Ring Opening in Epoxy, Propoxy Carbazole with Various Amines Using Ionic Liquid as Green Solvent

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Abstract The epoxides undergo ring-opening reaction smoothly with various amines in an ionic liquid namely 1-butyl-3-methylimidazolium tetrafluoroborate (bmim BF₄) under mild reaction conditions. All the reactions were carried out at ambient temperature to afford the corresponding β -aminoalcohols in excellent yields. The ionic liquid was recovered and reused in further reactions with very good efficiency.

Keywords Epoxides, Amines, Bmim BF₄, β -Amino Alcohols

1. Introduction

β -Adrenergic blocking agents (β -blockers)^{1, 3-11} mostly comprising of β -amino alcohols are of pharmaceutical significance and have received major attention due to their utility in the management of cardiovascular disorders including hypertension, angina pectoris, cardiac arrhythmias, and other disorders related to the sympathetic nervous system. Aryloxy β -amino alcohol functionality is the key pharmacophore in β -blockers. Propranolol is the prototype agent for this class of compounds, which affects β_1 and β_2 receptors. The classical approach and the most straight forward synthetic route for the preparation of β -amino alcohols, involve the heating of epoxide with an excess of amine at elevated temperature. Since some functional groups are sensitive to high temperature, a variety of activators such as alkali metal halides, metal perchlorates, metal tetrafluoroborates and metal triflates have been reported to carry out this reaction. 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. On the other hand, use of ionic liquids as alternatives to conventional organic solvents is increasing at a rapid rate in many areas of

chemistry, in particular in the area of organic synthesis. It is due to the fact that the ionic liquids provide green chemistry and ecofriendly technologies as they can be recycled many times without loss of efficiency². Ionic liquids have higher boiling points compared to organic solvents which have lower boiling points and this property makes ionic liquids as best alternatives to organic solvents. The bmim BF₄ belongs to the class of Ionic liquids which we have used in the current study and found it to be an effective reagent and solvent. By using ionic liquid, high product yields can be obtained, and a reduced amount of waste can be produced in a given reaction. Often the ionic liquid can be recycled and was reused for five runs without any loss of activity. Therefore it leads to a reduction of the costs of the processes. It must be emphasized that reactions in ionic liquids are not difficult to perform and usually require no special apparatus or methodologies. The reactions are often quicker and easier to carry out than in conventional organic solvents.

2. Results and Discussions

In this communication, we wish to report the exploitation of Ionic liquids, in particular bmim BF₄ as an efficient reaction medium for the ring opening of various epoxides with nitrogen nucleophiles under mild and moderate reaction conditions as shown in the schemes 1.

Scheme 1

In a typical experiment, epoxy, propoxy carbazole and amine derivatives were reacted in presence of bmim BF₄, at ambient temperature to obtain the corresponding β -amino alcohol derivatives and the obtained results were shown in the table 1. In all of the reactions, an equimolar amount of an

epoxide and amine were mixed, in which a suitable amount of bmim BF₄ was added. First, epoxy, propoxy carbazole (**1**) was subjected to the opening with various amines (**2a-e** and **3a**) in the presence of bmim BF₄. The reaction between compound **1** and compound **2a** was rather fast in the presence of bmim BF₄ and the corresponding β -amino alcohol **3a**, was obtained nearly in quantitative yield (91%) within 45 minutes at room temperature (Table 1, entry 1). A somewhat milder reaction between compound **1** and compound **2b** took place employing bmim BF₄ and compound **3b** was isolated in quantitative yield (85%) after 35 minutes at room temperature (Table 1, entry 2). In the

case of the reactions between compound **1** and the compound **2c**, in the presence of bmim BF₄ at room temperature obtained compound **3c** in quantitative yield (83%) after 50 minutes (Table 1, entry 3). On the other hand, the ring opening reactions of compound **1** with the secondary amines **2d** and **2e** were sluggish and had to be heated at 60°C for 120 minutes in the presence of bmim BF₄ (Table 1, entry 4 and 5). Compounds **3d**, **3e** were obtained in 85% and 79% respectively. Reaction of compound **1** and compound **3a** was performed at 60°C for 180 minutes in the presence of bmim BF₄ compound **3f** was isolated in 78% yield (Table 2, entry 1).

Table 1. Reaction of Compound with various amines

t	Amine	T (°C)	Time (min)	Yield (%)	Conventional reaction Temp./Time / % yield	Product
1	2a	rt	45	91	High/3h/70	3a
2	2b	rt	35	85	High/3h/72	3b
3	2c	rt	50	83	High/4h/65	3c
4	2d	60	120	79	High/6h/60	3d
5	2e	60	120	85	High/6h/65	3e

Table.2. Reaction of 3a ad as a hindered amine

Entr y	Amine	T (°C)	Time (min)	Yield (%)	Conventional reaction Temp./Time / % yield	Product
1	3a	60	180	78	High/7h/60	3f

The spectra (IR, NMR and Mass) for compound **3c** are given below as a typical example. Spectra for all the products are

given in the enclosed supplementary data (Figures 1-14).

IR spectrum of 3c

^1H NMR spectrum of 3c

Mass spectrum of 3c

3. Experimental Section

FT-IR spectra were recorded as KBr pellet on Nicolet 380 FT-IR instrument (Model Thermo Electron Corporation-Spectrum One). ^1H spectra were recorded on Varian 300 and 400 MHz spectrometers using CDCl_3 , $\text{DMSO}-d_6$ as solvents, and tetra methyl silane (TMS) as internal standard. Mass spectra were recorded on Agilent triple quadrupole mass spectrometer equipped with turbo ion spray interface at 375°C . All the organic extracts were dried over sodium sulfate after work-up. The dry reactions were carried out under nitrogen atmosphere with magnetic/mechanical stirring. Unless otherwise mentioned, all the solvents and reagents used were of LR grade. TLC was performed on precoated silica-gel plates, which were visualized using UV light and sulphuric acid/ethanol (5:95) charring.

3.1. General Procedure

To a mixture of epoxide (1 mol) and amine (1 mol) was added the bmim BF_4 (10 mol%). The resulting reaction mixture was stirred at ambient 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 product was extracted with di ethyl ether, followed by drying at 80°C under reduced pressure to afford the corresponding pure β -amino alcohol derivatives in excellent yields. All the products were confirmed by their ^1H NMR, IR and Mass spectrometry and compared with literature data.

3.2. Spectral Data for 3a

Compound 3a: IR (KBr): 3344 cm^{-1} (-OH); ^1H NMR (CDCl_3 ; 400 MHz): δ 8.5 (m, 2H, -carbazole), 7.4 (m, 4H, -Aromatic), 7.1 (m, 5H, -Carbazole), 6.4 (d, 1H, $J=6.8$ -carbazole), 4.1 (m, 5H, $-\text{CH}_2\text{-CH-CH}_2$), 3.85 (s, 3H, $-\text{OCH}_3$), 2.92 (m, 2H, $-\text{CH}_2$), 2.9 (m, 2H, $-\text{CH}_2$), 2.1 (bs, -NH); ^{13}C NMR (100 MHz, DMSO) (Fig.2.6): δ 48.48, 52.13, 54.95, 68.17, 68.69, 70.21, 100.13, 103.63, 109.71, 111.93, 112.21, 114.25, 118.42, 120.76, 121.49, 122.17, 124.26, 126.04, 139.29, 141.53, 148.15, 149.71, 155.11; MS: m/z (M+1) 407. HRMS: m/z calculated for $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_4$, 406.19 Found: $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_4$, 406.168

Compound 3b: IR (KBr, cm^{-1}): 3391, 3292, 2929, 1513, 1259, 1105, 717. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.22 (s,

¹H), 8.25 (d, J = 7.6 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.37–7.27 (m, 2H), 7.16 (t, J = 7.0 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 6.72–6.66 (m, 5H), 5.28 (s, 1H), 5.20 (t, J = 4.0 Hz, 1H), 4.27–4.16 (m, 3H), 3.61 (s, 3H), 3.43–3.35 (m, 1H), 3.24–3.16 (m, 1H). ¹³C NMR (100 MHz, DMSO-d₆): 154.9, 150.7, 143.0, 141.0, 138.9, 126.4, 124.5, 122.4, 121.7, 118.5, 114.6, 113.2, 110.9, 110.3, 103.8, 100.4, 70.2, 67.8, 55.3, 47.4. MS (m/z): 363 (M+1). HRMS. m/z Calculated for C₂₂H₂₂N₂O₃ 362.16 Found C₂₂H₂₂N₂O₃ 362.1459

Compound 3c: IR (KBr): 3620, 3567 and 3363 cm⁻¹ (-NH), 3095 and 3063 cm⁻¹ (-OH);

¹H NMR (300 MHz, dmsO): δ 11.2 (s, 2H, -NH), 8.2 (m, 2H, -Aromatic), 7.5 (m, 2H, -Aromatic), 7.3 (m, 4H, -Aromatic), 7.2 (m, 4H, -Aromatic), 6.6 (m, 2H, -Aromatic), 5.2 (m, 2H, -OH), 4.2 (m, 4H, -OCH₃), 4.0 (m, 2H, -CH), 2.8 (m, 4H, -CH₂); MS: m/z (M-1) 494 and (M+1) 496. HRMS m/z calculated: for C₃₀H₂₉N₃O₄ 495.58 Found: C₃₀H₂₉N₃O₄ 495.5689

Compound 3d: IR (KBr): 3401 cm⁻¹ (-OH), 3059 cm⁻¹ (-CH aromatic);

¹H NMR (300 MHz, CdCl₂): δ 8.2 (d, 1H, J=7.8, -Aromatic), 8.0 (s, 1H, -NH), 7.5–7.2 (m, 9H, -Aromatic), 6.8 (m, 5H, -Aromatic), 6.6 (d, 1H, J=8.0, -Aromatic), 4.2 (m, 4H, -OCH₂), 4.1 (m, 1H, -CH), 3.9 (m, 6H, -NCH₂), 3.0 (m, 3H, -OCH₂), 1.5 (s, 1H, -OH); MS: m/z (M+1) 497. HRMS m/z C₃₁H₃₂N₂O₄ for 496.61 Found C₃₁H₃₂N₂O₄ 496.5891

Compound 3e: IR (KBr): 3064 cm⁻¹ (-CH Aromatic), 2838 cm⁻¹ (-OCH₃);

¹H NMR (400 MHz, DMSO-d₆/TMS): δ 7.8 (m, 2H, -tosyl), 7.5 (m, 2H, -tosyl), 6.9 (m, 4H, -Aromatic), 4.3 (m, 2H, -OCH₂), 4.1 (m, 2H, -CH₂), 3.7 (s, 3H, -OCH₃), 2.4 (s, 3H, -CH₃); MS: m/z (M+1) 323. HRMS m/z calculated for C₃₃H₃₆N₂O₆: 556.66 Found C₃₃H₃₆N₂O₆: 556.6495

Compound 3f: IR (KBr): 3613 cm⁻¹ and 3530 cm⁻¹ (-NH), 3461 cm⁻¹ and 3400 cm⁻¹ (-OH);

¹H NMR (300 MHz, dmsO): δ 11.2 (s, 2H, -NH), 8.2 (m, 2H, -Aromatic), 7.5 (m, 2H, -Aromatic), 7.3 (m, 8H, -Aromatic), 6.8 (m, 2H, -Aromatic), 6.6 (m, 4H, -Aromatic), 5.1 (s, 2H, -OH), 4.2 (m, 8H, -CH₂), 3.9 (m, 2H, -CH), 3.6 (s, 3H, -OCH₃); MS: m/z (M) 645. HRMS m/z calculated for C₃₉H₃₉N₃O₆ 645.76 Found C₃₉H₃₉N₃O₆ 645.7496

4. Conclusions

In conclusion it has been demonstrated that ionic liquids can be used for the ring opening of epoxides with amines. Ionic liquid can be recycled several times. The details of experimental and spectral data for other compounds are available in the supplementary data.

Appendix - Supplementary Data

Figure 1. (3a) IR

Figure 2. (3a) ¹H NMR Figure 3. (3a) ¹³C NMR

Figure 4. (3b) IR

Figure 5. (3a) Mass

 Figure 6. (3b) ^1H NMR

Figure 7. (3b) Mass

Figure 8. (3c) IR

Figure 9. (3c) ^1H NMR

Figure 10. (3c) Mass

 Figure11. (3e) ¹H NMR

Figure 12. (3e) Mass

Figure 13. (3e) IR

Figure 14. (3f) ¹H NMR

Figure 15. (3f) Mass

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