

Highly Stereospecific S_N2-type Displacement of Sulfinyl by Hydroxy Group under Pummerer Conditions

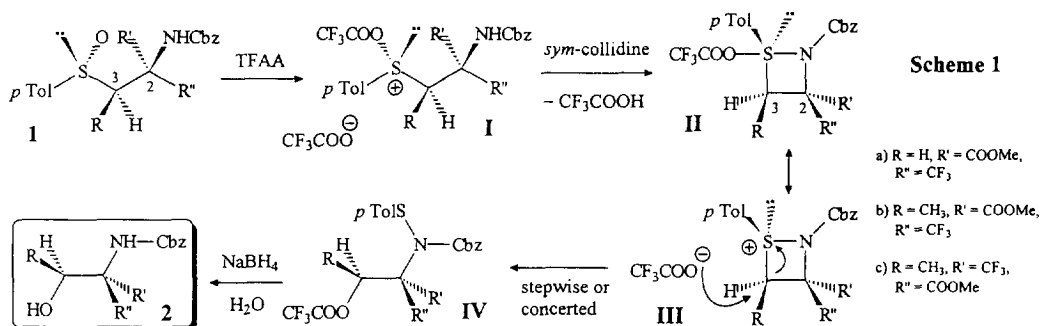
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Abstract: The trifluoroacetic anhydride promoted Pummerer reactions of *N*-Cbz α -amino- α -trifluoromethyl- β -*p*-tolylsulfinyl methyl butanoates **1b-c** occur in a highly stereospecific non-oxidative fashion (d.r. > 98:2), resulting in a S_N2-type displacement of the sulfinyl by hydroxy group and providing enantiomerically pure α -trifluoromethyl-*allo*-threonine **2b** and -threonine **2c** derivatives.
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The Pummerer rearrangement (PR) is a useful reaction, which usually produces α -substituted sulfides from the corresponding sulfoxides through an internal redox process, involving reduction of the sulfinyl group and oxidation of the α -carbon.¹ Reports have appeared on unusual PRs leading to final products in which the original sulfinyl bearing carbon has a lower oxidation state than expected.² We have recently reported that the PR promoted by trifluoroacetic anhydride (TFAA) on *N*-Cbz γ -trifluoro- β -aminosulfoxides like **1a** occurs in a "non-oxidative" fashion, producing *one-pot* the corresponding β -aminoalcohol **2a**.³ In order to get an insight into the stereochemical course of the process, and to exploit the reaction in the asymmetric synthesis of nitrogen substituted organofluorine chemicals, we have carefully investigated the PR of the *N*-Cbz γ -trifluoro- β -aminosulfoxides **1b** and **1c**,⁴ in which an additional stereogenic centre has been introduced at C-3, directly involved in the rearrangement (Scheme 1).



The best conditions for the reaction have been achieved by treating the sulfoxide **1b** in acetonitrile at 0 °C with TFAA (5 eq) and *sym*-collidine (3 eq). Then, water was added, followed by addition of an excess of NaBH₄. Routine work-up and purification delivered methyl *N*-Cbz α -trifluoromethyl *allo*-threoninate⁵ **2b** in 80% yield and excellent stereoselection (d.r. > 98:2).

The same procedure applied to the diastereoisomeric β -aminosulfoxide **1c**, having opposite configuration at C-2, provided the methyl threoninate **2c** in 70% yield (d.r. > 98:2).⁶ The C-3 stereochemistry of **2b** and **2c** was determined by esterification with both enantiomers of α -phenylpropionic acid,⁷ and allows to establish that the displacement of the sulfinyl by the hydroxy group occurs with inversion of configuration.

It has been previously demonstrated by experiments using deuterium labelling that no removal of C-3 proton occurred during the TFAA promoted PR of **1a**, and that the α -trifluoroacetoxy sulfenamide **IVa**, easily transformed in the ep *N*-Cbz trifluoroalaninol **2a**, is the product of the PR. In the light of these findings, the mechanism shown on Scheme 1 should be operating in the *one-pot* highly stereoselective desulfinylative-hydroxylation of **1b-c** to **2b-c**. The tricoordinate sulfur cation of **I**, formed as usual by action of TFAA, undergoes an intramolecular reaction with the β -nitrogen anion, formed by action of *sym*-collidine. The process produces the cyclic four membered σ -sulfurane **II**, having the carbamic nitrogen atom and the trifluoroacetoxy group at the apical positions,⁸ that could be conceived also as an acylaminosulfonium cation **III**. Subsequent breaking of the S-C with the formation of the CF₃COO-C bond occurs with inversion of configuration at C-3, affording the sulfenamide **IV**. No attempts were made to purify those intermediates. The protected β -hydroxy α -aminoacids **2b-c** were obtained by treatment of the crude **IVb-c** with NaBH₄/H₂O.

It can be seen that the C-2 stereogenic centre of **1b-c** does not affect the stereoselection of the process.

We are currently investigating full scope and limits of this reaction, that could represent a useful tool in sulfoxide mediate asymmetric synthesis.⁹

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