

Regioselective Opening of Epoxides to β -Amido Alcohols Under Solid-Liquid PTC Conditions

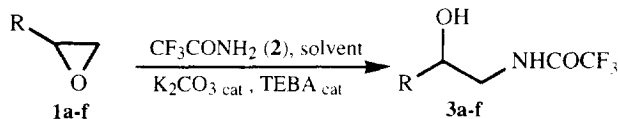
Domenico Albanese,* Dario Landini, Michele Penso

Centro CNR and Dipartimento di Chimica Organica e Industriale dell'Università
 Via Venezian 21, I-20133 Milano, Italy[#]

Abstract: A study on the ring opening of a number of epoxides **1** with trifluoroacetamide (**2**) under solid-liquid phase transfer catalysis (SL-PTC) conditions has been performed. The reaction is completely regioselective affording β -amido alcohols **3** deriving from the attack of the nucleophile to the less substituted carbon atom of the oxirane ring. © 1997 Elsevier Science Ltd.

In previous papers we have reported on the alkylation of trifluoroacetamide (**2**) under solid-liquid phase transfer catalysis (SL-PTC) conditions to give useful intermediates which can be easily converted into primary and secondary amines,¹ aminoesters² and aminoacids.³ These results indicate **2** as a valuable surrogate for the amino group and prompted us to extend this strategy to the ring opening of epoxides.

In the present paper we report a systematic study of the reaction of trifluoroacetamide (**2**) with a series of epoxides **1** under SL-PTC conditions, promoted by catalytic amounts of solid K_2CO_3 . The 1-*N*-(trifluoroacetamido)alcohols **3** thus obtained, can be converted by mild alkaline hydrolysis into the corresponding amino alcohols **4** whose importance as ligands for asymmetric catalysis, as drugs and building blocks in the synthesis of pharmaceuticals is well known.⁴



Scheme 1

RESULTS AND DISCUSSION

The reaction (Scheme 1) was performed by stirring at 90°C a heterogeneous mixture of the epoxide **1** (1 mol), triethylbenzylammonium chloride (TEBA) (**5**) (0.1 mol), anhydrous K_2CO_3 (0.1 mol), trifluoroacetamide (**2**) (2 mol) and dioxane as solvent until complete conversion of the substrate was reached (TLC analysis).

[#] E-mail: research@iumchz.chimorg.unimi.it

Under these reaction conditions β -amido alcohols **3** were isolated in 55-76% yield after 7.5-48 hours (Table 1).

Table 1.

epoxide 1	t(h)	yield(%)	β -amido alcohol 3
1a R = CH ₂ OPh	7.5 18	75 30 ^a	3a R = CH ₂ OPh
1b R = CH ₂ OBOM	27	76	3b R = CH ₂ OBOM
1c R = CH ₂ OAllyl	9	55	3c R = CH ₂ OAllyl
1d R = (<i>S</i>)-(+)-CH ₂ OBn	29	58	3d R = (<i>R</i>)-(-)-CH ₂ OBn
1e R = <i>n</i> -C ₆ H ₁₃	24	75	3e R = <i>n</i> -C ₆ H ₁₃
1f R = Ph	48	58	1f R = Ph

^a Without TEBA.

The reaction is completely regioselective affording in all cases β -amido alcohols **3** deriving from the attack of the nucleophile to the less substituted carbon atom of the oxirane ring. As a consequence of this behaviour the stereocenter of chiral epoxides was not supposed to be affected. In a control experiment (*S*)-(+)-2-benzyl glycidyl ether (**1d**) was used as a starting material affording 58% yield of the corresponding enantiopure amido alcohol **3d**, as revealed by ¹⁹F NMR analysis. The spectrum registered after treatment of **3d** with (*S*)-(+)-2-methoxy-2-phenyl-2-trifluoromethyl acetic acid chloride ("Mosher's acid chloride") showed a single signal for the trifluoromethyl group, whereas two well separated singlets were obtained by using (\pm) **3d**.⁵

[(Phenoxy)methyl]oxirane (**1a**) was chosen as the model substrate for studying the factors affecting the ring opening. The best results were obtained by working in polyethereal solvents such as DME, diglyme and dioxane, the latter being the most effective. The process did not proceed at all in less polar solvents such as toluene or chlorobenzene, whereas many by-products were formed in aprotic dipolar solvents such as CH₃CN and DMSO.

The presence of the PTC agent is essential for the good outcome of the reaction. In fact, in the absence of TEBA (**5**) the β -amido alcohol **3a** was formed in 30% yield only, after 18 hours. K₂CO₃ proved to be the most successful of the various basic reagents used to deprotonate **2**. With KHCO₃ the reaction is slower and furnishes **3a** in 47% yield together with 10% of 3-phenoxy-1,2-propanediol (**6**). Cs₂CO₃, CsF and TBAF gave scarce results both in terms of yield and reaction time.

The observed regiochemistry clearly indicate that the reaction proceeds through an S_N2 autocatalytic process promoted by catalytic amounts of anhydrous K₂CO₃ and TEBA. Trifluoroacetamide (**2**) reacts with solid K₂CO₃ at the phase boundary⁶ affording the potassium salt of trifluoroacetamide **7** which is transferred, in part by the PTC agent, into the organic medium where the reaction occurs. The strong catalytic effect of the PTC agent can be ascribed to the increased solubility and the higher reactivity of the CF₃CONH⁻Q⁺ (**8**) species with respect to that of CF₃CONH⁻K⁺ (**7**).⁷ The effective nucleophile **8** is regenerated through protonation by trifluoroacetamide (**2**).

The trifluoroacetamide group can be easily removed by mild alkaline hydrolysis, thus giving access to β -amino alcohols **4**. For example 1-amino-3-phenoxy-2-propanol (**4a**) was formed in 95% yield by treatment of **3a** with NaOH 3%/THF at 0°C.

It is also worth noting that the good stability of *O*-protected glycidols under the above reaction conditions enable the use of the corresponding β -amido alcohols **3** as polyfunctionalized C₃ building blocks bearing a stereocenter of known configuration.

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EXPERIMENTAL

Commercial trifluoroacetamide (**1**) was recrystallised from CHCl₃, mp 71-72°C, before use. K₂CO₃ was dried by heating at 140°C in vacuo (0.05 mmHg) for 6 h. Starting epoxides **1a,c-f** are commercially available. Product **1b** was prepared by a literature method.⁸ ¹H NMR and ¹⁹F NMR spectra were recorded in CDCl₃ at 300 Mhz and 282 Mhz, respectively, using TMS for the ¹H- and CFCl₃ for the ¹⁹F NMR spectra as external standards. ¹³C NMR spectra were recorded in CDCl₃ at 75.4 Mhz using CDCl₃ (δ = 76.9) as internal standard. The coupling constants are in Hz. Optical rotations were measured with a Perkin-Elmer 241 instrument. Melting points are corrected. Analytical TLC was performed using Merck precoated silica gel F₂₅₄ plates.

General Method for the Preparation of β -Trifluoroacetamido Alcohols **3a-f**

A mixture of the epoxide **1** (1 mmol), K₂CO₃ (0.1 mmol), TEBA **5** (0.1 mmol), trifluoroacetamide (**2**) and dioxane (0.25 ml) is stirred at 90°C until the starting material is no longer detectable (TLC analysis). After cooling, the crude is diluted with CH₂Cl₂, filtered on celite and the solvent is evaporated under reduced pressure. The residue is purified by flash or medium pressure liquid-chromatography (MPLC) on silica gel (230-400 mesh). Starting epoxide, reaction time, chromatographic eluant, yield and physical, spectroscopic and analytical data of amido alcohols **3a-f** are as follows.

1-N-(Trifluoroacetyl)-3-(phenoxy)propan-2-ol (3a). [(Phenoxy)methyl]oxirane (**1a**): 7.5h; EtOAc and petroleum ether (PE) (1:3). **3a**, 75%; mp 90-91°C; ¹H NMR (CDCl₃), δ , 7.30-6.80 (m, 6H), 4.23-4.15 (m, 1H), 4.05 (dd, 1H, ²J = 9.5, ³J = 3.9), 3.93 (dd, 1H, ²J = 9.5, ³J = 6.4), 3.76 (ddd, 1H, ²J = 13.9, ³J = 3.7, 6.6), 3.48 (ddd, 1H, ²J = 13.9, ³J = 7.1, 4.9), 2.70 (d, 1H, ³J = 4.6). ¹³C NMR (CDCl₃), δ , 157.9 (q, CO, ²J_{CF} = 37.1); 157.8, 129.7, 121.7, 114.4 (s, C_{arom}), 115.7 (q, CF₃, ¹J_{CF} = 287.9), 69.9 (s, C-3), 68.3 (s, C-2), 42.3 (s, C-1). ¹⁹F NMR (-75.79). *Anal. Calcd.* for C₁₁H₁₂F₃NO₃: C, 50.20; H, 4.60; N, 5.32. *Found*: C, 50.31; H, 4.56; N, 5.42.

1-N-(Trifluoroacetyl)-3-[(phenylmethoxy)methoxy]propan-2-ol (3b). [(Phenylmethoxy)methoxy]methyl] oxirane (**1b**): 27h; EtOAc and PE (1:3). **3b**, 76%; mp 43-45°C; ¹H NMR (CDCl₃), δ , 7.40-7.25 (m, 5H), 6.95 (bs, 1H), 4.78 (s, 2H), 4.61 (s, 2H), 3.94-3.85 (m, 1H), 3.69 (dd, 1H, ²J = 10.6, ³J = 3.6), 3.61 (ddd, 1H, ²J = 13.8, ³J = 3.7, 6.6), 3.54 (dd, 1H, ²J = 10.6, ³J = 6.2), 3.27 (ddd, 1H, ²J = 13.8, ³J = 7.5, 4.8), 3.06 (bs, 1H). ¹⁹F NMR (-76.35). *Anal. Calcd.* for C₁₃H₁₆F₃NO₄: C, 50.82; H, 5.25; N, 5.32. *Found*: C, 50.70; H, 5.27; N, 5.39.

1-N-(Trifluoroacetyl)-3-(2-propenyloxy)-propan-2-ol (3c). [(2-Propenyloxy)methyl] oxirane (**1c**): 9h; EtOAc and PE (1:2). **3c**, 55%; n_D²⁰ = 1.4290; ¹H NMR (CDCl₃), δ , 7.13 (bs, 1H), 5.93-5.80 (m, 1H), 5.28-5.16 (m, 2H), 3.98 (dt, 2H, ³J = 5.7, ⁴J = 1.4), 3.94 (m, 1H), 3.62 (ddd, 1H, ²J = 13.8, ³J = 3.9, 6.5), 3.52 (dd, 1H, ²J = 9.7, ³J = 3.9), 3.40 (dd, 1H, ²J = 9.7, ³J = 6.1), 3.32 (ddd, 1H, ²J = 13.8,

$^3J = 6.7, 5.2), 3.03$ (bs, 1H). ^{19}F NMR (-76.43). *Anal. Calcd.* for $\text{C}_8\text{H}_{12}\text{F}_3\text{NO}_3$: C, 42.30; H, 5.32; N, 6.17. *Found*: C, 42.24; H, 5.48; N, 6.19.

(**2R**)-(-)-1-*N*-(Trifluoroacetyl)-3-(phenylmethoxy)propan-2-ol (**3d**). (2*S*)-(+)-[(Phenyl methoxy)methyl] oxirane (**1d**); 29h; Et₂O and PE (3:2). **3d**, 58%; $[\alpha]_{\text{D}}^{20} = -52.17$, ($c = 1.15$, CH_2Cl_2); $n_{\text{D}}^{20} = 1.4841$, ^1H NMR (CDCl_3), δ , 7.48-7.21 (m, 5H), 6.85 (bs, 1H), 4.54 (s, 2H), 3.96 (m, 1H), 3.63 (ddd, 1H, $^2J = 13.9$, $^3J = 3.9, 6.6$), 3.57 (dd, 1H, $^2J = 9.6$, $^3J = 3.9$), 3.44 (dd, 1H, $^2J = 9.6$, $^3J = 6.2$), 3.32 (ddd, 1H, $^2J = 13.9$, $^3J = 7.0, 4.7$), 2.61 (bs, 1H). ^{19}F NMR (-76.41). *Anal. Calcd.* for $\text{C}_{12}\text{H}_{14}\text{F}_3\text{NO}_3$: C, 51.99; H, 5.09; N, 5.05. *Found*: C, 52.05; H, 5.17; N, 5.00. The "Mosher ester" of this compound [and of (\pm)-**3d**] was synthesized by treating 28 mg of **3d** (0.10 mmol) with 28 mg (0.11 mmol) of (+)-(*S*)-"Mosher's acid chloride", as reported in literature.⁹

1-*N*-(Trifluoroacetyl)-octan-2-ol (**3e**). 1,2-Epoxyoctane (**1e**); 24h; EtOAc and PE (1:4). **3e**, 75%; mp 69-70°C, ^1H NMR (CDCl_3), δ , 6.75 (bs, 1H), 3.81-3.69 (m, 1H), 3.61 (ddd, 1H, $^2J = 13.5$, $^3J = 3.2, 6.8$), 3.15 (ddd, 1H, $^2J = 13.5$, $^3J = 8.3, 4.6$), 1.83 (d, 1H, $^3J = 6.0$), 1.65-1.20 (m, 10H), 0.90 (t, 3H, $^3J = 6.0$). ^{19}F NMR (-76.39). *Anal. Calcd.* for $\text{C}_{10}\text{H}_{18}\text{F}_3\text{NO}_2$: C, 49.79; H, 7.52; N, 5.81. *Found*: C, 49.81; H, 7.52; N, 5.76.

1-*N*-(Trifluoroacetyl)-2-phenyl-1-ethanol (**1f**). Phenyl oxirane (**1f**); 48h; EtOAc and PE (1:4). **3f**, 58%; mp 76-78°C, ^1H NMR (CDCl_3), δ , 7.42-7.33 (m, 5H), 6.84 (bs, 1H), 4.87 (dd, 1H, $^2J = 8.5$, $^3J = 3.6$), 3.79 (ddd, 1H, $^2J = 13.6$, $^3J = 3.6, 7.3$), 3.37 (ddd, 1H, $^2J = 13.6$, $^3J = 8.5, 4.5$), 2.40 (bs, 1H). ^{19}F NMR (-76.43). *Anal. Calcd.* for $\text{C}_{10}\text{H}_{10}\text{F}_3\text{NO}_2$: C, 51.51; H, 4.32; N, 6.01. *Found*: C, 51.61; H, 4.45; N, 5.90.

Hydrolysis of 3a. 1-*N*-(Trifluoroacetyl)-3-(phenoxy)propan-2-ol (**3a**) (1 mmol, 263 mg) was dissolved in THF (1 ml) and NaOH 3% (2 mmol, 2.6 ml) was added. After stirring for 1h at 0°C the solvent was evaporated and the residue extracted with Et₂O. The ether solution was dried (MgSO_4), filtered and evaporated to give 159 mg of 1-amino-3-phenoxy-2-propanol (**4a**), yield 95%. mp 91-92 (lit.¹⁰ mp 90-91.5).

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- ^{19}F NMR (CDCl_3) of the Mosher's ester of (\pm) **3d**: δ , -71.912 (s, CE_3), -71.128 (s, CE_3), -76.630 (s, CE_3CO). ^{19}F NMR of the Mosher's ester of **3d**: δ , -72.106 (s, CE_3), -76.646 (s, CE_3CO).
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