Facile Ring Opening of Oxiranes with Aromatic Amines in Fluoro Alcohols

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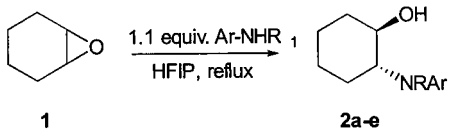
β-Amino alcohols are an important class of organic compounds[1] and are of considerable use in medicinal chemistry.[2] The most practical and widely used route to the synthesis of these compounds is the direct aminolysis of 1,2-epoxides;[1] however, these reactions, which are usually carried out with a large excess of ammonia or amines at elevated temperatures, often fail when poorly nucleophilic amines are concerned. Several useful modifications of the classical procedures have been reported: thus metal amides (Al, Mg, Li, Pb, and Si)[3] have been successfully employed in several cases although many functional groups are potentially incompatible with their use. To avoid drawbacks due to the basic medium, a variety of activators such as Lewis acids or metal salts can be introduced to effect the ring opening at room temperature.[4]

Due to the electron-withdrawing character of fluoroalkyl groups, fluoroalkyl alcohols have a high ability to form hydrogen bonds.[5] In our interest for the use of fluorous medium in organic synthesis,[6] we investigated the possible activation of oxirane ring opening by fluoroalkyl alcohols such as trifluoroethanol and hexafluoro-2-propanol, by hydrogen bonding. We report here the reaction of amines with epoxides in those solvents.

Scheme 1



1 **2a-e**

2a R_1 = H, Ar = Ph,
2b R_1 = Me, Ar = C_6H_5-
2c R_1 = H, Ar = *o*-Me-C_6H_4-
2d R_1 = H, Ar = α-naphthyl
2e R_1 = H, Ar = *p*-MeO-C_6H_4-

Table 1. Ring Opening of Cyclohexene Oxide (1) with Aromatic Amines

entry	product	duration[a]	yield (%)[b]
1.	**2a**	4	84
2.	**2b**	4	86
3.	**2c**	2.5	92
4.	**2d**	3	87
5.	**2e**	2.5	88

[a] Duration in hours. [b] Isolated yields.

Results and Discussion

Initially ring opening of cyclohexene oxide **1** was investigated with aniline in trifluoroethanol (TFE). Cyclohexene oxide was treated with 1.1 equiv of aniline at room temperature, and no reaction was observed. Ring opening of epoxide with aniline failed even at reflux temperature. Since hexafluoro-2-propanol (HFIP) is more acidic ($pK_a = 9.3$) than trifluoroethanol ($pK_a = 12.8$), ring opening was tried out in the former. Cyclohexene oxide (1 mmol) was treated with aniline (1.1 mmol) at room temperature in HFIP (1 mL). After 48 h, there was formation of 65% of amino alcohol **2a**. When the reaction was performed at reflux, 84% of amino alcohol **2a** was obtained after 4 h. The *trans*-configuration of **2a** was assigned by J_{H-H} coupling constants (ddd, $J = 10.7$, 9.4, 3.8 Hz) at 3.14 ppm for CH−NH in ^{1}H NMR spectrum. When the reaction was carried out in 2-propanol no reaction occurred, clearly showing the activating effect of HFIP (Scheme 1, Table 1).

The reaction could be generalized to various aromatic amines. As shown in Table 1, the reaction was also efficient with the secondary *N*-methylaniline. Steric hindrance of the aromatic amine does not have any profound effect on their reactivity toward ring opening of epoxide. Cyclohexene oxide underwent a ring opening reaction at reflux in HFIP with *o*-methylaniline and α-naphthylamine to afford the amino alcohols **2c**[4f] and **2d**,[4f] respectively, in high yields (Scheme 1, Table 1). However, the reaction failed with *p*-nitroaniline. With other cyclic epoxides, **3** and **5**, ring opening could also be achieved with aromatic amines in good yields (Scheme 2, Table 2).

When 1-dodecene oxide **7**, a terminal epoxide, was subjected to ring opening with the *N*-methylaniline, a mixture of both regioisomers **8b** and **9b** were obtained in the ratio of 90:10, the major product resulting from the attack of nucleophile at the less-substituted carbon

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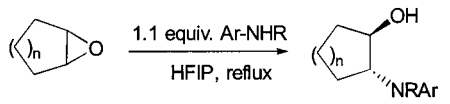
Scheme 2



3 n = 1 **4a** R = H, Ar = Ph, **4b** R = Me, Ar = Ph

5 n = 3 **6a** R = H, Ar = Ph, **6b** R = Me, Ar = Ph

Table 2. Epoxide Ring Opening with Aromatic Amines

entry	substrate	product	duration[a]	yield (%)[b]
6	**3**	**4a**	9	88
7		**4b**	6	81
8		**6a**	38	70[c]
9	**5**	**6b**	52	68[c]

[a] Duration in hours. [b] Isolated yields. [c] Some starting materials were recovered.

(Scheme 3). The regioisomers were separated by column chromatography. This selectivity is similar to that of reactions catalyzed by metal salts and triflates.[4f−i] Ring opening of styrene oxide with aniline resulted in an inextricable mixture. However, when the reaction was performed at room temperature, it afforded after 3 h the regioisomer **11a** (∼50%) accompanied by an unidentified mixture. The facile nature of the styrene ring opening prompted us to perform the reaction in the less acidic CF_3CH_2OH. After 6 h at room temperature, the reaction was complete and afforded 80% of **11a** as the single regioisomer. These high reactivity and selectivity are similar to that observed in the case of metal salts and strong Lewis acids.[4c]

An interesting feature of this method is that the aliphatic amines such as diethylamine, *n*-butylamine, benzylamine, and pyrrolidine failed to effect the ring opening under the similar reaction conditions even after 4 days at reflux. This is in sharp contrast with ring opening reactions facilitated with metal salts,[4a−e] but has already been observed in the case of $Cu(OTf)_2$-catalyzed reactions.[4f] Conversely, when the reaction was carried out in 2-propanol, without any promotor, no conversion was observed with aniline, but piperidine, which is more nucleophilic, underwent reaction to afford the corresponding amino alcohol **12**. Even though we do not have any support for the mechanism, we assume that HFIP forms an association with nucleophilic amines and deactivates them toward reaction with the epoxide. In contrast, in the case of less nucleophilic amines such as aniline, HFIP activates the epoxide ring probably through hydrogen bonding. To explore further, the following experiment was carried out: cyclohexene oxide was treated with an equimolar mixture of piperidine and aniline at reflux in HFIP (1 mL). Only product **2a** was formed after 10 h, but the conversion was only 40%**.** This experiment indicates that interaction between HFIP and piperidine resulted in two effects: HFIP deactivates piperidine toward ring opening and piperidine decreases the activating interaction between HFIP and the oxirane. Since 1 mL of HFIP corresponds to 10 equiv, this cannot be explained only by neutralization but by modified physical properties of HFIP in the presence of piperidine.[5a] A large amount of HFIP (5 mL) was required to obtain 72% conversion into **2a** after 9 h, and no product of reaction with piperidine was observed (Scheme 4). In 2-propanol the reaction occurred with piperidine, affording, after 30 h at reflux, the amino alcohol **12** in good yield with no traces of **2a**. Thus it seems that there are competitive effects of HFIP depending on the nucleophilicity of amines: an activation of the oxirane through hydrogen bonding, and a deactivation of amines.

To summarize, epoxide ring opening with aromatic amines was achieved by using HFIP as the solvent without any catalyst under neutral conditions, leading to high yields of the corresponding amino alcohols. Conversely, HFIP deactivates more-nucleophilic amines (alkylamines) toward oxirane ring opening.

Experimental Section

Amines and epoxides were obtained from Aldrich Chemical Co. and used as such. Products were characterized by comparison of their physical data with those of known samples. ^{1}H NMR spectra were performed at 200 MHz with $CDCl_3$ solutions. All yields refer to isolated products. TLC were performed on 0.25 mm Merck precoated silica plates (60F-254). Compounds **2a**−**e**,[4f] **4a**−**4bc**,[4f] **6a**−**6bc**,[4f] **8a**,[4f] **8b**,[4f] **9b**,[4f] **11a**,[4c,7] and **12**[8] were known.

Typical Experimental Procedure for Epoxide Ring Opening with Aromatic Amines. To a solution of epoxide (1 mmol) in HFIP (1 mL) was added aromatic amine (1.1 mmol). The solution was kept at reflux under argon atmosphere. The completion of the reaction was ascertained by GC. At the end of the reaction, HFIP was recovered by distillation, and the crude product was purified by column chromatography using 3−5% EtOAc in petroleum ether.

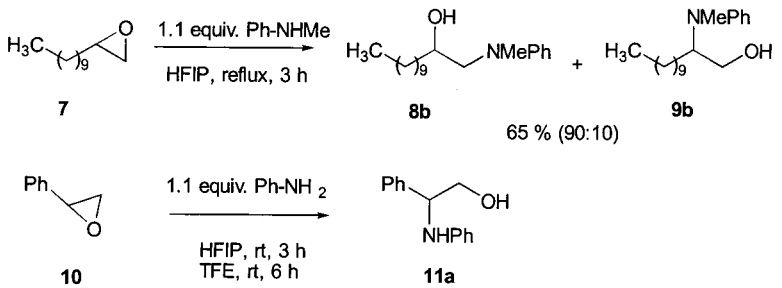
***trans*-2-(Phenylamino)cyclohexanol (2a)**: white solid (0.168 g, 84%); mp: 59−61 °C (lit[4f]: 58−59 °C); R_f 0.3 (10% EtOAc in petroleum ether); ^{1}H NMR δ 1.0 (m, 1H), 1.35 (m, 3H), 1.75 (m, 2H), 2.1 (m, 2H), 3.15 (ddd, J = 10.7, 9.8, 3.8 Hz, 1H), 3.3 (ddd, J = 9.9, 9.8, 4.4 Hz, 1H), 6.75 (m, 3H), 7.1 (m, 2H).

***trans*-2-(*N*-Methyl-*N*-phenylamino)cyclohexanol (2b):**[4f] viscous liquid (0.76 g, 86%); R_f 0.5 (10% EtOAc in petroleum ether); ^{1}H NMR δ 1.27 (m, 2H), 1.4 (m, 2H), 1.75 (m, 2H), 2.2 (m, 2H), 2.75 (s, 3H), 3.4 (ddd, J = 10.8, 9.7, 3.7 Hz, 1H), 3.65 (ddd, J = 10.3, 9.7, 4.7 Hz, 1H), 6.95 (m, 3H), 7.25 (m, 2H).

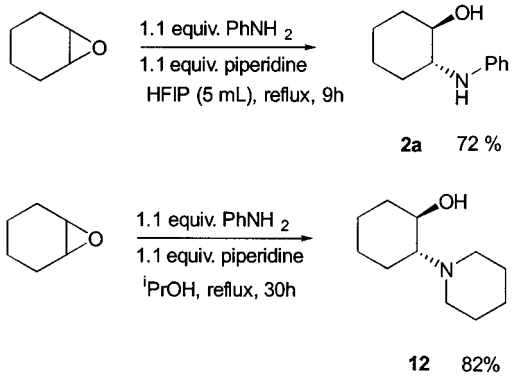
***trans*-2-(2-Methylphenylamino)cyclohexanol (2c):**[4f] liquid (0.190 g, 92%); R_f 0.3 (10% EtOAc in petroleum ether); ^{1}H NMR δ 1.1 (m, 1H), 1.4 (m, 3H), 1.8 (m, 2H), 2.15 (m, 2H), 2.2 (s, 3H), 3.2 (ddd, J = 10.9, 9.4, 3.8 Hz, 1H), 3.4 (ddd, J = 10.5, 9.4, 4.8 Hz, 1H), 6.7 (m, 1H), 6.8 (d, J = 7.9 Hz, 1 H), 7.1 (m, 2H).

***trans*-2-(α-Naphthylamino)cyclohexanol (2d)**: white solid (0.210 g, 87%); mp: 83−85 °C (lit[4f]: 84−85 °C); R_f 0.7 (10% EtOAc

Scheme 3



Scheme 4



in petroleum ether); ^{1}H NMR δ 1.15 (m, 4H), 1.4 (m, 2H), 1.8 (m, 2H), 2.2 (m, 2H), 3.4 (ddd, J = 10.9, 9.3, 3.9 Hz, 1H), 3.55 (ddd, J = 9.6, 9.3, 4.2 Hz, 1H), 6.8 (dd, J = 6.3, 0.9 Hz, 1H), 7.3 (m, 2H), 7.45 (m, 2H), 7.8 (m, 2H).

***trans*-2-(4-Methoxyphenylamino)cyclohexanol (2e)**: white solid (0.192 g, 88%); mp: 59−61 °C (lit[4f]: 58−59 °C); R_f 0.4 (10% EtOAc in petroleum ether); ^{1}H NMR δ 1.0 (m, 1H), 1.3 (m, 3H), 1.72 (m, 2H), 2.1 (m, 2H), 3.0 (ddd, J = 10.9, 9.3, 3.8 Hz, 1H), 3.3 (ddd, J = 9.5, 9.3, 3.9 Hz, 1H), 3.7 (s, 3H), 6.7 (d, J = 8 Hz, 2H), 6.8 (d, J = 8 Hz, 2H).

***trans*-2-(Phenylamino)cyclopentanol (4a)**: white solid (0.156 g, 88%); mp: 54−56 °C (lit[4f]: 54−55 °C); R_f 0.3 (10% EtOAc in petroleum ether); ^{1}H NMR δ 1.4 (m, 1H), 1.6 (m, 1H), 1.8 (m, 2H), 2.1 (m, 2H), 3.6 (m, 1H), 4.0 (m, 1H), 6.7 (m, 3H), 7.2 (m, 2H).

***trans*-2-(*N*-Methyl-*N*-phenylamino)cyclopentanol (4b):** [4f] colorless liquid (0.154 g, 81%); R_f 0.4 (10% EtOAc in petroleum ether); ^{1}H NMR δ 1.6−2.1 (m, 6H), 2.80 (s, 3H), 3.95 (m, 1H), 4.2 (m, 1H), 6.7−6.9 (m, 3H), 7.2 (m, 2H).

***trans*-2-(Phenylamino)cycloheptanol (6a)**: white solid (0.140 g, 70%); mp: 58−60 °C (Lit[4f]: 59−60 °C); R_f 0.3 (10% EtOAc in petroleum ether); ^{1}H NMR δ 1.2−1.8 (m, 9H), 2.0 (m, 1H), 3.2 (ddd, J = 10.6, 9.3, 3.3, 1H), 3.4 (ddd, J = 9.6, 9.3, 3.6 Hz, 1H), 6.7 (m, 3H), 7.2 (m, 2H).

***trans*-2-(*N*-Methyl-*N*-phenylamino)cycloheptanol (6b):** [4f] colorless liquid (0.147 g, 68%); R_f 0.4 (10% EtOAc in petroleum ether); ^{1}H NMR δ 1.38−1.80 (m, 9H), 2.1 (m, 1H), 2.74 (s, 3H), 3.5 (ddd, J = 10.6, 9.3, 2.4, 1H), 3.6 (ddd, J = 9.5, 9.3, 3.6 Hz, 1H), 6.85−7.0 (m, 3H), 7.26 (m, 2H).

1-(*N*-methyl-*N*-phenylamino)dodecan-2-ol (8b):[4f] colorless liquid, R_f 0.5 (10% EtOAc in petroleum ether); ^{1}H NMR δ 0.9 (t, J = 6.9 Hz, 3H), 1.3 (bs, 16H), 1.5 (m, 2H), 1.57 (m, 1H), 2.9 (s, 3H), 3.2 (m, 2H), 3.9 (m, 1H), 6.75−6.9 (m, 3H), 7.3 (m, 2H).

2-(*N*-methyl-*N*-phenylamino)dodecan-1-ol (9b):[4f] colorless liquid, R_f 0.45 (10% EtOAc in petroleum ether); ^{1}H NMR δ 0.88 (t, J = 6.9 Hz, 3H), 1.2 (bs, 17H), 1.5 (m, 1H), 2.7 (s, 3H), 3.6 (m, 2H), 3.95 (m, 1H), 6.7−6.9 (m, 3H), 7.2 (m, 2H).

2-Phenylamino-2-phenylethanol (11a)[7] (reaction performed in trifluoroethanol at room temperature): colorless liquid (0.115 g, 80%); R_f 0.5 (10% EtOAc in petroleum ether); ^{1}H NMR δ 3.75 (dd, ^1J = 11.0 Hz, ^2J = 7.0 Hz, 1H), 3.95 (dd, ^1J = 11.0 Hz, ^2J = 4.0 Hz, 1H), 4.5 (dd, ^2J = 7.0 Hz, ^2J = 4.0 Hz, 1H), 6.6−7.4 (m, 10H).

***trans*-2-(Piperidin-1-yl)cyclohexanol (12)**:[8] colorless oil (0.150 g, 82%); bp 150−152 °C (1 mmHg, Kugelrohr); ^{1}H NMR δ 1.02−1.34 (m, 6H), 1.62−1.84 (m, 8H), 2.12 (m, 1H), 2.12 (m, 1H), 2.48 (ddd, J = 11.0, 9.5, 3.3 Hz, 1H), 2.54 (m, 2 H), 2.68 (m, 2H), 3.45 (ddd, J = 9.6, 9.5, 2.8 Hz, 1H).

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