EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201300861

Tetrazole-Substituted Five, Six, and Seven-Membered Cyclic Amines Bearing Perfluoroalkyl Groups – Efficient Synthesis by Azido-Ugi Reaction

Olga I. Shmatova[a] and Valentine G. Nenajdenko*[a]

Keywords: Multicomponent reactions / Fluorine / Fluorinated compounds / Nitrogen heterocycles / Amines

The application of perfluoroalkylated cyclic imines in azido-Ugi reactions was studied. It was shown that the reaction allows access to five-, six- and seven-membered perfluoroalkylated cyclic amines connected to a tetrazole ring. The scope and limitations of this approach are discussed. When benzyl isocyanide was used in the azido-Ugi reaction, it was shown that the tetrazole products could easily be debenzylated by catalytic hydrogenation to form 1*H*-tetrazoles in excellent yields.

Introduction

The chemistry of organofluorine compounds is a rapidly developing area due to the importance of these substances for pharmaceutical applications and materials science.[1] The replacement of hydrogen by fluorine significantly changes the physicochemical and metabolic properties of the molecules. The conformational behaviour[2] of the molecules is also significantly influenced, and this can be exploited in the design of new drugs. Some fluorine-containing drugs are presented in Figure 1. Fluorinated amines and amino acids are very important in modern medicinal chemistry. Such fragments have improved metabolic stability and lower basicity. CF_3-substituted amines are only a little more basic than anilines. The resulting increased ability to penetrate the blood-brain barrier makes such amines in extremely high demand for drug discovery.[3]

Recently, we prepared cyclic imines bearing CF_3 and C_2F_5 groups[4] and started to investigate their chemical applications.[5] We supposed that α-polyfluoroalkylated cyclic imines would be a suitable starting point for azido-Ugi reactions for the incorporation into target tetrazole derivatives of saturated nitrogen heterocycles bearing polyfluoroalkyl moieties.

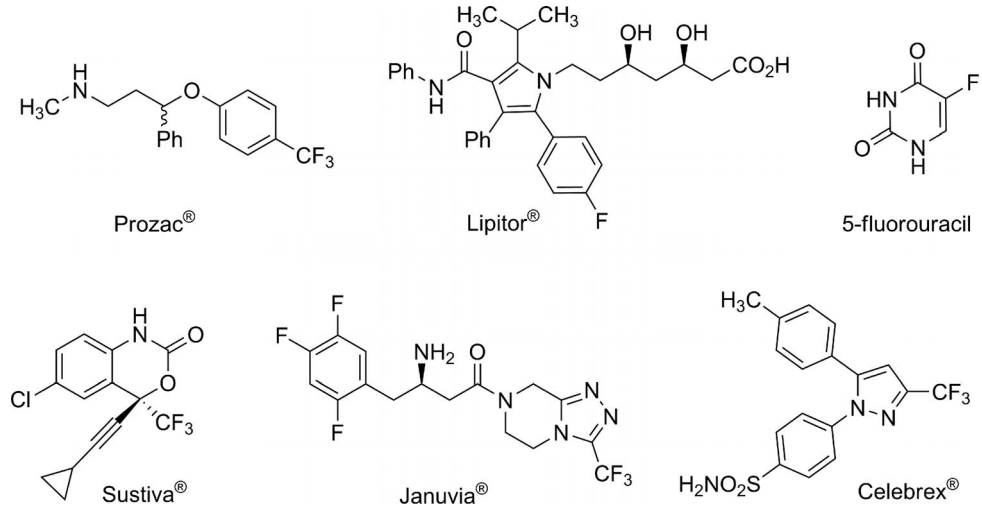


Figure 1. Some examples of fluorine-containing drugs.

Tetrazoles are a very important class of heterocycles that are widely used in medicinal chemistry,[6] materials chemistry,[7] organometallic and coordination chemistry,[8] and organocatalysis.[9] The biological activities of compounds containing tetrazole rings are usually attributed to the pos-

[a] Department of Chemistry, Moscow State University, Leninskie Gory, Moscow 119992, Russia
E-mail: nen@acylium.chem.msu.ru
Homepage:www.msu.ru

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201300861.

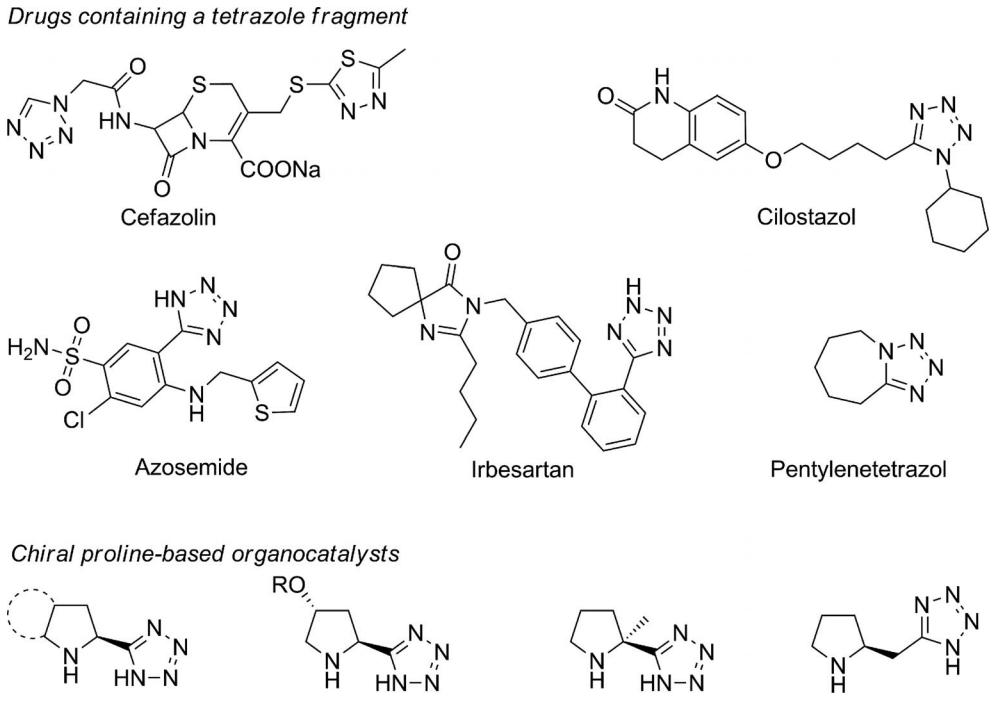


Figure 2. Applications of tetrazole derivatives in medicine and organocatalysis.

sibility of this moiety to mimic a carboxyl group[10] or a *cis*-amide bond.[11] A lot of drugs and drug candidates contain this fragment, and some of them are presented in Figure 2. Recently, some fluorine-containing tetrazoles were shown to be very effective against CNS disorders and also as imaging agents.[12]

Moreover, the interest in tetrazoles has increased due to the successful development of organocatalysis and the broad applications of proline-derived tetrazoles in this field (Figure 2). Recently, some examples of the use of organocatalysis for the preparation of fluorinated molecules,[13] and also of the application of fluorinated organocatalysts, have appeared in the literature.[14] These data clearly show that rapid progress is being made in this chemistry, especially in field of asymmetric synthesis.

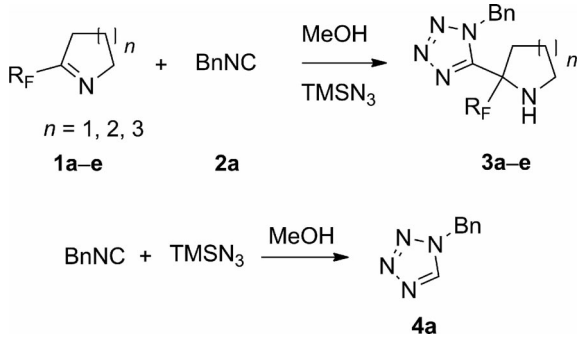
Isocyanide-based multicomponent reactions are effective methods for the synthesis of complex molecules.[15] The replacement of carboxylic acids (used in the classical Ugi reaction) with hydrazoic acids[16] opens up a direct route to various 1,5-substituted tetrazoles. With this in mind, we decided to work on a straightforward route to perfluoroalkylated cyclic imines bearing tetrazole rings using an azido-Ugi reaction.

Such compounds could be very interesting new organocatalysts with reduced basicity and reduced nucleophilicity of the amine nitrogen. It is known that the incorporation of a trifluoromethyl group in the α position to an amine functionality changes the basicity dramatically. For example, 2,2,2-trifluoroethylamine is five orders of magnitude less basic than ethylamine (pK_a 5.7 and 10.7, respectively, in water). Recently, Mykhailiuk et al. demonstrated an even higher difference for α-trifluoromethylated morpholine compared to the parent molecule (ΔpK_a = –5.9 in water).[17] As a result, iminium intermediates formed in organocatalytic reactions can be expected to have enhanced electrophilicities, which would lead to more efficient reactions and shorter reaction times (if the intermediate participates in the rate-determining step).

Results and Discussion

We started our investigation by studying the influence of the imine component on the reaction. It is well known that there are significant differences in the conformations of nitrogen heterocycles. For instance, compared to a piperidine ring, a pyrrolidine is flatter and more rigid, whereas an azepane is quite a flexible molecular fragment. The starting perfluoroalkylated cyclic imines could be easily prepared from commercially available materials.[4] $TMSN_3$ (TMS = trimethylsilyl) in methanol was used in all experiments as a convenient source of HN_3.

Cyclic imines **1a**–**e**, with various ring sizes and bearing a perfluoroalkyl group (i.e., CF_3 or C_2F_5), were used in azido-Ugi reactions with benzyl isocyanide (**2a**; Scheme 1). We found that perfluoroalkylated imines **1a**–**e** reacted with benzyl isocyanide **2a** in azido-Ugi reactions to give the corresponding tetrazoles (i.e., **3a**–**e**; Table 1). 2-CF_3 pyrroline **1a** was converted into the corresponding tetrazole (i.e., **3a**) in 54% yield. Similarly, the reactions with 2-CF_3-substituted tetrahydropyridine **1c** and tetrahydroazepine **1e** gave the desired products (i.e., **3c** and **3e**) in 80 and 50% yields, respectively. Thus, six-membered ring 2-CF_3-imine **1c** showed a better reactivity than five- and seven-membered ring imines **1a** and **1e**.



Scheme 1. $TMSN_3$-modified Ugi reaction with perfluoroalkyl cyclic imines, and formation of **4a** as a by-product.

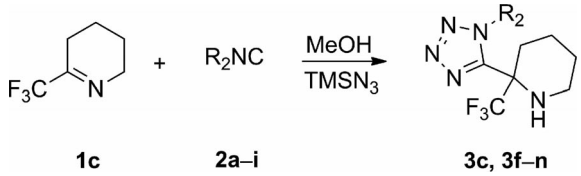
Table 1. Azido-Ugi reaction with perfluoroalkylated imines.

Entry	R_f	n	Imine	Product	Yield [%]
1	CF_3	1	**1a**	**3a**	54
2	C_2F_5	1	**1b**	**3b**	5[a]
3	CF_3	2	**1c**	**3c**	80
4	C_2F_5	2	**1d**	**3d**	22[a]
5	CF_3	3	**1e**	**3e**	50

[a] The major isolated product was **4a**.

Previously, we observed that 2-C_2F_5-substituted cyclic imines **1b**,**d** were much less reactive than trifluoromethylated derivatives **1a**,**c**,**e**, due to the very high steric demand of the C_2F_5 group.[5] This rule also applies to the azido-Ugi reaction. For 2-C_2F_5-pyrroline **1b**, the desired Ugi tetrazole (i.e., **3b**) was formed in trace amounts, in spite of our numerous attempts to improve the yield. Only a 5% yield of target compound **3b** was isolated, and the major by-product was *N*-benzyltetrazole (**4a**), which was isolated in 75% yield (Scheme 1). The desired reaction with C_2F_5-piperidine **1d** proceeded more quickly to give 22% of tetrazole **3d**, but again the major product was **4a**, which was isolated in 67% yield.

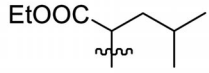
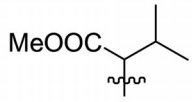
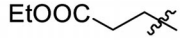
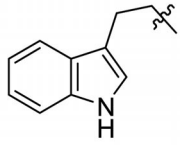
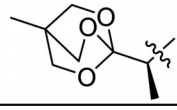
Then we investigated the influence of the isocyanide component on the reaction with CF_3-tetrahydropyridine **1c** (Scheme 2). We demonstrated that a wide variety of isonitriles **2a**–**j** reacted with imine **1c** to give CF_3-substituted piperidinyl tetrazoles **3c** and **3f**–**n** in high isolated yields (Table 2). Tetrazole surrogates of dipeptides containing 2-trifluoromethylated pipecolinic acid were isolated as pairs of diastereomers when natural amino-acid-derived isocyanides **2f**–**g**,**j** were used.



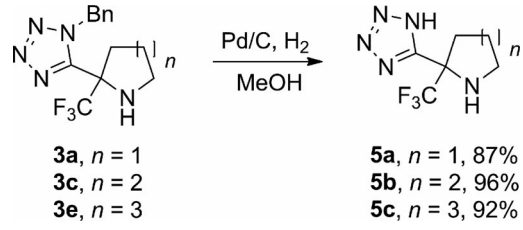
Scheme 2. Variation of the isocyanide component in the reaction with **1c**.

Finally, tetrazoles with different ring sizes that had been prepared by the Ugi reaction (i.e., **3a**,**c**,**e**) were debenzylated (Scheme 3) in the presence of a catalytic amount of palladium (10% on carbon) and hydrogen (1 atm.) in methanol. In all cases, almost quantitative yields were achieved. After filtration of the catalyst and evaporation of the solvent, no further purification of the products was required. The structures of products **5a**–**c** resemble the structures of tetrazole-proline analogues with perfluoroalkyl substituents in the α position. Our approach opens up a short and efficient route to such molecules.

Table 2. Influence of the isocyanide component on the reaction with imine **1c**.

Entry	R_2	Isonitrile	Product	Yield, %
1	Bn	**2a**	**3c**	80
2	*t*Bu	**2b**	**3f**	58
3	CH_2COOEt	**2c**	**3g**	62
4	allyl	**2d**	**3h**	80
5	Bu	**2e**	**3i**	81
6		**2f**	**3j**[a]	67
7		**2g**	**3k**[a]	67
8		**2h**	**3l**	84
9		**2i**	**3m**	77
10		**2j**	**3n**[a]	60

[a] A mixture of two diastereomers was isolated in a 1:1 ratio.



Scheme 3. Synthesis of *N*-unsubstituted tetrazoles **5**.

Conclusions

Perfluoroalkylated cyclic imines were used as substrates for the azido-Ugi reaction. The influence of imine and isocyanide components on the reaction was investigated to indicate lower activity of C_2F_5-substituted imines. The reaction gives tetrazoles connected to pyrrolidine, piperidine, or azepane rings bearing a perfluoroalkyl group in generally

good yields. New 1*H*-5-cyclic amino tetrazoles bearing a CF_3 group were synthesized by azido-Ugi reaction and subsequent debenzylation.

Experimental Section

General Remarks: One-dimensional NMR spectra (^1H, ^{19}F, and ^{13}C) were obtained with Jeol ECX-400, Bruker VRX-400, or Bruker AM-300 spectrometers. Chemical shifts are reported in parts per million (ppm) downfield from TMS. Deuterated solvent peaks were used as internal references: $CDCl_3$ at 7.27 and 77.00 ppm, [D_6]DMSO at 2.50 and 39.50 ppm, MeOD at 3.31 and 49.00 ppm. Chemical shifts for ^{19}F NMR spectroscopic data are referenced to $CFCl_3$ (0.0) or $PhCF_3$ (–63.90). High-resolution mass spectra (HRMS) were recorded using a Bruker Daltonics (MicroTOF-Q) instrument. Electrospray ionization (ESI) mass spectra (MS) were obtained from methanol or acetonitrile solution. TLC was carried out on precoated silica plates (Merck $60F_{254}$) with UV light visualization. Flash chromatography was performed using MP Silica 60 (320–630 mesh). All reagents were purchased from Aldrich unless otherwise stated. Starting cyclic imines were prepared by published methods.[4] Isonitrile **2j** was synthesized by a literature method.[15k]

General Procedure for the Ugi Reaction: The appropriate imine (1 mmol) was dissolved in dry MeOH (2 mL). The isocyanide (1.1 mmol) and $TMSN_3$ (1.1 mmol) were added, and the solution was stirred for several days (TLC control) at room temperature. When the product was a solid, it was purified by filtration and washing with cold methanol. When the product was soluble in methanol, the reaction solvent was evaporated, and the product was purified by column chromatography (hexane/ethyl acetate or dichloromethane).

1-Benzyl-5-[2-(trifluoromethyl)pyrrolidin-2-yl]-1*H*-tetrazole (3a): Yield 54%, white solid, m.p. 76–77 °C. ^1H NMR ($CDCl_3$): δ = 1.67–1.73 (m, 1 H), 1.88–1.97 (m, 1 H), 2.45–2.62 (m, 2 H, CH_2-C_q), 2.72 (br. s, 1 H, NH), 2.77–2.85 (m, 1 H, CH_2-N), 3.13–3.21 (m, 1 H, CH_2-N), 5.73 and 5.89 (2 d, $J_{H,H}$ = 15.07 Hz, 2 H, CH_2-Ar), 7.23–7.36 (m, 5 H, Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.2, 34.1 (CH_2-C_q), 47.2 (CH_2-N), 52.5 (CH_2-Ar), 66.9 (q, $J_{C,F}$ = 28.9 Hz, C_q), 125.5 (q, $J_{C,F}$ = 283.9 Hz, CF_3), 127.2 (Ar), 128.6 (Ar), 128.9 (Ar), 134.2 (C_q, Ar), 153.5 (C_q, tet) ppm. ^{19}F NMR ($CDCl_3$): δ = –76.9 (CF_3) ppm. IR: $\tilde{\nu}$ = 3370 (NH) cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{15}F_3N_5$ [M + H] 298.1274; found 298.1272.

1-Benzyl-5-[2-(pentafluoroethyl)pyrrolidin-2-yl]-1*H*-tetrazole (3b): Yield 5%, white solid, m.p. 50–51 °C. ^1H NMR ($CDCl_3$): δ = 1.58–1.68 (m, 1 H), 1.87–1.97 (m, 1 H), 2.49–2.56 (m, 1 H, CH_2-C_q), 2.62–2.76 (m, 2 H, CH_2-C_q and CH_2-N), 2.89 (br. s, 1 H, NH), 3.10–3.15 (m, 1 H, CH_2-N), 5.67 and 5.87 (2 d, $J_{H,H}$ = 15.07 Hz, 2 H, CH_2-Ar), 7.32–7.38 (m, 3 H, Ar), 7.22–7.24 (m, 2 H, Ar). ^{13}C NMR ($CDCl_3$): δ = 25.0, 34.2 (CH_2-C_q), 46.9 (CH_2-N), 52.5 (t, $J_{C,F}$ = 3.1 Hz, CH_2-Ar), 66.4 (t, $J_{C,F}$ = 23.8 Hz, C_q), 114.4 (tq, $J_{C,F}$ = 260.6, $J_{C,F}$ = 35.8 Hz, CF_2), 118.6 (qt, $J_{C,F}$ = 287.7, $J_{C,F}$ = 36.1 Hz, CF_3), 127.6 (Ar), 128.6 (Ar), 128.8 (Ar), 134.0 (C_q, Ar), 153.6 (C_q, tet) ppm. ^{19}F NMR ($CDCl_3$): δ = –79.3 (s, 3 F, CF_3), –118.4 and –120.1 (2 d, $J_{F,F}$ = 272.0 Hz, 2 F, CF_2). IR: $\tilde{\nu}$ = 3360 (NH) cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{15}F_5N_5$ [M + H] 348.1242; found 348.1233.

2-(1-Benzyl-1*H*-tetrazol-5-yl)-2-(trifluoromethyl)piperidine (3c): Yield 80%, white solid, m.p. 80–81 °C. ^1H NMR ($CDCl_3$): δ = 1.24–1.55 (m, 3 H), 1.75–1.96 (m, 4 H), 2.78–2.83 (m, 1 H, CH_2-N), 2.91–2.97 (m, 1 H, CH_2-N), 5.85 and 6.06 (2 d, $J_{H,H}$ = 14.72 Hz, 2 H, CH_2-Ar), 7.33–7.43 (m, 5 H, Ar). ^{13}C NMR ($CDCl_3$): δ = 19.8, 25.5, 28.9 (CH_2-C_q), 42.3 (CH_2-N), 53.0 (CH_2-Ar), 61.7 (q, $J_{C,F}$ = 27.5 Hz, C_q), 124.9 (q, $J_{C,F}$ = 284.3 Hz, CF_3), 127.6 (Ar), 128.6 (Ar), 128.7 (Ar), 133.9 (C_q, Ar), 150.5 (C_q, tet) ppm. ^{19}F NMR ($CDCl_3$): δ = –79.2 (CF_3) ppm. IR: $\tilde{\nu}$ = 3310 (NH) cm^{-1}. $C_{14}H_{16}F_3N_5$ (311.31): calcd. C 54.01, H 5.18, N 22.50; found C 54.10, H 5.15, N 22.53.

2-(1-Benzyl-1*H*-tetrazol-5-yl)-2-(pentafluoroethyl)piperidine (3d): Yield 22%, yellowish solid, m.p. 80–81 °C. ^1H NMR ($CDCl_3$): δ = 1.25–1.46 (m, 3 H), 1.74–1.98 (m, 4 H), 2.76–2.79 (m, 1 H, CH_2-N), 2.89–2.92 (m, 1 H, CH_2-N), 5.80 and 6.02 (2 d, $J_{H,H}$ = 14.85 Hz, 2 H, CH_2-Ar), 7.32–7.37 (m, 5 H, Ar). ^{13}C NMR ($CDCl_3$): δ = 19.7, 25.1, 28.8 (q, $J_{C,F}$ = 1.8 Hz, CH_2-C_q), 42.1 (CH_2-N), 53.0 (dd, $J_{C,F}$ = 5.9, $J_{C,F}$ = 1.5 Hz, CH_2-Ar), 61.6 (t, $J_{C,F}$ = 20.7 Hz, C_q), 114.5 (tq, $J_{C,F}$ = 263.5, $J_{C,F}$ = 36.2 Hz, CF_2), 118.6 (qt, $J_{C,F}$ = 287.6, $J_{C,F}$ = 36.2 Hz, CF_3), 128.4 (Ar), 128.5 (Ar), 128.7 (Ar), 133.7 (C_q, Ar), 150.5 (q, $J_{C,F}$ = 2.6 Hz, C_q, tet) ppm. ^{19}F NMR ($CDCl_3$): δ = –78.4 (s, 3 F, CF_3), –120.9 and –122.9 (2 d, $J_{F,F}$ = 275.4 Hz, 2 F, CF_2). IR: $\tilde{\nu}$ = 3300 (NH) cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{17}F_5N_5$ [M + H] 384.1218; found 384.1201.

2-(1-Benzyl-1*H*-tetrazol-5-yl)-2-(trifluoromethyl)azepane (3e): Yield 50%, white solid, m.p. 100–102 °C. ^1H NMR ($CDCl_3$): δ = 1.27–1.42 (m, 2 H), 1.45–1.63 (m, 3 H), 1.67–1.77 (m, 1 H), 2.02 (br. s, 1 H, NH), 2.41–2.55 (m, 2 H), 2.68–2.75 (m, 1 H, CH_2-N), 2.81–2.86 (m, 1 H, CH_2-N), 5.92 and 5.98 (2 d, $J_{H,H}$ = 15.26 Hz, 2 H, CH_2-Ar), 7.18–7.20 (m, 2 H, Ar), 7.33–7.38 (m, 3 H, Ar). ^{13}C NMR ($CDCl_3$): δ = 22.9, 29.4, 32.7, 33.8, 43.7 (CH_2-N), 53.1 (CH_2-Ar), 65.1 (q, $J_{C,F}$ = 26.4 Hz, C_q), 125.9 (q, $J_{C,F}$ = 287.3 Hz, CF_3), 127.2 (Ar), 128.4 (Ar), 128.9 (Ar), 134.5 (C_q, Ar), 153.6 (C_q, tet) ppm. ^{19}F NMR ($CDCl_3$): δ = –77.6 (CF_3) ppm. IR: $\tilde{\nu}$ = 3315 (NH) cm^{-1}. $C_{15}H_{18}F_3N_5$ (325.33): calcd. C 55.38, H 5.58, N 21.53; found C 55.40, H 5.62, N 21.58.

2-(1-*tert*-Butyl-1*H*-tetrazol-5-yl)-2-(trifluoromethyl)piperidine (3f): Yield 58%, white solid, m.p. 149–150 °C. ^1H NMR ($CDCl_3$): δ = 1.42–1.60 (m, 3 H), 1.84 (br. s, 10 H, NH and 3 CH_3), 1.92–1.99 (m, 2 H), 2.38–2.45 (m, 1 H, CH_2-C_q), 2.92–2.98 (m, 1 H, CH_2-N), 3.03–3.09 (m, 1 H, CH_2-N) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.1, 25.1, 31.2 (CH_2-C_q), 31.4 (CH_3), 42.61 (CH_2-N), 63.0 (q, $J_{C,F}$ = 26.9 Hz, C_q), 67.5 (C_q), 124.9 (q, $J_{C,F}$ = 285.6 Hz, CF_3), 151.9 (C_q, tet) ppm. ^{19}F NMR ($CDCl_3$): δ = –75.8 (CF_3) ppm. IR: $\tilde{\nu}$ = 3291 (NH) cm^{-1}. $C_{11}H_{18}F_3N_5$ (277.29): calcd. C 47.65, H 6.54, N 25.26; found C 47.68, H 6.64, N 25.11.

Ethyl {5-[2-(Trifluoromethyl)piperidin-2-yl]-1*H*-tetrazol-1-yl}acetate (3g): Yield 62%, white solid, m.p. 95–96 °C. ^1H NMR ($CDCl_3$): δ = 1.26 (t, $J_{H,H}$ = 7.17 Hz, 3 H, CH_3), 1.32–1.40 (m, 1 H), 1.49–1.53 (m, 1 H), 1.59–1.91 (m, 4 H), 2.20–2.29 (m, 1 H, CH_2-C_q), 2.90–2.96 (m, 2 H, CH_2-N), 4.24 (q, $J_{H,H}$ = 7.17 Hz, 2 H, CH_2-CH_3), 5.53 and 5.78 (2 d, $J_{H,H}$ = 17.15 Hz, 2 H, CH_2-Ar). ^{13}C NMR ($CDCl_3$): δ = 13.9 (CH_3), 19.6, 25.4, 28.5 (CH_2-C_q), 41.9 (C-5), 49.9 (CH_2-Ar), 61.4 (q, $J_{C,F}$ = 27.8 Hz, C_q), 62.3 (CH_2-CH_3), 124.6 (q, $J_{C,F}$ = 284.7 Hz, CF_3), 150.7 (C_q, tet), 165.8 (CO) ppm. ^{19}F NMR ($CDCl_3$): δ = –79.4 (CF_3) ppm. IR: $\tilde{\nu}$ = 3291 (NH), 1759 (CO) cm^{-1}. $C_{11}H_{16}F_3N_5O_2$ (307.27): calcd. C 43.00, H 5.25, N 22.79; found C 43.03, H 5.44, N 22.54.

2-(1-Allyl-1*H*-tetrazol-5-yl)-2-(trifluoromethyl)piperidine (3h): Yield 80%, white solid, m.p. 72–73 °C. ^1H NMR ($CDCl_3$): δ = 1.33–1.44 (m, 1 H), 1.52–1.64 (m, 2 H), 1.75–1.93 (m, 3 H), 2.16–2.25 (m, 1 H, CH_2-C_q), 2.91–2.95 (m, 1 H, CH_2-N), 2.99–3.05 (m, 1 H, CH_2-N), 5.31–5.37 (m, 3 H, CH_2=CH and CH_2-Ar), 5.47–5.52 (m, 1 H, CH_2=CH), 6.01–6.11 (m, 1 H, CH_2=CH) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.8, 25.5, 28.8 (CH_2-C_q), 42.3 (CH_2-N), 51.9 (CH_2-Ar), 61.6 (q, $J_{C,F}$ = 27.81 Hz, C_q), 120.2 (CH_2=CH), 124.7 (q, $J_{C,F}$ =

284.3 Hz, CF_3), 130.8 (CH_2=*C*H), 150.0 (C_q, tet) ppm. ^{19}F NMR ($CDCl_3$): δ = –79.6 (CF_3) ppm. IR: $\tilde{\nu}$ = 3294 (NH) cm^{-1}. $C_{10}H_{14}F_3N_5$ (261.25): calcd. C 45.97, H 5.40, N 26.81; found C 45.75, H 5.48, N 26.77.

2-(1-Butyl-1*H*-tetrazol-5-yl)-2-(trifluoromethyl)piperidine (3i): Yield 81%, white solid, m.p. 53–54 °C. ^1H NMR ($CDCl_3$): δ = 0.96 (t, $J_{H,H}$ = 7.34 Hz, 3 H, CH_3), 1.32–2.03 (m, 10 H), 2.13–2.27 (m, 1 H, CH_2-C_q), 2.87–2.92 (m, 1 H, CH_2-N), 3.02–3.07 (m, 1 H, CH_2-N), 4.61–4.80 (m, 2 H, *C*H_2-Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.4 (CH_3), 19.8, 19.9, 25.4, 28.8, 31.3 (*C*H_2-C_q), 42.1 (CH_2-N), 49.4 (*C*H_2-Ar), 61.5 (q, $J_{C,F}$ = 27.5 Hz, C_q), 124.7 (q, J = 284.3 Hz, CF_3), 150.0 (C_q, tet) ppm. ^{19}F NMR ($CDCl_3$): δ = –79.6 (CF_3) ppm. IR: $\tilde{\nu}$ = 3311 (NH) cm^{-1}. $C_{11}H_{18}F_3N_5$ (277.29): calcd. C 47.65, H 6.54, N 25.26; found C 47.78, H 6.62, N 25.21.

Ethyl 4-Methyl-2-{5-[2-(trifluoromethyl)piperidin-2-yl]-1*H*-tetrazol-1-yl}pentanoate (3j): Mixture of diastereomers, ratio 1:1, yield 67%, white solid, m.p. 77–78 °C. ^1H NMR ($CDCl_3$): δ = 0.83–0.93 (m, 12 H, 2 *C*H_3–CH), 1.10 and 1.18 (t, 6 H, $J_{H,H}$ = 7.13 Hz, *C*H_3-CH_2), 1.26–1.61 (m, 8 H), 1.74–1.84 (m, 6 H), 2.00–2.31 (m, 6 H), 2.82–3.00 (m, 4 H, *C*H_2-N), 4.03–4.17 (m, 4 H, *C*H_2-CH_3), 6.17 (dd, 1 H, $J_{H,H}$ = 8,49 Hz; $J_{H,H}$ = 6.14 Hz, *C*H-Ar) and 6.29 (t, 1 H, $J_{H,H}$ = 7.45 Hz, *C*H-Ar). ^{13}C NMR ($CDCl_3$): δ = 13.6 (*C*H_3), 13.9 (*C*H_3), 19.5, 19.7 (*C*H_3), 21.7 (*C*H_3), 21.9, 22.2, 22.4, 24.9, 25.0, 25.2, 25.3, 28.7 (*C*H_2-C_q), 28.8 (*C*H_2-C_q), 41.3, 41.5, 42.0 (*C*H_2-N), 42.1 (*C*H_2-N), 60.5 (*C*H-Ar), 60.7 (*C*H-Ar), 61.3 and 61.5 (q, $J_{C,F}$ = 27.5 Hz, C_q-CF_3), 61.9 (*C*H_2-CH_3), 62.0 (*C*H_2-CH_3), 124.6 (q, $J_{C,F}$ = 284.3 Hz, *C*F_3), 150.6 (C_q, tet), 150.7 (C_q, tet), 168.6 (*C*O), 168.8 (*C*O). ^{19}F NMR ($CDCl_3$): δ = –78.6, –79.0 (CF_3) ppm. IR: $\tilde{\nu}$ = 3275 (NH), 1758 (CO) cm^{-1}. $C_{15}H_{24}F_3N_5O_2$ (363.38): calcd. C 49.44, H 6.66, N 19.20; found C 49.44, H 6.60, N 19.20.

Methyl 3-methyl-2-{5-[2-(trifluoromethyl)piperidin-2-yl]-1*H*-tetrazol-1-yl}butanoate (3k): Mixture of diastereomers, ratio 1:1, yield 67%, white solid, m.p. 79–80 °C. ^1H NMR ($CDCl_3$): δ = 0.86 and 0.97 (d, 6 H, $J_{H,H}$ = 6.79 Hz, *C*H_3), 1.02 and 1.05 (d, 6 H, $J_{H,H}$ = 6.79 Hz, *C*H_3), 1.22–1.54 (m, 6 H), 1.69-2.12 (m, 8 H), 2.67–2.97 (m, 6 H), 3.60 and 3.66 (s, 6 H, *C*H_3-COO), 5.83 (d, 1 H, $J_{H,H}$ = 7.67 Hz, *C*H-Ar) and 6.06 (d, 1 H, $J_{H,H}$ = 8.11 Hz, *C*H-Ar) ppm. ^{13}C NMR ($CDCl_3$): δ = 18.8 (*C*H_3), 19.1 (*C*H_3), 19.5, 19.6, 19.8 (*C*H_3), 20.5 (*C*H_3), 25.2, 25.3, 28.7 (*C*H_2-C_q), 28.7 (*C*H_2-C_q), 31.7 (*C*H), 41.9 (*C*H_2-N), 41.9 (*C*H_2-N), 52.3, 52.4 (*C*H_3-COO), 61.4 and 61.5 (q, $J_{C,F}$ = 27.4 Hz and $J_{C,F}$ = 27.8 Hz, C_q), 67.3 (CH-Ar), 67.4 (CH-Ar), 124.5, 124.5 (q, $J_{C,F}$ = 284.3 Hz, *C*F_3), 150.6 (C_q, tet), 151.1 (C_q, tet), 168.1 (*C*O), 168.6 (*C*O) ppm. ^{19}F NMR ($CDCl_3$): δ = –78.8, –79.1 (CF_3) ppm. IR: $\tilde{\nu}$ = 3271 (NH), 1753 (CO) cm^{-1}. $C_{13}H_{20}F_3N_5O_2$ (335.33): calcd. C 46.56, H 6.01, N 20.89; found C 46.53, H 5.97, N 20.78.

Ethyl 3-{5-[2-(Trifluoromethyl)piperidin-2-yl]-1*H*-tetrazol-1-yl}-propanoate (3l): Yield 84%, yellow oil. ^1H NMR ($CDCl_3$): δ = 1.19 (t, $J_{H,H}$ = 7.17 Hz, 3 H, CH_3), 1.29–1.57 (m, 3 H), 1.74–1.86 (m, 3 H), 2.13–2.22 (m, 1 H), 2.81–3.10 (m, 4 H), 4.10 (q, $J_{H,H}$ = 7.17 Hz, 2 H, *C*H_2-CH_3), 4.86–4.93 (m, 2 H), 5.01–5.08 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.9 (CH_3), 19.6, 25.2, 28.6, 33.3, 41.9 (CH_2-N), 45.1 (*C*H_2-Ar), 61.0 (*C*H_2-CH_3), 61.4 (q, $J_{C,F}$ = 27.8 Hz, C_q), 124.6 (q, $J_{C,F}$ = 284.3 Hz, CF_3), 150.3 (C_q, tet), 170.0 (CO) ppm. ^{19}F NMR ($CDCl_3$): δ = –79.5 (CF_3) ppm. IR: $\tilde{\nu}$ = 3317 (NH), 1737 (CO) cm^{-1}. $C_{12}H_{18}F_3N_5O_2$ (321.30): calcd. C 44.86, H 5.65, N 21.80; found C 44.83, H 5.50, N 22.01.

3-(2-{5-[2-(Trifluoromethyl)piperidin-2-yl]-1*H*-tetrazol-1-yl}ethyl)-1*H*-indole (3m): Yield 77%, yellow solid, m.p. 108–110 °C. ^1H NMR ($CDCl_3$): δ = 1.25–1.55 (m, 3 H), 1.68 (br. s, 1 H, NH), 1.77–1.90 (m, 3 H), 2.65–2.72 (m, 1 H), 2.84–2.92 (m, 1 H), 3.44–3.51 (m, 1 H), 3.55–3.63 (m, 1 H), 4.89–4.96 (m, 1 H), 5.15–5.23 (m, 1 H), 7.04–7.05 (m, 1 H, Ar), 7.15–7.27 (m, 2 H, Ar), 7.38–7.40 (m, 1 H, Ar), 7.65–7.67 (m, 1 H, Ar), 8.41 (br., 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.5, 25.1, 25.5, 28.7, 41.5 (CH_2-N), 50.1 (*C*H_2-Ar), 61.4 (q, $J_{C,F}$ = 27.5 Hz, C_q), 110.6 (C_q, Ar), 111.4 (Ar), 118.0 (Ar), 119.4 (Ar), 121.9 (Ar), 122.8 (Ar), 124.7 (q, $J_{C,F}$ = 284.7 Hz, CF_3), 126.9 (C_q, Ar), 136.2 (C_q, Ar), 150.4 (C_q, tet) ppm. ^{19}F NMR ($CDCl_3$): δ = –79.2 (CF_3) ppm. IR: $\tilde{\nu}$ = 3329 (NH), 3400 (br., NH) cm^{-1}. $C_{17}H_{19}F_3N_6$ (364.37): calcd. C 56.04, H 5.26, N 23.06; found C 56.14, H 5.36, N 23.00.

2-{1-[1-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)ethyl]-1*H*-tetrazol-5-yl}-2-(trifluoromethyl)piperidine (3n): Mixture of diastereomers, ratio 1:1, yield 60%, white solid, m.p. 193–195 °C. ^1H NMR ($CDCl_3$): δ = 0.80, 0.81 (s, 6 H, *C*H_3-Cq), 1.35-1.66 (m, 12 H), 1.72–2.05 (m, 6 H), 2.55-2.79 (m, 4 H, *C*H_2-N and *C*H_2-C_q), 2.89–2.94, 3.05-3.08, (m, 2 H, *C*H_2-N), 3.87–3.93 (m, 12 H, 3 *C*H_2), 5.28 (q, 1 H, $J_{H,H}$ = 7.00 Hz, *C*H-CH_3) and 5.86 (q, 1 H, $J_{H,H}$ = 6.83 Hz, *C*H-CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1, 14.1 (*C*H_3-CH), 15.8 (*C*H_3-C_q), 19.8, 20.0, 24.7, 25.7, 29.3, 28.5 (*C*H_2-C_q), 30.7, 30.7 (*C*$_q$), 41.5, 42.0 (*C*H_2-N), 59.1, 59.2 (*C*H-CH_3), 61.5 (q, $J_{C,F}$ = 27.1 Hz, C_q-CF_3), 72.7, 72.7 (*C*H_2-O), 107.3, 107.6 (*C*$_q$), 124.8, 124.9 (q, $J_{C,F}$ = 284.7 Hz, $J_{C,F}$ = 284.3 Hz, *C*F_3), 152.1, 151.2 (C_q, tet) ppm. ^{19}F NMR ($CDCl_3$): δ = –78.7, –78.8 (CF_3) ppm. IR: $\tilde{\nu}$ = 3310 (NH) cm^{-1}. $C_{15}H_{22}F_3N_5O_3$ (377.36): calcd. C 47.74, H 5.88, N 18.56; found C 47.89, H 5.73, N 18.44.

1-Benzyl-1*H*-tetrazole (4a): White solid, m.p. 59 °C. ^1H NMR ($CDCl_3$): δ = 5.6 (s, 2 H, *C*H_2), 7.27–7.33 (m, 2 H, Ar), 7.39–7.42 (m, 3 H, Ar), 8.54 (s, 1 H, Ar) ppm. Spectroscopic data are in agreement with those in the literature.[18]

General Procedure for Debenzylation: A solution of the appropriate tetrazole (1 mmol) in abs. MeOH (10 mL) was treated with palladium (10% on carbon) and placed under hydrogen (1 atm.). The mixture was stirred at room temperature for a few hours (TLC control). The mixture was filtered through Celite, which was then washed with methanol, and the filtrate was concentrated to give the product as a white solid.

5-[2-(Trifluoromethyl)pyrrolidin-2-yl]-1*H*-tetrazole (5a): Yield 87%, white solid, m.p. 152–154 °C (decomp.). ^1H NMR ([D$_6$]DMSO): δ = 1.65–1.77 (m, 1 H), 1.81–1.94 (m, 1 H), 2.53–2.31 (m, 2 H, CH_2-C_q), 2.93–3.05 (m, 2 H, CH_2-N), 6.63 (br. s, NH_2^+) ppm. ^{13}C NMR ($CDCl_3$): δ = 24.9, 33.0 (CH_2-C_q), 46.8 (CH_2-N), 65.0 (q, $J_{C,F}$ = 28.5 Hz, C_q-CF_3), 125.9 (q, $J_{C,F}$ = 283.2 Hz, CF_3), 157.7 (C_q, tet) ppm. ^{19}F NMR ($CDCl_3$): δ = –76.9 (CF_3) ppm. IR: $\tilde{\nu}$ = (b) 3400 (NH) cm^{-1}. HRMS (ESI): calcd. for $C_5H_8N_5F_3$ [M + H] 208.0805; found 208.0806.

2-(1*H*-Tetrazol-5-yl)-2-(trifluoromethyl)piperidine (5b): Yield 96%, white solid, m.p. 228–230 °C (decomp.). ^1H NMR ([D$_6$]DMSO): δ = 1.04–1.16 (m, 1 H), 1.38–1.44 (m, 2 H), 1.68–1.76 (m, 1 H), 1.84–1.91 (m, 1 H, CH_2-C_q), 2.34–2.41 (m, 1 H, CH_2-C_q), 2.51–2.57 (m, 1 H, CH_2-N), 2.91–2.94 (m, 1 H, CH_2-C_q), 5.37 (br. s, NH_2^+) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 19.3, 23.5, 26.9 (*C*H_2-C_q), 41.3 (CH_2-N), 59.6 (q, $J_{C,F}$ = 27.5 Hz, C_q), 124.8 (q, $J_{C,F}$ = 284.0 Hz, *C*F_3), 154.9 (C_q, tet) ppm. ^{19}F NMR ($CDCl_3$): δ = –79.2 (CF_3) ppm. IR: $\tilde{\nu}$ = 3425 (b, NH) cm^{-1}. HRMS (ESI): calcd. for $C_7H_{10}N_5F_3$ [M + H] 222.0961; found 222.0959.

2-(1*H*-Tetrazol-5-yl)-2-(trifluoromethyl)azepane (5c): Yield 92%, white solid, m.p. 148–150 °C (decomp.). ^1H NMR ([D$_6$]DMSO): δ = 1.07–1.17 (m, 1 H), 1.32–1.41 (m, 2 H), 1.53–1.77 (m, 3 H), 2.18–2.24 (m, 1 H, CH_2-C_q), 2.47–2.53 (m, 1 H, CH_2-C_q), 2.79–2.91 (m, 2 H, CH_2-N) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 22.4, 29.2, 32.0, 32.5, 42.9 (CH_2-N), 62.6 (q, $J_{C,F}$ = 26.3 Hz, C_q-CF_3), 126.3 (q, $J_{C,F}$

= 288.0 Hz, CF_3), 157.8 (C_q, tet) ppm. ^{19}F NMR ($CDCl_3$): δ = –77.8 (CF_3) ppm. IR: $\tilde{\nu}$ = 3352 (NH) cm^{-1}. HRMS (ESI): calcd. for $C_8H_{12}N_5F_3$ [M + H] 236.1118; found 236.1111.

Supporting Information (see footnote on the first page of this article): Copies of the ^1H NMR, ^{13}C NMR and ^{19}F NMR of compounds **3a**–**n** and **5a**–**c**.

Acknowledgments

The authors thank the Russian Foundation for Basic Research (RFBR 11-03-01167-a, 12-03-31582, and 12-03-00292) for financial support for this work.

[1] a) T. Hiyama (Ed.), *Organofluorine Compounds. Chemistry and Applications*, Springer, Berlin, Germany, **2000**; b) R. D. Chambers (Ed.), *Fluorine in Organic Chemistry*, Blackwell, Oxford, UK, **2004**; c) P. Kirsch (Ed.), *Modern Fluoroorganic Chemistry: Synthesis Reactivity, Applications*, Wiley-VCH, Weinheim, Germany, **2004**; d) K. Uneyama (Ed.), *Organofluorine Chemistry*, Blackwell, Oxford, **2006**; e) *Fluorine in the Life Sciences*, *ChemBioChem* **2004**, *5*, 559–722; f) P. Maienfisch, *Chimia* **2004**, *58*, 92–162; g) A. Tressaud, *Fluorine-Containing Agrochemicals: An Overview of Recent Developments*, in: *Advances in Fluorine Science*, vol. 2 (Ed.: G. Theodoridis), Elsevier, Amsterdam, **2006**, p. 121–175; h) J. P. Bégué, D. Bonnet-Delpon (Eds.), *Bioorganic and Medicinal Chemistry of Fluorine*, John Wiley & Sons, Hoboken, **2008**; i) A. Tressaud, G. Haufe (Eds.), *Fluorine and Health. Molecular Imaging*, *Biomedical Materials and Pharmaceuticals*, Elsevier, Amsterdam, **2008**, p. 553–778.

[2] a) L. Hunter, *Beilstein J. Org. Chem.* **2010**, *2*, no. 6; b) D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308–319.

[3] S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330.

[4] N. E. Shevchenko, E. S. Balenkova, G.-V. Röschenthaler, V. G. Nenajdenko, *Synthesis* **2010**, 120–126.

[5] a) I. L. Odinets, O. I. Artyushin, K. A. Lyssenko, N. E. Shevchenko, V. G. Nenajdenko, G.-V. Röschentaler, *J. Fluorine Chem.* **2009**, *130*, 662–666; b) O. I. Shmatova, N. E. Shevchenko, E. S. Balenkova, G.-V. Röschenthaler, V. G. Nenajdenko, *Eur. J. Org. Chem* **2013**, accepted; c) N. E. Shevchenko, O. I. Shmatova, E. S. Balenkova, G.-V. Röschenthaler, V. G. Nenajdenko, *Eur. J. Org. Chem.* **2013**, accepted; d) O. I. Shmatova, N. E. Shevchenko, E. S. Balenkova, G.-V. Röschenthaler, V. G. Nenajdenko, *Mendeleev Commun.* **2013**, *23*, 92–93.

[6] a) V. Bavetsias, J. H. Marriott, C. Melin, R. Kimbell, Z. S. Matusiak, F. T. Boyle, A. L. Jackman, *J. Med. Chem.* **2000**, *43*, 1910–1926; b) R. S. Upadhayaya, S. Jain, N. Sinha, N. Kishore, R. Chandra, S. K. Arora, *Eur. J. Med. Chem.* **2004**, *39*, 579–592; c) V. A. Ostrovskii, R. E. Trifonov, E. A. Popova, *Russ. Chem. Bull.* **2012**, *61*, 768–780; d) R. N. Butler, in: *Comprehensive Heterocyclic Chemistry*, vol. 5, part 4.13 (Eds.: A. R. Katritzky, C. W. Rees), Elsevier Science, Ltd. **1984**, p. 791–838.

[7] H. Gao, J. M. Shreeve, *Chem. Rev.* **2011**, *111*, 7377–7436.

[8] a) E. A. Popova, R. E. Trifonov, V. A. Ostrovskii, *ARCIVOC* **2012**, 45–65; b) G. Aromí, L. A. Barrios, O. Roubeau, P. Gamez, *Coord. Chem. Rev.* **2011**, *255*, 485–546.

[9] a) D. A. Longbottom, V. Franckevičius, S. V. Ley, *Chimia* **2007**, *61*, 247–256; b) M. Bhanushali, C.-G. Zhao, *Synthesis* **2011**, *12*, 1815–1830; c) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713–5743; d) C. Nájera, J. M. Sansano, *Chem. Rev.* **2007**, *107*, 4584–4681; e) M. Limbach, *Chem. Biodiversity* **2006**, *3*, 119–133; f) Y.-Y. Wu, Z. Chai, X.-Y. Liu, G. Zhao, S.-W. Wang, *Eur. J. Org. Chem.* **2009**, 904–911; g) H. Torii, M. Nakadai, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem.* **2004**, *116*, 2017–2020; *Angew. Chem. Int. Ed.* **2004**, *43*, 1983–1986; h) A. Hartikka, P. I. Arvidsson, *Eur. J. Org. Chem.* **2005**, 4287–4295; i) A. J. A. Cobb, D. M. Shaw, S. V. Ley, *Synlett* **2004**, 558–560; j) A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, J. B. Gold, S. V. Ley, *Org. Biomol. Chem.* **2005**, *3*, 84–96; k) N. S. Chowdari, M. Ahmad, K. Albertshofer, F. Tanaka, C. F. Barbas III, *Org. Lett.* **2006**, *8*, 2839–2842; l) K. R. Knudsen, C. E. T. Mitchell, S. V. Ley, *Chem. Commun.* **2006**, 66–68; m) C. E. T. Mitchell, S. E. Brenner, S. V. Ley, *Chem. Commun.* **2005**, 5346–5348; n) A. Prieto, N. Halland, K. Anker, *Org. Lett.* **2005**, *7*, 3897–3900; o) A. J. A. Cobb, D. A. Longbottom, D. M. Shaw, S. V. Ley, *Chem. Commun.* **2004**, 1808–1809; p) Y. Yamamoto, N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 5962–5963; q) D. B. Ramachary, C. F. Barbas III, *Org. Lett.* **2005**, *7*, 1577–1580; r) S.-T. (A.) Tong, P. W. R. Harris, D. Barker, M. A. Brimble, *Eur. J. Org. Chem.* **2008**, 164–170.

[10] a) R. J. Herr, *Bioorg. Med. Chem.* **2002**, *10*, 3379–3393; b) J. Roh, K. Vávrová, A. Hrabálek, *Eur. J. Org. Chem.* **2012**, 6101–6118.

[11] a) L. V. Myznikov, A. Hrabalek, G. I. Koldobskii, *Chem. Heterocycl. Compd.* **2007**, 3–13; b) B. C. H. May, A. D. Abell, *J. Chem. Soc. Perkin Trans. 1* **2002**, 172–178; c) A. Rajasekaran, P. P. Thampi, *Eur. J. Med. Chem.* **2004**, *39*, 273–279.

[12] a) J. Shirai, T. Yoshikawa, M. Yamashita, Y. Yamamoto, M. Kawamoto, N. Tarui, I. Kamo, T. Hashimoto, Y. Ikeura, *Bioorg. Med. Chem.* **2011**, *19*, 6430–6446; b) J. J. Hale, S. G. Mills, M. MacCoss, P. E. Finke, M. A. Cascieri, S. Sadowski, E. Ber, G. G. Chicchi, M. Kurtz, J. Metzger, G. Eiermann, N. N. Tsou, F. D. Tattersall, N. M. J. Rupniak, A. R. Williams, W. Rycroft, R. Hargreaves, D. E. MacIntyre, *J. Med. Chem.* **1998**, *41*, 4607–4614; c) T. G. Hamill, H. D. Burns, *J. Labelled Compd. Radiopharm.* **2004**, *47*, 99–106; d) F. T. Chin, C. L. Morse, H. U. Shetty, V. W. Pike, *J. Labelled Compd. Radiopharm.* **2006**, *49*, 17–31.

[13] a) N. Shibata, E. Suzuki, Y. Takeuchi, *J. Am. Chem. Soc.* **2000**, *122*, 10728–10729; b) B. Török, M. Abid, G. London, J. Esquibel, M. Török, S. C. Mhadgut, P. Yan, G. K. S. Prakash, *Angew. Chem.* **2005**, *117*, 3146–3149; *Angew. Chem. Int. Ed.* **2005**, *44*, 3086–3089; c) D. A. Nagib, M. E. Scott, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 10875–10877; d) T. Furukawa, N. Shibata, S. Mizuta, S. Nakamura, T. Toru, M. Shiro, *Angew. Chem.* **2008**, *120*, 8171–8174; *Angew. Chem. Int. Ed.* **2008**, *47*, 8051–8054; e) G. K. S. Prakash, F. Wang, T. Stewart, T. Mathew, G. A. Olah, *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 4090–4094.

[14] a) L. E. Zimmer, C. Sparr, R. Gilmour, *Angew. Chem.* **2011**, *123*, 12062–12074; *Angew. Chem. Int. Ed.* **2011**, *50*, 11860–11871; b) Y. J. Zhao, Y. H. Pan, S. B. D. Sim, C. H. Tan, *Org. Biomol. Chem.* **2012**, *10*, 479–485; c) G. Valero, X. Company, R. Rios, *Chem. Eur. J.* **2011**, *17*, 2018–2037; d) D. Cahard, X. Xu, S. Couve-Bonnaire, X. Pannecoucke, *Chem. Soc. Rev.* **2010**, *39*, 558–568; e) S. Lectard, Y. Hamashima, M. Sodeoka, *Adv. Synth. Catal.* **2010**, *352*, 2708–2732; f) A. Wittkopp, P. R. Schreiner, *Chem. Eur. J.* **2003**, *9*, 407–414; g) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673; h) B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, *7*, 1967–1969; i) S. H. McCooey, S. J. Connon, *Angew. Chem.* **2005**, *117*, 6525–6528; *Angew. Chem. Int. Ed.* **2005**, *44*, 6367–6370; j) J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296–18304.

[15] a) V. Nenajdenko (Ed.), *Isocyanide Chemistry*, Wiley-VCH, Weinheim, Germany, **2012**; b) A. Dömling, I. Ugi, *Angew. Chem.* **2000**, *112*, 3300–3344; *Angew. Chem. Int. Ed.* **2000**, *39*, 3168–3210; c) J. Zhu, *Eur. J. Org. Chem.* **2003**, 1133–1144; d) A. Dömling, *Chem. Rev.* **2006**, *106*, 17–89; e) A. V. Gulevich, A. G. Zhdanko, R. V. A. Orru, V. G. Nenajdenko, *Chem. Rev.* **2010**, *110*, 5235–5331; f) V. G. Nenajdenko, A. V. Gulevich, E. S. Balenkova, *Tetrahedron* **2006**, *62*, 5922–5930; g) A. V. Gulevich, N. E. Shevchenko, E. S. Balenkova, G.-V. Röschenthaler, V. G. Nenajdenko, *Synlett* **2009**, 403–406; h) V. G. Nenajdenko, A. V. Gulevich, K. Yu. Chernichenko, N. V. Sokolova, E. S. Balenkova, *Mendeleev Commun.* **2011**, *21*, 245–246;

i) A. V. Gulevich, N. E. Shevchenko, E. S. Balenkova, G.-V. Röschentaler, V. G. Nenajdenko, *Tetrahedron* **2008**, *64*, 11706–11712; j) A. V. Gulevich, I. V. Shpilevaya, V. G. Nenajdenko, *Eur. J. Org. Chem.* **2009**, 3801–3808; k) A. G. Zhdanko, V. G. Nenajdenko, *J. Org. Chem.* **2009**, *74*, 884–887; l) V. G. Nenajdenko, A. V. Gulevich, N. V. Sokolova, A. V. Mironov, E. S. Balenkova, *Eur. J. Org. Chem.* **2010**, 1445–1449; m) A. V. Gulevich, L. S. Koroleva, O. V. Morozova, V. N. Bakhvalova, V. N. Silnikov, V. G. Nenajdenko, *Beilstein J. Org. Chem.* **2011**, *7*, 1135–1140.

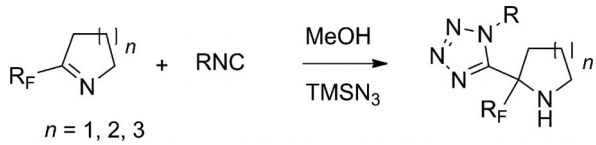
[16] a) T. Nixey, M. Kelly, D. Semin, C. Hulme, *Tetrahedron Lett.* **2002**, *43*, 3681–3684; b) M. Giustiniano, T. Pirali, A. Massarotti, B. Biletta, E. Novellino, P. Campiglia, G. Sorba, G. C. Tron, *Synthesis* **2010**, *23*, 4107–4118; c) M. Nayak, S. Batra, *Tetrahedron Lett.* **2010**, *51*, 510–516; d) C. Kalinski, M. Umkehrer, S. Gonnard, N. Jäger, G. Ross, W. Hiller, *Tetrahedron Lett.* **2006**, *47*, 2041–2044; e) S. Achatz, A. Dömling, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6360–6362; f) L. E. Kaim, L. Grimaud, in: *Isocyanide Chemistry* (Ed.: V. Nenajdenko), Wiley-VCH, Weinheim, Germany, **2012**, chapter 5, p. 167–171.

[17] a) M. Morgenthaler, E. Schweizer, A. Hoffmann-Röder, F. Benini, R. E. Martin, G. Jaeschke, B. Wagner, H. Fischer, S. Bendels, D. Zimmerli, J. Scheider, F. Diederich, M. Kansy, K. Müller, *ChemMedChem* **2007**, *2*, 1100–1115; b) A. V. Shcherbatiuk, O. S. Shyshlyk, D. V. Yarmoliuk, O. V. Shishkin, S. V. Shishkina, V. S. Starova, O. A. Zaporozhets, S. Zozulya, R. Moriev, O. Kravchuk, O. Manoilenko, A. A. Tolmachev, P. K. Mykhailiuk, *Tetrahedron* **2013**, *69*, 3796–3804.

[18] G. Aridoss, K. K. Laali, *Eur. J. Org. Chem.* **2011**, 2827–2835.

Received: June 13, 2013
Published Online: ■

Fluorinated Heterocycles



n = 1, 2, 3

The application of perfluoroalkyl cyclic imines in azido-Ugi reactions was demonstrated. The reaction was very general, and almost any 2-substituted imines bearing CF_3 or C_2F_5 could be used to prepare tetrazole derivatives. When benzyl isocyanide was used in the azido-Ugi reaction, the tetrazole products could easily be debenzylated by hydrogenolysis.

Keywords: Multicomponent reactions / Fluorine / Fluorinated compounds / Nitrogen heterocycles / Amines

