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A Versatile Synthesis of Amino Trifluoromethyl Ketones and Alcohols

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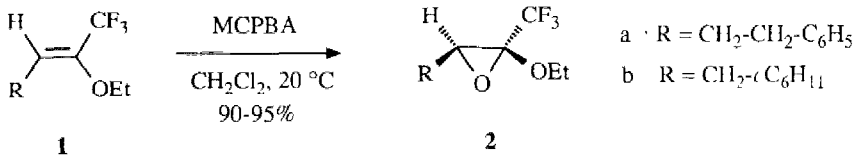
Abstract: *A short selective and general route to α-amino trifluoromethyl ketones and corresponding alcohols is described via an easy epoxidation of 1-CF_3 enol ethers followed by an opening with various secondary amines*

α-Amino and α-peptidyl fluoromethyl ketones and corresponding alcohols are a very important class of protease inhibitors [1] This interest, especially in the elastase and aspartyl protease field, has stimulated much attention.[2] Unfortunately, no general synthesis has been described due to the lack of easily available fluorinated synthons. Some particular methods are limited to the preparation of β-primary amino or β-peptidyl trifluoromethyl alcohols [2f,3,4] Another strategy, based on an epoxide opening by an amine, has been described only for 1-perfluoroalkyl epoxyethanes [5]

We report here a general preparation of α-amino trifluoromethyl ketones and stereochemically pure β-amino alcohols starting from readily available 1-CF_3 enol ethers [6] Recently, using a Wittig reaction with ethyl trifluoroacetate, we have described a direct and easy method of preparation of fluorinated enol ethers **1** in pure Z configuration.[7]

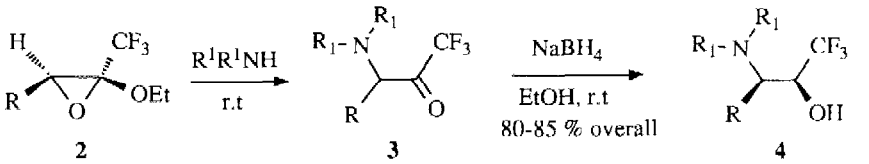
In a general way, the presence of a perfluoroalkyl group on an olefin is expected to decrease the reactivity towards electrophilic reagents. In particular, the classical method of epoxidation with peracids is unsuccessful. The preparation of such perfluoroalkyl epoxides has been described by basic ring closure of bromohydrins.[8] In the case of **1**, we could expect that the presence of the ethoxy group would counterbalance the effect of the trifluoromethyl group, although **1** has been shown to be unreactive towards protonation [6a,9]

Indeed, in methylene chloride at room temperature, in the presence of m-chloroperbenzoic acid (MCPBA), enol ethers **1** led to corresponding epoxyethers **2** in very high yields[10] (90-95 %).



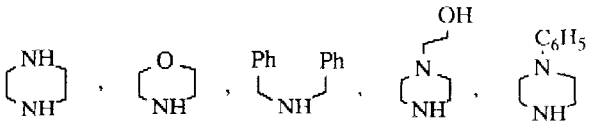
1 **2**

Cleavage of epoxyethers **2** by a wide variety of secondary amines was performed at room temperature to give regioselectively trifluoromethylated α-amino ketones **3**, which were immediately reduced by $NaBH_4$ into the pure (R,S-S,R) diastereomer of aminoalcohols **4**[11] as determined by chemical and NMR correlations.[12] The overall yield from **2** is about 85 %. The diastereoselectivity, already observed in the parent series in the case of bulky amino groups,[13] follows the Felkin Anh model.



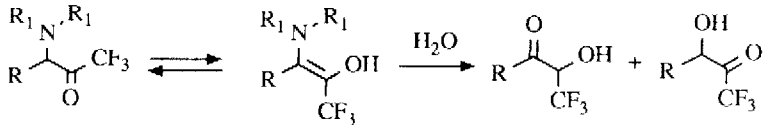
2 **3** **4**

4a { R = CH_2-CH_2-C_6H_5 ; R_1-NH-R_1 = Morpholine

R_1-NH-R_1 = 

We should note that the α-amino trifluoromethylated ketones are less stable than corresponding the

α amido ketones [3,4] Attempts for their purification (chromatography on SiO_2) readily led to a mixture of α-hydroxy ketones **5** and **6** resulting from the hydrolysis of the enolic form of ketones **3** [21]



3 **5** **6**

In summary, this communication describes a new alternative for the synthesis of α-amino trifluoromethyl ketones and corresponding aminoalcohols from easily available enol ethers **1**. The synthetic utility of this method is illustrated by the stereoselectivity of formation of β-amino alcohols by the new easy formation of fluoroalkyl epoxyethers that could be opened by any nucleophilic reagents leading directly to various α-functionalized trifluoromethyl ketones.

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10. **2a**: bp 110 °C/15mmHg, ^{19}F NMR δ -75.8, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7 2 (m, 5H), 3.8 (m, 2H), 3 23 (m, 2H), 2.74 (m, 2H), 1 92 (m, 2H), 1.18 (t, *J* = 7Hz, 3H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 140.5, 128.5, 128.23, 126.17, 121 9 (CF_3, q, *J* = 281Hz), 81.6 (C-CF_3, q J=39.2), 68.68, 61 11, 31.66, 28.32, 16.08.
11. **Typical procedure: Preparation of aminoalcohol 4a**: A mixture of epoxide **2a** (0 660 g, 2.54 mmol) and morpholine (1.1 g, 12 7 mmol, 5 equiv) was stirred under argon atmosphere for 3 h (if amine is solid, the reaction was performed in toluene [1 mL], the reaction time was then 36 h) Excess of amine was distilled under reduced pressure. The crude product was reduced following a classical procedure (4 equ. of sodium borohydride in ethanol at room temperature) The excess of hydride was decomposed with acetaldehyde After evaporation of solvent under reduced pressure, addition of 30 mL of 15% NaOH, extraction with ether, the combined organic fractions were washed with brine and dried over $MgSO_4$ Evaporation of solvent under reduced pressure and then bulb-to-bulb distillation gave 655 mg (85 % yield) of a pure diastereomer **4a**: ^{19}F NMR ($CDCl_3$) δ -75 81 (d, *J* 7 8 Hz); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7 25 (m, 5H), 5 2 (br s, OH), 3 70 (m, 4H), 3 63 (dq, , *J* 7 8 Hz, *J* 2 Hz), 2.9 (m, 7H), 1.9 (dm, 2H), ^{13}C NMR ($CDCl_3$) δ 140.77, 128.4, 128 24, 126.34, 124 (q, J = 280 Hz), 69 1 (q, J = 29 6), 67.34, 65.8, 62.33, 52 0, 49 46, 34.03, 29.95. **4a**,HCl. mp 170°C
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