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Mild cleavage of aliphatic epoxides with substituted anilines on alumina

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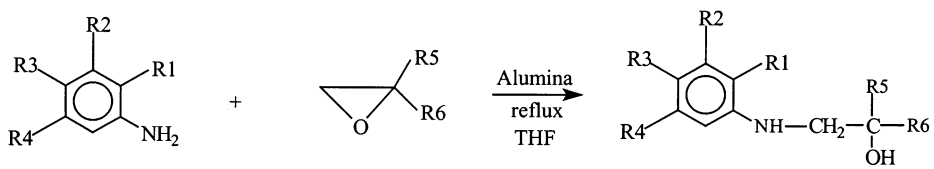
Abstract—Aluminum oxide has been used in the ring opening of epoxides by anilines. This new heterogeneous reaction competes favourably with the usual reactions and the products obtained are of high purity. The yields of the amino-alcohols are uniformly good and the recovered alumina could be used in a new attempt without alteration. © 2002 Published by Elsevier Science Ltd.

Due to their ease of formation and wide reactivity with nucleophiles, oxiranes are used as starting materials and intermediates in organic synthesis. The nucleophilic opening of these epoxides has been studied extensively since it provides a suitable route to the formation of C–C, C–N, C–O or C–S σ-bonds.[1–4]

There are several references to the opening of epoxides with alcohols, thiols and amines, but aromatic amines have received less attention. The first example of basic alumina-promoted opening of an epoxide by aniline was described by Posner.[5]

Interest in the use of alumina as a reagent for organic synthesis is increasing because of its safety, low cost and long shelf life. Moreover, alumina can be used to solve some of the environmental problems associated with organic reagents.[6,7]

The cleavage of epoxides by anilines using classical procedures is difficult. The reaction required an excess of strong inorganic base, a long reaction time, or both and the yields of the corresponding secondary alcohols were low (yields<25%). Recently, new methods using activators/promoters have been developed and used.[8]



6. R1=OH; R2=R3=R4=H
7. R1=R2=R3=R4=H
8. R1=H; R2=R3=R4=OCH_3
9. R1=F; R2=R3=R4=H
10. R1=R4=H; R2-R3=-O-$(CH_2)_2$-O-
11. R1=R2=R3=H; R4=Cl
12. R1=R2=R4=H; R3=COOEt

1. R5=H; R6=CH_2-O-$(CH_2)_2$-C_6H_5
2. R5-R6= -$(CH_2$-$CH_2)_2$-N-CH_2-C_6H_5
3. R5=H; R6=CH_2-O-α-Naphthyl
4. R5=H; R6=-CH_2-Cl
5. R5=H; R6=$C_{16}H_{32}OCH_2$-

13. R1=OH; R2=R3=R4=R5=H; R6=CH_2-O-$(CH_2)_2$-O-C_6H_5
14. R1=R2=R3=R4=R5=H; R6=CH_2-O-$(CH_2)_2$-O-C_6H_5
15. R1=H; R2=R3=R4=OCH_3; R5=H, R6=CH_2-O-$(CH_2)_2$-O-C_6H_5
16. R1=F; R2=R3=R4=H; R5-R6=-$(CH_2$-$CH_2)_2$-N-CH_2-C_6H_5
17. R1=H; R2-R3=-O-$(CH_2)_2$-O; R4=H; R5-R6= -$(CH_2$-$CH_2)_2$-N-CH_2-C_6H_5
18. R1=R2=R3=H; R4=Cl; R5=H; R6=-CH_2-O-$(CH_2)_2$-O-C_6H_5
19. R1=R2=R4=H; R3=COOH; R5=H; R6=-CH_2-O-α-Naphthyl
20. R1=R2=R3=H; R4=Cl; R5=H; R6=CH_2-CH(CH_2)O
21. R1=R2=R3=H; R4=Cl; R5=H; R6= $C_{16}H_{32}OCH_2$-

Scheme 1.

Keywords: 1,2-epoxides; aluminum oxide; anilines; ring opening.
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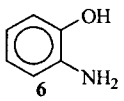
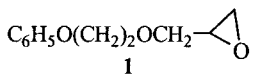
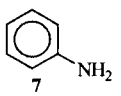
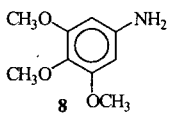
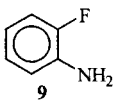
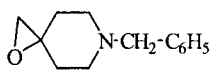
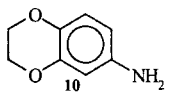
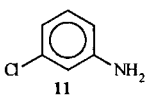
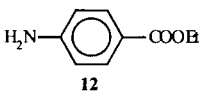
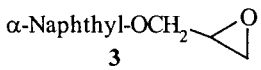
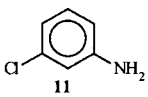
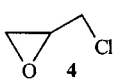
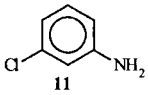
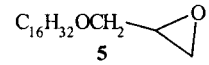
These include Lewis acids such as cerium chloride ($CeCl_3 \cdot 7H_2O$),[8a] tantalum chloride ($TaCl_5$),[8b] diisopropoxyaluminium trifluoroacetate;[8c] metal complexes as $(Cu(OTf)_2)$[8d] or $(Sn(OTf)_2)$[8e] and other activating agents such as trifluoroethanol, hexafluoro-2-propanol.[8f] Although a wide choice of activators is available, many are associated with one or other limitation. We have developed a new method to achieve this conversion, which involves stirring a heterogeneous mixture of unactivated commercially available alumina, the epoxide and the corresponding aniline in tetrahydrofuran (THF) at reflux temperature for 6 h (Scheme 1). The opening of oxiranes with anilines over alumina was rapid and clean, affording the corresponding amino-alcohols in good yield. Moreover, this procedure facilitates the recovery of the alumina, which is easily separated from the crude of reaction by filtration, washing in methanol several times and drying at 100°C during 6 h. The alumina can be used at least three times in these conditions.

The reaction conditions reported in the general procedure are the most effective of a variety of conditions studied in this work. The high purity of the obtained products and the ease of this method for the rapid synthesis of amino-alcohols makes it inherently attractive.

The ring opening takes place in a completely regioselective fashion, affording the desired compound as the only product and the corresponding isomer was not detected. The results obtained in the reaction of alkyloxirane (**1**) with the substituted or unsubstituted aniline are similar (entries 1, 2 and 3). However, the reaction with ethyl *p*-aminobenzoate did not give the desired compound, but rather the corresponding acid (**19**) in low yield (entry 7). It is sometimes desirable to open an epoxide in the presence of other functional groups; in the case of the bifunctional epoxide **2**, the treatment produced analytically pure amino-alcohols in acceptable yield after column chromatography purification (entries 4 and 5). A less satisfactory result was obtained when epichlorohydrin was used. In this case, in addition to the desired product (**20**) other secondary compounds were detected. Epoxides containing a lipophilic group (alkyl substituent) like (**5**) are compatible with

Table 1. Nucleophilic opening of oxiranes by anilines over chromatographic alumina[a] (reflux in THF for 6 h)

Entry	Aniline (3 mmol)	Epoxide (1 mmol)	Product	Yield(%)[b]
1	 **6**	 **1**	**13**	75
2	 **7**	**1**	**14**	70
3	 **8**	**1**	**15**	65
4	 **9**	 **2**	**16**	59
5	 **10**	**2**	**17**	68
6	 **11**	**1**	**18**	74
7	 **12**	 **3**	**19**	38
8	 **11**	 **4**	**20**	42
9	 **11**	 **5**	**21**	78

a) Aluminum oxide-90 standardised (activity II-III) b) All yields represent purified products

this procedure, and the desired compound is produced in acceptable yield (entry 9). All products gave satisfactory IR, ^{1}H NMR, ^{13}C NMR and HRMS spectra, consistent with the structures.[9] The course of the reaction is easily followed by TLC analysis. In summary, we present an easy method of generating β-hydroxyethylanilines in acceptable yield by ring opening of epoxides using aluminium oxide.

General procedure

In general, the reaction involves reflux (6 h) of a suspension of 1 mmol of the epoxide in THF (15 mL) in the presence of 3 mmol of the corresponding aniline and 6 g of aluminium oxide-90 standardised (activity II–III). Filtration of alumina followed by removal of volatile material under vacuum gave the crude of the reaction. The obtained residue was purified by column chromatography on silica gel with hexane/ethyl acetate as eluent. The yield of various alcohols (**13**–**21**) prepared in these conditions are listed in Table 1. The filtered alumina was recovered by washing in methanol and drying at 100°C for 6 h.

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9. Significant analytical data of the new compounds:
13: IR (KBr), ν (cm^{-1}): 3300, 1276, 1105. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 3.26 (m, 2H, CH_2-N-); 3.64 (m, 2H, CH_2-O-); 3.90 (m, 1H, CH-O-); 4.13 (t, $J=5$, 4H, CH_2-O-); 6.65 (m, 3H, Ar); 6.94 (m, 3H, Ar); 7.18 (m, 4H, Ar). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ (ppm): 46.6 (CH_2, CH_2-N); 67.3 (CH_2, CH_2-O-); 69.1 (CH, CH-O-); 70.1 (CH_2, CH_2-O-); 73.8 (CH_2, CH_2-O-); 113.2 (CH, C-2, C-6); 114.7 (CH, C-3, C-5); 117.7 (CH, C-4); 121.1 (CH, C-4′); 129.3 (CH, C-2′, C-6′); 129.6 (CH, C-3′, C-5′); 148.3 (CH, C-1); 158.6 (CH, C-1′).
14: IR (NaCl), ν (cm^{-1}): 3400, 1280, 1122. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 3.26 (m, 2H, CH_2-N); 3.58 (m, 1H, CH_2-O-); 3.80 (m, 1H, CH-O-); 4.10 (m, 4H, CH_2-O-); 6.62 (m, 4H, Ar); 6.92 (m, 3H, Ar); 7.24 (m, 2H, Ar). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ (ppm): 46.9 (CH_2, CH_2-N); 67.3 (CH_2, CH_2-O-); 69.2 (CH, CH-O-); 70.0 (CH_2, CH_2-O-); 73.6 (CH_2, CH_2-O-); 112.6 (CH, C-3, C-6); 114.6 (CH, C-2′, C-6′); 118.2 (CH, C-4, C-5); 121.1 (CH, C-3′, C-5′); 129.5 (CH, C-4′); 136.9 (C, C-1); 144.2 (C, C-1′); 158.4 (C, C-2).
15: IR (NaCl), ν (cm^{-1}): 3500, 1210, 1126. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 3.25 (m, 2H, CH_2-N-); 3.64 (m, 2H, CH_2-O-); 3.75 (m, 9H, CH_3-O-); 3.83 (m, 1H, CH-O-); 4.09 (m, 4H, CH_2-O-); 5.86 (s, 2H, C-2H, C-6H); 6.89 (m, 3H, Ar); 7.28 (m, 2H, Ar). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ (ppm): 47.2 (CH_2, CH_2-N-); 55.9 (CH_3, CH_3-O-); 61.1 (CH_3, CH_3-O-); 67.2 (CH_2, CH_2-O-); 68.9 (CH, CH-O-); 70.1 (CH_2, CH_2-O-); 73.8 (CH_2, CH_2-O-); 90.7 (CH, C-2; C-6); 114.5 (CH, C-2′, C-6′); 121.0 (CH, C-4′); 129.5 (CH, C-3′, C-5′); 145.1 (C, C-1′); 153.8 (C, C-3, C-4, C-5); 158.4 (C, C-1).
16. IR (NaCl), ν (cm^{-1}): 3480, 1224, 1105. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.68 (t, $J=5$, 4H, CH_2-C); 2.40 (m, 2H, CH_2-N); 2.63 (m, 2H, CH_2-N); 3.12 (d, $J=6$, 2H, CH_2-N); 3.54 (s, 2H, CH_2-Ar); 4.21 (t, $J=6$, 1H, NH-); 6.68 (m, 2H, Ar); 7.00 (m, 2H, Ar); 7.31 (m, 5H, Ar). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ (ppm): 35.3 (CH_2, CH2-C); 49.2 (CH_2, CH_2-N); 54.2 (CH_2, -CH_2-Ar); 63.2 (CH_2, -CH_2-N-); 69.7 (C, C-4); 112.5 (CH, C-5); 114.2 (d, $J=21$, C-3); 117.0 (CH, $J=8$, C-4); 124.5 (CH, $J=8$, C-6); 126.9 (CH, C-4′); 128.2 (CH, C-2′, C-6′); 129.1 (CH, C-3′, C-5′); 136.2 (C, C-1′) 138.9 (C, C-1); 153.2 (C, $J=240$, C-2).
17. IR (NaCl), ν (cm^{-1}): 3500, 1260, 1120. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.66 (m, 4H, CH_2-C-); 2.32 (m, 2H, CH_2-N-); 2.60 (m, 2H, CH_2-N); 2.80 (bs, 2H, OH, NH-); 3.02 (s, 2H, CH_2-N-); 3.53 (s, 2H, CH_2-N); 4.19 (m, 4H, CH_2-O-); 6.20 (d, $J=9$, 1H, H-8); 6.22 (s, 1H, H-5); 6.64 (d, $J=9$, 1H, H-7); 7.32 (m, 5H, Ar). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ (ppm): 35.4 (CH_2, CH_2-C); 49.2 (CH_2, CH_2-N); 55.6 (CH_2, CH_2-N); 63.1 (CH_2, CH_2-Ar); 64.2 (CH_2, CH_2-O-); 64.7 (CH_2, CH_2-O-); 69.4 (C, C-4); 102.2 (CH, C-5); 107.2 (CH, C-7); 117.6 (CH, C-8); 127.0 (CH, C-4′); 128.2 (CH, C-2′, C-6′); 129.2 (CH, C-3′, C-5′); 135.8 (C, C-1′); 138.2 (C, C-6); 143.6 (C, C-8a); 143.9 (C, 4a).
18. IR (NaCl) ν (cm^{-1}): 3300, 1262, 1127. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 3.18 (m, 2H, CH_2-N); 3.60 (m, 2H, CH_2-O); 3.86 (m, 2H, CH_2-O); 4.10 (m, 3H, CH_2-O and CH-O); 5.20 (m, 1H, NH); 6.48 (m, 3H, Ar); 6.94 (m, 4H, Ar); 7.24 (m, 2H, Ar). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ (ppm):46.3 (CH_2, CH_2-N); 67.2 (CH_2, CH_2-O); 68.9 (CH-O); 70.0 (CH_2, CH_2-O); 73.6 (CH_2, CH_2-O); 111.5 (CH, Ar); 112.6 (CH, Ar); 114.6 (CH, C-2′, C-6′); 117.3 (CH, Ar); 121.2 (CH, Ar); 129.6 (CH, C-3′, C-5′); 130.2 (CH,

Ar); 134.6 (C, C-3); 149.2 (C, C-1′); 158.4 (C, C-1). **19**. IR (NaCl) ν (cm^{-1}): 3400, 1230, 1120. ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 3.82 (m, 2H, CH_2-N); 4.18 (m, 2H, CH_2-O); 4.28 (m, 1H, CH-O); 7.14 (m, 2H, Ar); 7.42 (m, 4H, Ar); 7.76 (m, 5H, Ar).

20. IR (NaCl) ν (cm^{-1}): 3300, 1240, 1080. ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 3.04 (m, 2H, CH_2-N); 3.60 (m, 1H, CH-O); 3.80 (m, 1H, CH-O); 4.05 (m, 1H, CH-O); 6.45 (m, 1H, Ar); 6.66 (m, 1H, Ar); 7.10 (m, 1H, Ar). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ (ppm): 41.5 (CH_2, CH_2-N); 69.3 (CH_2, CH_2-O); 71.2 (CH, CH-O); 115.6 (CH, Ar); 117.9 (CH, Ar); 130.2 (CH, Ar); 135,2 (C, C-3); 149,5 (C, C-1).

21. IR (NaCl) ν (cm^{-1}): 3390, 1262, 1200. ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 0.88 (t, $J=7$, 3H, CH_3); 1.26 (m, 24H, CH_2-); 1.48 (m, 2H, CH_2-); 1.98 (m, 2H, CH_2-); 2.38 (m, 2H, CH_2-N); 3.65 (m, 5H, CH_2-O); 5.32 (bs, 1H, NH); 6.44 (m, 1H, Ar); 6.66 (m, 2H, Ar); 7.05 (t, $J=7.6$, 1H, Ar).