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Biomimetic Transamination of α-Keto Perfluorocarboxylic Esters. An Efficient Preparative Synthesis of β,β,β-Trifluoroalanine

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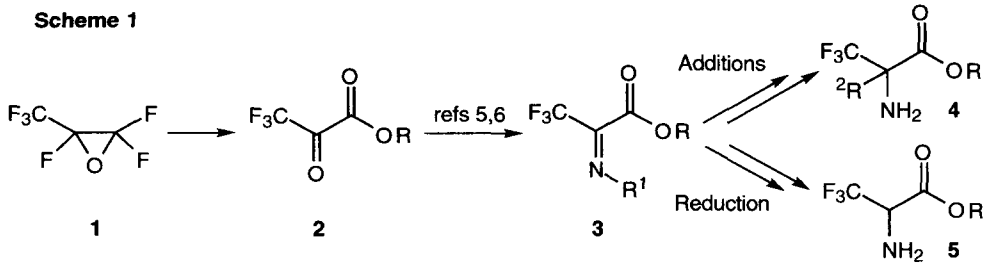
Abstract: An efficient large-scale preparative synthesis of biologically interesting β,β,β-trifluoroalanine through the biomimetic transamination of the ethyl trifluoropyruvate has been developed. The azomethine—azomethine isomerization of the *N*-(1-phenyl)ethylimine of ethyl trifluoropyruvate to the *N*-(1-phenyl)ethylidene alanine ethyl ester, a key stage of the process, was found to occur under the mild reaction conditions, in a triethylamine solution at rt. The proposed working mechanistic rationale accounting for the easiness of the isomerization and its stereochemical outcome, involves unusual non-asymmetric [1,5]-proton shift transfer from the methine carbon to the enolate oxygen. © 1997 Elsevier Science Ltd.

INTRODUCTION

One of the most remarkable achievements of fluoro-bio-organic chemistry in the past two decades, has been concerned with the development of chemistry-pharmacology of fluoro-amino acids and related compounds.[1,2] The fascinating manifold biological properties of this man-made class of amino acids and their importance in bio-organic and medicinal chemistry are well documented by the recent flux of research in this area.[2-4] One of our projects in the field has been devoted to the synthesis of particularly challenging type of fluoro-amino acids, α-trifluoromethyl-α-amino carboxylic acids.[5] In 1986 we have introduced *N*-substituted imines of alkyl trifluoropyruvate **3** (Scheme 1), readily available from commercial and inexpensive hexafluoropropene oxide (**1**) or trifluoropyruvates **2**, as highly promising electrophilic synthons of the trifluoroalanine and demonstrated general principles for its further elaboration to the series of α-trifluoromethyl-α-amino acids **4** *via* additions to the C,N double bond of **3** of organometallic reagents, π-rich aromatic compounds or enamines, as well as

Scheme 1



cycloaddition reactions.[5a-c,e,f,i] The extraordinary electrophilicity of the C,N double bond in **3** (R^1 = acyl) provides easy yet regioselective introduction of virtually any desired amino acid side-chain in synthons **3** allowing for efficient general approach to the family of α-trifluoromethyl-α-amino acids **4**. This methodology has been further elaborated by *Burger* and associates and applied for the synthesis of numerous α-trifluoromethyl-α-amino acids and peptides.[6] Recently, promising attempts to develop asymmetric versions of this method have been reported.[7,8]

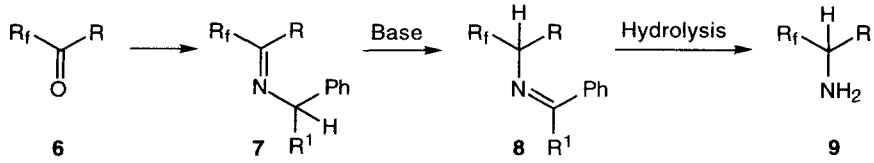
Synthesis and biological properties of trifluoroalanine **5**, a simplest member of the α-trifluoromethyl-α-amino acids family, has been of particular interest.[6,9-11] Among the various syntheses of trifluoroalanine **5** reported so far,[2] reduction of appropriate imines **3** seems to be the most direct because, in contrast to other multi-stage methods, only one functional group transformation, an imine to an amine, is necessary. Thus, trifluoroalanine **5** can be prepared starting from *N*-acyl imines **3** *via* three-stage procedure including reduction of the C,N double bond followed by deprotection of the amino and carboxyl groups.[5c,6a,12] However, because of non-direct preparation of corresponding *N*-acyl imines **3** and their exceptionally high hydrolyzability, necessitating usage of dry atmosphere for all manipulations with these compounds, this approach is obviously expensive and quite inconvenient for large scale preparation of **5**. Therefore, taking into account appealing biological properties of **5**, synthetically simple and practically useful method for its preparation would be highly desirable to provide required availability of β,β,β-trifluoroalanine **5** for biological and chemical studies.

RESULTS AND DISCUSSION

Recently we have developed biomimetic, reducing agent-free, reductive amination methodology, referred to as a [1,3]-Proton Shift Reaction (PSR), for transformation of fluoroalkyl carbonyl compounds to the corresponding amino derivatives (Scheme 2). Synthetic potential of the method has been demonstrated with the efficient preparation of various fluoroalkyl-, fluoroarylamines[13] and β-amino acids[14] **9** (R = Alk, Ar, $CH_2COOAlk$, respectively) starting with appropriate carbonyl compounds **6** and benzylamine. A key reaction stage of the method is a base-catalyzed [1,3]-proton shift within 1,3-azaallylic system of imines **7**, **8** which provides intramolecular reduction-oxidation process *via* biomimetic transposition of the imine functionality. Equilibrium of this azomethine-azomethine isomerization is nearly entirely shifted to aldimines **8** (R^1 = H) which are much more thermodynamically stable than corresponding ketimines **7**. Desired amino compounds **9** can be easily released from *Schiff* bases **8** by an acidic hydrolysis under the mild reaction conditions. The recently developed asymmetric version of this biomimetic PSR, a transformation of enantiopure **7** (R^1 = Me) to enantiomerically enriched **8** (up to 97% ee),[15] renders the method synthetically powerful and practical approach to biomedicinally important fluoro-amino compounds.

Our experience in the PSR clearly revealed that this methodology might be effectively applied for preparing α-fluoroalkylglycines in general, and trifluoroalanine **5** in particular, starting with the corresponding α-keto

Scheme 2



6 **7** **8** **9**

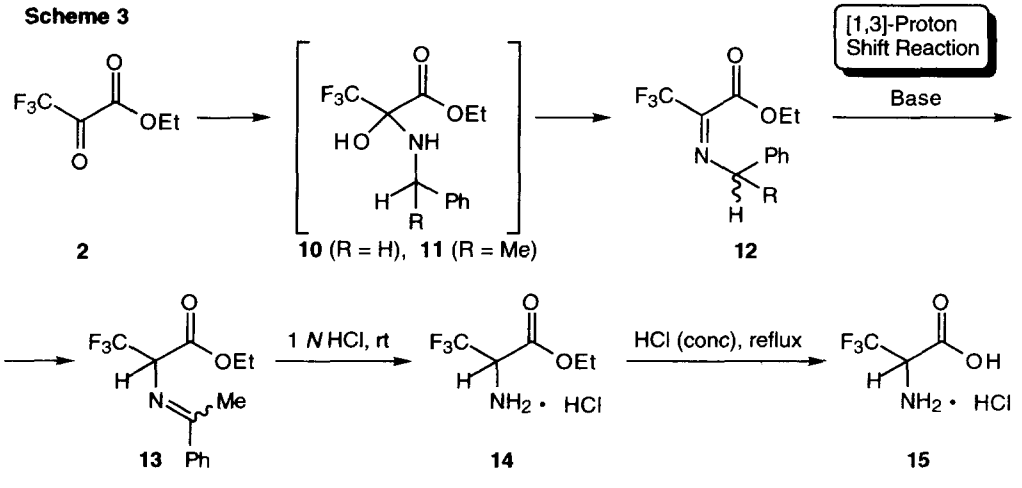
$R_f = C_nF_{2n+1}$, n = 1-7; $(CF_2)_nH$, n = 0-4; R = Alk, Ar, Bn, $CH_2COOAlk$; R^1 = H, Me

carboxylic esters.[5k] However, as we have shown earlier,[5c] *N*-benzylimine, as well as other *N*-alkylimines of trifluoropyruvate are very difficult to prepare by direct condensation between the amine and alkyl trifluoropyruvate **2**, due to the exceptionally high stability of the corresponding *hem*-aminoalkohols **10** (Scheme 3) towards dehydration. By contrast, *N*-(1-phenyl)ethylimine of ethyl trifluoropyruvate **12**, in racemic or (*R*)-enantiomerically pure form, can be easily prepared in high isolated yield (81-83%) by the direct condensation under the standard reaction conditions we normally employ for preparing fluoroalkyl-containing *Schiff* bases.[13b] The reasons behind the dramatic difference in the reactivity of *hem*-aminoalkohols **10**, **11**, that is brought about by the presence of the methyl group, are rather of electronic than steric origin, as it was shown that aniline[5c] and 2,4,6-trimethylaniline[16] are also readily react with alkyl trifluoropyruvates under the similar reaction conditions to afford the corresponding imines.

Isomerization of *rac*-*N*-(1-phenyl)ethylimine **12** to ketimine **13** was found to proceed under the surprisingly mild reaction conditions (*vide infra*). Thus, complete transformation of **12** to **13** was achieved in a triethylamine solution at room temperature in 6 hrs or at reflux in 30 min. In the latter case a sizable amount of by-products (some 10%) was detected by NMR, while the room temperature reaction occurred very cleanly to afford the desired isomerized product in 92% isolated yield. Addition to a solution of ketimine **12** in triethylamine catalytic amounts of more strong bases DABCO or DBU substantially accelerated the isomerization of **12** to **13**, however decreased the isolated yield of targeted **13**. Isomerization of enantiomerically pure (*R*)-**12**, under the same reaction conditions, gave the similar chemical outcome (89% of **13**), however without any reliably detectable enantiomeric excess. Mild acidic hydrolysis (1*N* HCl, rt) of *Schiff* base **13** provided selectively ethyl ester of amino acid **14** which could be further hydrolyzed to free trifluoroalanine hydrochloride **15** by conc. hydrochloric acid at reflux. Thus, the overall process has certain synthetically attractive characteristic that render this biomimetic approach an immediately useful alternative to the existing orthodox methods, heavily relying on the application of the reducing agents.[6a] Of the advantages, direct preparation of imine **12** and its high-yield yet very simple transformation to trifluoroalanine *Schiff* base **13** through biomimetic PSR, employing regular triethylamine instead of a reducing agent, should be pointed out. The efficiency of the method was demonstrated with preparing over 50 g of amino acid **15**, and it seems there are no difficulties in further increasing the scale of the synthesis.

Apart from synthetic result, the amazing easiness of the isomerization of ketimine **12** to *Schiff* base **13** and

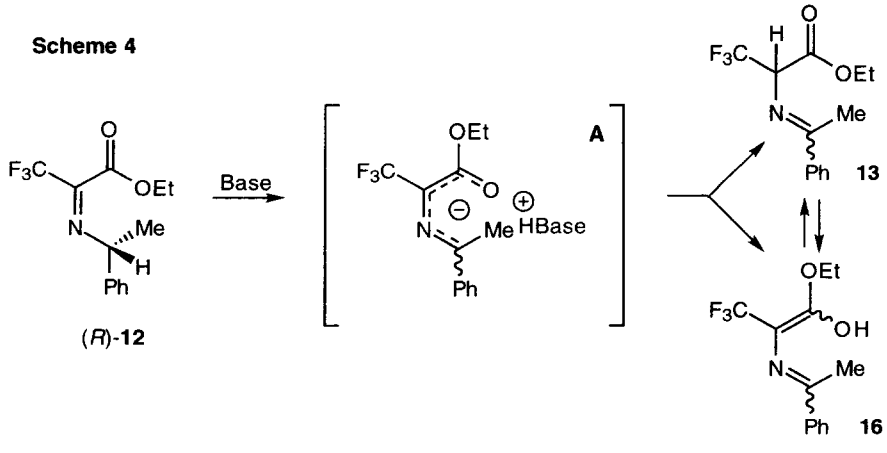
Scheme 3



stereochemical outcome of (*R*)-**12** isomerization deserve discussing. Our recent studies into the azomethine—azomethine isomerizations of the *Schiff* bases derived from fluoroalkyl carbonyl compounds and arylmethylamines have revealed that while the position of the isomerization equilibrium is overwhelmingly controlled by the electron-withdrawing effect of the perfluoroalkyl group, the observed rates of [1,3]-proton transfer are strongly influenced by a mix of several factors including both CH acidity and steric availability of the transferring proton and the nature, a basicity and steric properties, of the base catalyst used.[13c,d] In full agreement with these, we have recently found that the isomerizations of enantiomerically pure *N*-(1-phenyl)ethylimines **7** (Scheme 2, R = alk, aryl; R^1 = Me) to *N*-(1-phenyl)ethylidene derivatives **8** (R = alk, aryl; R^1 = Me) could be achieved in the highly enantioselective manner (*vide supra*), however only under the forced reaction conditions, such as the prolong (over 120 hrs) heating (150 °C) in triethylamine solution or application of strong bases (DBU) in a submolar amount,[15] as compared with the rather mild conditions required to accomplish the isomerizations of the corresponding *N*-benzyl derivatives **7** (R = alk, aryl; R^1 = H) to *Schiff* bases **8** (R = alk, aryl; R^1 = H).[13b] Basing on these data, the easiness of the isomerization of *N*-(1-phenyl)ethylimine **12** to *Schiff* base of alanine **13** (Scheme 3) was totally unexpected. A plausible rationale for the phenomenon observed should account also for the stereochemical outcome of the isomerization of enantiomerically pure (*R*)-**12**, that gave almost racemic product **13**.

Since the mechanism of the hydrocarbon azomethine—azomethine isomerization was shown to involve the 1,3-azaallylic carbanions as intermediates,[17] we can assume the formation of carbanion **A** (Scheme 4) as a possible intermediate in the isomerization of *N*-(1-phenyl)ethylimine **12** to *Schiff* base **13**. The ethoxycarbonyl group on starting **12** could participate in the delocalization of the developing negative charge in **A** rendering it more thermodynamically stable relative to the corresponding intermediate 1,3-azaallylic carbanions involved in the isomerizations of *N*-(1-phenyl)ethylimines derived from fluoroalkyl ketones. Accordingly, one can suggest that greater thermodynamic stability of carbanion **A**, provided by the presence of the ester group on starting substrate **12**, would be the underlying reason for the observed easiness of the isomerization of **12** to *Schiff* base of alanine **13**. Concerning the stereochemical outcome of the isomerization, we can assume that the evolution of anion **A** to a covalent state could proceed through formation of the carbon—hydrogen bond, a regular [1,3]-proton transfer, to give directly product **13** or *via* formation of the oxygen—hydrogen bond, an unusual [1,5]-proton transfer, yielding enolate **16**. If the former pathway takes place, the reaction would have chance to occur in asymmetric

Scheme 4



sense, while realization of the latter, a non-asymmetric route, gives rise to achiral product **16**. Since compound **13**, in which the methine (C-H) is activated by the three electron-withdrawing substituents is obviously prone racemization, the observed stereochemical outcome could be a result of both assumed reaction pathways. To get insight into the stereochemical course of the isomerization we conducted a series of additional experiments. Thus, we have investigated enantiomeric composition of *Schiff* base **13** at the points of 10%, 25%, 50% and 75% conversion of (*R*)-**12** to **13**. In all cases, regardless of the extent of the isomerization, product **13** was found to be racemic, within the limits of the chiral HPLC analysis used. Furthermore, we have found that compound **13** underwent isotopic exchange, at α-position, in a solution NEt_3/MeOH-d_4 with a rate about 10 times lower than the isomerization of **12** to **13** under the same reaction conditions. These data suggest that while the racemization of *Schiff* base **13** definitely takes place during the isomerization, it could hardly account alone for the formation of optically inactive product **13**. Moreover, considering steric availability of the corresponding carbon and oxygen atoms in intermediate **A** (Scheme 4), as well as a relative thermodynamic stability of enolate **16**, the protonation of the oxygen atom to give **16**, a non-asymmetric route, might be more favorable process over the regular [1,3]-proton transfer.

In conclusion, we have demonstrated that the biomimetic PSR methodology can be effectively applied to transamination of α-keto perfluorocarboxylic esters, that is exemplified with the efficient preparative large-scale synthesis of biologically interesting β,β,β-trifluoroalanine hydrochloride (**15**). The present reducing agent-free biomimetic transamination approach, employing simple set of reaction conditions and inexpensive reagents, would be an attractive alternative to the previously reported methods traditionally involving external reducing agents. The working mechanistic rationale for the unexpected easiness of the isomerization of *N*-(1-phenyl)ethylimine **12** to *Schiff* base of trifluoroalanine **13** and its stereochemical outcome, postulates the participation of the ester group in a stabilization of the intermediate carbanion and its non-asymmetric evolution to the covalent state *via* [1,5]-proton transfer from the methine carbon to the enolate oxygen.

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EXPERIMENTAL SECTION

General. For standard laboratory praxis and techniques see related paper, ref. 13b. All reagents, unless otherwise stated, are commercially available and were used as received. Hexafluoropropene oxide (97% purity) was purchased from Oakwood; # 3257. Ethyl trifluoropyruvate **2** was prepared from the hexafluoropropene oxide according to the corresponding literature procedure.[18] ^1H and ^{19}F NMR spectra were recorded at 299.95 and 282.24 MHz, respectively. Chemical shifts refer to tetramethylsilane (TMS) and $CFCl_3$ as the internal standards. Monitoring of the reactions by GLC were performed using a fused silica capillary column. Melting points were taken in open capillaries and are uncorrected. Enantiomeric compositions of *Schiff* base **13** were determined by chiral HPLC analysis using Chiral OJ (Daicel) column. Eluent: *n*-hexane/EtOH as 5/1 (volume).

Yields refer to isolated yields of products of greater than 95% purity as estimated by capillary GC and/or ^1H and ^{19}F NMR spectrometry. All new compounds were characterized by ^1H, ^{19}F and elemental analysis.

Ethyl 2-*N*-(1-phenylethyl)imino-3,3,3-trifluoropropionate (12). The starting ethyl trifluoropyruvate **2** (85.0 g, 0.50 mol) was first dissolved in 160 mL of toluene in 250-300 mL round-bottomed flask equipped with a reflux condenser, a Dean-Stark trap and a magnetic stirring bar. *N*-(1-phenyl)ethylamine (66.7 g, 0.55 mol) and 1 mol % of *p*-toluenesulfonic acid monohydrate were added at 5 °C to the reaction flask, and the mixture was stirred at reflux. After the reaction was complete (theoretical amount of water removed, and monitoring by GLC, TLC and ^1H, ^{19}F NMR), the solvent was removed *in vacuo* and imine **12** was purified by distillation. Yield of **12** 83% (113.4 g); bp 81-84 °C at 0.2 mm Hg. ^1H NMR ($CDCl_3$) δ 1.29 (t, 3H, J = 7.2 Hz), 1.42 (d, 3H, J = 6.8 Hz), 4.15 (q, 2H, J = 7.2 Hz), 5.08 (q, 1H, J = 6.8 Hz), 7.25-7.34 (m, 5H); ^{19}F NMR δ -68.02 (s). Anal. Calcd for $C_{13}H_{14}F_3NO_2$: C, 57.14; H, 5.16; N, 5.13; F, 20.86. Found: C, 57.39; H, 5.24; N, 5.19; F, 20.63.

Enantiomerically pure (*R*)-ethyl 2-*N*-(1-phenylethyl)imino-3,3,3-trifluoropropionate was prepared in 81% yield using the same procedure on 0.05 mol scale; $[\alpha]_D^{25}$ 120.1 (*c* 1, $CHCl_3$).

***N*-(1-phenyl)ethylidene-3,3,3-trifluoroalanine ethyl ester (13).** Imine **12** (110.0 g) was dissolved in 100 mL of triethylamine and the mixture was stirred at rt. Progress of the isomerization was monitored by NMR or GLC and upon completion, any undissolved solid was removed by filtration and TEA was evaporated *in vacuo*. The residual material was dried *via* an oil pump, to remove completely TEA, and purified by distillation. Yield of **13** 92% (101.2 g); bp 98-101 °C at 0.2 mm Hg. ^1H NMR ($CDCl_3$) δ 1.20 (t, 3H, J = 7.2 Hz), 2,39 (s, 3H), 4.09 (q, 2H, J = 7.2 Hz), 5.16 (q, 1H, J = 7.4 Hz), 7.38-7.42 (m, 3H), 7.79-7.83 (m, 2H); ^{19}F NMR δ -72.06 (q, J = 7.4 Hz). Anal. Calcd for $C_{13}H_{14}F_3NO_2$: C, 57.14; H, 5.16; N, 5.13; F, 20.86. Found: C, 57.21; H, 5.18; N, 5.12; F, 20.74.

3,3,3-Trifluoroalanine ethyl ester hydrochloride (14). The starting *Schiff* base **13** (100.0 g) was dissolved in 300 mL of ether and 100 mL of 1 *N* HCl was added under stirring at ambient temperature. Progress of the hydrolysis was monitored by TLC and upon completion (20-30 min) aqueous layer was separated, washed with ether and evaporated *in vacuo* to give crystalline hydrochloride **14** purified by recrystallization from acetonitrile. Yield of **14** 71.5 g (94%); mp 153-157 °C. ^1H NMR (CD_3OD) δ 1.29 (t, 3H, J = 7.1 Hz), 4.19 (q, 2H, J = 7.1 Hz), 5.31 (q, 1H, J = 7.8 Hz); ^{19}F NMR δ -68.31 (d, J = 7.8 Hz). Anal. Calcd for $C_5H_9ClF_3NO_2$: C, 28.93; H, 4.37; N, 6.75. Found: C, 29.01; H, 4.40; N, 6.69.

3,3,3-Trifluoroalanine hydrochloride (15).[19,20] Amino acid **15** (50.5 g, 83%) was prepared from ethyl ester **14** according to the literature procedures described for the hydrolysis of the corresponding methyl ester[19,20] (hydrolysis by conc. HCl, 12 hrs at 90 °C); mp 205 °C (decomposition). ^1H NMR (CD_3OD) δ 5.09 (q, 1H, J = 7.8 Hz); ^{19}F NMR δ -71.10 (d, J = 7.8 Hz).

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