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# The Effect of Substituents on the Feasibility of Azomethine—Azomethine Isomerization: New Synthetic Opportunities for Biomimetic Transamination

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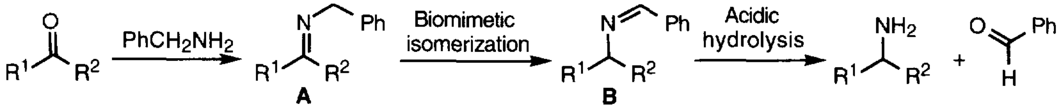
***Abstract:*** The azomethine—azomethine isomerization of the *Schiff* bases derived from fluoroalkyl carbonyl compounds and arylmethylamines has been studied as a function of substitution on the amine site. The present study indicates that regardless of the nature of the substitution, the position of the isomerization equilibrium is overwhelmingly controlled by the electron-withdrawing effect of the perfluoroalkyl group, while the reaction rate strongly depends on both CH acidity and steric availability of the transferring proton. Specifically, we have found that the presence of electron-releasing substituent on the phenyl of the benzylamine site largely retards the isomerization of the corresponding imines. In contrary, azomethine—azomethine isomerizations of the imines derived from the benzylamines containing electron-withdrawing substituent on the phenyl ring or picolylamines, possessing electron-deficient pyridine ring, occur with remarkably higher reaction rates as compared with the established isomerizations of *N*-benzylimines. In particular, the use of 4-picolylamine allows for truly biomimetic one-stage transamination of fluorocarbonyl compounds to afford the *Schiff* bases of the corresponding amines. The exciting synthetic aspects of this finding are demonstrated by the improved procedure for transamination of certain fluoroalkyl carbonyl compounds representing aldehydes, ketones, and β-keto carboxylic acids.

## Introduction

Biological transamination,[1] *i.e.* the enzyme-catalyzed interconversion of α-amino and α-keto carboxylic acids, involves the azomethine—azomethine isomerization of the corresponding *Schiff* bases derived from pyridoxal and pyridoxamine.[2] This isomerization, providing intramolecular oxidation—reduction process, represents the most ideal solution to the reductive amination of carbonyl compounds (Scheme 1) and can not be rivaled for the efficiency by the purely chemical methods using reducing reagents.[3] Unfortunately, the azomethine system of the *Schiff* bases derived from common carbonyl compounds and amines, was shown to be rather immobile necessitating strong nucleophilic catalysis, such as NaOMe in MeOH, for the isomerization to occur with the equilibrium normally not favoring the targeted products.[4] Thus, no generalized synthetic methods which make use of azomethine—azomethine isomerization have been developed till now.[5]

Recently we have discovered that, in strike contrast to the hydrocarbon imines,[4] the *Schiff* bases derived from fluoroalkyl carbonyl compounds and benzylamine (Scheme 1, **A**), under the mild reaction conditions in the presence of such a weak base as triethylamine (TEA) easily undergo azomethine—azomethine isomerization to afford aldimines **B** in excellent chemical yields.[6,7] The salient feature of these isomerizations is that the equilibrium between **A** and **B** is shifted nearly entirely toward the *N*-benzylidene derivatives **B** which can be readily hydrolyzed to release the desired amino compounds. The synthetic value of this reducing agent-free

**Scheme 1.**



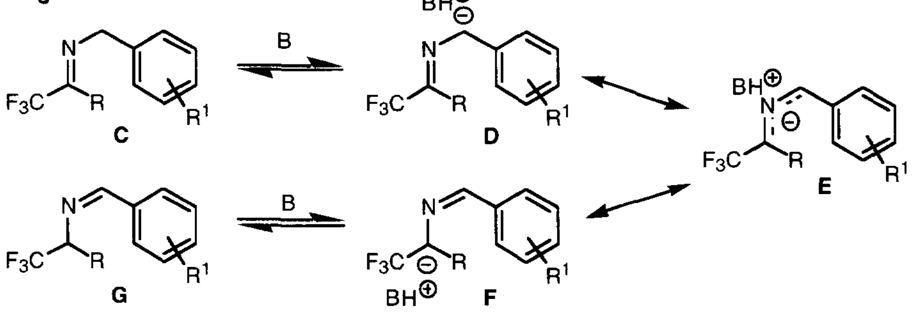
$R^1$ = fluoroalkyl, fluoroaryl; $R^2$ = H, alkyl, aryl, benzyl, COOR, $CH_2COOR$

biomimetic transamination process, referred to as a base-catalyzed [1,3]-proton shift reaction (PSR), have been demonstrated by the efficient preparation of structurally varied α-fluoroalkyl(aryl)amines,[6] α- and β-amino acids[7] starting with the appropriate fluoro-carbonyl compounds and benzylamine (Scheme 1). Due to the simplicity of the experimental procedure, the low cost of the required reagents and high yields of the targeted products, PSR is emerging as a convenient and preparatively useful generalized method for the synthesis of fluorine-containing amino compounds of a wide range of potential biomedicinal application.[8] However, for that exciting synthetic potential to be realized to the full, all factors influencing feasibility of PSR must be studied in greater detail. Previous investigations into the PSR have been focused on the effects of substituents at the imine carbon of *N*-benzyl imines **A** on the rate and equilibrium of their isomerizations to *Schiff* bases **B**, while the influence of the isomerization by substitution on the amine site has not received due attention. In this paper we present a full account of our studies into the effects of substitution on the phenyl of *N*-benzyl moiety in *Schiff* bases **A** on their isomerizations to aldimines **B**.[9]

## Results and Discussion

The mechanism of the hydrocarbon imines azomethine—azomethine isomerization was shown to involve intermediate azaallylic anion **E** (Figure 1) evolution of which to the covalent state **C** or **G** is controlled by the thermodynamic preference of **D** or **F**, respectively.[4] On this basis, the dramatic difference in the reactivity between hydrocarbon and fluorinated azomethines can be easily rationalized by taking into account strong electron-withdrawing effect of the trifluoromethyl group.[10] Obviously, the trifluoromethyl group, effectively delocalizing negative charge, might encourage thermodynamic preference of **F** over **D** to afford, upon the protonation, *N*-benzylidene derivative **G**. Furthermore, we have demonstrated that the rates of the isomerizations of trifluoromethyl *N*-benzylimines **C** to *N*-benzylidene derivatives **G** markedly depend on the nature of substituent R at the imine carbon and increase in the following order: R = perfluoroalkyl ≈ alkoxycarbonyl >> aryl >> hydrogen > alkyl ≈ benzyl.[6,7] For instance, the isomerization of *N*-benzylimine of trifluoroacetophenone **C** (R = Ph) to **G** readily occurred in triethylamine (TEA) solution at 14-16 °C for 24 h, while the transformation of the imine **C**, derived from benzyl trifluoromethyl ketone (R = $CH_2Ph$), to **G** was achieved only in boiling TEA for 48 h.[6d] The difference in the reactivity observed was accounted for by the opposite effect of the phenyl and benzyl groups on the equilibration of the intermediate azaallylic carbanions, facilitating and retarding the isomerization, respectively. This working rationale well accounts for marked difference in the reactivity of all previously studied *N*-benzylimines derived from fluorinated aldehydes, ketones

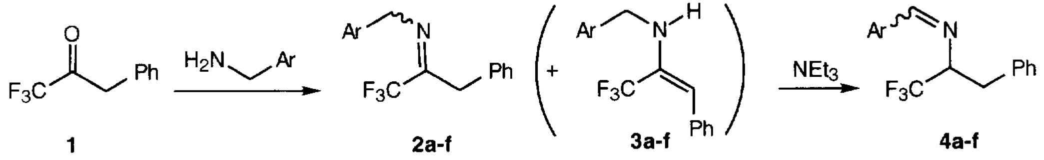
**Figure 1.**



B = Base; $R^1$ = Electron-withdrawing or electron-releasing substituent and keto esters.[6,7] It is also consistent with the data reported on the azomethine—azomethine isomerizations of unsymmetrically *para*-monosubstituted *N*-benzylidene benzylamines, for which the equilibrium constants were found to be adequately correlated by the *Hammett* equation.[4k] Accordingly, it was reasonable to assume that introduction of an electron-releasing substituent $R^1$ on the phenyl of the *N*-benzyl moiety in **C** (R = $CH_2Ph$) might destabilize **D** favoring thermodynamic stability of **F** and thus would overcome the retarding effect of the benzyl group facilitating the isomerization of **C** to **G**.

To realize this opportunity we designed a series of *N*-benzyl imines **2a-f** (Scheme 2) bearing electron-releasing and electron-withdrawing substituents on the phenyl ring. Imines **2a-f** were synthesized *via* direct condensation of benzyl trifluoromethyl ketone (**1**) with the appropriate benzylamine in the presence of *p*-toluenesulfonic acid. *Schiff* bases **2a,e** were isolated in a mixture with the corresponding enamines **3a,e**, while **2b-d,f** were obtained as individual compounds. According to NMR spectra, imines **2a-f** and their enamines are geometrically homogeneous (>95%). However, when considering the isomerization outcome, these properties of the starting material are not important as it is known that both syn—anti and imine—enamine isomerizations are much more mobile than the relative triad azomethine—azomethine prototropy under study.[4a,11] Since all starting **2,3a-f** and final **4a-f** compounds proved chemically stable to and well-separable by GLC, the isomerizations of **2,3a-f** to **4a-f** were conducted in the same flask by heating the mixture of 1 mmol of each **2,3a-f** in TEA solution at 78±1 °C. Each isomerization was repeated under the same reaction

**Scheme 2**



Ar = Ph (**a**); 4-MeO-$C_6H_4$ (**b**); 3,4-$(MeO)_2$-$C_6H_3$ (**c**); 2,4$(MeO)_2$-$C_6H_3$ (**d**); 4-F-$C_6H_4$ (**e**); 4-$CF_3$-$C_6H_4$ (**f**)

**Table 1. TEA-Catalyzed Isomerization of 2,3a-f to 4a-f**[a]

| Entry | Imine **1**, Ar | reaction time<br>3 h<br>ratio[b] **2**/**4** | <br>12 h<br>ratio[b] **2**/**4** | <br>23 h<br>ratio[b] **2**/**4** | Yield,[c]<br>% |
|---|---|---|---|---|---|
| 1 | (**a**) $C_6H_5$[d] | 49/51 | 15/85 | 4/96 | 92[e] |
| 2 | (**b**) 4-MeO-$C_6H_4$[f] | 70/30 | 30/70 | 15/85 | 94[g] |
| 3 | (**c**) 3,4-$(MeO)_2$-$C_6H_3$ | 56/44 | 18/82 | 8/92 | 87[h] |
| 4 | (**d**) 2,4-$(MeO)_2$-$C_6H_3$ | 92/8 | 85/15 | 73/27 | 90[i] |
| 5 | (**e**) 4-F-$C_6H_4$[j] | 46/54 | 10/90 | <1/99 | 95[k] |
| 6 | (**f**) 4-$CF_3$-$C_6H_4$ | <1/99 | — | — | 92[l] |

[a] All reactions were run in TEA solution at 78±1 °C. [b] Determined by GLC and $^{19}F$ NMR analyses. The number given for **2** is a sum of ketimine **2** and the corresponding enamine. Aldimines **4**, according to NMR, are geometrically homogeneous (Z > 95%). [c] Isolated yield of Schiff bases **4** after completion (> 97% of **2**) of the isomerization. [d] Initial 1/2.4 enamine/ketimine mixture. [e] See ref. 6c. [f] Initial 1/16 enamine/ketimine mixture. [g] Complete isomerization in 71 h. [h] Complete isomerization in 52 h. [i] Complete isomerization in 183 h. [j] Initial 1/2.3 enamine/ketimine mixture. [k] Complete isomerization in 42 h. [l] Complete isomerization less than in 3 h.

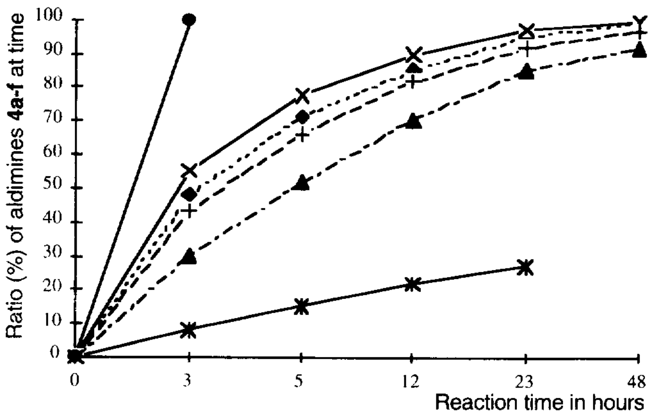


Figure 2. TEA-Catalyzed Isomerization of **2,3a-f** to **4a-f**.
Curve ◆ — **a**, ▲ — **b**, ✢ — **c**, ✳ — **d**, X — **e**, ● — **f**

conditions as an individual experiment to afford pure **4a-f**. After the definite reaction period, the extent of isomerization of **2,3a-f** to **4a-f** was determined immediately by GLC and $^{19}$F NMR analyses of the reaction mixture. The results are collected in Table 1 and graphically represented in Fig. 2. In agreement with the data reported for the isomerizations of fluorine-free azomethines,[4] the initial rates of the transformations of **2,3a-f** to **4a-f** were found to follow approximately first-order kinetics (Fig. 2). The striking feature of the isomerizations studied was the remarkable effect of the electronic nature of substituents on the reaction rates. Thus, the isomerization of *p*-trifluoromethyl substituted ketimine **2f** to aldimine **4f** was entirely completed in 3 h (entry 6), while the conversion of MeO-containing derivatives **2b,d** to **4b,d** took 71 and 183 h, respectively (entries 2,4). The effects of *para*-fluorine (**2e** to **4e**, entry 5) and *meta*-, *para*-dimethoxy (**2c** to **4c**, entry 3) substitutions on the isomerization rates were not so pronounced. The imines **2c,e** were transformed to *N*-benzylidene derivatives **4c,e**, respectively, with the rates similar to that of unsubstituted **2a** isomerization to **4a** (entry 1). The marked difference in the reaction rates of the isomerizations of two dimethoxy substituted imines **2c,d** to **4c,d** (entry 3 *vs* 4) could be accounted for by the opposite electronic effects of *para*- and *meta*-methoxy groups in **2c**, while in **2d** the both methoxy groups work in a coherent manner.[12] By contrast, the influence of the substitutions on the position of the equilibrium between **2a-f** and **4a-f** was not observed. Despite the marked difference in the reaction rates, all imines **2a-f** were completely ($K$ = **4**/**2** >30) isomerized to **4a-f**, which were isolated with high chemical yields and fully characterized.

The data obtained (Table 1, Fig. 2) suggest that, in contrast to our assumption, introduction of the electron-withdrawing substituents on the phenyl of the *N*-benzyl group in the starting imines **2** accelerated their isomerizations to **4**. Moreover, we have found that *p*-trifluoromethyl substituted ketimine **2f** readily underwent isomerization to **4f** in TEA solution at room temperature (18 °C, 24 h) similarly to the *N*-benzylimine of trifluoroacetophenone which bears both carbanion stabilizing the trifluoromethyl and phenyl groups at the imine carbon. These results indicate that our idea on the factors influencing the azomethine—azomethine isomerization is not complete. The observed outcome can be rationalized with the following arguments: a) the investigated substitutions influence the CH-acidity of the methylene protons of the *N*-benzyl moiety in **2**, facilitating the abstraction of the proton if an electron-withdrawing substituent is introduced; b) the substitution on the phenyl of the *N*-benzyl moiety in **2** can not rival the effect of the trifluoromethyl group for the control over the position of the equilibrium between azomethines **2** and **4**. Since the CH-acidity of the benzyl protons might be affected also by the nature of substituents on the imine carbon,[13] this amended rationale reasonably accounts for the significant difference in the rates of previously studied isomerizations of the *N*-benzylimines derived from various fluoroalkyl carbonyl compounds,[6,7] and is quite consistent with the data reported for isomerizations of fluorine-free azomethines.[4]

To survey the generality of the effects revealed, we decided to investigate the isomerizations of the imines derived from ketone **1** and picolylamines, in which the electron-deficient nature of the pyridine ring, instead of the substituted phenyl, was envisioned to enhance the CH-acidity of the methylene protons. An attempt to prepare the corresponding imine by the direct condensation between ketone **1** and 4-picolylamine gave rather unexpected result. Thus, the reaction of **1** with the amine in boiling toluene afforded *Schiff* base **7a** in respected chemical yield (77%) (Scheme 3). It follows, that the isomerization of the intermediate ketimine, which can be detected (<10%) by NMR on the initial stage of the reaction, occurred exceptionally easily *via* a thermal self-catalytic or the initial 4-picolylamine-catalyzed manner. Whatever the source of this reactivity, the synthetic result, a truly biomimetic one-stage transamination of benzyl trifluoromethyl ketone (**1**) to Schiff base of amine **7a**, was impressive. By contrast, 3-picolylamine reaction with ketone **1** gave expected imine **5**, as the main product (85.6%), in a mixture with its enamine **6** (12.7%) and only a minute amount of the isomerized product **7b** (1.7%). Ketimine **5** was purified to individual state by column chromatography and its isomerization to **7b** was studied under the different reaction conditions (Table 2). We have found that transformation of **5** to **7b** can be conducted simply by heating of **5** in toluene solution at reflux (entry 1); however, formation of a sizable amount of decomposition products was also observed. The isomerization conducted in the neat 3-picolylamine (entry 2) proceeded more easily, to provide the complete transformation of **5** to **7b** at room temperature in 50 h. These results indicate that the formation of 4-pyridyl derivative **7a** in the related reaction, could also occur through the both pathways, but apparently with the higher reaction rate, since the influence of CH-acidity of the

**Scheme 3**

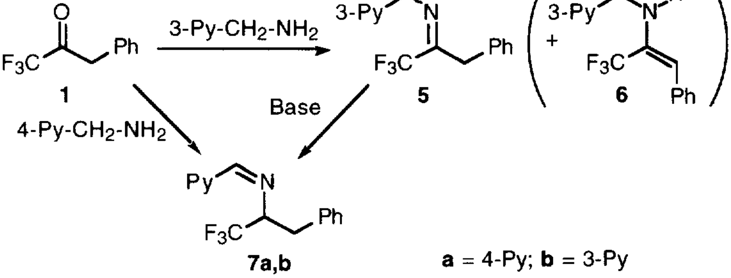


**Table 2. Isomerization of Ketimine 5 to Aldimine 7b**[a]

| Entry | Base | Ratio[b], % | | |
|---|---|---|---|---|
| | | Enamine **6**[c] | Ketimine **5**[c] | Aldimine **7b**[c] |
| 1 | — | 10 | 17 | 73[d] |
| 2 | $NH_2$-$CH_2$-3-Py | 5 | 13 | 82[e] |
| 3 | $C_6H_5N$ | 13 | 82 | 5 |
| 4 | DBU | — | — | 100[j] |
| 5 | $NEt_3$ | 14 | 14 | 72[f] |
| 6 | $NHEt_2$ | 4 | 2 | 94[g] |
| 7 | $NH_2CH_2Ph$ | 3 | 1 | 96[i] |
| 8 | NH-*i*-$Pr_2$ | 13 | 2 | 85[h] |
| 9 | (-)-Nicotine | 12 | 80 | 8 |

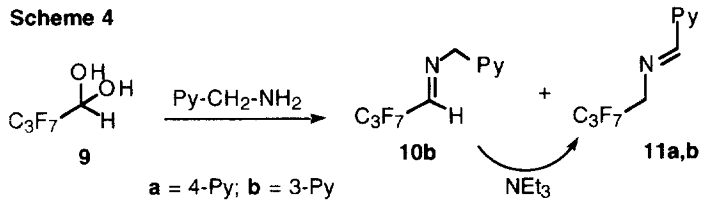
[a] All reactions were run the solution of the base indicated at room temperature for 23 h. [b] Determined by GLC and $^{19}$F NMR analyses. [c] According to NMR, are geometrically homogeneous (> 95%). [d] Up to 25% of byproducts ($^{19}$F NMR). [e] Up to 12% of byproducts ($^{19}$F NMR) after the completion of the isomerization in 50 h. [f] Complete isomerization in 58 h. [g] Complete isomerization in 35 h. [h] Up to 15% of byproducts ($^{19}$F NMR) after the completion of the isomerization in 48 h. [i] Up to 13% of byproducts ($^{19}$F NMR) after the completion of the isomerization in 35 h. [j] Complete isomerization in less than 10 min.

methylene protons is more pronounced in this case; the negative charge of the derived carbanion can be distributed onto the 4-pyridyl nitrogen. 2-Picolylamine reaction with ketone **1** shown atypical behavior giving rise to a mixture of many products.

With these results in hand, we next explored the effect of nature of a base-catalyst on the rate of the isomerization of **5** to **7b**. We chose a series of amines differ for the basicity and steric properties as well. The results are collected in Table 2. As can be seen in the Table, pyridine was the less effective in catalyzing the isomerization producing only minute amount of **7b** in 23 h at room temperature (entry 3). By contrast, DBU-catalyzed isomerization occurred exothermically providing complete transformation of **5** to **7b** in a few minutes (entry 4). In the series of *N*-alkyl amines, less sterically demanding that triethylamine (entry 5), diethyl- and benzylamine (entries 6,7) were found to be substantially more effective in catalyzing the isomerization, while the difference between triethylamine and di-*i*-propylamine was not so pronounced (entries 5 *vs* 8). The dependence of the catalytic activity of a base on its steric properties is clearly demonstrated by the (-)-nicotine-catalyzed isomerization (entry 9), the outcome of which, was found to be very similar to that of pyridine-catalyzed isomerization (entry 3 *vs* 9). This result suggests that despite the pyrrolidine nitrogen of the nicotine is much more basic than its pyridine one, the former is probably too sterically shielded to realize the proton transfer. It is also worth noting that the rates of the reactions catalyzed by isosteric *N*-benzyl and 3-picolylamine were significantly different, that might be accounted for by the difference in the basicity of these amines. In spite of the difference in the reaction rates, all reactions, except for pyridine and (-)-nicotine-catalyzed, resulted in the complete transformation of **5** to **7b** with $K > 30$, thus implying that the nature of the base used has no detectable influence on the isomerization equilibrium. These data (Table 2), support the above assumption that the rate-determining step in the isomerization under study is the abstraction of the methylene proton, that, in turn, is a function of the CH-acidity and steric availability of the transferring proton.

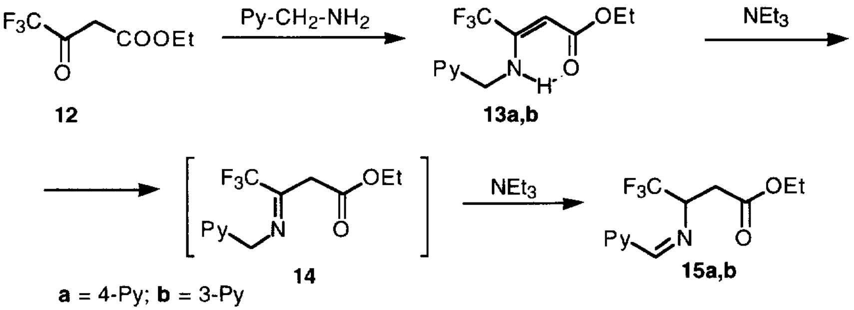
Finally, to demonstrate the generality of the discovered effects influencing the isomerization of the imines derived from trifluoromethyl ketone **1**, for transamination of other classes of fluorinated carbonyl compounds, we investigated reactions of 3- and 4-picolylamines with fluoroalkyl aldehydes and β-keto esters. The isomerizations of *N*-benzylimines of perfluoroalkyl aldehydes are known to proceed under the milder reaction conditions as compared with the isomerization of *N*-benzylimine of ketone **1**. Thus, the TEA-catalyzed isomerization of *N*-benzylimine of perfluorobutyraldehyde could be completed in 89 h at 14-18 °C or in 21 h at 50 °C.[6d] Accordingly, we expected that synthetically advantageous one-step transamination of fluoroaldehydes with 4-picolylamine would also take place. Indeed, the reaction of perfluorobutyraldehyde hydrate (**9**) with 4-picolylamine afforded directly the isomerized product **11a** (Scheme 4). The condensation of aldehyde **9** with 3-picolylamine gave the expected aldimine **10b**. Treatment of **10b** with triethylamine at room temperature resulted in the complete transformation of **10b** to **11b** in a few minutes, that is dramatically easier as compared with the mentioned above isomerization of the *N*-benzyl derivative. Preliminary results showed that the pattern of reactivity revealed for the condensations of ketone **1** and aldehyde **9** with 3- and 4-picolylamines might be common for the reactions of *n*-alkyl *n*-perfluoroalkyl ketones and *n*-perfluoroalkyl aldehydes.

**Scheme 4**



Transamination of fluorinated β-keto carboxylic esters *via* PSR is of particular interest, since the ready available by this method β-amino acids are of high biomedicinal

**Scheme 5**



interest.[7,14,15] Previously we have shown that condensation of β-per(poly)fluoroalkyl-β-keto esters with benzylamine gives rise to the corresponding enamino derivatives stabilized by the intramolecular hydrogen bond. These compounds were found to undergo two sequential [1,3]-proton shift transfers, azomethine—enamine and azomethine—azomethine isomerizations, to give Schiff bases of the targeted β-amino acids only under the forced reaction conditions.[7g] Thus, realization of the opportunity to facilitate this transformation, offered by the present results, would be highly desirable. In contrast to ketone **1** and aldehyde **9**, the condensation of trifluoroacetoacetate **12** with 4-picolylamine gave enamine **13a** as the main reaction product in a mixture with aldimine **15a** in a ratio 10 to 1, respectively. Complete isomerization of **13a** to **15a** was found to occur in TEA solution at room temperature in less than 4 h. Condensation of keto ester **12** with 3-picolylamine afforded the only enamine **13b**, however, its isomerization to Schiff base **15b** proved also highly facile to be completed in TEA solution at room temperature for 36 h. These results suggest that regardless the stability of the initial **13a,b** and complex reaction sequence involving azomethine—enamine and azomethine—azomethine isomerizations through the intermediate ketimines **14**, electron-deficient nature of the pyridine ring facilitates the overall outcome affording final Schiff bases **15a,b** under the mild reaction conditions.

In conclusion, we have found that the rate of biomimetic transamination of the given fluorocarbonyl compounds *via* PSR can be controlled by the nature of substitution on the *N*-site of the starting imine. Specifically, the application of benzylamine analogs containing electron-withdrawing substituent on the phenyl ring or picolylamines, remarkably facilitate the azomethine—azomethine isomerization allowing us to achieve truly biomimetic one-stage transamination of fluoroalkyl aldehydes and ketones to the corresponding amines. In contrary, the presence of electron-releasing substituent on the phenyl of the benzylamine largely retards the isomerization rate. However, no influence of the substitutions studied on the position of the isomerization equilibrium, which is directed by the strong electron-withdrawing effect of the fluoroalkyl group, was detected. The synthetic aspects of these results are demonstrated by the improved procedure for transamination of certain fluoroalkyl carbonyl compounds representing aldehydes, ketones, and β-keto carboxylic acids. The present study amends our mechanistic rationale for the azomethine—azomethine isomerization. Thus, the feasibility of the isomerization is a function of a) CH acidity and steric availability of the transferring proton, and b) the thermodynamic stability of competing azaallylic anions. While the latter factor controls the position of the isomerization equilibrium, the former properties influence the reaction rate. The practical importance of this study is that the conclusions drawn from these data should allow for the rational design of more practical methodology of biomimetic transamination which would expand the scope and utility of this reaction.

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## EXPERIMENTAL SECTION

***General.*** For standard laboratory praxis and techniques see related paper, ref. 6d. $^{1}$H, $^{19}$F and $^{13}$C NMR spectra, unless indicated, were recorded of CDCl$_3$ solutions at 299.95, 282.24 and 75.42 MHz, respectively. Chemical shifts refer to tetramethylsilane (TMS) and CFCl$_3$ as the internal standards. Unless otherwise stated, $R_f$ values are taken using *n*-hexane/ethyl acetate (4:1) as an eluting system.

Yields refer to isolated yields of products of greater than 95% purity as estimated by capillary GC and/or $^{1}$H and $^{19}$F NMR spectrometry. All new compounds were characterized by $^{1}$H, $^{19}$F, $^{13}$C NMR and by mass spectrometry or elemental analysis.

The syntheses of *N*-benzylimines **2a-f** were carried out according to the general procedure given in the ref. 6d.

***N*-(1,1,1-Trifluoro-3-phenyl-*iso*-propylidene)benzylamine (2a)** (in a 1.3/1 mixture with corresponding enamine **3a**):[6d] 89.5%, $R_f$ 0.31. $^{1}$H NMR $\delta$ 3.92 (s, 1.12H), 4.69 (s, 1.12H) (ketimine **2a**), 3.65 (br.s, 0.44H), 4.06 (d, 0.88H, $J_{HH}$ = 4.5 Hz), 6.10 (s, 0.44H) (enamine **3a**), 7.16-7.35 (m, 10H); $^{19}$F NMR $\delta$ -68.61 (s, 1.3F) (enamine **3a**), -72.94 (s, 1.7F) (ketimine **2a**); MS m/z 277 (M$^+$, 16), 186 (M$^+$-PhCH$_2$, 4), 91 (100), 65 (19).

***N*-(1,1,1-Trifluoro-3-phenyl-*iso*-propylidene)-4-methoxybenzylamine (2b)**: 84%, $R_f$ 0.27. $^{1}$H NMR $\delta$ 3.79 (s, 3H), 3.91 (s, 2H), 4.63 (s, 2H), 6.84-6.86 (m, 2H), 7.15-7.35 (m, 7H); $^{19}$F NMR $\delta$ -72.93 (s, 3F); MS m/z 307 (M$^+$, 5), 121 (100), 91 (13).

***N*-(1,1,1-Trifluoro-3-phenyl-*iso*-propylidene)-3,4-dimethoxybenzylamine (2c)**: 84%, $R_f$ 0.15. $^{1}$H NMR $\delta$ 3.85 (s, 3H), 3.86 (s, 3H), 3.92 (s, 2H), 4.63 (s, 2H), 6.71-7.03 (m, 3H), 7.17-7.34 (m, 5H); $^{19}$F NMR $\delta$ -72.94 (s, 3F); MS m/z 337 (M$^+$, 12), 152 (10), 151 (100), 91 (10).

***N*-(1,1,1-Trifluoro-3-phenyl-*iso*-propylidene)-2,4-dimethoxybenzylamine (2d)**: 67%, $R_f$ 0.24. $^{1}$H NMR $\delta$ 3.77 (s, 3H), 3.80 (s, 3H), 3.94 (s, 2H), 4.65 (br.s, 2H), 6.44-6.48 (m, 2H), 7.17-7.32 (m, 6H); $^{19}$F NMR $\delta$ -72.53 (s, 3F); $^{13}$C NMR $\delta$ 33.36 (s), 50.39 (s), 55.45 (q, $J_{CF}$ = 8.1 Hz), 98.63 (s), 104.30 (s), 118.73 (s), 121.93 (q, $J_{CF}$ = 279.3 Hz), 127.10 (s), 128.47 (s), 129.02 (s), 129.81 (s), 134.22 (s), 157.82 (q, $J_{CF}$ = 32.3 Hz), 158.13 (s), 160.37 (s); MS m/z 337 (M$^+$, 6), 151 (100), 121 (30), 91 (24), 77 (12), 65 (11).

***N*-(1,1,1-Trifluoro-3-phenyl-*iso*-propylidene)-4-fluorobenzylamine (2e)** (in a 2.3/1 mixture with corresponding enamine **3e**): 92%, $R_f$ 0.33. $^{1}$H NMR $\delta$ 3.91 (s, 1.4H), 4.63 (s, 1.4H) (ketimine **2e**), 3.60 (br.s, 0.3H), 4.02 (br.s, 0.6H), 6.10 (s, 0.3H) (enamine **3e**), 6.96-7.35 (m, 9H); $^{19}$F NMR $\delta$ -68.72 (s, 0.9F), -115.42 (m, 0.3F) (enamine **3e**), -73.07 (s, 2.1F), -116.11 (m, 0.7F) (ketimine **2e**); MS m/z 295 (M$^+$, 9), 204 (M$^+$-PhCH$_2$, 1), 109 (100), 91 (10).

***N*-(1,1,1-Trifluoro-3-phenyl-*iso*-propylidene)-4-trifluoromethylbenzylamine (2f)**: 78%, $R_f$ 0.30. $^{1}$H NMR $\delta$ 3.92 (s, 2H), 4.70 (br.s, 2H), 7.15-7.18 (m, 2H), 7.25-7.40 (m, 5H), 7.56-7.59 (m, 2H); $^{19}$F NMR $\delta$ -63.02 (s, 3F), -73.17 (s, 3F); $^{13}$C NMR $\delta$ 33.68 (s), 54.85 (s), 119.77 (q, $J_{CF}$ = 279.1 Hz), 124.17 (q, $J_{CF}$ = 271.8 Hz), 125.48 (q, $J_{CF}$ = 3.8 Hz), 127.35 (s), 127.85 (s), 128.23 (s), 129.18 (s), 133.41 (s), 141.88 (s), 158.68 (q, $J_{CF}$ = 32.8 Hz); MS m/z 345 (M$^+$, 22), 235 (13), 159 (100), 109 (17), 91 (40). Enamine **3f**: 27%, $R_f$ 0.42. $^{1}$H NMR $\delta$ 3.72 (br.s, 1H), 4.13 (s, 2H), 6.13 (s, 1H), 7.22-7.33 (m, 7H), 7.54-7.57 (m, 2H); $^{19}$F NMR $\delta$ -63.06 (s, 3F), -68.68 (s, 3F); MS m/z 345 (M$^+$, 74), 326 (10), 235 (10), 186 (16), 166 (16), 159 (100), 117 (33), 109 (24), 91 (30).

**Isomerizations of 2a-f to *N*-Benzylidene Derivatives 4a-f.** The isomerizations of **2,3a-f** to **4a-f** were carried out according to the general procedure given in the ref. 6d. Reaction time and yields are given in Table 1.

***N*-Benzylidene-1,1,1-trifluoro-3-phenyl-*iso*-propylamine (4a)**:[6d] $R_f$ 0.39. $^1$H NMR δ 3.06, 3.26 (ABX, 2H, $J_{AB}$ = 13.2 Hz, $J_{AX}$ = 2.1 Hz, $J_{BX}$ = 10.8 Hz), 3.78 (dqd, 1H, $J_{HH}$ = 10.8 Hz, $J_{HF}$ = 7.1 Hz, $J_{HH}$ = 2.1 Hz), 7.09-7.65 (m, 10H), 7.66 (s, 1H); $^{19}$F NMR δ -75.36 (d, 3F, $J_{HF}$ = 7.1 Hz); MS m/z 277 (M, 24), 186 (M-PhCH$_2$, 100).

***N*-(4-Methoxybenzylidene)-1,1,1-trifluoro-3-phenyl-*iso*-propylamine (4b)**: $R_f$ 0.28. $^1$H NMR δ 3.04, 3.25 (ABX, 2H, $J_{AB}$ = 13.5 Hz, $J_{AX}$ = 2.7 Hz, $J_{BX}$ = 10.5 Hz), 3.78 (dqd, 1H, $J_{HH}$ = 10.5 Hz, $J_{HF}$ = 6.8 Hz, $J_{HH}$ = 2.7 Hz), 6.87-6.90 (m, 2H), 7.12-7.22 (m, 5H), 7.57-7.60 (m, 3H); $^{19}$F NMR δ -75.41 (d, 3F, $J_{HF}$ = 6.8 Hz); MS m/z 307 (M$^+$, 19), 306 (12), 216 (M$^+$-PhCH$_2$, 100), 189 (70), 147 (12), 139 (30), 121 (12), 109 (13), 104 (10), 91 (55), 77 (29), 65 (20), 63 (12), 51 (20).

***N*-(3,4-Dimethoxybenzylidene)-1,1,1-trifluoro-3-phenyl-*iso*-propylamine (4c)**: $R_f$ 0.21. $^1$H NMR δ 3.05, 3.25 (ABX, 2H, $J_{AB}$ = 13.8 Hz, $J_{AX}$ = 2.7 Hz, $J_{BX}$ = 10.2 Hz), 3.74 (dqd, 1H, $J_{HH}$ = 10.2 Hz, $J_{HF}$ = 6.8 Hz, $J_{HH}$ = 2.7 Hz), 6.81-6.83 (m, 1H), 6.99-7.02 (m, 1H), 7.09-7.12 (m, 2H), 7.18-7.26 (m, 3H), 7.38-7.39 (m, 1H), 7.58 (s, 1H); $^{19}$F NMR δ -75.31 (d, 3F, $J_{HF}$ = 6.8 Hz); MS m/z 337 (M$^+$, 33), 246 (M$^+$-PhCH$_2$, 100), 219 (54), 204 (10), 151 (16), 109 (11), 91 (45), 77 (18), 65 (20), 51 (15).

***N*-(2,4-Dimethoxybenzylidene)-1,1,1-trifluoro-3-phenyl-*iso*-propylamine (4d)**: $R_f$ 0.19. $^1$H NMR δ 3.07, 3.25 (ABX, 2H, $J_{AB}$ = 13.8 Hz, $J_{AX}$ = 3.3 Hz, $J_{BX}$ = 9.9 Hz), 3.72 (s, 3H), 3.78 (dqd, 1H, $J_{HH}$ = 9.9 Hz, $J_{HF}$ = 8.7 Hz, $J_{HH}$ = 3.3 Hz), 3.84 (s, 3H), 6.37 (d, 1H, $J_{HH}$ = 2.4 Hz), 6.53 (dd, 1H, $J_{HH}$ = 8.7 Hz, $J_{HH}$ = 2.4 Hz), 7.12-7.27 (m, 5H), 7.97 (d, 1H, $J_{HH}$ = 8.7 Hz), 8.11 (s, 1H); $^{19}$F NMR δ -75.30 (d, 3F, $J_{HF}$ = 8.7 Hz); $^{13}$C NMR δ 36.14 (s), 55.55 (s), 73.65 (q, $J_{CF}$ = 26.8 Hz), 98.06 (s), 105.60 (s), 117.26 (s), 127.55 (q, $J_{CF}$ = 280.7 Hz), 126.66 (s), 128.44 (s), 129.15 (s), 130.02 (s), 136.77 (s), 160.55 (s), 161.33 (s), 163.76 (s); MS m/z 337 (M$^+$, 16), 246 (M$^+$-PhCH$_2$, 100), 219 (13), 215 (10), 177 (25), 164 (14), 162 (11), 149 (47), 91 (22), 77 (11), 65 (11).

***N*-(4-Fluorobenzylidene)-1,1,1-trifluoro-3-phenyl-*iso*-propylamine (4e)**: $R_f$ 0.42. $^1$H NMR δ 3.04, 3.26 (ABX, 2H, $J_{AB}$ = 13.2 Hz, $J_{AX}$ = 2.4 Hz, $J_{BX}$ = 10.5 Hz), 3.76 (dqd, 1H, $J_{HH}$ = 10.5 Hz, $J_{HF}$ = 6.8 Hz, $J_{HH}$ = 2.4 Hz), 6.99-7.65 (m, 10H); $^{19}$F NMR δ -75.42 (d, 3F, $J_{HF}$ = 6.8 Hz), -108.68 (m, 1F); MS m/z 295 (M$^+$, 26), 294 (18), 204 (M$^+$-PhCH$_2$, 100), 200 (13), 177 (81), 127 (62), 109 (38), 108 (26), 107 (21), 91 (76), 77 (17), 75 (11), 65 (26), 63 (11), 51 (19).

***N*-(4-Trifluoromethylbenzylidene)-1,1,1-trifluoro-3-phenyl-*iso*-propylamine (4f)**: $R_f$ 0.40. $^1$H NMR δ 3.05, 3.29 (ABX, 2H, $J_{AB}$ = 13.2 Hz, $J_{AX}$ = 2.7 Hz, $J_{BX}$ = 10.5 Hz), 3.81 (dqd, 1H, $J_{HH}$ = 10.5 Hz, $J_{HF}$ = 6.8 Hz, $J_{HH}$ = 2.7 Hz), 7.06-7.09 (m, 2H), 7.19-7.26 (m, 3H), 7.62-7.65 (m, 3H), 7.73-7.75 (m, 2H); $^{19}$F NMR δ -63.45 (s, 3F), -75.35 (d, 3F, $J_{HF}$ = 6.8 Hz); MS m/z 345 (M$^+$, 21), 344 (12), 254 (62), 227 (34), 200 (18), 177 (25), 159 (12), 91 (100), 65 (17).

**General Procedure for the Transamination of Benzyl Trifluoromethyl Ketone (1), 4,4,4,3,3,2,2-Heptafluorobutyraldehyde Hydrate (9) and Ethyl Trifluoroacetoacetate (12) with Pycolilamines.** The carbonyl compound (1 equiv), the appropriate amine (1.1 equiv) and *p*-toluenesulfonic acid (3-5 mol%) were dissolved in dry and degassed toluene (50-100 mL) in a round bottom flask under oxygen-free argon atmosphere. The flask was equipped with a reflux condenser and a Dean-Stark trap and the mixture was heated to reflux until theoretical amount of water was removed. The reaction was additionally controlled by GLC, TLC and $^{19}$F NMR, and upon the completion the solvent was removed *in vacuo*. The imine products were purified by column chromatography on $SiO_2$.

***N*-(4-Pyridylmethylidene)-1,1,1-trifluoro-3-phenyl-*iso*-propylamine (7a)**, obtained directly by the condensation between ketone **1** and 4-picolylamine: 77%, $R_f$ 0.47 (ethyl acetate/hexane as 1/1). $^1$H NMR δ 3.04, 3.30 (ABX, 2H, $J_{AB}$ = 13.5 Hz, $J_{AX}$ = 2.4 Hz, $J_{BX}$ = 10.5 Hz), 3.82 (dqd, 1H, $J_{HH}$ = 10.5 Hz, $J_{HF}$ = 8.8 Hz, $J_{HH}$ = 2.4 Hz), 7.05-7.08 (m, 2H), 7.20-7.26 (m, 3H), 7.46-7.49 (m, 2H), 7.58 (s, 1H), 8.66-8.88 (m, 2H); $^{19}$F NMR δ -75.95 (d, $J_{HF}$ = 8.8 Hz); MS m/z 278 ($M^+$, 14), 200 (31), 187 (M-$PhCH_2$, 26), 167 (33), 91 (100), 65 (16), 51 (14).

***N*-(1,1,1-Trifluoro-3-phenyl-*iso*-propylidene)-3-pyridylmethylamine (5)** (in a 9/1 mixture with corresponding enamine **6**): 95.6%, $R_f$ 0.45 (ethyl acetate/hexane as 1/1). $^1$H NMR δ 3.94 (s, 2H), 4.66 (s, 2H), 7.16-7.37 (m, 6H), 7.61-7.65 (m, 1H), 8.45-8.52 (m, 2H); $^{19}$F NMR δ -73.22 (s, 3F); MS m/z 278 ($M^+$, 6), 187 (M-$PhCH_2$, 36), 92 (100), 91 (30), 65 (33). Enamine **6**: $^1$H NMR δ 4.10 (s, 2H), 6.15 (s, 1H), 7.22-7.37 (m, 6H), 7.52-7.56 (m, 1H), 8.39 (m, 1H), 8.51-8.53 (m, 1H); $^{19}$F NMR δ -68.88 (s). Anal. Calcd for $C_{15}H_{13}F_3N_2$: C, 64.74; H, 4.71; N, 10.07; F, 20.48. Found: C, 64.52; H, 4.75; N, 10.19; F, 20.34.

Isomerization of the mixture **5**,**6** to aldimine **7b**. The mixture (9/1) of ketimine **5** with the corresponding enamine **6** (3g) was dissolved in 5 mL of dry TEA and the resultant solution was left at room temperature (22-25 °C) for 48 h. Upon the completion of the isomerization (>99%, monitored by $^{19}$F NMR), the solvent was removed *in vacuo* and aldimine **7b** was purified by column chromatography on $SiO_2$. ***N*-(3-Pyridylmethylidene)-1,1,1-trifluoro-3-phenyl-*iso*-propylamine (7b)**: 89.5%, $R_f$ 0.57 (ethyl acetate/hexane as 1/1). $^1$H NMR δ 3.06, 3.30 (ABX, 2H, $J_{AB}$ = 13.8 Hz, $J_{AX}$ = 3.0 Hz, $J_{BX}$ = 10.5 Hz), 3.83 (dqd, 1H, $J_{HH}$ = 10.5 Hz, $J_{HF}$ = 6.8 Hz, $J_{HH}$ = 3.0 Hz), 7.07-7.10 (m, 2H), 7.18-7.28 (m, 3H), 7.32-7.37 (m, 1H), 7.66 (s, 1H), 8.06-8.10 (m, 1H), 8.65-8.69 (m, 2H); $^{19}$F NMR δ -75.37 (d, 3F, $J_{HF}$ = 6.8 Hz); MS m/z 278 ($M^+$, 22), 277 (14), 200 (39), 187 ($M^+$-$PhCH_2$, 75), 167 (25), 160 (45), 92 (10), 91 (100), 78 (18), 77 (11), 65 (20), 64 (11), 63 (14), 51 (17).

***N*-(4-Pyridylmethylidene)-4,4,4,3,3,2,2-heptafluorobutylamine (11a)** obtained directly by the condensation between aldehyde **9** and 4-picolylamine: 63%, $R_f$ 0.35 (ethyl acetate/hexane as 1/2). $^1$H NMR δ 4.25 (td, 2H, $J$ = 15.3 Hz, $J$ = 1.5 Hz), 7.27-7.69 (m, 2H), 8.38 (s, 1H), 8.71-8.73 (m, 2H); $^{19}$F NMR δ -81.15 (t, 3F, $J$ = 8.6 Hz), -117.84 (m, 2F), -127.58 (s, 2F). Anal. Calcd for $C_{16}H_{14}F_3N$: C, 69.30; H, 5.09; N, 5.05; F, 20.56. Found: C, 69.44; H, 5.17; N, 5.07; F, 20.34. Anal. Calcd for $C_{10}H_7F_7N_2$: C, 41.68; H, 2.45; N, 9.72; F, 46.15. Found: C, 41.45; H, 2.47; N, 9.80; F, 46.21.

***N*-(4,4,4,3,3,2,2-Heptafluoropropylidene)-3-pyridylmethylamine (10b)**, : 74%, $R_f$ 0.28 (ethyl acetate/hexane as 1/2.5). $^1$H NMR δ 4.88 (s, 2H), 7.30-7.35 (m, 1H), 7.61-7.65 (m, 1H), 7.80-7.84 (m, 1H), 8.55-8.59 (m, 2H); $^{19}$F NMR δ -80.97 (t, 3F, $J_{F\text{-}F}$ = 8.6 Hz), -118.84 (m, 2F), -127.93 (s, 2F); $^{13}$C NMR δ 61.73 (s), 123.82 (s), 132.14 (s), 135.74 (s), 149.30 (s), 149.34 (s), 151.60 (t, $J_{CF}$ = 27.5 Hz), because of the low intensity and many coupling CF constants, carbon resonances of perfluoroalkyl group are obscured. Anal. Calcd for $C_{10}H_7F_7N_2$: C, 41.68; H, 2.45; N, 9.72; F, 46.15. Found: C, 41.59; H, 2.44; N, 9.76; F, 46.11.

For the isomerization of **10b** to **11b** the procedure described for **7b** was followed. ***N*-(3-Pyridylmethylidene)-4,4,4,3,3,2,2-heptafluorobutylamine (11b)**: 78%, $R_f$ 0.34 (ethyl acetate/hexane as 1/2.5). $^1$H NMR δ 4.28 (td, 2H, $J$ = 15.5 Hz, $J$ = 1.8 Hz), 7.33-7.39 (m, 1H), 7.64 (s, 1H), 8.07-8.11 (m, 1H), 8.67-8.72 (m, 2H); $^{19}$F NMR δ -81.17 (t, 3F, $J$ = 8.5 Hz), -117.91 (m, 2F), -127.60 (s, 2F). Anal. Calcd for $C_{10}H_7F_7N_2$: C, 41.68; H, 2.45; N, 9.72; F, 46.15. Found: C, 41.41; H, 2.50; N, 9.67; F, 46.28.

**Ethyl 3-*N*-(4-pyridylmethyl)amino-4,4,4-trifluoro crotonate (13a)** (in a mixture 10/1 with isomerized product **15a** obtained by the direct condensation of keto ester **12** with 4-picolylamine): **13a**, 64% , $R_f$ 0.29 (ethyl acetate/hexane as 1/1). $^1$H NMR δ 1.29 (t, 3H, $J$ = 7.2 Hz), 4.18 (q, 2H, $J$ = 7.2 Hz), 4.49 (m, 2H), 5.24 (s, 1H), 7.20-7.22 (m, 2H), 8.58-8.60 (m, 3H); $^{19}$F NMR δ -66.99 (s). **Ethyl 3-(*N*-4-pyridylmethylidene)amino-4,4,4-trifluorobutyrate (15a)**: 13%, $R_f$ = 0.36. $^1$H NMR δ 1.21 (t, 3H, $J$ = 7.2 Hz), 2.92 (m, 2H), 4.11 (m, 2H), 4.29 (m, 1H), 7.63-7.65 (m, 2H), 8.43 (s, 1H), 8.72-8.74 (m, 2H); $^{19}$F NMR δ -75.49 (d, $J_{HF}$ = 6.8 Hz); $^{13}$C NMR δ 14.20 (s), 34.23 (q, $J_{CF}$ = 1.7 Hz), 61.31 (s), 67.81 (q, $J_{CF}$ = 29.11 Hz), 122.40 (s), 124.00 (q, $J_{CF}$ = 280.0 Hz), 141.75 (s), 150.66 (s), 165.73 (s), 169.67 (s). Anal. Calcd for $C_{12}H_{13}F_3N_2O_2$: C, 52.56; H, 4.78; N, 10.22. Found: C, 52.34; H, 4.73; N, 10.05.

Treatment of the mixture (10/1) of **13a/15a** with TEA, as described for **7b**, resulted in the formation of **15a** as an individual product isolated by column chromatography on $SiO_2$ in 86% yield.

**Ethyl 3-*N*-(3-pyridylmethyl)amino-4,4,4-trifluorocrotonate (13b)**: 76.5%, $R_f$ 0.40 (ethyl acetate/hexane as 1/1). $^1$H NMR δ 1.27 (t, 3H, $J$ = 7.2 Hz), 4.15 (q, 2H, $J$ = 7.2 Hz), 4.50 (m, 2H), 5.22 (s, 1H), 7.28-7.33 (m, 1H), 7.62-7.66 (m, 1H), 8.48 (br.m, 1H), 8.56-8.58 (m, 2H); $^{19}$F NMR δ -66.99 (s, 3F); $^{13}$C NMR δ 14.38 (s), 45.68 (q, $J_{CF}$ = 2.9 Hz), 60.05 (s), 86.60 (q, $J_{CF}$ = 5.7 Hz), 122.18 (q, $J_{CF}$ = 276.8 Hz), 123.80 (s), 133.47 (s), 134.92 (s), 148.00 (q, $J_{CF}$ = 31.1 Hz), 148.97 (s), 149.44 (s), 169.84 (s). Anal. Calcd for $C_{12}H_{13}F_3N_2O_2$: C, 52.56; H, 4.78; N, 10.22. Found: C, 52.44; H, 4.75; N, 9.98.

For the isomerization of **13b** to **15b** the procedure described for **7b** was followed. **Ethyl 3-(*N*-3-pyridylmethylidene)amino-4,4,4-trifluorobutyrate (15b)**: 91%, $R_f$ 0.42 (ethyl acetate/hexane as 1/1). $^1$H NMR δ 1.20 (t, 3H, $J$ = 7.2 Hz), 2.93 (m, 2H), 4.13 (m, 2H), 4.28 (m, 1H), 7.30-7.68 (m, 2H), 8.06-8.13 (m, 1H), 8.65-8.75 (m, 2H); $^{19}$F NMR δ -75.55 (d, 3F, $J_{HF}$ = 6.8 Hz). Anal. Calcd for $C_{12}H_{13}F_3N_2O_2$: C, 52.56; H, 4.78; N, 10.22. Found: C, 52.50; H, 4.76; N, 10.18.

## References

1 Braunstein, A.E.; Kritsmann, M.G. *Biochimiya* **1937**, *2*, 242, 859.

2 (a) Greenstein, J.P.; Winitz, M. *Chemistry of the Amino Acids*; Krieger Publishing Company: Malabar, Florida, 1984 (reprint edition); Vol. 1, Chapter 6, pp 569-687. (b) Snell, E.E. In *Chemical and Biological Aspects of Pyridoxal Catalysis*; Fasella, P.M., Braunstein, A.E., Rossi-Fanelli, A., Eds.; Macmillan: New York, 1963; pp 1-12. (c) *Pyridoxal Catalysis: Enzymes and Model Systems*; Snell, E.E., Braunstein, A.E., Severin, E.S., Torchinsky, Yu.M., Eds.; Interscience: New York, 1968. (d) Jencks, W.P. *Catalysis in Chemistry and Enzymology*, McGraw-Hill: New York, 1969; pp 143-145. (e) Guirard, B.M.; Snell, E.E. In *Comprehensive Biochemistry*; Florkin, M., Stotz, E.H., Eds.; Elsevier: New York, 1964; Vol. 15, Chapter 5. (f) Bruice, T.C.; Benkovic, S.J. *Bioorganic Mechanisms*; W.A.Benjamin: New York: 1966; Vol. 2, Chapter 8.

3 For reviews on reductive aminations see: (a) Emerson, W.S. *Organic Reactions*, Wiley: New York, 1948; Vol.14, Chapter 3. (b) Gibson, M.S. *The Chemistry of the Amino Group*; Patai, S., Ed.; Interscience Publishers: New York, 1968. (c) Dayagi, S.; Degani, Y. *The Chemistry of the Carbon-Nitrogen Double Bond*; Patai, S., Ed.; Wiley: New York, 1970. (d) Lane, C.F. *Synthesis* **1975**, 135. (e) Gribble, G.W.; Jasinski, J.M.; Pellicone, J.T.; Panetta, J.A. *Synthesis* **1978**, 766. (f) Hutchins, R. O.; Natale, N. *Org. Prep. Proced. Int.* **1979**, *11* (5), 20. For publications: (g) Barney, C.L.; Huber, E.W.; McCarthy, J.R. *Tetrahedron Lett.* **1990**, *31*, 5547. (h) Love, B.E.; Ren, J. *J. Org. Chem.* **1993**, *58*, 5556. (i) Abdel-Magid, A.; Carson, K.G.; Harris, B.D.; Maryanoff, C.A.; Shah, R.D. *J. Org. Chem.* **1996**, *61*, 3849.

4 (a) Layer, R.W. *Chem. Rev.* **1963**, 489. (b) Ingold, C.K.; Shoppee, C.W. *J. Chem. Soc.* **1929**, 1199. (c) Shoppee, C.W. *J. Chem. Soc.* **1931**, 1225. (d) Baddar, F.G. *J. Chem. Soc.* **1950**, 136. (e) Baddar, F.G.; Iskander, Z. *J. Chem. Soc.* **1954**, 203. (f) Baddar, F.G.; Iskander, Z. *J. Chem. Soc.* **1954**, 209.

(g) Witkop, B.; Beiler, T.W. *J. Am. Chem. Soc.* **1954**, *76*, 5589. (h) Cram, D.J.; Guthrie, R.D. *J. Am. Chem. Soc.* **1965**, *87*, 397. (i) Guthrie, R.D.; Jaeger, D.A.; Meister, W.; Cram, D.J. *J. Am. Chem. Soc.* **1971**, *93*, 5137. (j) Jaeger, D.A.; Cram, D.J. *J. Am. Chem. Soc.* **1971**, *93*, 5153. (k) Smith, P.A.S.; Dang, C.V. *J. Org. Chem.* **1976**, *41*, 2013. (l) Jaeger, D.A.; Broadhurst, M.D.; Cram, D.J. *J. Am. Chem. Soc.* **1979**, *101*, 717.

5 Some progress was achieved with application of synthetic pyridoxamine analogs for asymmetric synthesis of α-amino acids in aqueous medium and in the presence of metal ions. (a) Williams, R.M. *Synthesis of Optically Active α-Amino Acids*; in *Organic Chemistry Series*; Vol. 7, Baldwin, J.E., Magnus, P.D., Eds.; Pergamon Press: Oxford, 1989, Chapter 8. (b) Kuzuhara, H.; Ando, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1925; and papers cited therein.

6 (a) Soloshonok, V.A.; Yagupol'skii, Yu.L.; Gerus, I.I.; Kukhar, V.P. *Zh. Org. Khim.* **1988**, *24*, 993; *Chem. Abst.* **1989**, *110*, 134824. (b) Kukhar, V.P.; Soloshonok, V.A.; Galushko, S.V.; Rozhenko, A.B. *Dokl. Akad. Nauk SSSR* **1990**, *310*, 886; *Chem. Abstr.* **1991**, *113*, 78920w. (c) Soloshonok, V.A.; Kirilenko, A.G.; Kukhar, V.P.; Resnati, G. *Tetrahedron Lett.* **1994**, *35*, 3119. (d) Ono, T.; Kukhar, V.P.; Soloshonok, V.A. *J. Org. Chem.* **1996**, *61*, in press.

7 (a) Soloshonok, V.A.; Yagupol'skii, Y.L.; Kukhar, V.P. *Zh. Org. Khim.* **1988**, *24*, 1638; *Chem. Abstr.* **1989**, *110*, 154827b. (b) Khotkevich, A.B.; Soloshonok, V.A.; Yagupol'skii, Y.L. *Zh. Obshch. Khim.* **1990**, *60*, 1005; *Chem. Abstr.* **1991**, *113*, 171274y. (c) Soloshonok, V.A.; Kirilenko, A.G.; Kukhar, V.P.; Resnati, G. *Tetrahedron Lett.* **1993**, *34*, 3621. (d) Soloshonok, V.A.; Kirilenko, A.G.; Galushko, S.V.; Kukhar, V.P. *Tetrahedron Lett.* **1994**, *35*, 5063. (e) Soloshonok, V.A.; Kirilenko, A.G.; Fokina, N.A.; Shishkina, I.P.; Galushko, S.V.; Kukhar, V.P.; Svedas, V.K.; Kozlova, E.V. *Tetrahedron: Asymmetry* **1994**, *5*, 1119. (f) Soloshonok, V.A.; Kirilenko, A.G.; Fokina, N.A.; Galushko, S.V.; Kukhar, V.P.; Svedas, V.K.; Resnati, G. *Tetrahedron: Asymmetry* **1994**, *5*, 1225. (g) Soloshonok, V.A.; Kukhar, V.P. *Tetrahedron* **1996**, *52*, 6953.

8 For general discussion of biological activity and importance of fluorinated amino compounds see: (a) Welch, J. T.; Eswarakrischnan, S. *Fluorine in Bioorganic Chemistry*; Wiley: New York, 1991. (b) *Selective Fluorination in Organic and Bioorganic Chemistry*; Welch, J. T., Ed.; American Chemical Society: Washington, 1991. (c) *Biomedicinal Aspects of Fluorine Chemistry*; Filler, R.; Kobayashi, Y., Eds.; Kodansha LTD: Tokyo, Elsevier: Amsterdam - New York - Oxford, 1982. (d) Sieler, M.; Jung, M. J.; Koch-Waser, *Enzyme-Activated Irreversible Inhibitors*; Elsevier: Amsterdam, 1978. (e) *Fluorine-Containing Amino Acids: Synthesis and Properties;* Kukhar, V.P.; Soloshonok, V.A., Eds.; Wiley: Chichester, 1994. (f) *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R.E.; Smart, B.E.; Tatlow, J.C., Eds.; Plenum Press: New York, 1994. (g) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123; and references cited therein.

9 Preliminary communication: (b) Soloshonok, V.A.; Ono, T. *SYNLETT* **1996**, in press.

10 Yagupol'skii, L.M.; Il'chenko, A.Y.; Kondratenko, N.V. *Russ. Chem. Rev.* **1974**, *43*, 32.

11 Harada, K. In *Chemistry of the Carbon-Nitrogen Double Bond*; Patai, S., Ed.; Interscience: London, 1970; pp 69-147.

12 The steric effect of *o*-methoxy group in **2d** should also be taken into account.

13 Reutov, O.A.; Beletskaya, I.P.; Butin, K.P. *CH-Acids*; Pergamon: Oxford, 1978.

14 For most recent reviews on β-amino acids see: *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E. Ed.; VCH Publisher: New York, scheduled to appear in 1996. For general reviews on fluorine-containing amino acids see ref. 8e

15 In addition to ref. 7, for biocatalytic preparation of enantiomerically pure fluorinated β-amino acids see: (a) Soloshonok, V.A.; Svedas, V.K.; Kukhar, V.P.; Kirilenko, A.G.; Rybakova, A.V.; Solodenko, V.A.; Fokina, N.A.; Kogut, O.V.; Galaev, I.Y.; Kozlova, E.V.; Shishkina, I.P.; Galushko, S.V. *SYNLETT* **1993**, 339. (b) Soloshonok, V.A. in *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E. Ed.; VCH Publisher: New York, scheduled to appear in 1996.

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