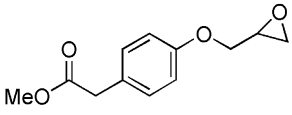
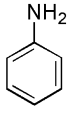
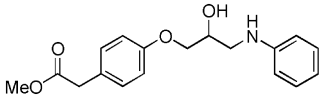
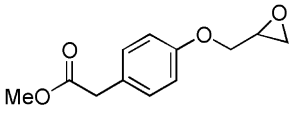
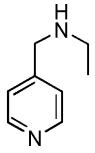
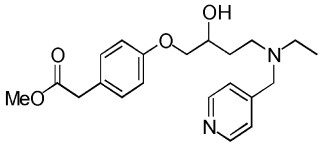
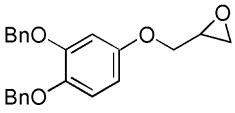
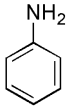
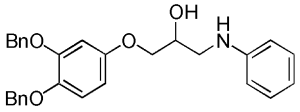
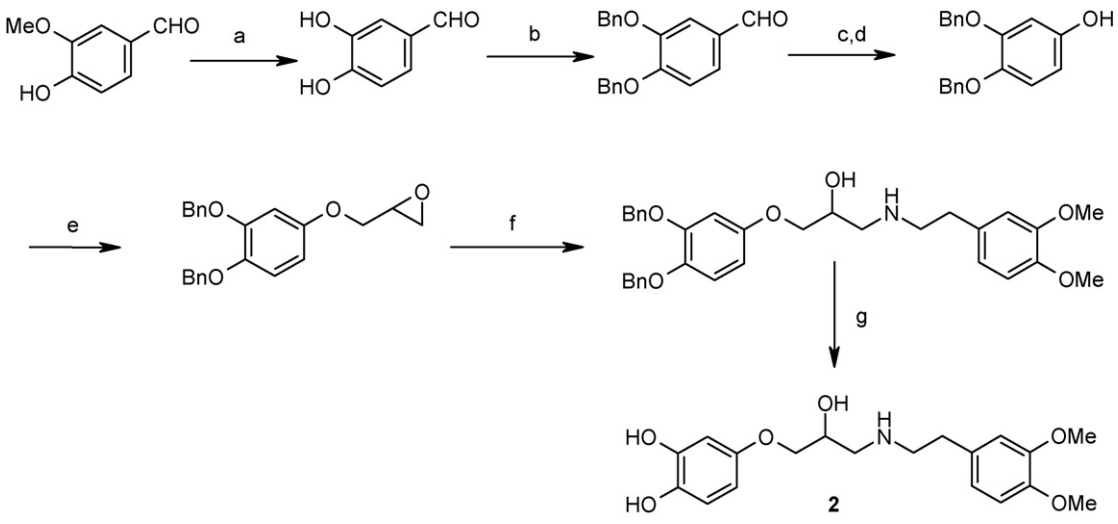
l.				3.0	89
m.				1.5	90
n.				2.0	88
o.				2.0	87
p.				2.0	89
q.				3.0	88
r.				2.5	90
s.				2.0	92
t.				2.5	89
u.				2.0	90

[a] All products were characterized by ^{1}HNMR, IR and mass spectroscopy.
[b] Isolated and unoptimized yield.

at room temperature to afford β-amino alcohol in good yield. This β-amino alcohol was treated with Pd/C under hydrogen atmosphere to deprotect the benzyl groups and to obtain the final synthetic catecholamine of 1-(3,4-dihydroxyphenoxy)-3-(3′,4′-dimethoxyphenyl)-ethylamino-2-propanol (RO363) **2** in very good yield (Scheme 3).

3. Conclusion

In conclusion, the present methodology describes a simple, convenient and efficient procedure for the regioselective ring opening of various epoxides with a variety of amines using a catalytic (10% mol) amount of samarium triflate. The notable



Reagents: a) HBr, AcOH b) benzylbromide, K_2CO_3, acetone c) *m*-CPBA d) NaOH-EtOH e) epichlorohydrin, K_2CO_3, acetone f) 3,4-dimethoxyphenylethyl amine, $Sm(OTf)_3$, RT g) Pd/C

Scheme 3.

features of this procedure are mild reaction conditions, excellent regioselectivity, cleaner reactions, improved yields, enhanced reaction rates and simplicity in operation, which makes it a useful and attractive process for the synthesis of β-amino alcohols of biological and synthetic importance. The high catalytic nature of samarium triflate and its wide applicability would make this protocol an attractive alternative over existing methods.

4. Experimental section

4.1. General methods

IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectro-photometer. ^{1}H NMR spectra were recorded on Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. The spectroscopic data of products was compared with the data reported in the literature.

4.2. General procedure

To a mixture of epoxide (2 mmol) and amine (2 mmol) in dichloromethane (10 mL) was added samarium triflate (0.2 mmol) at 0 °C and the resulting mixture was stirred at room temperature for a specified period (Table 1). The progress of the reaction was monitored by TLC. After complete conversion of the starting material, as indicated by TLC, the reaction mixture was diluted with methylene dichloride (20 mL) and washed twice with water followed by brine solution. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude product, which was purified by column chromatography (silicagel 60–120 mesh) using ethyl acetate and *n*-hexane (3:7) to afford pure β-amino alcohol.

4.3. Spectral data for selected compounds

4.3.1. 2-(N, N-Phenyl, methylamino)-2-phenylethanol (d)

IR (KBr): ν 3407, 3059, 3028, 2884, 2815, 1598, 1504, 1450, 1378, 1320, 1202, 1109, 1065, 1032, 995, 902, 843, 750, 696 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.45 (brs, 1H, OH), 2.70 (s, 3H), 4.10 (t, 2H, J = 7.5 Hz), 5.10 (t, 1H, J = 7.5 Hz), 6.80 (t, 1H, J = 7.5 Hz), 6.90 (d, 2H, J = 7.5 Hz), 7.07–7.18 (m, 2H), 7.25–7.35 (m, 5H). EIMS: *m/z* (%): 227 (M^+ 16), 202 (100), 185 (15), 169 (10), 156 (18), 133 (10), 121 (15), 105 (20), 95 (22), 79 (35), 63 (10), 52 (20).

4.3.2. 2-(N, N-Pyridyl, ethylamino)-2-phenylethanol (j)

IR (KBr): ν 3369, 3034, 2969, 2930, 1658, 1603, 1550, 1452, 1414, 1379, 1277, 1220, 1056, 760, 704 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.12 (t, 3H, J = 6.5 Hz), 2.55–2.75 (m, 4H), 3.30 (brs, 1H), 3.80-3.95 (m, 2H), 4.70 (dd, 1H, J = 9.0, 3.5 Hz), 7.20–7.40 (m, 7H), 8.50–8.60 (m, 2H). EIMS: *m/z* (%): 256 (M^+ 10), 225 (55), 197 (15), 164 (12), 150 (100), 134 (25), 121 (20), 105 (45), 92 (80), 77 (30), 65 (21), 51 (25).

4.3.3. Trans-2-(N, N-Pyridyl, ethylamino)-cyclohexanol (k)

^{1}H NMR ($CDCl_3$): δ 1.10 (t, 3H, J = 7.0 Hz), 1.15–1.35 (m, 6H), 1.70–1.90 (m, 3H), 2.30–2.40 (brs, 1H), 2.45–2.65 (m, 2H), 3.30–3.45 (m, 2H), 3.85 (d, 1H, J = 12.5 Hz), 7.20 (d, 2H, J = 7.0 Hz), 8.55 (d, 2H, J = 7.0 Hz).

4.3.4. 2-(N, N-Pyridyl, ethylamino)-hexane-2-ol (l)

IR (KBr): ν 3377, 2930, 2864, 1603, 1548, 1459, 1414, 1378, 1058, 1000, 777, 717 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.90 (t, 3H, J = 6.5 Hz), 1.08 (t, 3H, J = 7.0 Hz), 1.30–1.45 (m, 6H), 2.30–2.25 (m, 3H), 2.60–2.70 (m, 1H), 2.90 (brs, 1H), 3.45 (d, 1H, J = 9.5 Hz), 3.58–3.65 (m, 1H), 3.82 (d, 1H, J = 9.5 Hz), 7.20 (d, 2H, J = 6.0 Hz), 8.55 (d, 2H, J = 6.0 Hz). EIMS: *m/z* (%): 236 (M^+ 12), 220 (10), 204 (15), 194 (18), 179 (15), 162 (20), 149

(100), 133 (10), 106 (15), 92 (65), 71 (10), 65 (40), 56 (15), 43 (20).

4.3.5. 1-(3, 4-diphenoxy-phenoxy)-3-phenylamino-propan-2-ol (u)

^{1}H NMR ($CDCl_3$): δ 3.25 (q, 1H, $J = 7.5$ Hz), 3.40 (dd, 1H, $J = 7.5$ and 3.0 Hz), 3.95 (t, 2H, $J = 6.0$ Hz), 4.15–4.21 (m, 1H), 5.05 (s, 2H), 5.10 (s, 2H), 6.35 (dd, 1H, $J = 8.5$ and 2.0 Hz), 6.55 (d, 1H, $J = 3.0$ Hz), 6.62 (d, 2H, $J = 6.5$ Hz), 6.70 (t, 1H, $J = 4.5$ Hz), 6.80 (d, 1H, $J = 6.0$ Hz), 7.12 (t, 2H, $J = 6.5$ Hz), 7.25–7.45 (m, 10H). EIMS: *m/z* (%): 455 (M^+ 10), 438 (10), 380 (25), 362 (15), 304 (21), 257 (12), 240 (12), 196 (18), 150 (20), 132 (12), 106 (45), 101 (28), 91 (100), 79 (40), 65 (40), 51 (10), 43 (21).

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