Tetrahedron 64 (2008) 11706–11712

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

The Ugi reaction with CF_3-carbonyl compounds: effective synthesis of α-trifluoromethyl amino acid derivatives

Anton V. Gulevich [a], Nikolay E. Shevchenko [a], Elisabeth S. Balenkova [a], Gerd-Volker Röschenthaler [b,*], Valentine G. Nenajdenko [a,*]

[a] Department of Chemistry, Moscow State University 119991, Leninskije Gory, Moscow, Russia
[b] Institute of Inorganic and Physical Chemistry, University of Bremen, 28334 Leobener Str., Bremen, Germany

ARTICLE INFO

Article history:
Received 10 July 2008
Received in revised form
16 September 2008
Accepted 2 October 2008
Available online 10 October 2008

Keywords:
Ugi Reaction
Fluoral
Dipeptides
Opine
Fluorine chemistry

ABSTRACT

The Ugi reaction with CF_3-carbonyl compounds is described in detail. The method is efficient for the multicomponent preparation of α-trifluoromethyl (Tfm) amino acids, α-Tfm containing dipeptides, and iminodicarboxylic acids. In addition, the first protected CF_3-opine derivative was prepared. The scope, limitations, and stereochemistry of the approach are discussed.

1. Introduction

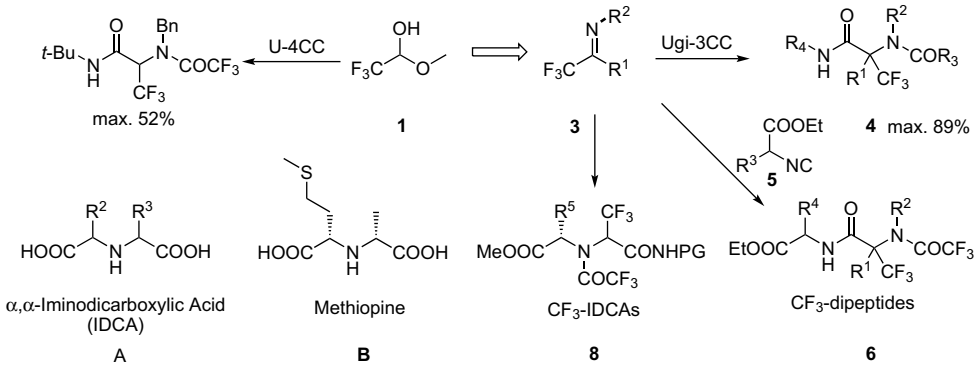
The Ugi multicomponent reaction (U-MCR) has attracted considerable interest owing to its exceptional synthetic efficiency and extensive diversity-generating ability.[1] The development of new types of components can increase the synthetic potential of the reaction. Herein we focus our attention on polyfluorocarbonyl compounds possessing high carbonyl activity and other unique properties.[2] The fluorine-modified Ugi reaction can result in important fluorine-containing compounds, especially derivatives of α-CF_3 amino acids (α-Tfm Aas), which could become interesting candidates for combinatorial chemistry to generate libraries of trifluoromethyl peptides and peptide mimetics. Fluorinated amino acids and their small peptides have found a wide range of applications in enzymology, pharmaceutical, medicinal, and agricultural chemistry.[3] α-Tfm Aas attract considerable interest in modern peptide chemistry due to the unique stereoelectronic properties of the trifluoromethyl group.[4] CF_3-containig peptides can be very effective peptidomimetics, for example, mimics of natural peptides or micromolecular inhibitors of some matrix metalloproteinases.[5] Also, the α-Tfm group strongly effects the proteolytic stability of peptides and their interaction with enzyme or receptor subsites.[6]

Usually, the preparation of polyfluorinated peptides is based on the condensation of the corresponding amino acids.[7] However, effective noncondensation-type synthesis of trifluoroalanine dipeptides has also been developed.[8] Isocyanide-based approaches to α-Tfm peptides have been described. As an example, α-CF_3-substituted dipeptide building blocks can be obtained by a [4+1]-cycloaddition of hexafluoroacetone or trifluoropyruvate derived *N*-acylimines and isocyanoacetic acid derivatives with subsequent acidic hydrolysis of the cycloadducts.[9] The Ugi reaction with CF_3-substituted isocyanides or CF_3-carboxylic acid was also used for the multicomponent preparation of α-Tfm alanine peptides.[10] One example of the Ugi reaction with trifluoroacetaldehyde was reported in 2007 but, in this paper, there was no isolated products, spectroscopic data, or complete experimental procedures. The authors only measured the anti-microbial activity but no evidence of the Ugi reaction with CF_3CHO was given.[11] Therefore, the multicomponent Ugi reaction involving CF_3-carbonyl compounds or imines is still unexplored.

It is well-known that polyfluorocarbonyl compounds differ from non-fluorinated analogs in carbonyl activity and other properties.[4] We supposed that CF_3-carbonyl compounds could be

* Corresponding authors. Tel.: +49 (0)421 218 2493; fax: +49 (0)421 218 4267 (G.-V.R.); tel.: +7 495 939 2276; fax: +7 495 932 8846 (V.G.N.).
E-mail addresses: gvr@chemie.uni-bremen.de (G.-V. Röschenthaler), nen@acylium.chem.msu.ru (V.G. Nenajdenko).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.10.004



Scheme 1. The Ugi reaction with CF_3-carbonyl compounds.

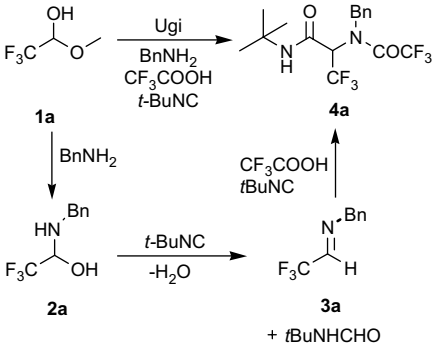
interesting for the Ugi reaction. In this paper, we report the Ugi reaction with polyfluorocarbonyl compounds as a new approach to α-Tfm amino acids derivatives, dipeptides, and iminodicarboxylic acids (Scheme 1).

2. Results and discussions

Trifluoroacetaldehyde (fluoral) methylhemiacetal **1a** is the most convenient and commercially available form of gaseous trifluoroacetaldehyde (bp −18.8 to −17.5 °C). We have found that **1a** reacts directly in the Ugi four component condensation (U-4CC) with benzylamine, CF_3COOH, and *tert*-butyl isocyanide, but the expected product **4a** was formed in 21% yield only (Table 1). This fact can be explained by the ability of trifluoroacetaldehyde to form a stable hemiaminal **2a**.[12] *tert*-Butyl isocyanide is supposed to be both the isocyanide component and dehydrating agent.[13] Indeed, using 2 and 3 equiv of isocyanide slightly increased the yield of **4a** up to 28 and 34% correspondingly.

We have investigated several dehydrating agents for promotion of the reaction, and MS 4 Å was found to be the most effective, giving the target molecule **4a** in 52% yield. Other CF_3-carbonyl compounds namely trifluoroacetone and trifluoroacetophenone form the products in yields not exceeding 50% even with MS 4 Å promotion.

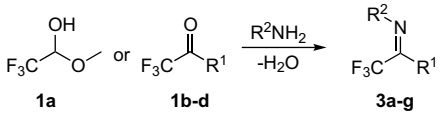
Table 1
The Ugi reaction with fluoral methylhemiacetal



Entry	Conditions[a]	Yield (%)
1	CF_3COOH (1 equiv), *t*-BuNC (1 equiv)	21
2	CF_3COOH (1 equiv), *t*-BuNC (2 equiv)	28
3	CF_3COOH (1 equiv), *t*-BuNC (3 equiv)	34
4	$(CF_3CO)_2O$ (1 equiv), *t*-BuNC (2 equiv)	39
5	CF_3COOH (1 equiv), *t*-BuNC (1 equiv), $Ti(i\text{-}PrO)_4$	15
6	CF_3COOH (1 equiv), *t*-BuNC (1 equiv), MS 4 Å	52

[a] Compound **1a** (1 equiv), $BnNH_2$ (1 equiv), CH_2Cl_2, rt, 0.1 M.

Table 2
Synthesis of CF_3-imines



Entry	R^1	R^2	Product **3**	Yield (%)
1[a]	H	Bn	**3a**	50
2[a]	H	(*S*)-Me(Ph)CH	**3b**	51
3[b]	CH_3	*i*-Pr	**3c**	83
4[b]	CH_3	Bn	**3d**	85
5[c]	Ph	Bn	**3e**	93
6[d]	CF_3	4-$MeOC_6H_4$	**3f**	77
7[d]	CF_3	$BnCH_2$	**3g**	81

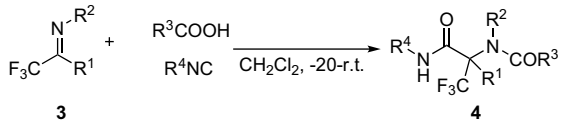
[a] PhMe/TsOH (cat), reflux.
[b] $TiCl_4/NEt_3/CH_2Cl_2$.
[c] C_6H_6/AcOH, reflux with Dean–Stark apparatus.
[d] $POCl_3/NEt_3/CH_2Cl_2$.

To increase yields, pure imines were prepared according to the modified literature procedures [14] (Table 2) and tested in the Ugi reaction conditions. Using a model experiment (entry 1, Table 3; Scheme 2), optimal conditions were found to be CH_2Cl_2, 0.1 M, −20 °C to rt, 12 h.

Only strong acids such as $CH_2ClCOOH$ (pK_a 2.85), $CHCl_2COOH$ (pK_a 1.48), CCl_3COOH (pK_a 0.7), and CF_3COOH (pK_a 0.23) gave the desired Ugi products. Weaker acids such as 4-$NO_2C_6H_4COOH$ (pK_a 3.44), PhCOOH (pK_a 4.2), and AcOH (pK_a 4.75) reacted with no success. This fact can be explained by the lower basicity of the imines

Table 3
Synthesis of α-Tfm amino acids derivatives via Scheme 2

Entry	Imine	R^1	R^2	R^3	R^4	Product	Yield (%)
1	**3a**	H	Bn	CF_3	*t*-Bu	**4a**	89
2	**3a**	H	Bn	CH_2Cl	4-$MeOC_6H_4CH_2$	**4b**	60
3	**3a**	H	Bn	$CHCl_2$	4-$MeOC_6H_4CH_2$	**4c**	58
4	**3a**	H	Bn	CCl_3	Bn	**4d**	75
5	**3a**	H	Bn	CF_3	Bn	**4e**	88
6	**3c**	CH_3	*i*-Pr	CF_3	Bn	**4f**	64
7	**3c**	CH_3	*i*-Pr	CCl_3	Bn	**4g**	40
8	**3c**	CH_3	*i*-Pr	CF_3	4-MeC_6H_4	**4h**	57
9	**3d**	CH_3	Bn	CF_3	Bn	**4i**	70
10	**3d**	CH_3	Bn	CF_3	*t*-Bu	**4j**	73
11	**3e**	Ph	Bn	CF_3	Bn	**4k**	45
12	**3e**	Ph	Bn	CF_3	*t*-Bu	—	—
13	**3f**	CF_3	4-$MeOC_6H_4$	CF_3	Bn	—	—
14	**3g**	CF_3	CH_2CH_2Ph	CF_3	Bn	—	—



Scheme 2. Synthesis of α-Tfm amino acids.

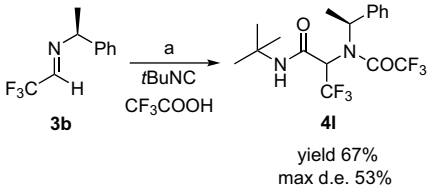
due to the strong electron withdrawing effect of the CF_3 moiety. Trifluoroacetic acid is the reagent of choice for further investigations.

Imines of fluoral **3a** and trifluoroacetones **3c**,**d** reacted smoothly (entries 1–10, Table 3). Trifluoroacetophenone imine **3e** reacted worse (entry 9), possibly, due to lower electrophilicity of the imine group and its sterically hindered structure. Unfortunately, the most bulky imines of hexafluoroacetone containing aryl **3f** or alkyl **3g** substituents did not give Ugi products at all. In general, the structure of the isocyanide has no serious effect on the reaction, except for the reaction of trifluoroacetone imine **3e** with *t*-BuNC (Table 3, entry 12). Aliphatic, aromatic, and sterically hindered isocyanides react straightforwardly. Consequently, we have demonstrated that imines **3** are more effective starting materials for the Ugi reaction than CF_3-carbonyl compounds. Imines **3a**–**e** gave several derivatives of trifluoroalanine, α-Tfm alanine and α-Tfm phenylalanine in good yields using this very simple procedure.

In the case of isocyanoacetic acid derivatives **5** this method opens a new multicomponent one-step route to orthogonally protected semi-natural dipeptides containing natural amino acid residue and α-Tfm substituted amino acid fragments (Scheme 3). It is notable that the Ugi multicomponent reaction with CF_3-imines is a general approach to construct a broad variety of α-Tfm dipeptides. All compounds were isolated in good yields as a mixture of diastereomers (~1:1), this is usual for Ugi reaction. [15]

Asymmetric multicomponent reactions (AMCRs) are a topical field of modern stereoselective synthesis.[15] Chiral amines (the most common is commercially available α-methylbenzylamine) were used to control the formation of a new stereogenic center in the Ugi-MCR.[16] Usually no high stereoselectivity is observed in the Ugi reaction (3CC or 4CC modification) with α-methylbenzylamine (max de is 60%).[15]

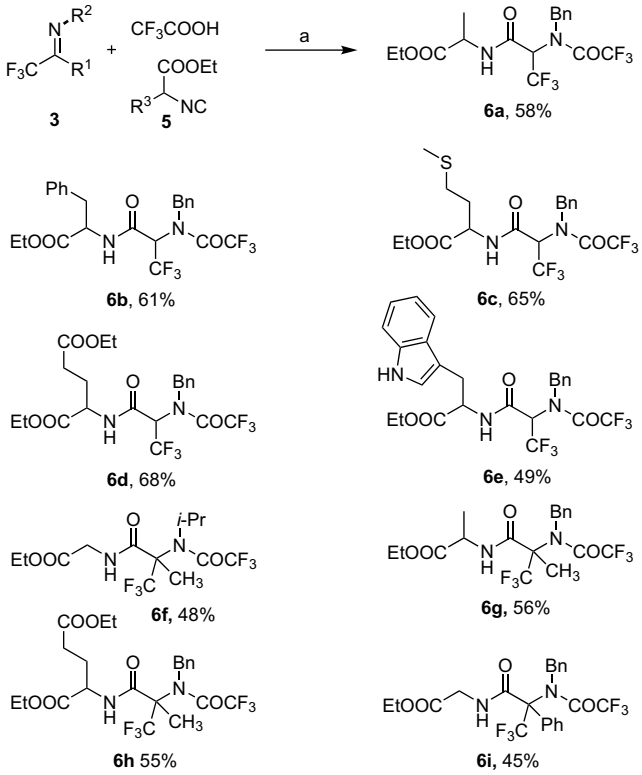
We have investigated the stereochemistry of the reaction using chiral imine **3b** and the bulky *tert*-butyl isocyanide (Scheme 4). Under suitable conditions (temperature, solvents), the stereoselectivity of the fluoro-modified reaction is comparable with the selectivity of the standard Ugi reaction without fluorinated substrate. Trifluoroalanine derivative **4l** was obtained in 67% yield with de up to 53%. Further development in this direction is under investigation.



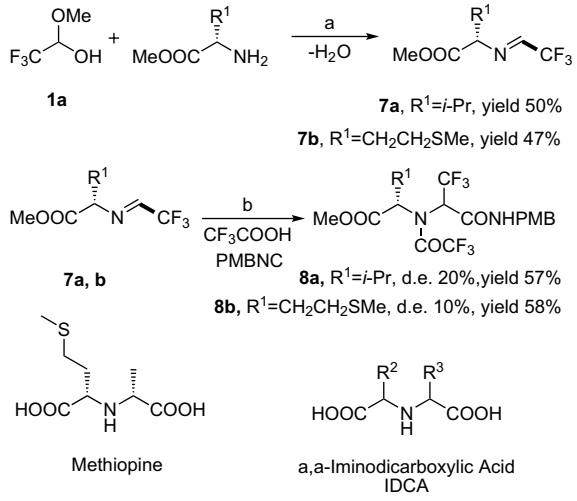
Scheme 4. Diastereoselective modification of the reaction: (a) MeOH, 0.1 M, −20 °C, 24 h.

Esters of α-aminoacids can be conveniently used as chiral auxiliaries since they are available in both enantiomeric forms. Moreover, in several synthetic applications in the field of peptidomimetics their structure may also be retained.[1] However, diastereomeric excesses of the reaction are often only moderate and strongly influenced by the structure of the side chain of the α-amino acid.[17]

The previously unknown imine of fluoral and aminoacid (L-valine[18]) **7a** was synthesized and introduced in the Ugi reaction with 4-methoxybenzylisocyanide (PMBNC). Unfortunately the maximum de was only 20% (Scheme 5). Product **8a** is a fluorinated orthogonally protected analog of α,α-iminodicarboxylic acid (IDCA). IDCAs and their derivatives can be isolated from several types of poisonous mushrooms.[19] IDCA is structural fragment of a series of synthetic dipeptides, which have been demonstrated to be potent pharmaceutically active ACE-inhibitors [20] and inhibitors of some other enzymes.[21] IDCA is a framework of opines, specific markers of crown gall tumors produced by the parasitic bacterium *Agrobacterium tumefaciens*.[22] As an example, fluorinated orthogonally protected methiopine analog **8b** was prepared in good yield (Scheme 5).



Scheme 3. Synthesis of α-Tfm dipeptides: (a) CH_2Cl_2, −20 °C to rt.



Scheme 5. Synthesis of IDCAs: (a) Toluene, reflux; (b) CH_2Cl_2: 0.1 M, −20 °C, 24 h.

3. Conclusion

In conclusion, the Ugi reaction with CF_3-carbonyl compounds was described. We have investigated the reaction of fluoral hemiacetal in U-4CC conditions and found that MS 4 Å can promote the reaction. It was found that CF_3-imines are more effective precursors in comparison with CF_3-carbonyl compounds. The method is simple and an efficient approach to α-Tfm amino acids and orthogonally protected semi-natural CF_3-containing dipeptides and CF_3-iminodicarboxylic acids. Also the first CF_3-opine derivative was prepared. We believe that our research can open a new frontier of multicomponent chemistry, efficient for the synthesis of fluorine-containing compounds.

4. Experimental section

4.1. General procedure for Ugi-4CC

Benzylamine (1 mmol) and trifluoroacetaldehyde methylhemiacetal **1a** were dissolved in CH_2Cl_2 (10 mL) and CF_3COOH (1 mmol) and *tert*-Butyl isocyanide was added at 20 °C. The mixture was stirred for 12 h and treated with a mixture of EtOH/HCl(aq) (10:1, 0.5 mL) to remove isocyanide remains. The solvent was removed in vacuo and the residue was purified by column chromatography (hexanes/ethyl acetate 4:1).

4.2. MS 4 Å promoted Ugi-4CC reaction

Benzylamine (1 mmol) and trifluoroacetaldehyde methylhemiacetal **1a** were dissolved in CH_2Cl_2 (10 mL). MS 4 Å (400 mg), CF_3COOH (1 mmol), and *tert*-Butyl isocyanide were added at 20 °C. The mixture was stirred for 12 h and treated with a mixture of EtOH/HCl(aq) (10:1, 0.5 mL) to remove isocyanide remains. The solvents were removed in vacuo and the residue was purified by column chromatography (hexanes/ethyl acetate 4:1).

4.2.1. N^2-Benzyl-N^1-(tert-butyl)-3,3,3-trifluoro-N^2-(trifluoroacetyl)alaninamide **4a**

Yield 89% (342 mg), white solid, mp 71–73 °C. R_f (hexanes/ethyl acetate 3:1) 0.7; IR (Nujol, cm^{-1}) 3351 (NH), 1703 (CONH), 1673 ($COCF_3$); ^1H NMR ($CDCl_3$, 200 MHz): 1.19 (s, 9H), 4.70–5.13 (m, 3H), 5.7 (br s, 1H), 7.32–7.50 (m, 5H); ^{19}F NMR ($CDCl_3$, 188 MHz): −69.4 (s, 0.73×3F), −68.4 (s, 0.27×3F), −67.7 (s, 3F); ^{13}C NMR ($CDCl_3$, 50 MHz): 28.0, 50.7, 52.4, 59.0 (q, *J* 31.1 Hz), 116.1 (q, *J* 288.3 Hz, CF_3), 123.5 (q, *J* 285.4 Hz, CF_3), 127.0, 128.2, 128.9, 134.6, 159.0 (q, *J* 36.7 Hz), 159.5; HRMS (EI) calculated for $C_{16}H_{18}F_6N_2O_2$ 384.1273; found 384.1264.

4.3. General procedure for Ugi-3CC

Imine **3** or **7** (1 mmol) was dissolved in CH_2Cl_2 (10 mL) and carboxylic acid (1 mmol) and isocyanide was added at −20 °C. The mixture was allowed to warm up to ambient temperature and stirred for 12 h and treated with a mixture of EtOH/HCl(aq) (10:1, 0.2 mL) to remove isocyanide remains. The solvents were removed in vacuo and the residue was purified by column chromatography.

4.3.1. N^2-Benzyl-N^2-(chloroacetyl)-3,3,3-trifluoro-N^1-(4-methoxybenzyl)alaninamide **4b**

Yield 60% (257 mg), colorless oil. R_f (hexanes/ethyl acetate 2:1) 0.7; IR (film, cm^{-1}) 2870, 1660; ^1H NMR ($CDCl_3$, 400 MHz): 3.76 (s, 3H), 3.80–3.85 (m, 1H), 4.10–4.23 (m, 1H), 4.25–4.30 (m, 2H), 4.83 (d, *J* 17.9 Hz, 1H), 5.18 (d, *J* 17.9 Hz, 1H), 6.13 (q, *J* 7.6 Hz, 1H), 6.77–6.86 (m, 3H), 7.10–7.15 (m, 4H), 7.27–7.32 (m, 2H), 7.8 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): 41.9, 43.2, 49.1, 55.2, 56.3 (q, *J* 30.7 Hz), 114.0, 123.0 (q, *J* 283.2 Hz), 125.4, 127.7, 128.7, 128.9, 129.2, 136.0, 159.0, 162.1, 169.9. HRMS (EI): calculated for $C_{20}H_{20}ClF_3N_2O_3$ 428.1115; found 428.1129.

4.3.2. N^2-Benzyl-N^2-(dichloroacetyl)-3,3,3-trifluoro-N^1-(4-methoxybenzyl)alaninamide **4c**

Yield 58% (268 mg), colorless oil. R_f (hexanes/ethyl acetate 2:1) 0.6; IR (Nujol, cm^{-1}) 2870, 1670; ^1H NMR ($CDCl_3$, 400 MHz): 3.77 (s, 3H), 4.30 (d, *J* 5.6 Hz, 1H), 4.48 (d, *J* 5.6 Hz, 1H), 4.94 (d, *J* 18.2 Hz), 5.23 (d, *J* 18.2 Hz), 5.96 (s, 1H), 6.0 (m, 1H), 6.80 (d, *J* 8.6 Hz), 7.13 (d, *J* 8.6 Hz, 2H), 7.27–7.40 (m, 5H), 7.5 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): 43.3, 44.2, 55.2, 57.1 (q, 32.2 Hz), 63.9, 66.3, 114.0, 122.9 (q, *J* 290.0 Hz), 125.3, 127.6, 129.2, 135.3, 136.7, 159.1, 161.7, 167.4. HRMS (EI): calculated for $C_{20}H_{19}Cl_2F_3N_2O_3$ 462.0725; found 462.0744.

4.3.3. N^1,N^2-Dibenzyl-3,3,3-trifluoro-N^2-(trichloroacetyl)-alaninamide **4d**

Yield 75% (350 mg), white solid, mp 105–108 °C. R_f (hexanes/ethyl acetate 3:1) 0.7; IR (Nujol, cm^{-1}) 3434, 1697, 1673; ^1H NMR ($CDCl_3$, 200 MHz): 4.07–4.52 (m, 3H), 4.55–5.01 (m, 1H), 5.3 (br s, 1H), 6.1 (br s, 1H), 7.18–7.55 (m, 10H); ^{19}F NMR ($CDCl_3$, 188 MHz): −65.1 (s, 3F). HRMS (EI): calculated for $C_{19}H_{16}Cl_3F_3N_2O_2$ 466.0230; found 466.0230.

4.3.4. N^1,N^2-Dibenzyl-3,3,3-trifluoro-N^2-(trifluoroacetyl)-alaninamide **4e**

Yield 88% (368 mg), white solid, mp 86–88 °C. R_f (hexanes/ethyl acetate 3:1) 0.8; IR (Nujol, cm^{-1}) 3278, 1714, 1658; ^1H NMR ($CDCl_3$, 200 MHz): 3.98–4.15 (m, 1H), 4.22–4.37 (m, 1H), 4.75–4.90 (m, 1H), 5.02–5.16 (m, 2H), 6.3 (br s, 1H), 7.10–7.40 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz): 43.9, 51.2, 59.0 (q, *J* 31.1 Hz), 116.2 (q, *J* 288.3 Hz, CF_3), 121.4 (q, *J* 284.6 Hz, CF_3), 127.3, 127.7, 127.8, 128.4, 128.8, 128.9, 133.9, 136.5, 159 (q, *J* 38.2 Hz), 160.6; ^{19}F NMR ($CDCl_3$, 188 MHz, 20 °C) −69.3 (s, 0.78×3F), −68.3 (s, 0.23×3F), −67.8 (s, 0.23×3F), −67.1 (s, 0.78×3F); HRMS calculated for $C_{19}H_{16}F_6N_2O_2$ 418.1116; found 418.1111.

It was found that ^{19}F NMR spectra of trifluoroalanine derivatives **4a**–**c** and **6a**–**e** have interesting multipets, which supposed to be signals of rotamers. We have demonstrated that multiplets disappear if the spectrum measured at 60 °C and, consequently, certain signals correspond to rotamers (See Supplementary data).

Substituted derivatives **4f**,**h** and **6f**,**h**,**i** were obtained in hydrate form. In ^{13}C NMR of these compounds the signal of $COCF_3$ (q, ∼158 ppm) group transform to the signal of $C(OH)_2CF_3$ group (q, ∼98 ppm).

4.3.5. N-Benzyl-3,3,3-trifluoro-2-[isopropyl(trifluoroacetyl)amino]-2-methylpropanamide·H_2O **4f**

Yield 64% (246 mg), white solid, mp 161–163 °C. R_f (hexanes/ethyl acetate 3:1) 0.8; IR (Nujol, cm^{-1}) 3375, 1717, 1673; ^1H NMR (CD_3OD, 400 MHz): 1.30 (d, *J* 6.8 Hz, 3H), 1.33 (d, *J* 6.8 Hz, 3H), 1.60 (9s, 3H), 3.85 (sept., *J* 6.9 Hz, 1H), 4.46 (d, *J* 16.2 Hz, 1H), 4.72 (d, *J* 16.2 Hz, 1H), 7.15–7.30 (m, 5H); ^{19}F NMR ($CDCl_3$, 188 MHz): −74.0 (s, 3F), −71.0 (s, 3F); ^{13}C NMR (CD_3OD, 100 MHz): 18.9, 23.5, 23.7, 45.4, 48.2, 67.6 (q, *J* 29.3 Hz), 97.9 (q, *J* 33.7 Hz), 123.3 (q, *J* 289.3 Hz, CF_3), 125.9 (q, *J* 287.0 Hz, CF_3), 127.7, 128.0, 129.3, 137.6, 170.9. HRMS (EI): calculated for $C_{16}H_{18}F_6N_2O_2$ 384.1273; found 384.1273.

4.3.6. N-Benzyl-3,3,3-trifluoro-2-[isopropyl(trichloroacetyl)-amino]-2-methylpropanamide **4g**

Yield 50% (216 mg), white solid, mp 126–128 °C. R_f (hexanes/ethyl acetate 3:1) 0.7; IR (Nujol, cm^{-1}) 3429, 1697, 1673; ^1H NMR ($CDCl_3$, 400 MHz): 1.51 (d, *J* 6.3 Hz, 3H), 1.62 (d, *J* 6.3 Hz, 3H), 1.98 (s, 3H), 4.38–4.43 (m, 1H), 4.58–4.64 (m, 1H), 5.11 (sept., *J* 6.3 Hz, 1H), 5.9 (br s, 1H), 7.23–7.37 (m, 5H); ^{19}F NMR ($CDCl_3$, 188 MHz): −68.6 (s, 3F); ^{13}C NMR (CD_3OD, 100 MHz): 19.8, 21.9, 44.4, 52.1, 71.3 (q, *J*

27.8 Hz), 94.3, 125.1 (q, *J* 288.1 Hz), 127.7, 127.8, 128.8, 137.6, 162.1, 167.0. HRMS (CI, NH_3): calculated for $C_{16}H_{18}Cl_3F_3N_2O_2$ 432.0386; found 432.0384.

4.3.7. 3,3,3-Trifluoro-2-[isopropyl(trifluoroacetyl)amino]-2-methyl-N-(4-methylphenyl)propanamide·H_2O **4h**

Yield 57% (219 mg), white solid, mp 143–145 °C. R_f (hexanes/ethyl acetate 3:1) 0.8; IR (Nujol, cm^{-1}) 3347, 1702; ^1H NMR (DMSO-d_6, 400 MHz): 1.30 (d, *J* 6.8 Hz, 6H), 1.73 (s, 3H), 2.32 (s, 3H), 3.86 (sept., *J* 6.8 Hz, 1H), 7.17 (d, *J* 8.1 Hz, 2H), 7.26 (d, *J* 8.1 Hz, 2H), 8.18 (s, 1H); ^{19}F NMR ($CDCl_3$, 188 MHz): −63.4 (s, 3F), −70.7 (s, 3F); ^{13}C NMR (DMSO-d_6, 100 MHz): 18.5, 20.6, 22.9, 23.3, 46.3, 65.7 (q, *J* 27.8 Hz), 97.4 (q, *J* 32.9 Hz), 121.8 (q, *J* 290.6 Hz), 124.5 (q, *J* 288.8 Hz), 128.5, 129.4, 131.0, 138.2, 167.0. HRMS (EI): calculated for $C_{16}H_{18}F_6N_2O_2$ 384.1272; found 384.1254.

4.3.8. N-Benzyl-2-[benzyl(trifluoroacetyl)amino]-3,3,3-trifluoro-2-methylpropanamide **4i**

Yield 70% (302 mg), white solid, mp 125–127 °C. R_f (hexanes/ethyl acetate 3:1) 0.8; IR (Nujol, cm^{-1}) 3372, 1714, 1673; ^1H NMR ($CDCl_3$, 200 MHz): 1.62 (s, 3H), 4.90 (d, *J* 4.9 Hz, 2H), 4.90 (AB-system, *J* 19.1 Hz, 2H), 6.0 (br s, 1H), 7.20–7.55 (m, 10H); ^{19}F NMR ($CDCl_3$, 188 MHz): −71.3 (3F, s), −69.3 (3F, s); ^{13}C NMR ($CDCl_3$, 50 MHz): 19.1, 44.3, 48.6, 68.1 (q, *J* 26.9 Hz), 116.0 (q, *J* 288.3 Hz), 125.4 (q, *J* 289.7 Hz), 125.6, 127.7, 127.8, 128.8, 136.9, 137.1, 158.4 (q, *J* 36.7 Hz), 165.6. HRMS (EI): calculated for $C_{20}H_{18}F_6N_2O_2$ 432.1272; found 432.1283.

4.3.9. 2-[Benzyl(trifluoroacetyl)amino]-N-(tert-butyl)-3,3,3-trifluoro-2-methylpropanamide **4j**

Yield 73% (290 mg), colorless oil. R_f (hexanes/ethyl acetate 3:1) 0.8; IR (film, cm^{-1}) 3480, 1716, 1697; ^1H NMR ($CDCl_3$, 200 MHz): 1.35 (s, 9H), 1.52 (s, 3H), 4.60 (d, *J* 19.1 Hz, 1H), 5.03 (d, *J* 19.1 Hz, 1H), 5.5 (br s, 1H), 7.21–7.53 (m, 5H); ^{19}F NMR ($CDCl_3$, 188 MHz): −70.8 (s, 3F), −68.8 (s, 3F); ^{13}C NMR ($CDCl_3$, 50 MHz): 19.1, 28.4, 48.6, 52.2, 68.5 (q, *J* 26.85 Hz), 116.1 (q, *J* 288.3 Hz, CF_3), 125.6 (q, *J* 288.3 Hz, CF_3), 125.7, 127.6, 128.9, 137.1, 158.3 (q, *J* 36.7 Hz), 164.2. HRMS (EI): calculated for $C_{17}H_{20}F_6N_2O_2$ 398.1429; found 398.1428.

4.3.10. N^1,N^2-Dibenzyl-3,3,3-trifluoro-2-phenyl-N^2-(trifluoroacetyl)alaninamide **4k**

Yield 40% (200 mg), white solid, mp 124–126 °C. R_f (hexanes/ethyl acetate 3:1) 0.8; IR (Nujol, cm^{-1}) 3347, 1744, 1698; ^1H NMR ($CDCl_3$, 200 MHz): 3.87 (d, *J* 16.1 Hz, 1H), 4.39–4.62 (m, 3H), 4.98 (d, *J* 15.1 Hz, 1H), 7.02–7.48 (m, 15H); ^{19}F NMR ($CDCl_3$, 188 MHz): −76.3 (3F, s), −67.5 (3F, s); ^{13}C NMR ($CDCl_3$, 50 MHz): 44.9, 47.9, 72.5, 97.3 (q, *J* 32.9 Hz), 124.5 (q, *J* 290.6 Hz, CF_3), 124.9 (q, *J* 292.1 Hz, CF_3), 127.4, 128.0, 128.1, 128.2, 128.3, 128.5, 128.7, 129.1, 132.1, 136.1, 136.4, 167.2. HRMS (EI): calculated for $C_{25}H_{20}F_6N_2O_2$ 494.1429; found 494.1425.

4.3.11. N^1-(tert-Butyl)-3,3,3-trifluoro-N^2-[(1S)-1-phenylethyl]-N^2-(trifluoroacetyl)alaninamide **4l** *(mixture of diastereomers, ~3.35:1)*

Yield 67% (270 mg), colorless oil. R_f (hexanes/ethyl acetate 4:1) 0.6; IR (film, cm^{-1}) 3465, 1739, 1720; ^1H NMR ($CDCl_3$, 400 MHz): 1.06 (s, 0.23×9H), 1.33 (s, 0.77×9H), 1.60–1.75 (m, 3H), 3.90–4.10 (m, 1H), 5.40–5.50 (m, 1H), 6.3 (br s, 1H), 7.28–7.45 (m, 5H); ^{19}F NMR ($CDCl_3$, 188 MHz): −68.2, −68.1 (ds, 3F), −61.8 (s, 0.77×3F), −61.7 (s, 0.23×9F). HRMS (EI): calculated for $C_{17}H_{20}F_6N_2O_2$ 398.1429; found, 398.1421.

4.3.12. Ethyl N-benzyl-3,3,3-trifluoro-N-(trifluoroacetyl)-alanylalaninate **6a** *(mixture of diastereomers, ~1:1)*

Yield 58% (250 mg), colorless oil. R_f (hexanes/ethyl acetate 3:1) 0.7; IR (film, cm^{-1}) 3450, 1729, 1700; ^1H NMR ($CDCl_3$, 200 MHz): 1.15–1.48 (m, 6H), 4.07–4.52 (m, 3H), 4.67–5.21 (m, 3H), 6.5 (br s, 1H), 7.12–7.60 (m, 5H); ^{19}F NMR ($CDCl_3$, 188 MHz): −69.4 (d, *J* 13.8 Hz, 0.76×3F), −68.3 (s, 0.33×3F), −67.9 (s, 0.12×3F), −67.5 (dd, *J* 27.6 Hz, 0.76×3F); ^{13}C NMR ($CDCl_3$, 50 MHz): 14.0, 17.4, 17.98, 48.5, 48.7, 51.05, 51.42, 58.9 (q, *J* 31.1 Hz), 61.8, 116.0 (q, *J* 288.3 Hz, CF_3), 128.6 (q, *J* 284.0 Hz, CF_3), 127.3, 127.7, 128.5, 128.9, 133.6, 134.0, 160.0, 160.1, 164.8 (m), 171.9, 172.0. Several peaks in ^{13}C NMR spectrum are duplicated. HRMS (EI): calculated for $C_{17}H_{18}F_6N_2O_4$ 428.1171; found 428.1152.

4.3.13. Ethyl N-benzyl-3,3,3-trifluoro-N-(trifluoroacetyl)-alanylphenylalaninate **6b** *(mixture of diastereomers, ~1:1)*

Yield 61% (307 mg), colorless oil. R_f (hexanes/ethyl acetate 3:1) 0.7; IR (film, cm^{-1}) 3342, 1749, 1685; ^1H NMR ($CDCl_3$, 200 MHz): 1.25 (t, *J* 7.0 Hz, 3H), 2.95–3.20 (m, 2H), 4.17 (q, *J* 7.0 Hz, 2H), 4.42–5.15 (m, 4H), 6.15–6.50 (m, 1H), 6.95–7.52 (m, 10H); ^{19}F NMR ($CDCl_3$, 188 MHz): −69.3 (d, *J* 22.4 Hz, 0.76×3F), −68.5–68.0 (m, 0.35×3F), −67.9 (s, 0.12×3F), −67.0 (dd, *J* 75.9 Hz, 0.76×3F); ^{13}C NMR ($CDCl_3$, 50 MHz): 37.3, 37.4, 51.5 (m), 53.4, 53.6, 59.3 (m), 61.8, 116.0 (q, *J* 288.5 Hz, CF_3), 129.3 (q, *J* 288.5 Hz, CF_3), 127.1, 127.3, 127.4, 128.4, 128.6, 128.8, 129.1, 129.2, 133.4, 133.6, 135.1, 135.3, 160.0, 160.3, 170.4, 170.5, 171.5 (q, *J* 7.2 Hz). Several peaks in ^{13}C NMR spectrum are duplicated. HRMS (EI): calculated for $C_{23}H_{22}F_6N_2O_4$ 504.1484; found 504.1489.

4.3.14. Ethyl N-benzyl-3,3,3-trifluoro-N-(trifluoroacetyl)-alanylmethioninate **6c** *(mixture of diastereomers, ~1:1)*

Yield 65% (320 mg), yellow oil. R_f (hexanes/ethyl acetate 3:1) 0.7; IR (film, cm^{-1}) 3345, 1687; ^1H NMR ($CDCl_3$, 200 MHz): 1.19–1.34 (m, 3H), 1.79–2.20 (m, 5H), 2.26–2.47 (m, 2H), 4.20 (d, *J* 7.3 Hz, 2H), 4.30–4.55 (m, 1H), 4.60–5.15 (m, 3H), 6.40–6.90 (m, 1H), 7.15–7.50 (m, 5H); ^{19}F NMR ($CDCl_3$, 188 MHz): −68.7 (d, *J* 7.0 Hz, 0.79×3F), −67.7–67.3 (m, 0.31×3F), −67.2 (s, 0.12×3F), −66.2 (dd, *J* 43.1 Hz, 0.79×3F); ^{13}C NMR ($CDCl_3$, 50 MHz): 14.0, 15.3, 29.3, 29.6, 30.7, 31.09, 50.1, 51.8, 52.1, 59.3 (m), 62.0, 116.0 (q, *J* 288.3 Hz, CF_3), 122.9 (q, *J* 285.6 Hz, CF_3), 127.6, 127.9, 128.8, 129.0, 129.1, 133.4, 157.7 (q, *J* 28.2 Hz), 160.3, 160.5, 170.8, 171.0. Several peaks in ^{13}C NMR spectrum are duplicated. HRMS (EI): calculated for $C_{19}H_{22}F_6N_2O_4S$ 488.1204; found 488.1211.

4.3.15. Diethyl N-benzyl-3,3,3-trifluoro-N-(trifluoroacetyl)-alanylglutamate **6d** *(mixture of diastereomers, ~1:1)*

Yield 68% (350 mg), colorless oil. R_f (hexanes/ethyl acetate 3:1) 0.6; IR (film, cm^{-1}) 3351, 1629, 1693; ^1H NMR ($CDCl_3$, 200 MHz): 1.15–1.33 (m, 6H), 1.82–2.43 (m, 4H), 4.05–4.40 (m, 5H), 4.65–5.17 (m, 3H), 6.60–7.10 (m, 1H), 7.15–7.45 (m, 5H); ^{19}F NMR ($CDCl_3$, 188 MHz): −69.3 (s, 0.74×3F), −68.5–67.5 (m, 0.31×3F), −67.2 (s, 0.53×3F), −67.0 (dd, *J* 51.7 Hz, 0.74×3F); ^{13}C NMR ($CDCl_3$, 50 MHz): 14.0, 26.2, 26.8, 29.7, 30.0, 51.5, 52.0, 52.4, 59.4 (m), 60.7, 60.9, 61.8, 61.9, 116.0 (q, *J* 288.6 Hz, CF_3), 122.7 (q, *J* 284.3 Hz, CF_3), 127.5, 127.6, 128.5, 128.9, 133.6, 133.7, 158.5 (m), 160.5, 160.7, 170.6, 170.8, 172.7, 173.1. Several peaks in ^{13}C NMR spectrum are duplicated. HRMS (EI): calculated for $C_{21}H_{24}F_6N_2O_6$ 514.1539; found 514.1529.

4.3.16. Ethyl N-benzyl-3,3,3-trifluoro-N-(trifluoroacetyl)-alanyltryptophanate **6e** *(mixture of diastereomers, ~1:1)*

Yield 49% (266 mg), yellow oil. R_f (hexanes/ethyl acetate 3:1) 0.6; IR (film, cm^{-1}) 3382, 1687; ^1H NMR ($CDCl_3$, 200 MHz): 1.10–1.30 (m, 3H), 3.15–3.35 (m, 2H), 4.00–4.20 (m, 2H), 4.40–4.55 (m, 4H), 6.22–6.47 (m, 1H), 6.90–7.55 (m, 10H), 8.00–8.20 (m, 1H); ^{19}F NMR ($CDCl_3$, 188 MHz, 20 °C): −68.6 (d, *J* 20.7 Hz, 0.74×3F), −68.0–67.3 (m, 0.51×3F), −66.2 (dd, *J* 87.9 Hz, 0.74×3F); ^{19}F NMR ($CDCl_3$, 188 MHz, 60 °C): −68.6 (s, 3F), −66.4 (s, 3F); ^{13}C NMR ($CDCl_3$, 50 MHz): 13.8, 13.9, 27.0, 51.7, 53.2, 53.4, 59.6 (m), 61.8, 109.0, 109.1, 111.3, 111.4, 116.0 (q, *J* 288.3 Hz, CF_3), 118.2, 118.3, 119.5, 122.0, 122.3, 122.8 (q, *J* 284.1 Hz, CF_3), 123.0, 127.2, 127.4, 127.6, 128.5, 128.8, 128.9, 133.3, 136.0, 136.1, 158.3 (m), 160.1, 160.6, 170.8, 170.9. Several peaks in ^{13}C NMR spectrum are duplicated. HRMS (EI): calculated for $C_{25}H_{23}F_6N_3O_4$ 543.1593; found 543.1598.

4.3.17. Ethyl N-{3,3,3-trifluoro-2-[isopropyl(trifluoroacetyl)-amino]-2-methylpropanoyl}glycinate·H_2O ***6f***

Yield 48% (150 mg), colorless oil.; R_f (hexanes/ethyl acetate 3:1) 0.6; IR (film, cm^{-1}) 3471, 1239, 1720; ^1H NMR ($CDCl_3$, 400 MHz): 1.20–1.29 (m, 6H), 1.33 (d, *J* 7.1 Hz, 3H), 1.60 (s, 3H), 3.92 (sept., *J* 7.1 Hz, 1H), 4.03 (d, *J* 17.9 Hz, 1H), 4.20 (q, *J* 7.1 Hz, 2H), 4.42 (d, *J* 17.9 Hz, 1H), 4.5 (br s, 1H); ^{19}F NMR ($CDCl_3$, 188 MHz): −79.2 (q, *J* 6.9 Hz, 0.32×3F), −78.0 (s, 0.69×3F), −75.6 (q, *J* 6.9 Hz, 0.32×3F), −74.48 (s, 0.69×3F); ^{13}C NMR ($CDCl_3$, 100 MHz): 13.8, 18.4, 21.3, 23.1, 42.2, 46.3, 62.5, 65.7 (q, *J* 27.8 Hz), 96.0 (q, *J* 33.7 Hz), 122.4 (q, *J* 292.0 Hz, CF_3), 124.3 (q, *J* 289.1 Hz, CF_3), 168.2, 169.7. HRMS (EI): calculated for $C_{13}H_{18}F_6N_2O_4$ 365.0936 (M−CH_3), 311.1219 (M−CF_3); found 365.0947 (M−CH_3), 311.1225 (M−CF_3).

4.3.18. Ethyl 2-({2-[benzyl(trifluoroacetyl)amino]-3,3,3-trifluoro-2-methylpropanoyl}amino)propanoate ***6g*** *(mixture of diastereomers, ~1:1)*

Yield 56% (250 mg), colorless oil. R_f (hexanes/ethyl acetate 3:1) 0.6; IR (film, cm^{-1}) 3322, 1727, 1708; ^1H NMR ($CDCl_3$, 200 MHz): 1.28 (t, *J* 7.1 Hz, 3H), 1.46 (t, *J* 8.5 Hz, 3H), 1.57 (s, 3H), 4.70–4.37 (m, 2H), 4.45–4.73 (m, 2H), 5.07 (d, *J* 19.1 Hz, 1H), 6.35–6.67 (m, 1H), 7.22–7.52 (m, 5H); ^{19}F NMR ($CDCl_3$, 188 MHz): −71.7, −73.7(ds, 3F), −69.4, −69.3 (ds, 3F); ^{13}C NMR ($CDCl_3$, 50 MHz): 13.9, 17.8, 18.0, 18.9, 48.6, 48.9, 61.7, 61.8, 68.0 (q, *J* 26.9), 115.9 (q, *J* 288.3 Hz, CF_3), 125.3 (dq, *J* 288.4 Hz, CF_3), 125.6, 127.6, 127.7, 128.8, 128.9, 136.8, 136.9, 158.4 (q, *J* 36.8 Hz), 164.7, 164.8, 172.4, 172.5. Several peaks in ^{13}C NMR spectrum are duplicated. HRMS (CI, NH_3): calculated for $C_{18}H_{20}F_6N_2O_4$ 442.1327; found 442.1320.

4.3.19. Diethyl N-{2-[benzyl(trifluoroacetyl)amino]-3,3,3-trifluoro-2-methylpropanoyl}glutamate·H_2O ***6h*** *(mixture of diastereomers, ~1:1)*

Yield 55% (290 mg), colorless oil. R_f (hexanes/ethyl acetate 3:1) 0.6; IR (film, cm^{-1}) 3351, 1729, 1693; ^1H NMR ($CDCl_3$, 200 MHz): 1.10–1.40 (m, 6H), 1.56 (s, 3H), 1.30–2.91 (m, 4H), 3.95–4.48 (m, 6H), 4.70, 4.62 (ds, 1H), 5.3 (br s, 0.5H), 7.0 (br s, 0.5H), 7.13–7.50 (m, 5H); ^{19}F NMR ($CDCl_3$, 188 MHz): −81.1 (s, 0.5×3F), −80.2 (s, 0.5×3F), −77.1 (s, 0.5×3F), −76.7 (s, 0.5×3F); ^{13}C NMR ($CDCl_3$, 100 MHz): 13.5, 13.8, 13.9, 14.0, 15.9, 16.1, 23.2, 24.7, 29.8, 31.3, 46.4, 46.5, 55.0, 56.6, 60.6, 61.9, 62.1, 63.7, 66.0 (m), 97.6 (m), 121.6 (dq, *J* 286.2 Hz, CF_3), 123.7 (dq, *J* 286.3 Hz, CF_3), 127.0, 127.5, 127.8, 128.0, 128.1, 138.1, 137.9, 168.0, 168.4, 172.6, 173.2, 177.0. Several peaks in ^{13}C NMR spectrum are duplicated. HRMS (EI): calculated for $C_{22}H_{26}F_6N_2O_6$ 528.1695; found 528.1694.

4.3.20. Ethyl N-benzyl-3,3,3-trifluoro-2-phenyl-N-(trifluoroacetyl)-alanylglycinate·H_2O ***6i***

Yield 45% (220 mg), white solid, mp 112–115 °C. R_f (hexanes/ethyl acetate 3:1) 0.7; IR (Nujol, cm^{-1}) 3328, 1756, 1737, 1724; ^1H NMR ($CDCl_3$, 400 MHz): 1.33 (3H, t, *J* 7.1 Hz), 3.98 (1H, d, *J* 16.2 Hz), 4.20 (1H, d, *J* 17.7 Hz), 4.29 (2H, q, *J* 7.1 Hz), 4.46–4.65 (3H, m), 7.10–7.40 (10H, m); ^{19}F NMR ($CDCl_3$, 188 MHz): 77.0 (s, 3F), 67.2 (s, 3F); ^{13}C NMR ($CDCl_3$, 100 MHz): 14.0, 42.6, 47.9, 62.8, 72.6 (q, *J* 27.1 Hz), 96.7 (q, *J* 32.9 Hz), 122.1 (q, *J* 291.3 Hz), 124.2 (q, *J* 289.4 Hz), 127.3, 128.1, 128.2, 128.2, 128.4, 129.1, 132.1, 136.6, 167.5, 169.5. HRMS (EI): calculated for $C_{22}H_{20}F_6N_2O_4$ 490.1327; found, 490.1336.

4.3.21. Methyl N-(2,2,2-trifluoroethylidene)-L-valinate ***7a***

A solution of fluoral monomethylacetale **1a** (6.5 g, 50 mmol), L-valine methyl ether (6.55 g, 50 mmol) and TsOH·H_2O (0.1 g) in toluene was stirred at reflux with Dean–Stark trap for 2 h. The solvent was removed in vacuo and the residue was distilled, Yield 50% (5.2 g), colorless liquid, bp 75–78 °C/20 Torr. R_f (hexanes/ethyl acetate 4:1) 0.8; $[\alpha]_D^{20}$ −67.43 (*c* 0.0476, CH_2Cl_2); IR (film, cm^{-1}) 2925, 1745; ^1H NMR ($CDCl_3$, 400 MHz): 0.91 (d, *J* 6.8 Hz, 3H), 0.92 (d, *J* 6.8 Hz, 3H), 2.34 (sept., *J* 6.8 Hz, 1H), 3.73–3.77 (m, 4H), 7.63 (q, *J* 3.3 Hz, 1H); ^{19}F NMR ($CDCl_3$, 188 MHz): −71.5; ^{13}C NMR ($CDCl_3$, 100 MHz): 18.0, 19.1, 31.5, 52.2, 77.8, 118.3 (q, *J* 275.2 Hz, CF_3), 151.7 (q, *J* 38.8 Hz, CF_3), 170.2. Anal. Calcd for $C_8H_{12}F_3NO_2$: C, 45.50; H, 5.73; N, 6.63. Found C, 50.41; H, 5.61; N, 6.82.

4.3.22. Methyl N-(2,2,2-trifluoroethylidene)-L-methioninate ***7b***

Compound **7b** was prepared according to the procedure for **7a**, yield 47%, colorless liquid, bp 70 °C/8 Torr. R_f (hexanes/ethyl acetate 4:1) 0.8; $[\alpha]_D^{25}$ −73.3 (*c* 0.0481, CH_2Cl_2); IR (film, cm^{-1}) 2923, 1741; ^1H NMR ($CDCl_3$, 400 MHz): 2.03 (s, 3H), 2.08–2.38 (m, 3H), 2.50–2.58 (m, 1H), 3.71 (s, 3H), 4.22–4.29 (m, 1H), 7.7 (q, *J* 3.3 Hz); ^{19}F NMR ($CDCl_3$, 188 MHz): −72.5; ^{13}C NMR ($CDCl_3$, 100 MHz): 14.9, 29.6, 30.8, 52.5, 68.9, 118.3 (q, *J* 275.2 Hz, CF_3), 152.8 (q, *J* 38.1 Hz, CF_3), 170.0. Anal. Calcd for $C_8H_{12}F_3NO_2S$: C, 39.5; H, 4.97; N, 5.76. Found C, 39.60; H, 4.90; N, 5.81.

4.3.23. Methyl N-(trifluoroacetyl)-N-(2,2,2-trifluoro-1-{[(4-methoxybenzyl)amino]carbonyl}ethyl)-D-valinate ***8a*** *(mixture of diastereomers, ~1:1.5, according to GC–MS)*

Yield 57% (270 mg), white solid, mp 117–122 °C. R_f (hexanes/ethyl acetate 4:1) 0.7; IR (Nujol, cm^{-1}) 3311, 1747, 1710, 1658; ^1H NMR ($CDCl_3$, 400 MHz): 0.64–0.72 (m, 0.043×6H), 0.90–1.08 (m, 0.84×6H), 1.17–1.25 (m, 0.12×6H), 1.95–2.25 (m, 0.77×1H), 2.55–2.70 (m, 0.23×1H), 3.60–3.80 (m, 6H), 4.12–4.27 (m, 1H), 4.30–4.47 (m, 2H), 4.60–4.70 (m, 0.16×1H), 4.75–4.85 (m, 0.14×1H), 5.05–5.13 (q, *J* 7.8 Hz, 0.33×1H), 5.18–5.26 (q, *J* 7.8 Hz, 0.39×1H), 6.0 (br s, 0.41×1H), 6.4 (br s, 0.13×1H), 6.83–6.90 (m, 2H), 6.9 (br s, 0.43×1H), 7.15–7.23 (m, 2H); ^{19}F NMR ($CDCl_3$, 188 MHz): −69.3 (s, 0.043×6F), −68.41 (s, 0.068×6F), −67.5–66.7 (m, 0.52×6F), −62.0 (s, 0.2×6F), −60.2 (s, 0.17×6F); ^{13}C NMR ($CDCl_3$, 100 MHz): 169.2, 169.1, 161.4, 159.9, 159.2, 158.2 (m), 129.3, 129.1, 128.9, 122.7 (dq, *J* 284.7 Hz), 115.8 (q, *J* 286.2 Hz), 114.2, 60.1, 65.9, 65.6, 63.5 (q, *J* 32.2 Hz), 60.8 (q, *J* 32.2 Hz), 62.2, 52.7, 52.6, 43.8, 43.7, 29.1, 29.5, 29.1, 29.0, 19.7, 18.8, 18.5. Several peaks in ^{13}C NMR spectrum are duplicated. Anal. Calcd for $C_{19}H_{22}F_6N_2O_5$: C, 48.31; H, 4.69; N, 5.93. Found C, 48.31; H, 4.61; N, 5.82. HRMS (EI): calculated for $C_{19}H_{22}F_6N_2O_5$ 472.1433; found, 472.1427.

4.3.24. Methyl N-(trifluoroacetyl)-N-(2,2,2-trifluoro-1-{[(4-methoxybenzyl)amino]carbonyl}ethyl)-D-methioninate ***8b*** *(mixture of diastereomers, ~1:1.1, according to GC–MS)*

Yield 58% (290 mg), white solid, mp 122–125 °C. R_f (hexanes/ethyl acetate 4:1) 0.7; IR (Nujol, cm^{-1}) 3286, 1745, 1712, 1658; ^1H NMR ($CDCl_3$, 400 MHz): 1.80–1.90 (m, 0.66×1H), 2.03–2.11 (m, 3H), 2.17–2.30 (m, 0.4×3H), 2.43–2.85 (m, 3H), 3.63 (s, 0.21×6H), 3.72 (s, 0.18×6H), 3.75–3.83 (m, 0.62×6H), 3.98–4.07 (m, 0.22×2H), 4.29–4.52 (m, 2H), 4.66–5.03 (m, 0.78×2H), 6.3 (br s, 0.42×1H), 6.80–6.92 (m, 2H), 7.12–7.25 (m, 2H), 7.7 (br s, 0.38×1H); ^{19}F NMR ($CDCl_3$, 188 MHz): −76.7 (s, 0.077×6F), −69.8–69.1 (m, 0.27×6F), −68.9 (s, 0.22×6F), −68.3 (s, 0.17×6F), −67.7 (s, 0.21×6F), −63.0 (br s, 0.055×6F); ^{13}C NMR ($CDCl_3$, 100 MHz): 170.6, 169.8, 168.9, 160.6, 160.0, 159.2, 159.2, 157.3 (m), 129.1, 129.0, 128.7, 128.3, 122 (dq, *J* 283.4 Hz), 115.3 (dq, *J* 288.3 Hz), 114.1, 144.0, 60.5 (q, *J* 32.2 Hz), 60.0, 58.9, 58.8, 55.1, 53.2, 52.8, 52.4, 51.9, 43.6, 43.3, 43.6, 31.8, 31.4, 30.6, 30.3, 30.0, 29.5, 15.1, 15.0. Several peaks in ^{13}C NMR spectrum are duplicated. Anal. Calcd for $C_{19}H_{22}F_6N_2O_5S$: C, 45.24; H, 4.40; N, 5.55. Found C, 45.18; H, 4.49; N, 5.48. HRMS (EI): calculated for $C_{19}H_{22}F_6N_2O_5S$ 504.1154; found, 504.1157.

Acknowledgements

The authors thank the Deutsche Forschungsgemeinschaft (436 RUS 113/812/0-1) and Russian Science Support Foundaition for financial support of this work.

Supplementary data

General information, synthesis of imines **1a–e** and copies of all ^{1}H, ^{13}C, and ^{19}F spectra. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.10.004.

References and notes

1. (a) Marcaccini, S.; Torroba, T. *Nat. Protocols* **2007**, *2*, 632–639; (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89; (c) *Multicomponent Reactions*; Zhu, J., Bienamé, H., Eds.; WILEY-VCH: Weinheim, 2005; (d) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133–1144; (e) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210.
2. (a) *Fluorine-Containing Synthons*; Soloshonok, V. A., Ed.; ACS Symposium Series 911; ACS: Washington, DC, 2005; (b) Kirsch, P. *Modern Fluoroorganic Chemistry. Synthesis, Reactivity, Applications*; WILEY-VCH: Weinheim, 2004.
3. (a) Smits, R.; Cadicamo, C. D.; Burger, K.; Koksch, B. *Chem. Soc. Rev.* **2008**, *37*, 1727–1739; (b) Qiu, X.-L.; Meng, W.-D.; Qing, F.-L. *Tetrahedron* **2004**, *60*, 6711–6745; (c) Sutherland, A.; Willis, C. L. *Nat. Prod. Rep.* **2000**, *17*, 621–631; (d) *Fluorine-containing Amino Acids. Synthesis and Properties*; Kukhar, P., Soloshonok, V. A., Eds.; WILEY: Chichester, UK, 1994; (e) *Biomedical Aspects of Fluorine Chemistry*; Filler, R., Kobayashi, Y., Yagupolskii, K. M., Eds.; Elsevier: Amsterdam, 1993.
4. (a) Druzhinin, S. V.; Balenkova, E. S.; Nenajdenko, V. G. *Tetrahedron* **2007**, *63*, 7753–7808; (b) Zanda, M. *New J. Chem.* **2004**, *28*, 1401–1411; (c) Jäckel, C.; Koksch, B. *Eur. J. Org. Chem.* **2005**, 4483–4503.
5. Moldeni, M.; Pesenti, C.; Sani, M.; Volonterio, A.; Zanda, M. *J. Fluorine Chem.* **2004**, *125*, 1735–1743.
6. Koksch, B.; Sewald, N.; Hofmann, H.-J.; Burger, K.; Jakubke, H.-J. *J. Pept. Sci.* **1997**, *3*, 157–167.
7. (a) Hodgson, D. R. W.; Sanderson, J. M. *Chem. Soc. Rev.* **2004**, *33*, 422–430; (b) Thust, S.; Koksch, B. *Tetrahedron Lett.* **2004**, *45*, 1163–1165.
8. (a) Guo, Y.; Fujiwara, K.; Uneyama, K. *Org. Lett.* **2006**, *5*, 827–829; (b) Osipov, S. N.; Sewald, N.; Kolomiets, A. F.; Fokin, A. V.; Burger, K. *Tetrahedron Lett.* **1996**, *37*, 615–618.
9. Koksch, B.; Mütze, K.; Osipov, S. N.; Golubev, A. S.; Burger, K. *Tetrahedron Lett.* **2000**, *41*, 3825–3828.
10. (a) Burger, K.; Hollweck, W.; Koksch, B. *Tetrahedron* **1998**, *54*, 5915–5928; (b) Sewald, N.; Hollweck, W.; Mütze, K.; Schierlinger, C.; Seymour, L. C.; Gaa, K.; Burger, K.; Koksch, B.; Jakubke, H. D. *Amino Acids* **1995**, *8*, 187–194.
11. Dömling, A.; Achatz, S.; Beck, B. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5483–5486.
12. See for example: Gong, Y.; Kato, K. *J. Fluorine Chem.* **2001**, *108*, 83–86.
13. We have found the traces of the imine **3c** and *t*-BuNHCHO in the reaction mixture.
14. See for example: (a) Fluoral imines: Ono, T.; Kukhar, V. P.; Soloshonok, V. A. *J. Org. Chem.* **1996**, *61*, 6563–6569; (b) Trifluoroacetone imines: Barten, J. A.; Lork, E.; Röschenthaler, G.-V. *J. Fluorine Chem.* **2004**, *125*, 1039–1049; (c) Berbasov, D. O.; Ojemaye, I. D.; Soloshonok, V. A. *J. Fluorine Chem.* **2004**, *125*, 603–607 Trifluoroacetophenone imines; (d) Hexafluoroacetone imines: see Ref. 8a and Supplementary data.
15. Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602–1634.
16. Gulevich, A. V.; Balenkova, E. S.; Nenajdenko, V. G. *J. Org. Chem.* **2007**, *72*, 7878–7885 and references therein.
17. Yamada, T.; Motoyama, N.; Taniguchi, T.; Kazuta, Y.; Miyazawa, T.; Kuwata, S.; Matsumoto, K.; Sugiura, M. *Chem. Lett.* **1987**, 723–726.
18. L-Valine is one of the most bulky natural amino acid having the best selectivity in the Ugi reaction (see Ref. 17).
19. Fushiya, S.; Yamada, S.; Matsuda, M.; Nozoe, S. *Tetrahedron Lett.* **1994**, *35*, 8201–8204.
20. (a) Chilton, W. S.; Petit, A.; Chilton, M.-D.; Dessaux, Y. *Phytochemistry* **2001**, *58*, 137–142; (b) Moore, L. W.; Chilton, W. S.; Canfield, M. L. *Appl. Environ. Microbiol.* **1997**, 201–207; (c) Tempe, J. In *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*; Weinstein, B., Ed.; Marcel Dekker: New York, NY, 1993; Vol. 7, pp 1134–1170; (d) Szegedi, E.; Czakó, M.; Otten, L. *Mol. Plant-Microbe Interact.* **1996**, *9*, 139–143; (e) Firmin, J. L.; Fenwick, G. R. *Nature* **1978**, *276*, 842–844.
21. (a) Hayashi, K.; Nunami, K.; Kato, J.; Yoneda, N.; Kubo, M.; Ochiai, T.; Ishida, R. *J. Med. Chem.* **1989**, *32*, 289–301; (b) Vincent, N.; Remond, G.; Portevin, B.; Serkiz, B.; Laubie, M. *Tetrahedron Lett.* **1982**, *23*, 1677–1680.
22. (a) Fournie-Zaluski, M. C.; Chaillet, P.; Soroca-Lucas, E.; Marcais-Collado, H.; Costentin, J.; Roques, B. P. *J. Med. Chem.* **1983**, *26*, 60–65; (b) Maycock, A. L.; DeSousa, D. M.; Payne, L. G.; Ten Broeke, J.; Wu, M. T.; Patchett, A. A. *Biochem. Biophys. Res. Commun.* **1981**, *102*, 963–969.