



## Unusual Non-Oxidative Pummerer Rearrangement of $\gamma$ -Trifluoro- $\beta$ -aminosulfoxides

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**Abstract:** Trifluoroacetic anhydride promoted Pummerer rearrangement of  $\gamma$ -trifluoro- $\beta$ -amino sulfoxides **1** follows an unusual pathway, in which a migration of the *p*-tolylthio group to the nitrogen atom provides the corresponding  $\alpha$ -sulfenamidotrifluoroacetates **5**. The usual removal of the proton in  $\alpha$  to the sulfinyl moiety does not take place, as shown by maintenance of deuterium during the rearrangement. This procedure is exploited for the stereoselective synthesis of 2D- and 2H- (*R*)-2-amino-3,3,3-trifluoropropan-1-ol **10**.

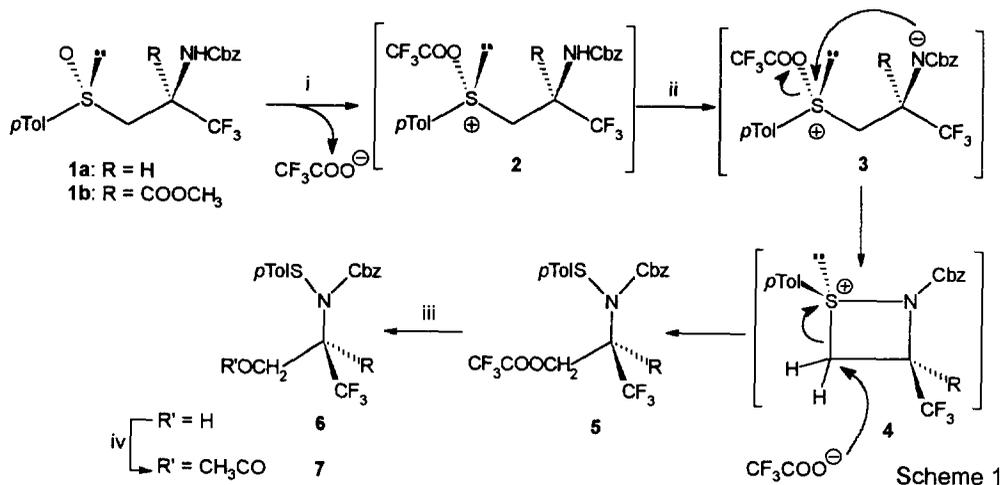
The synthesis of optically pure fluorine containing molecules with a high degree of functionalization is an exciting challenge for an organic chemist.<sup>1</sup> The fascinating and unique properties of fluorinated analogues of naturally occurring structures largely justify the efforts made in this field.<sup>2</sup>

Our interest in the synthesis of non racemic fluorinated amines and aminoacids brought us to develop a route to  $\gamma$ -fluoro- $\beta$ -enaminosulfoxides, which can be stereoselectively reduced to the corresponding amines.<sup>3</sup> Now we wish to report the unusual outcome of the trifluoroacetic anhydride promoted Pummerer rearrangement of the  $\gamma$ -trifluoro- $\beta$ -aminosulfoxides **1**, that occurs through a migration of the *p*-tolylthio group to the nitrogen atom and the consequent formation of the  $\alpha$ -sulfenamidotrifluoroacetates **5**, instead of the expected  $\alpha$ -carbon oxidation to give the corresponding  $\alpha$ -trifluoroacetoxy- $\beta$ -aminosulfide.

Sulfoxides bearing nitrogen atoms, including  $\beta$ -aminosulfoxides, are reported to undergo normal Pummerer rearrangements,<sup>4</sup> the only example of non-oxidative Pummerer reaction we are aware of, was reported by Uchida and Oae for various alkyl-(*o*-carbamoyl)phenyl sulfoxides, which afforded 1,2-benzisothiazole derivatives upon treatment with Lewis acids.<sup>5</sup>

As outlined in Scheme 1, when (*R<sub>S</sub>*,2*S*)-**1a** was treated with trifluoroacetic anhydride and *sym*-collidine in acetonitrile at 0°C, the sulfenamide **5a** was surprisingly recovered in good yield as the only product. A mildly basic work up of the reaction provided, in 90% yield, the alcohol **6a**,<sup>6</sup> whose structure was confirmed by *O*-acetylation to **7a**. The sulfenamide **5a** is clearly the product of an abnormal Pummerer rearrangement. In the most likely reaction path the *sym*-collidine, acting as a proton scavenger on **2a**, produces the zwitterionic intermediate **3a**: the preferential proton removal from the NH may be due to the fluorosubstitution, that

enhances the acidity of the carbamic proton. Nitrogen atom binding to the positively charged sulfur atom and S-O bond breaking produces the four membered ring **4a**. Attack of the trifluoroacetoxy anion on the CH<sub>2</sub>, which occurs with a cleavage of the S-C bond, gives the  $\alpha$ -sulfenamidotrifluoroacetate **5a**.

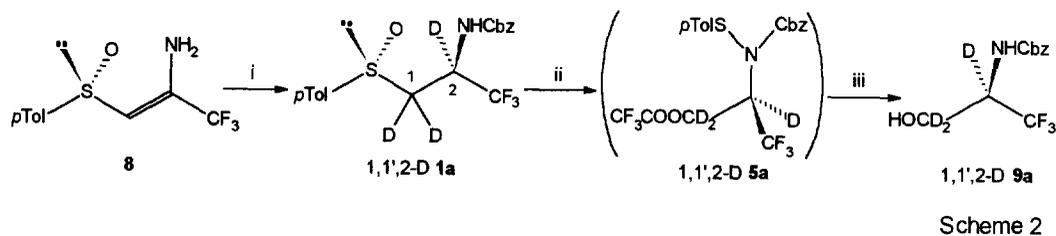


Key: i) Trifluoroacetic anhydride, acetonitrile, 0°C. ii) *sym*-Collidine. iii) K<sub>2</sub>CO<sub>3</sub>. iv) Acetic anhydride, triethylamine.

### Scheme 1. Pummerer rearrangement of $\gamma$ -trifluoro- $\beta$ -aminosulfoxides **1**.

The formation of a  $\sigma$ -sulfurane intermediate (pentavalent sulfur), stabilized by the presence of two electron withdrawing ligands on sulfur (the trifluoroacetoxy group and the carbamic nitrogen), may be also conceived as an alternative pathway.<sup>7</sup>

The 1,1',2-D-labelled  $\beta$ -aminosulfoxide (*R<sub>S</sub>,2S*)-**1a** was prepared from the primary  $\beta$ -enaminosulfoxide **8** by preliminary exchange with D<sub>2</sub>O, reduction with NaBD<sub>4</sub> in dry THF and subsequent treatment with benzyl chloroformate (Scheme 2).<sup>8</sup>



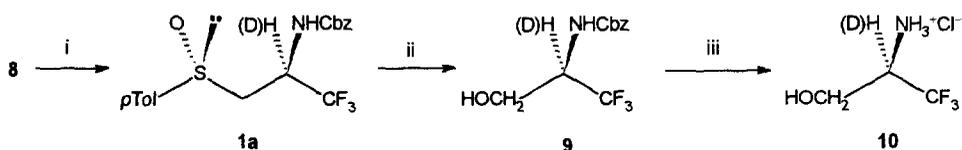
Key: i) a: D<sub>2</sub>O; b: NaBD<sub>4</sub>, dry THF, 0°C to r.t.; c: Benzyl chloroformate, K<sub>2</sub>CO<sub>3</sub> 50%, dioxane. ii) TFAA, *sym*-collidine, 0°C; iii) a: K<sub>2</sub>CO<sub>3</sub>, H<sub>2</sub>O; b: NaBH<sub>4</sub>.

### Scheme 2. Synthesis and Pummerer rearrangement of 1,1',2-D-**1a**.

When submitted to the Pummerer rearrangement, (*R<sub>S</sub>*,2*S*)-1,1',2-D-**1a** afforded the sulfenamide 1,1',2-D-**5a**, that was reduced *in situ* with NaBH<sub>4</sub> to the *N*-Cbz-aminoalcohol 1,1',2-D-**9a**, which was found to have retained the original labelling, thus confirming that the reaction does not involve the H-1 removal. Esterification of (*R*)-**9a** with enantiomerically pure (*S*)- $\alpha$ -phenylpropionic acid provided only one diastereoisomeric ester, thus establishing that the C-2 stereogenic centre remains untouched during the rearrangement.

In the light of these findings we re-examined the Pummerer rearrangement of the  $\beta$ -methoxycarbonyl- $\beta$ -aminosulfoxide **1b** and *in situ* reduction of the resulting intermediate, key steps in the synthesis of (*R*)- and (*S*)- $\alpha$ -trifluoromethyl-serine.<sup>9</sup> Also in this case, upon treatment of **1b** with trifluoroacetic anhydride and *sym*-collidine the corresponding sulfenamide **5b** was cleanly isolated (Scheme 1),<sup>10</sup> thus showing that this abnormal non-oxidative Pummerer rearrangement could be a general pathway for the trifluoroacetic anhydride promoted Pummerer reaction of  $\gamma$ -trifluoro- $\beta$ -aminosulfoxides **1**.

This procedure represents a straightforward route to  $\beta$ -fluoro- $\alpha$ -aminoalcohols, as shown in the stereoselective synthesis of 2-H and 2-D-(*R*)-trifluoroalaninol hydrochloride **10** (Scheme 3).



Scheme 3

Key: i) a: L-Selectride® (NaBD<sub>4</sub>); b: Benzyl chloroformate, K<sub>2</sub>CO<sub>3</sub> 50% (quantitative). ii) a: TFAA, *sym*-collidine, 0°C; b: K<sub>2</sub>CO<sub>3</sub>, H<sub>2</sub>O; c: NaBH<sub>4</sub>. (86%) iii) a: H<sub>2</sub>/Ra-Ni; b: 1N HCl (93%).

### Scheme 3. Synthesis of 2-H and 2-D-trifluoroalaninol **10**.

The  $\beta$ -aminosulfoxides 2-H- and 2-D-**1a** were obtained by stereoselective reduction of the primary  $\beta$ -enaminosulfoxide **8** with, respectively, L-Selectride® and NaBD<sub>4</sub>.<sup>3,11</sup> The 2-H and 2-D-*N*-Cbz-aminoalcohol **9** were obtained *one-pot* from **1a**, in 85% yield, upon treatment with trifluoroacetic anhydride/*sym*-collidine, and reduction with NaBH<sub>4</sub> of the sulfenamide formed in the rearrangement. Hydrogenolysis of the benzyl carbamate and treatment with 1N aqueous HCl afforded the 2-H and 2-D labelled **10**. The unfluorinated naturally occurring analogue is contained in ergonovine (D-lysergic acid L-2-propranolamide), an important ergot alkaloid. Further investigations are presently being carried out in order to fully exploit this method in the synthesis of more complex fluorinated aminoacids and aminoalcohols.

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## REFERENCES AND NOTES

1. Resnati, G. *Tetrahedron* **1993**, *49*, 9385-9445.
2. Banks, R. E.; Tatlow, J. C.; Smart, B. E. *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum Press: New York, 1994. Welch, J.T.; Eswarakrishnan, S. *Fluorine in bioorganic chemistry*; Wiley: New York, 1990. Filler, R.; Kobayashi, Y. *Biomedical aspects of fluorine chemistry*; Kodansha Ltd.: Tokyo, 1981. Kukhar, V.P.; Soloshonok, V.A. *Fluorine Containing Amino Acids*; Kukhar, V.P.; Soloshonok, V.A. Eds.; Wiley: New York, 1994.
3. Bravo, P.; Crucianelli, M.; Zanda, M. *Tetrahedron Lett.*, **1995**, *36*, 3043-3046.
4. For an overview of the Pummerer reaction of sulfoxides with a nitrogen nucleophile, see De Lucchi, O.; Miotti, U.; Modena, G. *Organic Reactions*; Paquette, L. A. Ed.; John Wiley and Sons: New York, 1991, Vol. 40; pp. 242-251. See also Duréault, A.; Carreaux, F.; Depezay, J.C. *Synthesis*, **1991**, 150-155; Pyne, S. G.; Hajipour, A. R. *Tetrahedron*, **1994**, *50*, 13501-13510 and references cited therein.
5. Uchida, Y.; Oae, S. *Gazz. Chim. Ital.*, **1987**, *117*, 649-654.
6. Spectroscopic data for **5a**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.4 - 7.0 (9 H, m, ArH), 5.41 (1 H, m, HC-N), 5.35 and 5.31 (1 H, br d,  $J = 12.2$  Hz,  $\text{OCH}_2\text{Ph}$ ), 4.79 (1 H, br dd,  $J = 11.6$  and 9.3 Hz,  $\text{CF}_3\text{COOHCH}$ ), 4.60 (1 H, br dd,  $J = 11.6$  and 9.3 Hz,  $\text{CF}_3\text{COOHCH}$ ), 2.31 (3 H, br s,  $\text{ArCH}_3$ );  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  - 72.11 (3 F, br signal,  $\text{CF}_3\text{CO}$ ), - 75.94 (3 F, br signal,  $\text{CF}_3\text{CH}$ ). Selected data for **6a**:  $^1\text{H}$  NMR (acetone- $\text{D}_6$ ):  $\delta$  7.5-7.1 (9 H, m, ArH), 5.28 (2 H, br s,  $\text{OCH}_2\text{Ph}$ ), 5.16 (1 H, ddq,  $J = 8.7$ , 4.6 and 8.5 Hz, HC-N), 4.33 (1 H, br dd,  $J = 5.8$  and 5.2 Hz, HO), 4.13 (1 H, br ddd,  $J = 11.6$ , 8.7 and 5.8 Hz, HOHCH), 4.00 (1 H, br ddd,  $J = 11.6$ , 8.7 and 5.8 Hz, HOHCH), 2.30 (3 H, br s,  $\text{ArCH}_3$ );  $^{19}\text{F}$  NMR (acetone- $\text{D}_6$ ):  $\delta$  - 67.47 (br d,  $J = 8.5$  Hz);  $^{13}\text{C}$  ( $\text{CDCl}_3$ ):  $\delta$  158.18 (s,  $\text{COO}$ ), 123.96 (q,  $^1J_{\text{C,F}} = 283.5$  Hz,  $\text{CF}_3$ ), 69.74 (t,  $^1J_{\text{C,H}} = 149$  Hz,  $\text{HOCH}_2$ ), 61.99 (dq,  $^1J_{\text{C,H}} = 142$  and  $^2J_{\text{C,F}} = 29$  Hz,  $\text{CHCF}_3$ ), 57.92 (t,  $^1J_{\text{C,H}} = 145.5$  Hz,  $\text{OCH}_2\text{Ph}$ ), 21.17 (q,  $^1J_{\text{C,H}} = 126.5$  Hz,  $\text{ArCH}_3$ ); EI/MS (70 eV):  $m/z$  (%) 385 ( $\text{M}^+$ , 100), 341 ( $\text{M}^+ - \text{CO}_2$ , 20), 250 ( $\text{M}^+ - \text{Cbz}$ , 40), 123 ( $\text{pTolS}^+$ , 90), 91 ( $\text{PhCH}_2^+$ , 100); FT-IR ( $\text{cm}^{-1}$ ): 3459; 1714.
7. Oae, S. *Organic Sulfur Chemistry: Structure and Mechanism*, CRC Press: Boca Raton, 1991, pp. 18-21.
8. Deuterium percentage was of 75% in position 1 (it was kept at this level on purpose) and > 95% in 2. Not exhaustively deuterated **1** was present as an equimolar mixture of 1-monodeuterated diastereoisomers and an half quantity of product not deuterated in 1, all detectable in the  $^1\text{H}$ -NMR spectrum.
9. Bravo, P.; Soloshonok, V. A.; Viani, F.; Zanda, M. *Gazz. Chim. Ital.*, **1995**, *125*, 149-150.
10. Spectroscopic data for **5b**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.4-7.1 (9 H, m, ArH), 5.26 and 4.58 (2 H, br signals,  $\text{CF}_3\text{COOCH}_2$ ), 5.22 (2 H, br s,  $\text{OCH}_2\text{Ph}$ ), 3.73 (3 H, br s,  $\text{OCH}_3$ ), 2.33 (3 H, br s,  $\text{ArCH}_3$ );  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  - 74.16 (3 F, br signal,  $\text{CF}_3\text{CO}$ ), - 76.28 (3 F, br signal,  $\text{CF}_3\text{-C-C}$ ).
11. The 2-D labelling of ( $R_S, 2S$ )-**1** was > 95% as showed by the disappearance of the  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ ) signal at  $\delta$  3.81 (m, 1 H, HC-N) and the simplification of the complex signal at  $\delta$  3.03-2.66 (m, 2 H,  $\text{SCH}_2$ ) to give two doublets at  $\delta$  3.00 and 2.70 (1 H,  $J = 12$  Hz).

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