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Facile ring opening of 2,3-epoxy-steroids with aromatic amines in ionic liquids

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ABSTRACT

Efficient ring opening of steroidal 2,3-epoxides with stoichiometric amount of aromatic amines has been carried out using an ionic liquid ($[bmim]^+[BF_4]^-$) both as solvent and catalyst. The reactions were completely regio- and stereoselective in each case. The aminoalcohol products have chair conformations in ring A. The ionic liquid-mediated ring opening can efficiently be carried out with aliphatic amines like morpholine as well.

1. Introduction

The vicinal amino alcohol moiety is a main structural feature in a vast number of naturally occurring and synthetic molecules. Among the synthetic derivatives, chiral auxiliaries for asymmetric synthesis and pharmacologically active compounds represent the two most prominent groups of compounds [1]. Derivatives of pharmacological importance include various androstanes with 2-amino-3-ol functionality that are used as potent neuromuscular blocking agents [2]. Similar steroidal compounds have been shown to inhibit proliferation of leukemia cells [3,4]. Accordingly, several patents and publications report on methods leading to steroidal amino alcohols [5–9], but there are only a few examples for the synthesis of aryl amino derivatives [10,11]. A 5α-hydroxy-10β-phenylamino steroid was synthesized by heating the corresponding 5α,10α-epoxide for 100 h at 60 °C in the presence of boron–trifluoride–etherate reagent and a 100-fold excess of aniline [10]. The formation of amino alcohols instead of the expected aziridines was reported in the reaction of 5α,6α-epoxy steroids in the presence of five equivalents of aniline and boron–trifluoride–etherate reagent in dichloromethane [11].

One of the most widely used methods for the synthesis of vicinal amino alcohols is the direct aminolysis of the corresponding epoxy-derivatives, mainly due to the facile synthesis of the latter compounds from the readily available olefins in an optically pure form [1]. However, the ring opening of epoxides usually requires the use of high excess of the amine, elevated temperature and long reaction time. The

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aminolysis with deactivated or aromatic amines as reagents is especially problematic. Subsequently, several methods have been developed to enhance the reactivity of epoxides towards nucleophilic cleavage by aromatic amines. These include the use of metal triflates [12,13], metal halides [14], zirconium sulfophenyl phosphonate [15], transition metal based Lewis acids [16], fluoro alcohols [17] and silica gel [18]. Currently, ionic liquids are widely used both as solvents and catalysts in several reactions because of the enhanced reaction rates and improved selectivities that can be achieved by these protocols [19,20]. Simple epoxides have also been shown to undergo smooth ring-opening with aryl amines in various ionic liquids like 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]$^+$[BF_4]$^-$) or 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]$^+$[PF_6]$^-$) as solvent [21].

In this paper, the application of this latter method to the regio- and stereoselective ring opening of 2,3-epoxy-steroids with aromatic amines is presented. The results are compared to those obtained using conventional organic solvents.

2. Experimental

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Inova 400 spectrometer at 400.13 and 100.62 MHz, respectively. Chemical shifts δ are reported in ppm relative to $CHCl_3$ (7.26 and 77.00 ppm for ^{1}H and ^{13}C, respectively). GLC analyses were carried out with a HP-5890/II gas chromatograph using a 15 m HP-5 column. Infrared (IR) spectra were recorded in KBr pellets using an Avatar330 FT-IR instrument. Elemental analyses were measured on a 1108 Carlo Erba apparatus.

2.1. *General procedure for the ring opening of epoxides in ionic liquid*

In a typical procedure, the steroidal epoxide (0.2 mmol), the aromatic amine (0.2 mmol) and 600 mg [bmim]$^+$[BF_4]$^-$ were placed under argon in a Schlenk-tube equipped with a magnetic stirrer and a septum inlet and a reflux condenser with a balloon on the top. The reaction mixture was heated at 100 °C for 8 h. The mixture was extracted three times with 3 ml diethyl ether. The etheral extract was analyzed by TLC and after removal of diethyl ether, by ^{1}H NMR. The products were purified by column chromatography (silica gel, ethyl acetate/hexane (30:70)) and were crystallized from diethyl ether.

Any volatiles were removed from the ionic liquid *in vacuo* and new load of starting materials (steroid and aromatic amine) for the next run were added to the ionic liquid and the atmosphere was changed to argon. The consecutive runs were conducted for the same reaction time.

2.2. *Characterization of the products*

3α-*Hydroxy*-2β-((4′-*methyl*-*phenyl*)-*amino*)-5α-*androst*-17-*one* (**3a**). ^{1}H NMR(δ,$CDCl_3$): 6.95(d, 8.4 Hz, 2H, 3′,5′-H); 6.50(d, 8.4 Hz, 2H, 2′,6′-H); 3.98(brs, 1H, 3-H); 3.51(brs, 1H, 2-H); 2.50–0.75(m, 26H, ring protons); 2.20(s, 3H, 4′-H_3); 0.99(s, 3H, 19-H_3); 0.83(s, 3H, 18-H_3). ^{13}C NMR(δ,$CDCl_3$): 221.0; 144.9; 129.9; 126.7; 113.0; 68.4; 55.5; 54.7; 51.3; 47.8; 38.9; 38.5; 36.2; 35.8; 34.6; 32.2; 31.6; 30.7; 27.8; 21.7; 20.3; 20.2; 15.1; 13.9. MS (*m*/*z*/rel. int.): 395 (M$^+$)/100, 377/23, 364/8, 349/11, 308/13, 160/27, 107/36, 43/28. IR(CH_2Cl_2, ν (cm^{-1})): 3608, 3481, 3419. Analysis calculated for $C_{26}H_{37}NO_2$ (395.58): C, 78.94; H, 9.43; N, 3.54; found: C, 78.52; H, 9.68; N, 3.24. Yield: 82%.

3α-*Hydroxy*-2β-((4′-*hydroxy*-*phenyl*)-*amino*)-5α-*androst*-17-*one* (**3b**). ^{1}H NMR (δ,$CDCl_3$): 6.67(d, 8.3 Hz, 2H, 3′,5′-H); 6.45(d, 8.3 Hz, 2H, 2′,6′-H); 3.97(brs, 1H, 3-H); 3.45(brs, 1H, 2-H); 2.50–0.60(m, 26H, ring protons); 0.95(s, 3H, 19-H_3); 0.80(s, 3H, 18-H_3). MS (*m*/*z*/rel. int.): 397(M$^+$)/100, 306/34, 162/23, 109/35. Analysis calculated for $C_{25}H_{35}NO_3$ (397.56): C, 75.53; H, 8.87; N, 3.52; Found: C, 75.20; H, 9.11; N, 3.31. Yield: 56%

3α-*Hydroxy*-2β-(*phenyl*-*amino*)-5α-*androst*-17-*one* (**3c**). ^{1}H NMR(δ,$CDCl_3$): 7.13(t, 8.4 Hz, 2H, 3′,5′-H); 6.66(t, 8.4 Hz, 1H, 4′-H); 6.55(d, 8.4 Hz, 2H, 2′,6′-H); 3.96(s, 1H, 3-H); 3.55(s, 1H, 2-H); 2.50–0.60(m, 26H, ring protons); 0.98(s, 3H, 19-H_3); 0.82(s, 3H, 18-H_3) ^{13}C NMR(δ,$CDCl_3$): 220.1; 147.1; 129.3; 117.4; 112.8; 68.3; 55.4; 54.4; 51.3; 47.8; 38.8; 38.3; 36.1; 35.2; 34.6; 32.1; 31.5; 30.7; 27.8; 21.7; 20.2; 15.0; 13.9. MS (*m*/*z*/rel. int.): 381 (M$^+$)/73, 306/100, 288/40, 243/43, 93/72. Analysis calculated for $C_{25}H_{35}NO_2$ (381.56): C, 78.70; H, 9.24; N, 3.67; found: C, 78.49; H, 9.01; N, 3.85. Yield: 48%.

3α-*Hydroxy*-2β-((4′-*acetyl*-*phenyl*)-*amino*)-5α-*androst*-17-*one* (**3d**). ^{1}H NMR(δ,$CDCl_3$): 7.78(d, 8.4 Hz, 2H, 3′,5′-H); 6.52(d, 8.4 Hz, 2H, 2′,6′-H); 3.98(brs, 1H, 3-H); 3.67(brs, 1H, 2-H); 2.50–0.65(m, 26H, ring protons); 2.48(s, 3H, C(O)CH_3); 0.99(s, 3H, 19-H_3); 0.83(s, 3H, 18-H_3). ^{13}C NMR(δ,$CDCl_3$): 220.1; 196.4; 150.9; 130.9; 127.9; 111.5; 67.9; 55.3; 53.8; 51.3; 47.8; 38.6; 37.6; 36.0; 35.7; 34.6; 32.1; 31.5; 30.6; 27.7; 26.0; 21.7; 20.1; 15.1; 13.8. MS (*m*/*z*/rel. int.): 423 (M$^+$)/78, 408/6, 395/10, 336/8, 308/16, 288/100, 218/55, 139/30. Analysis calculated for $C_{27}H_{37}NO_3$ (423.59): C, 76.56; H, 8.80; N, 3.31; found: C, 76.11; H, 9.01; N, 3.58.Yield: 45%.

3α-*Hydroxy*-2β-((4′-*nitro*-*phenyl*)-*amino*)-5α-*androst*-17-*one* (**3e**). ^{1}H NMR(δ,$CDCl_3$): 8.05(d, 8.5 Hz, 2H, 3′,5′-H); 6.62(d, 8.5 Hz, 2H, 2′,6′-H); 3.97(brs, 1H, 3-H); 3.48(brs, 1H, 2-H); 2.48–0.60(m, 26H, ring protons); 0.95(s, 3H, 19-H_3); 0.82(s, 3H, 18-H_3). ^{13}C NMR(δ,$CDCl_3$): 221.2; 152.1; 138.0; 126.4; 111.2; 67.7; 55.2; 53.9; 51.4; 47.8; 38.5; 37.4; 36.0; 35.7; 34.5; 32.0; 31.4; 30.8; 27.8; 21.7; 20.1; 15.0; 13.8. MS (*m*/*z*/rel. int.): 426(M$^+$)/100, 396/55, 339/17, 208/35, 191/50. Analysis calculated for $C_{25}H_{34}N_2O_4$ (426.55): C, 70.40; H, 8.03; N, 6.57; found: C, 70.77; H, 8.15; N, 6.75. Yield: 56%.

2β,3α-*Dihydroxy*-5α-*androst*-17-*one* (**4**) was obtained as a side product and was characterized by ^{1}H and ^{13}C NMR only. The chemical shifts of 2-H and 3-H as well as those of C-2 and C-3 correspond well to the chemical shifts of the analogous 2β,3α-dihydroxy-cholestane [22]. ^{1}H NMR(δ,$CDCl_3$): 3.88(m, 2H, 2-H, 3-H); 2.50–0.75(m, 26H, ring protons); 0.98(s, 3H, 19-H_3); 0.84(s, 3H, 18-H_3). ^{13}C NMR(δ,$CDCl_3$): 221.2; 71.7; 70.5; 55.3; 51.5; 47.8; 40.5; 39.0; 36.2; 35.8; 34.5; 31.8; 31.6; 30.8; 27.9; 21.7; 20.2; 14.5; 13.9.

2α,3α-*Epoxy*-17-((4′-*methyl*-*phenyl*)-*imino*)-5α-*androstane* (**5**) was obtained as a side product and was characterized by ^{1}H NMR and GC-MS. ^{1}H NMR(δ,$CDCl_3$): 6.965(d, 8.0 Hz, 2H, 3′,5′-H); 6.59(d, 8.0 Hz, 2H, 2′,6′-H); 3.12 (m, 2H, 2-H, 3-H); 2.50–0.60(m, 26H, ring protons); 2.22(s, 3H, 4′-H_3); 0.95(s, 3H, 19-H_3); 0.78(s, 3H, 18-H_3). MS (*m*/*z*/rel. int.): 377(M$^+$)/83; 362/93; 186/100; 144/21; 91/31.

2β-*Hydroxy*-3α-((4′-*methyl*-*phenyl*)-*amino*)-5α-*androst*-17-*one* (**7**). ^{1}H NMR(δ,$CDCl_3$): 6.96(d, 8.4 Hz, 2H, 3′,5′-H); 6.52(d, 8.4 Hz,

2H, 2′,6′-H); 4.02(brs, 1H, 2-H); 3.51(brs, 1H, 3-H); 2.50–0.75(m, 26H, ring protons); 2.20(s, 3H, 4′-H_3); 1.06(s, 3H, 19-H_3); 0.85(s, 3H, 18-H_3). ^{13}C NMR(δ,$CDCl_3$): 221.0; 144.7; 129.8; 126.6; 113.1; 69.4; 55.4; 53.7; 51.4; 47.8; 40.8; 40.5; 35.9; 35.8; 34.5; 31.6; 30.8; 29.1; 28.0; 21.7; 20.2; 20.1; 14.6; 13.9. MS (*m*/z/rel. int.): 395 (M^+)/100, 377/24, 362/6, 324/7, 288/15, 172/81, 107/82, 83/37. Analysis calculated for $C_{26}H_{37}NO_2$ (395.58): C, 78.94; H, 9.43; N, 3.54; found: C, 79.15; H, 9.12; N, 3.35. Yield: 45%.

3. Results and discussion

3.1. *Ring opening of 2α,3α-epoxy-5α-androstan-17-one with 4-methyl-aniline*

2α,3α-Epoxy-5α-androstan-17-one (**1**, Scheme 1) was reacted with 4-methyl-aniline (**2a**) in $[bmim]^+[BF_4]^-$, $[bmim]^+[PF_6]^-$ and Bu_4NBr at 100 °C. At this temperature all of the ionic liquids gave homogeneous solutions of the reagents. In $[bmim]^+[BF_4]^-$ ring opening took place smoothly with total conversion of the steroidal epoxide in 2 h using only one equivalent of the amine reagent. The products (and any unreacted starting material) were extracted by diethyl ether and the extracts were analyzed by TLC and ^{1}H NMR to determine the conversion of the substrate and the selectivity of the reaction. Ring opening was completely regio- and stereoselective, affording 3α-hydroxy-2β-((4′-methyl-phenyl)-amino)-5α-androst-17-one (**3a**, Scheme 1) together with 2β,3α-dihydroxy-5α-androst-17-one (**4**) as a side product (in less than 5%). The ionic liquid $[bmim]^+[BF_4]^-$ could be reused several times and no loss of activity or selectivity was observed even after the third run. **3a** was purified by column chromatography and the exact structure was determined by various spectroscopic methods (^{1}H, ^{13}C, ^{31}P NMR, 2D NMR techniques including ^{1}H-^{1}H-COSY, HSQC, HMBC and NOESY, as well as MS, see below).

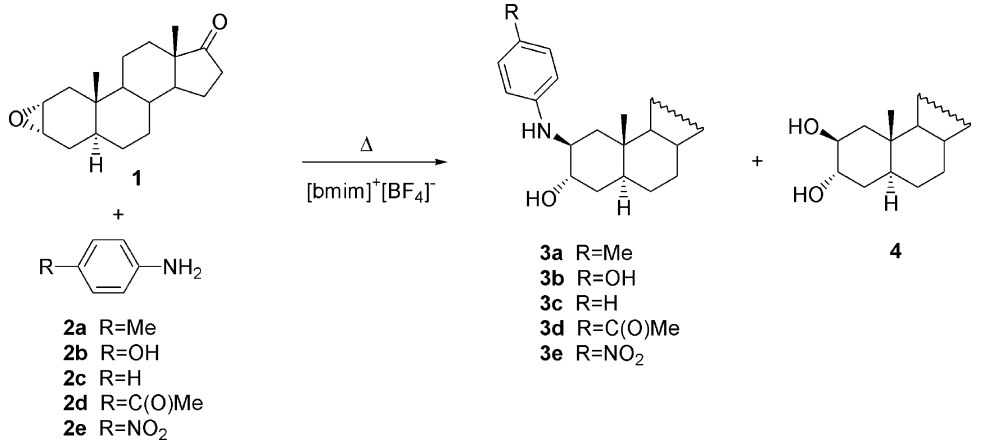
The formation of **4** can be explained by the presence of water impurity in ILs. This assumption is supported by the fact that the deliberate addition of water to the 1,2-ethanediol solution of **1** and **2a** resulted in an increase in the yield of **4** (see below). A product with an analogous structure had been obtained before in the acid-catalyzed ring opening of 2α,3α-epoxycholestane in the presence of water [22].

Poor results were obtained using the other room temperature ionic liquid $[bmim]^+[PF_6]^-$, only 30% conversion was achieved under the same reaction conditions (100 °C, 2 h). Bu_4NBr completely failed to induce any ring opening. The low reactivity of **1** in epoxide ring opening reaction in $[bmim]^+[PF_6]^-$ can be explained by the fact that this IL cannot be considered as innocent solvent due to partial hydrolysis and formation of species with 'PF_2' fragments [23].

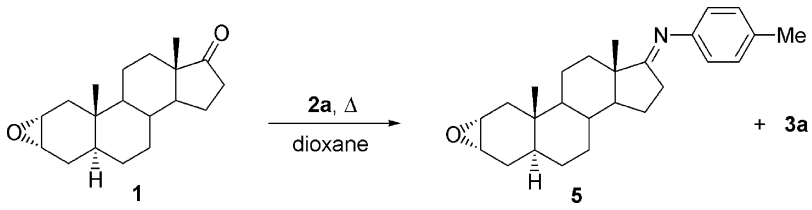
As a comparison, ring opening was attempted in 1,2-ethanediol, a usual solvent for the synthesis of 2-alkylamino-3-ol derivatives [8]. In the presence of a five-fold excess of 4-methyl-aniline 40% conversion was observed after 8 h heating at 100 °C. The two products, **3a** and **4** were obtained in a 1/1 ratio. Upon addition of water (10% based on the amount of 1,2-ethanediol) to the mixture composed of the substrate, 4-methyl-aniline (five equivalent based on the amount of epoxide) and of 1,2-ethanediol (0.5 ml/0.1 mmol epoxide), 60% conversion was achieved and the **3a**/**4** ratio changed to 1/2. The use of aprotic solvents, like 1,4-dioxane [24] was completely inefficient. According to GC and GC-MS measurements, only 3% of ring-opening product **3a** was obtained upon heating the epoxide with five-fold excess of 4-methyl-aniline (**2a**) at 100 °C for 8 h. However, a new derivative, which was proved to be the imine **5** (Scheme 2) according to ^{1}H NMR and GC-MS measurements, was obtained in 73% yield. (Formation of imine as a side reaction was observed before, during the condensation of 2α,3α-epoxy-5α-androstan-17-one with boiling aqueous *n*-butylamine [9].) The use of one equivalent of **2a** led to **5** in 40% yield and no ring-opening product was detected. As water have been found to catalyze ring-opening in several cases [9,24], the reaction of 4-methyl-aniline (**2a**) and **1** was carried out again under similar conditions (four equivalents of **2a**, 100 °C, 8 h in 1,4-dioxane), but in this case in the presence of 10% water (based on the amount of 1,4-dioxane). The results were almost the same as before, the formation of **3a** and **5** was observed in 4% and 63% yields, respectively.

3.2. *Determination of the structure of the ring opening-product (3a)*

The ^{1}H and ^{13}C chemical shifts of the A-ring nuclei have been assigned unequivocally by using ^{1}H-^{1}H COSY, HSQC and HMBC



Scheme 1 – Ring opening of 2α,3α-epoxy-5α-androstan-17-one (1) with aromatic amines in $[bmim]^+[BF_4]^-$.



Scheme 2 – Reaction of 2α,3α-epoxy-5α-androstan-17-one (1) with 4-methyl-aniline (2a) in 1,4-dioxane.

spectra (in $CDCl_3$ as solvent). The two protons with high chemical shifts (3.51 ppm and 3.98 ppm) correspond to 2-H and 3-H, respectively. 2-H was distinguished by the coupling with a geminal pair at 1.70 ppm attached to a carbon with a chemical shift of 38.5 ppm. This carbon nucleus gave a cross peak with 19-H_3 (at 0.99 ppm) in the HMBC spectrum, so it was assigned as C-1. On the other hand, the carbon atom that is attached to the geminal pair at 1.40 ppm and 1.80 ppm, giving cross peaks with the proton at 3.98 ppm in the ^1H-^1H COSY spectrum, showed no coupling to 19-H_3 in HMBC, so it can be assigned as C-4. Accordingly, the product is a 2-amino-3-ol derivative. In the NOESY spectrum, 3-H (at 3.98 ppm) gave intense cross peaks with both of the protons of the geminal pair at C-4 (1.40 and 1.80 ppm) and also with 2-H (3.51 ppm). A weak interaction was also observed between 3-H and 19-H_3 (at 0.99 ppm). This is in accordance with a 2β-amino-3α-ol structure where the A-ring is in a chair conformation and both 2-H and 3-H are in equatorial positions.

The stereoselectivity of the reaction is consistent with the classical *trans*-diaxial opening of cyclic epoxides which maximizes orbital overlap and controls regioselectivity (formation of 3α-ol products) in spite of the presence of the 19-CH_3 group in β position [25–27]. However, it should be noted that in contrast with 3α-hydroxy-2β-arylamino steroids **3a–3e**, 3α-hydroxy-2β-alkylamino derivatives adopt a twist-boat conformation of A-ring in $CDCl_3$ as it has been reported for 3α-hydroxy-2β-(4-morpholinyl)-5α-androst-17-one (**3f**) [28]. This is in accordance with our own results that showed prominent cross peaks between 3-H (3.89 ppm) and 19-H_3 (0.90) as well as between 3-H and 4β-H (1.84 ppm) in the NOESY spectra of **3f**, while no interactions were observed between the 3-H–2-H (2.58 ppm) and the 3-H–4α-H (1.51 ppm) pairs. The twist-boat conformation of ring A of **3f** had been interpreted by the stabilization of this conformation by a combination of relief of steric strain on the β-face of ring A and formation of a hydrogen bond between the 3α-OH and 2β-N. However, in polar solvents like DMSO, where intermolecular hydrogen bonds with the solvent molecules are dominating, the A-ring of **3f** has been reported to exist in chair conformation [28].

In our case, the chair conformation of ring A observed even in apolar solvents can be explained by the poor nucleophilic nitrogen of the arylamino group. The lack of an intramolecular hydrogen bond is confirmed by the infrared spectrum of **3a** in CH_2Cl_2 that contains three sharp bands at 3608 cm^{-1} (νOH), 3481 cm^{-1} ($\nu_{as}NH_2$) and 3419 cm^{-1} ($\nu_{s}NH_2$).

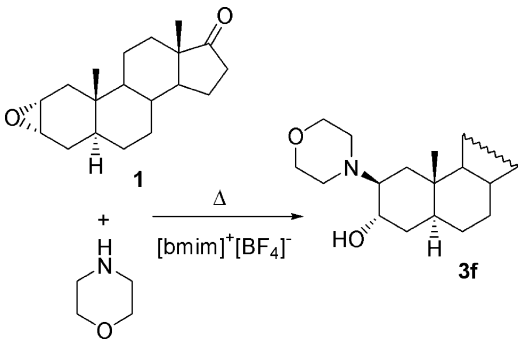
3.3. *Other ring opening reactions in ionic liquids*

Ring opening of 2α,3α-epoxy-5α-androstan-17-one (**1**) has been carried out using various other aromatic amine nucleophiles (**2b–2e**, Scheme 1) in $[bmim]^+[BF_4]^-$ as solvent. The amines **2b–2d** were considerably less reactive than **2a** (Table 1), both conversions and selectivities were poorer than with **2a** and there was also a considerable loss of activity when the ionic liquid was reused (Table 1, entries 2, 4). The only side product was 2β,3α-dihydroxy-5α-androst-17-one (**4**) again. No aminoalcohol was obtained in the presence of **2e**, even when it was used in five-fold excess compared to the epoxide **1**. Although epoxide ring opening in the presence of 4-nitroaniline is usually problematic, there are a few examples when the reaction had been carried out successfully using $BiCl_3$ [29] and $Sn(OTf)_2$ or $Cu(OTf)_2$ [12] as catalysts. In our case, $Sn(OTf)_2$ was completely ineffective even when it was used in two-fold excess compared to the epoxide. However, the use of the same

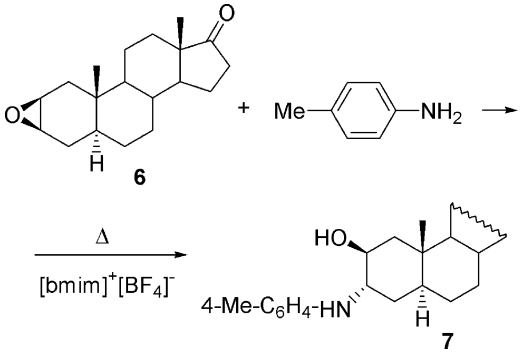
Table 1 – Reaction of 2α,3α-epoxy-5α-androstan-17-one (1) with aromatic amines (2a–2e) in $[bmim]^+[BF_4]^-$ [a]

Entry	Product	Run 1		Run 2		Run 3	
		Conversion (%)[b]	Selectivity (%)[b,c]	Conversion (%)[b]	Selectivity (%)[b,c]	Conversion (%)[b]	Selectivity (%)[b,c]
1	**3a**	100	>95	100	>95	100	>95
2	**3b**	70	86	55	84	40	85
3	**3c**	75	80				
4	**3d**	66	78	50	79	35	76
5[d]	**3e**	20	<5				
6[d,e]	**3e**	100	73				

[a] Reaction conditions: **1**/amine = 1/1; 100 °C, 8 h in $[bmim]^+[BF_4]^-$.
[b] Determined by ^1H NMR.
[c] Side product: 2β,3α-dihydroxy-5α-androst-17-one (**4**).
[d] Reaction time: 24 h.
[e] In the presence of LiOTf. **1**/LiOTf = 1/2.



Scheme 3 – Ring opening of 2α,3α-epoxy-5α-androstan-17-one (1) with morfoline.



Scheme 4 – Ring opening of 2β,3β-epoxy-5α-androstan-17-one (6) with 4-methyl-aniline (2a).

amount of LiOTf led to the formation of 3α-hydroxy-2β-((4′-nitro-phenyl)-amino)-5α-androst-17-one (**3e**) in 73% yield (in 24 h at 100 °C) according to the ^{1}H NMR spectrum of the crude reaction mixture (Table 1, entry 6). At the same time, LiOTf dissolved in dioxane was equally effective leading to the same product in 65% after heating the reaction mixture for 24 h.

The products **3b–3e** were all proved to be the 3α-hydroxy-2β-amino derivatives according to their NMR spectra.

As a comparison, 2α,3α-epoxy-5α-androstan-17-one (**1**) was also reacted with an aliphatic amine, morpholine. No reaction was observed either in $[bmim]^+[BF_4]^-$ or 1,2-ethanediol with one equivalent of the amine. Upon using morpholine in five-fold excess, **3f** (Scheme 3) was obtained in 70% and 80% yield after heating at 100 °C for 8 h in $[bmim]^+[BF_4]^-$ and 1,2-ethanediol, respectively.

2β,3β-Epoxy-5α-androstan-17-one (**6**) was found to be less reactive than **1**. It could be converted to 2β-hydroxy-3α-((4′-methyl-phenyl)-amino)-5α-androst-17-one (**7**, Scheme 4) in 45 % isolated yield in the presence of one equivalent of 4-methylaniline.

4. Conclusion

Ionic liquid promoted ring opening can be successfully used for the conversion of steroidal 2,3-epoxides into vicinal arylamino-alcohols. The strength of this methodology is shown by its tolerance towards the various functional groups of the aromatic amine, as well as by the application of amine in stoichiometric amount to the epoxide substrate. Also, the comparison of our results with those obtained in the reaction of the 2α,3α-epoxy-steroid with 4-methylaniline in conventional organic solvents, clearly shows the superiority of the use of ionic liquids. It has been shown that LiOTf dissolved in $[bmim]^+[BF_4]^-$ can even induce ring opening in the presence of 4-nitroaniline.

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