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# Improved Ritter reaction with $CF_3$-containing oxirane for an access to central units of protease inhibitors

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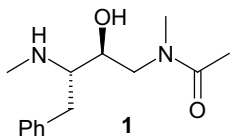
ABSTRACT

The influence of fluorinated alcohols on the $BF_3{\cdot}Et_2O$-promoted Ritter type reaction has been investigated. Trifluoroethanol/$BF_3{\cdot}Et_2O$ system allowed access to the central unit of protease inhibitors by the ring opening of fluorinated epoxide **2** with various nitriles.



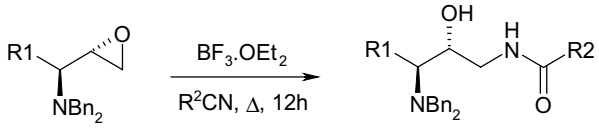
Diaminopropanols and corresponding amidopropanols constitute one of the most common central units of various protease inhibitors such as β- or γ-secretase,[1] HIV protease,[2] cathepsins,[3] or plasmepsins.[4] The scaffold **1** (Fig. 1) is a typical example of 1,3-diaminoalkan-2-ol-based structure of inhibitors.

Hydroxylethylamine motifs can be easily obtained by oxirane ring opening reactions, which furthermore allow the access of a wide structural diversity of compounds. Recently, Concellón et al. described an easy access to 1,3-diaminoalkan-2-ols by a ring opening of amino epoxides through a Ritter reaction with nitriles.[5] This reaction permitted a direct and selective introduction of an acylamino function and offers an excellent alternative to the classical aminolysis of oxiranes. Furthermore, the reaction provided the diaminoalcohol with a protection different for each amino group, what is particularly useful for further coupling to prepare inhibitors (Scheme 1).




**1**

**Figure 1.**

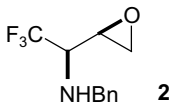



**Scheme 1.**

In our general search for new inhibitors of aspartyl proteases,[6] we developed an easy and diastereoselective synthesis of the trifluoromethyl epoxide **2** (Fig. 2).[6a]

Fluorine atoms when incorporated into peptidomimetic structures or amino acids can provide interesting changes in biological properties related to altered physico chemical properties such as high hydrophobicity and higher stability toward metabolic processes.[7] Fluoroalkyl groups are also good mimics of naturally occurring hydrophobic residues such as isopropyl or benzyl.

Ring opening of epoxide **2** can offer a general access to a wide range of polyfunctional molecules. For an easy entry to the trifluoromethyl analogue of scaffold **1**, we investigated the Ritter reaction with the amino oxirane **2**.




**2**

**Figure 2.**

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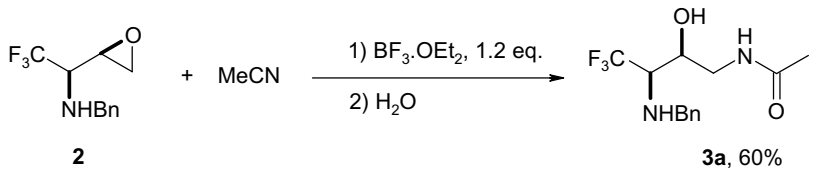
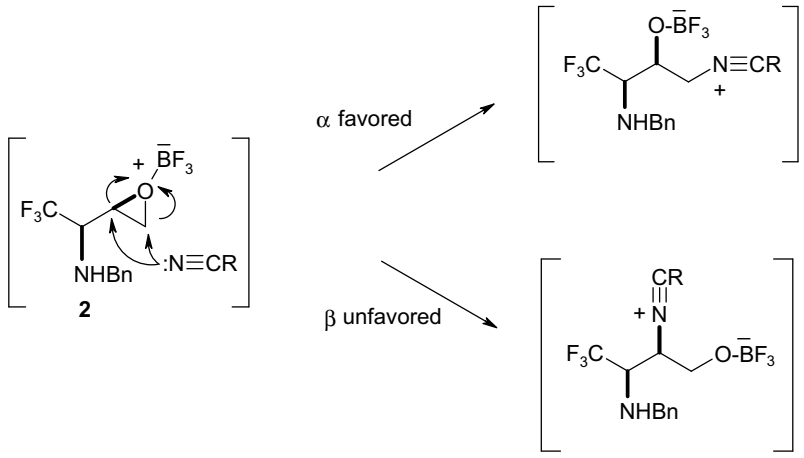



**Scheme 2.**




**Scheme 3.**

We first carried out the reaction with acetonitrile under reported conditions.[8] Epoxide **2** was warmed at reflux in acetonitrile used as the solvent, in the presence of 1.2 equiv of $BF_3{\cdot}OEt_2$. After hydrolysis, the corresponding trifluoromethyl alcohol **3a** was obtained, in a 60% yield (Scheme 2).

The ring opening of the epoxide **2** is regioselective, occurring on the terminal position (Scheme 3). For non-fluorinated epoxides, this selectivity was explained based on steric grounds. From **2**, according to the mechanism proposed by Concellón,[8] this regioselectivity was also expected, the generation of a nitrilium ion being easier on a remote position from the electron-withdrawing $CF_3$ group (Scheme 3). It is interesting to note that the presence of a non-protected amine function in **2** is not an obstacle for the reaction.

The large excess of nitrile used as the solvent limits the reaction to liquids, and it is not compatible with structurally more complex nitriles. The reaction was then investigated by using $CH_2Cl_2$ as the solvent and nitriles as reagents under $BF_3{\cdot}OEt_2$ catalysis (Scheme 3). With 4 equiv of MeCN, no reaction occurred at room temperature, and a complex mixture was obtained at reflux. We previously reported that hexafluoroisopropanol (HFIP) or trifluoroethanol (TFE), when used as solvents, could promote oxirane ring opening with nucleophiles.[9] We then explored this reaction in fluorinated alcohols. Surprisingly from **2**, no reaction occurred in HFIP or TFE used as solvents alone. When 1.2 equiv of $BF_3{\cdot}OEt_2$ was added in HFIP, only traces of the desired product were obtained. This might be due to a complexation of HFIP with the nitrile function, which decreases the reactivity of the latter. The reaction was then conducted with acetonitrile in $CH_2Cl_2$ in the presence of $BF_3{\cdot}OEt_2$ (1.2 equiv) and only 1.2 equiv HFIP or TFE (Table 1).

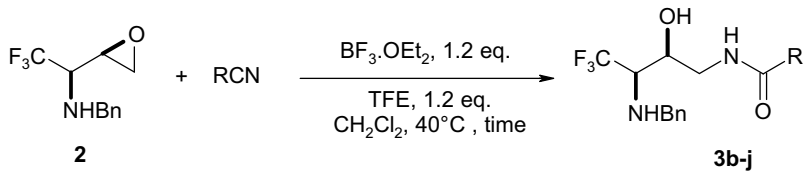
At room temperature, with 1.2 equiv of HFIP, 40% of the corresponding product **3a** was obtained after 24 h. Increasing the quantity of HFIP did not change the yield and the reaction rate. In contrast, reaction time significantly decreased when the reaction was performed at reflux (1.5 h vs 24 h). Under similar conditions, TFE appeared to be a better additive with an improved yield in product **3a** (67% at rt (entry 4) and 65% at 40 °C (entry 5)). Among different solvents used (ether, THF, $ClCH_2CH_2Cl$, or toluene), only $CH_2Cl_2$ provided clean reaction. The reaction was then extended to various nitriles under these optimized conditions (Scheme 4, Table 2).

**Table 1**
Ritter reaction in DCM and activated with fluorinated alcohols

| Entry | MeCN (equiv) | Solvent | $T$ (°C) | Time (h) | Yield of **3a**[a] (%) |
|---|---|---|---|---|---|
| 1 | 4 | $CH_2Cl_2$ | rt | 24 | 0 |
| 2 | 4 | $CH_2Cl_2$/HFIP (1.2) | rt | 24 | 40 |
| 3 | 4 | $CH_2Cl_2$/HFIP (1.2) | 40 | 1.5 | 50 |
| 4 | 4 | $CH_2Cl_2$/TFE (1.2) | rt | 24 | 67 |
| 5 | 4 | $CH_2Cl_2$/TFE (1.2) | 40 | 1.5 | 65 |

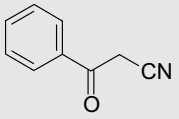
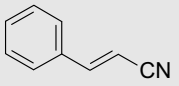
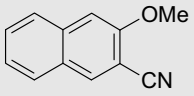
[a] Isolated yield.

Yields obtained in the ring opening of epoxide **2** with alkyl (entries 1 and 2), aromatic (entries 3–5), and functionalized nitriles (entries 7–9) were moderate to good, ranging from 44% to 78%. From the *p*$NO_2$ phenyl nitrile, and the reaction led to a complex mixture (entry 6), **3f** could not be isolated. Clearly, the success of this reaction is due to synergic effects of trifluoroethanol and $BF_3{\cdot}Et_2O$, since both reactions performed in TFE alone and in $CH_2Cl_2$ with $BF_3{\cdot}Et_2O$ were unsuccessful. This activating effect of $BF_3{\cdot}Et_2O$ in fluoro-alcohols had previously been observed in other reactions investigated in the laboratory.[10] In the same connection, Prakash recently reported that $BF_3{\cdot}2TFE$ complex behaves as a superacidic catalyst.[11] However, its preparation is not straightforward. For our Ritter reaction, we assumed that such a complex could be generated in situ and promote the ring opening. In order to validate this hypothesis, $^1H$ NMR experiments were performed on a mixture $1BF_3{\cdot}Et_2O/2TFE$ in $CDCl_3$. In starting partners, $^1H$




**Scheme 4.**

**Table 2**
Ritter reaction with various nitriles

| Entry | RCN | Time (h) | Product | Yield in **3**[a] (%) |
|---|---|---|---|---|
| 1 | BuCN | 1.5 | **3b** | 44 |
| 2 | *t*BuCN | 1.5 | **3c** | 52 |
| 3 | PhCN | 3.5 | **3c** | 78 |
| 4 | *p*-MeO–PhCN | 1.5 | **3d** | 73 |
| 5 | *p*-Cl–PhCN | 3 | **3e** | 47 |
| 6 | *p*-$NO_2$–PhCN | 24 | **3f** | Mixture |
| 7 |  | 6 | **3g** | 74 |
| 8 |  | 3 | **3h** | 68 |
| 9 |  | 2 | **3i** | 58 |

[a] Isolated yield.

NMR chemical shifts of methylene protons are 3.90 ppm ($J_{H-F}$ = 8.5 Hz) for TFE and 4.17 ppm ($J_{H-H}$ = 7 Hz) for $BF_3{\cdot}Et_2O$. In the resulting mixture, methylenes of the major compound are shielded to 4.0 ppm for $CH_2$–$CF_3$, and deshielded to 4.06 ppm for $CH_2$–$CH_3$. The shift for $CH_2$–$CF_3$ ($\Delta\delta$ = 0.1) is weaker than that described for the difference between TFE and $BF_3{\cdot}2$TFE ($\Delta\delta$ = 0.35)[11] suggesting that the latter complex was not formed. However, exchanges between $BF_3$ ligands, even partial, are sufficient to promote the reaction.

In conclusion, we have described a new and easy access to trifluoromethyl diamino alcohols by the ring opening of a trifluoromethyl amino epoxide **2** by the Ritter reaction with nitriles in the presence of $BF_3{\cdot}OEt_2$ and trifluoroethanol.[12] This method presents the great interest to provide a direct access to the central core of most protease inhibitors with a diversity of structure. The yields are moderate to good, and it is important to note that the presence of a free amino function does not influence the reaction.

## Acknowledgments

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12. *Typical procedure for the synthesis of N-(3-benzylamino-4,4,4-trifluoro-2-hydroxy-butyl)-acetamide* (**3a**): To a solution of trifluoromethylated epoxide **2** (100 mg, 0.43 mmol) in dichloromethane (1 mL), nitrile (1.7 mmol) and trifluoroethanol (40 μL, 0.5 mmol) were added at 0 °C. Then $BF_3{\cdot}OEt_2$ (60 μL, 0.5 mmol) was introduced to the reaction mixture and warmed at reflux until the disappearance of the starting material (monitored by $^{19}F$ NMR). The reaction mixture was then hydrolyzed by a saturated aqueous solution of $Na_2CO_3$ (5 mL), and was extracted with dichloromethane (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was then purified by chromatography on silica gel (82 mg, 65%). IR: 3306; 2936; 1655 $cm^{-1}$. $^{19}F$ NMR (188 MHz, $CDCl_3$, $CFCl_3$ as internal standard): $\delta$ −71.9 (d, $J$ = 7.4 Hz, $CF_3$). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.24 (m, 5H), 4.64 (ddd, $J$ = 10.1, 8.1, 2.2 Hz, 1H), 4.06 (d, $J$ = 13.2 Hz, 1H), 3.80 (m, 2H), 3.61 (dd, $J$ = 8.3, 13.5 Hz, 1H), 2.90 (m, 1H), 1.90 (s, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 164.5, 139.0, 128.5, 128.3, 127.5, 126.2 (q, $J$ = 287.3 Hz, **C**$F_3$), 76.2, 59.7 (q, $J$ = 26.4 Hz, **C**H$CF_3$), 58.0, 51.6, 13.8.