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A Novel Synthesis of β-Trifluoromethyl-Substituted Isoserine *via* Intramolecular Rearrangement of Imino Ethers

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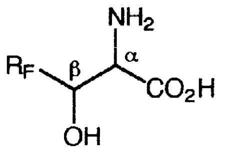
Abstract: The methodology for the construction of β-trifluoromethyl-substituted isoserine is reported. The fluorinated α-hydroxy-β-imino esters which are the precursors to amino acid derived isoserine were formed firstly *via* a base catalyzed intramolecular rearrangement of imino ethers, and the subsequent conversions of these compounds resulted in the formation of the designed isoserines and the related fluorinated compounds.

The study of fluoroalkyl β-hydroxy-α-amino acids (**1**) and its regioisomer α-hydroxy-β-amino acids (**2**) has become an area of intense interest and the important targets in organic synthesis due to their biological activities of inhibitors of enzymes. The three important utilities from these compounds have attracted considerable attention: 1) utilization for the treatment of a wide variety of human disorders,[1] 2) performance as the peptidomimetic units and chiral auxiliaries in organic synthesis,[2] 3) important precursors to the corresponding fluoroalkyl peptidyl ketones which have been shown to be effective inhibitors of proteolytic enzymes.[3] Despite of this large interest in fluoroalkyl-α-amino acids, only few methods are available for the synthesis of these compounds.[4] Furthermore, the properties of fluoroalkyl substituted α-hydroxy-β-amino acids (**2**) have been unexplored because of the lack of methods for their preparations.[5, 6]



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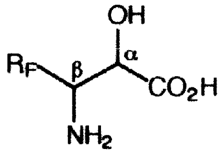

2 (R_F=CF_3; HCF_2; C_3F_7)

Recently, Naito *et al.*[7] reported the synthesis of non-fluorinated imino alcohols by means of intramolecular rearrangement of imino ethers which was similar to our approach, but they failed to obtain α-hydroxy-β-amino esters. In our ongoing project directed toward the synthesis of β-fluoroalkyl substituted amino acids[8] and the related isoserine (**2**), we discovered a novel, facile and efficient method for the general synthesis of α-hydroxy-β-imino-γ-fluorinated esters (**5**) and successfully applied this protocol to the synthesis of our target products (**2**).

The imino ethers (**4**) were simply prepared from the fluorinated imidoyl chlorides[9] with commercially available glycolate compounds under the basic conditions in good yields, and subsequently converted into **5**

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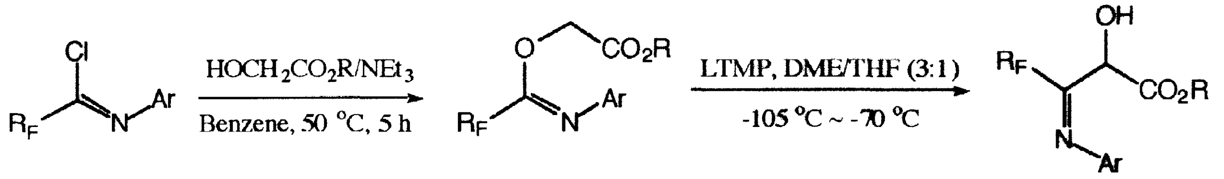
by lithium 2,2,6,6-tetramethylpiperidide (LTMP) catalyzed intramolecular addition-elimination reaction.[10] Our preliminary experiments showed that LDA also served as the efficient base to complete this intramolecular rearrangement at low temperature, but the yields were 10 % lower in average than those obtained under LTMP conditions. The reaction temperature was kept between -105 °C and -70 °C because the higher temperature (> -50 °C) caused much more complex results in this reaction (Scheme 1).



3 **4** **5**

$R_F = CF_3, HCF_2, C_3F_7$;
Ar = p-C_6H_4OMe;
R = Me, Et, Bn, *t*-Bu.

Isolated yield: 71 % ~ 92%

Isolated yield: 81 % ~ 89%

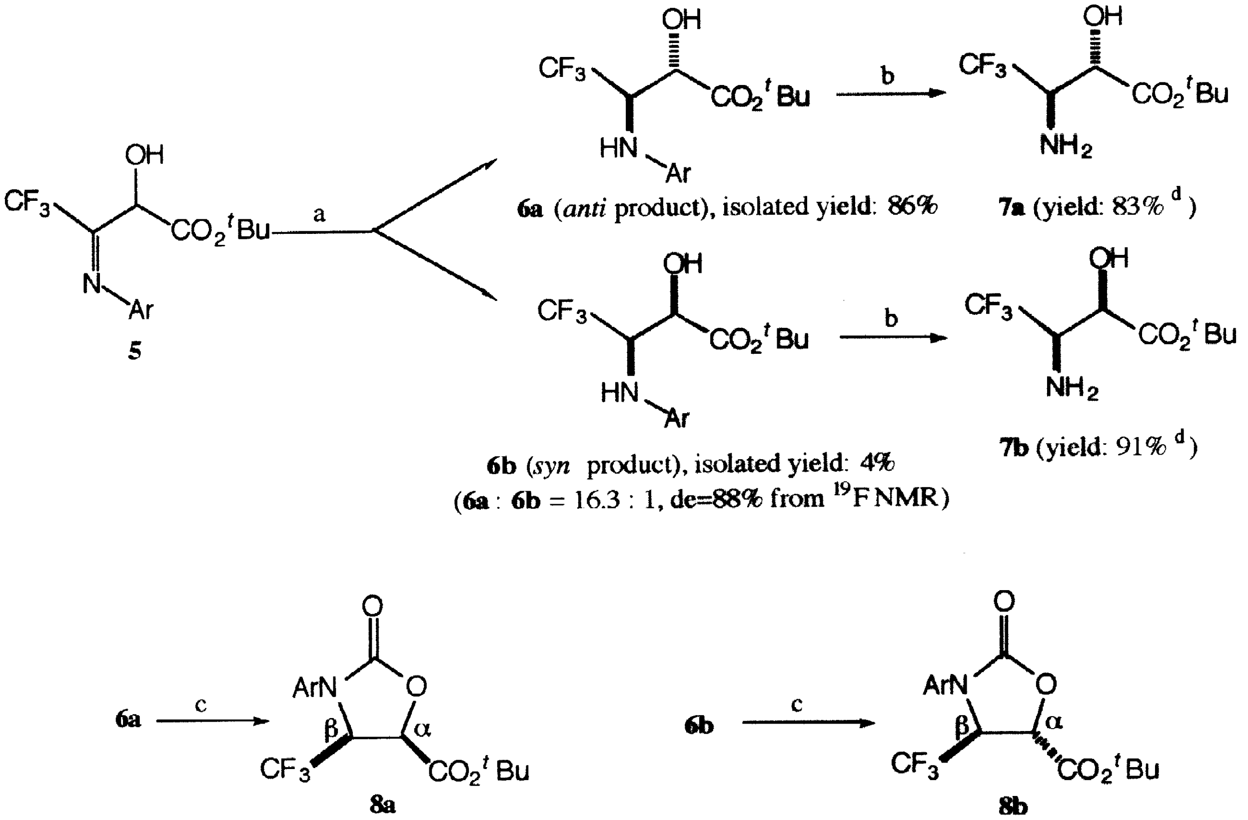
Scheme 1

To our knowledge, the formation of fluorinated α-hydroxy β-imino esters (**5**) by treatment of fluorinated imino ethers (**4**) with LTMP base through the intramolecular rearrangement was the first example of constructing such kind of important and unique fluorinated compounds. The reactions that afforded the compounds **5** *via* compounds **4** were generally applicable to the preparations of the fluorinated α-hydroxy-β-imino ethyl esters (entries 2, 5, and 6 in Table 1) and other esters, such as methyl, *t*-butyl, and benzyl (entries 1, 3, and 4 in Table 1), which would be easily deprotected to generate carboxylic acids.

Table 1. The Isolated Yields of Base-Catalyzed Intramolecular Rearrangement Products (**5**)

Entry	1	2	3	4	5	6
R_F	CF_3	CF_3	CF_3	CF_3	HCF_2	C_3F_7
R	Me	Et	Bn	*t*-Bu	Et	Et
Yield of **5** (%)	81	83	83	89	87	81

The diastereoselective reductions of imine esters (**5**) with $NaBH_4$-$ZnCl_2$ system in isopropanol-THF (1:1), which is known to reduce imino alcohols with the high *anti*-stereoselectivity,[11] afforded *anti* product **6a** predominantly. The two diastereomers of **6a** and **6b** could be easily separated by column chromatography to provide pure *anti*- and *syn*- products **6a** and **6b** in 86% and 4% isolated yields, respectively. The further treatment of compounds **6** with CAN in CH_3CN-H_2O solvent system gave the final products **7a** and **7b** in good yields, which are the important precursors to the final products α-hydroxy-β-amino acids (**2**, R_F= CF_3). The assignment for *syn*- and *anti*- stereochemistry of compounds **6a** and **6b** was based on the analysis of coupling constants between H_α and H_β in the cyclized five membered compounds **8a** and **8b** obtained from **6a** and **6b**, respectively, and the chemical shift of CF_3 group on ^{19}F NMR of compounds **7b** comparing to the reported data (Scheme 2).[5, 12]



5

6a (*anti* product), isolated yield: 86%

7a (yield: 83% d)

6b (*syn* product), isolated yield: 4%
(**6a** : **6b** = 16.3 : 1, de=88% from ^{19}F NMR)

7b (yield: 91% d)

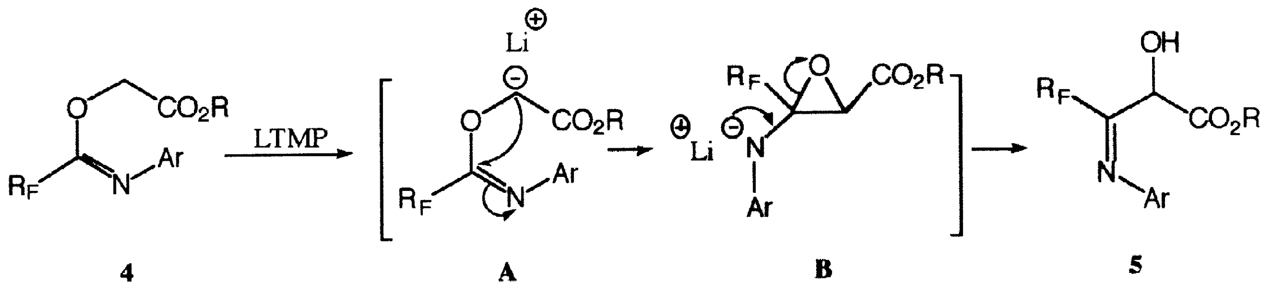
8a

8b

a) $NaBH_4$ (0.3 eq.), $ZnCl_2$ (0.2 eq.), *i*-PrOH/THF (1:1), -80 °C ~ rt, 6 h. b) CAN (1.1 eq.) CH_3CN/H_2O (1:1), rt, 1h. c) Triphosgene (0.5 eq.), *i*-Pr_2NEt (3.0 eq), CH_2Cl_2, 40 °C, 8 h. d) based on ^{19}F NMR.

Scheme 2

One possible explanation for this interesting intramolecular rearrangement is proposed in Scheme 3. An S_N2 type displacement of hydroxyl group or alkoxyl group attached to α-carbon bearing trifluoromethyl or perfluoroalkyl group with carbanions is known to be difficult.[13]



4 A B 5

Scheme 3

The carbanion intermediates (**A**) of the imino ether which are generated with LTMP *in situ*, would undergo the intramolecular nucleophilic attack to the electrophilic imino carbon to form the epoxy intermediates (**B**) at low reaction temperature, and the subsequent regeneration of imino bond and ring opening reaction of the epoxide moiety would lead to the formation of desired α-hydroxy-β-imino esters (**5**).

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10. Typical procedure for the preparation of compounds **5**:

    a) Preparation of LTMP base: To a solution of 2,2,6,6-tetramethylpiperidine (240 mg, 1.7 mmol) in freshly distilled solvent (DME/THF=1.2 ml/0.4 ml) cooled down to 0 °C by ice-water bath under Argon atmosphere, n-BuLi in hexane (1.7 mmol) was added dropwisely and then stirred for additional 30 min.

    b) Intramolecular rearrangement: The LTMP solution was cooled down to -105 °C with EtOH/liq. N_2 bath, and the solution of trifluoromethyl imino ether (1 mmol) in freshly distilled solvent (DME/THF =1.2 ml/0.4 ml) was added dropwisely to the LTMP solution over 10 min, and the temperature of the reaction solution was then raised slowly up to -70 °C over 1 h period (reaction was monitored by TLC). After all starting material was gone from TLC, 10 ml of diethyl ether was added and the reaction mixture was quenched with 10 ml of aq. NH_4Cl, the organic layer was then washed twice with 10 ml of chilly brine and dried over $MgSO_4$. Purification of products through column chromatography (silica gel, EtOAc/ hexane = 1/4), gave the light yellowish oily product.

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12. NMR data for compounds **7** and **8** (C_6F_6 as an internal reference in $CDCl_3$):

    7a: ^{19}F NMR: δ= 88.8 ppm (d, J_{FH}= 7.3 Hz, CF_3); **7b**: ^{19}F NMR: δ= 85.9 ppm (d, J_{FH}= 7.4 Hz, CF_3); (The reported data[5] of ^{19}F NMR for methyl *syn*-2-hydroxy-4,4,4-trifluoro-3-aminobutanoate: δ= 86.1ppm, d, J_{FH}= 7.4Hz);

    8a: ^{19}F NMR: δ= 91.8 ppm (d, J_{FH}= 5.6 Hz, CF_3); ^{1}H NMR: δ= 5.08 ppm (d, $J_{\alpha\beta}$= 8.1 Hz, α-H); δ= 4.80 ppm (dq, $J_{\alpha\beta}$= 8.1 Hz, J_{HF} = 5.6 Hz, β-H);

    8b: ^{19}F NMR: δ= 85.9 ppm (d, J_{FH}= 5.8 Hz, CF_3); ^{1}H NMR: δ= 4.81 ppm (d, $J_{\alpha\beta}$= 3.0 Hz, α-H); δ= 4.66 ppm (dq, $J_{\alpha\beta}$= 3.0 Hz, J_{HF} = 5.8 Hz, β-H).
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