Journal of Fluorine Chemistry 148 (2013) 14–18

Contents lists available at SciVerse ScienceDirect

Journal of Fluorine Chemistry

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

Cycloaddition of N-substituted imines of trifluoropyruvate with diazomethane: Efficient synthesis of 2-(trifluoromethyl)aziridine-2-carboxylates

Yuliya V. Rassukana *, Ludmyla V. Bezgubenko, Petro P. Onys'ko, Anatoly D. Synytsya

Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Kyiv 02660, 5 Murmans'ka St, Ukraine

ARTICLE INFO

Article history:
Received 26 December 2012
Received in revised form 11 January 2013
Accepted 15 January 2013
Available online 28 January 2013

Keywords:
Trifluoropyruvate imines
Aziridinecarboxylic acids
Diazomethane
Triazolinecarboxylates
Cycloaddition

ABSTRACT

A convenient synthesis for 2-trifluorometylaziridine-2-carboxylates and respective acids, based on reaction of N-substituted trifluoropyruvate imines 1 with diazomethane, was developed.

1. Introduction

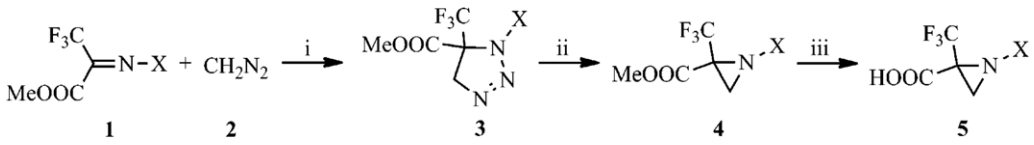
Fluorinated amino acids attracted much attention as potential enzyme inhibitors, antibacterial and antitumor agents etc. [1]. Introduction of fluorine atoms leads to profound changes in their physico-chemical and biological properties, such as high electronegativity, high lipophilicity, steric demand that increases with a number of fluorine atoms, and pharmacokinetic profile [1,2a,b]. On the other hand, aziridinocaboxylates, due to the strain associated with three-membered ring, have been widely used as versatile building blocks for the synthesis of a variety of pharmaceutically and biologically important molecules [3]. Furthermore, they are found among naturally occurring products [3]. At the same time there are only few examples of fluorinated aziridinecarboxylates [4], and free aziridinecarboxylic acids bearing trifluoromehyl group, to the best of our knowledge, are unknown so far. Therefore, the elaboration of efficient methods for the synthesis of compounds combining in their structure fragments of aziridine and fluorinated amino acid is a challenging task.

2. Results and discussion

Herein we wish to disclose a convenient method for the preparation of novel α-trifluoromethylated aziridine-2-carboxylic acids based on cycloaddition of N-substituted iminotrifluoropropionates with diazomethane. It is worthwhile to note that cycloaddition of imines with diazomethane was reported to proceed by different routes depending on substituents at azomethine bond. Thus, N-trifluoroacetylimine of trifluoropyruvate undergoes cycloaddition to form respective aziridine [4a], whereas N-benzoylimine of hexafluoroacetone gives [1 + 4]-cycloadduct [5]. We studied cycloaddition with diazomethane for a series of trifluoropyruvate imines **1a–g** essentially differing in polar and sterical characteristics of substituent at the nitrogen atom. It was found that in all cases the reaction leads initially to a mixture of [2 + 3] and [2 + 1] cycloaddition products, triazolines **3** and aziridines **4**. The observed ratio **3**/**4** depends on substituent X at nitrogen atom and is sensitive even to small impurities in staring compounds. Thus, the use of freshly distilled imines **1** leads to increase in **3**–**4** ratio. In case of N-phenyliminotrifluoropyruvate **1a** we managed to isolate triazolinecarboxylate **3a** and fully characterize it by spectral and analytical data. Triazolines **3** upon heating or/and in the presence of acidic catalysts (CF_3COOH, HCl) readily eliminate nitrogen to afford respective aziridinecarboxylates **4** in high yields (Scheme 1). Slow transformation **3** → **4** occurs even at room temperature and is completed within several months. It is to be noted that from experimental viewpoint the preparation of aziridinecarboxylates **4** is convenient and very simple: virtually pure aiziridines **4** are obtained merely upon exposing the ethereal solution of respective imine **1** and diazomethane **2** overnight at room temperature followed by heating in an organic solvent in the presence of acidic catalyst.

* Corresponding author. Tel.: +38 044 5732594; fax: +38 044 5732643.
E-mail address: juravi@rambler.ru (Y.V. Rassukana).

0022-1139/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jfluchem.2013.01.019



Scheme 1. Reagents and conditions: (i) Et_2O, r.t., overnight; (ii) Δ, CF_3COOH; (iii) THF, 1 M aq NaOH, 0 °C to r.t.; 10% aq citric acid, 0 °C to r.t.

The spectral and analytical data of compounds obtained are in complete agreement with their structure. Triazoline- (**3**) and aziridinecarboxylates **4** give clearly distinguishable ^{19}F NMR characteristics (δ_F −74.3 ÷ −76.2 ppm and −72.9 ÷ −73.6 ppm, respectively) that allow easy monitoring of the process and identification of the products in the reaction mixture. The transformation **3** → **4** is accompanied by a downfield shift of fluorine signals of CF_3 group and essential upfield displacement of hydrogen and carbon NMR signals of endocyclic CH_2 group. Generation of a new chiral center upon formation of compounds **3**, **4** is an additional evidence to the fact that ring closure involves imine carbon atom. This is clearly revealed in magnetic non-equivalence of diastereotopic hydrogen atoms of CH_2 group in the ^1H NMR spectra of compounds **3**, **4**. In five member heterocycles **3** NCH_2 proton signals reveal themselves as two doublets of AB system (δ_A 4.8–4.9, δ_B 5.0–5.1 ppm, $^2J_{AB}$ 17.6–18.3 Hz), whereas in three-member heterocycles **4** - as poorly resolved separate multiplets (δ_A 2.6–3.1 ppm, $^2J_{AB}$ 0.6–2 Hz, δ_B 3.0–3.5 ppm, $^4J_{HF}$ 1–2 Hz). Moreover, spin-spin coupling of the NCH_2 group signals on magnetic nuclei (^{31}P and ^{19}F) situated on both atoms of the C–N diad, revealed in ^1H, ^{13}C NMR spectra of compound **4h** [δ (NCH_A) 2.63 ppm, $^3J_{HP}$ = 11.4 Hz, δ (NCH_B) 3.02 ppm, $^3J_{HP}$ = 15.3 Hz, $^4J_{HF}$ 2 Hz, $^2J_{AB}$ 2 Hz; δ_C 32.9 ppm, $^2J_{CP}$ 6.3 Hz, $^2J_{CF}$ 2.5 Hz] unequivocally proves the formation of aziridine cycle.

Upon treatment with aq NaOH in THF, aziridinecarboxylates **4** were converted into respective water soluble free acids **5** representing the first examples of 2-(trifluoromethyl)aziridine-2-carboxylic acids. In case of dimethyl 2-trifluoromethylaziridine-1,2-dicarboxylate **3f** we managed to carry out selective hydrolysis of 2-COOMe group leading to respective aziridine-2-carboxylic acid **5f**.

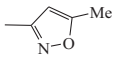
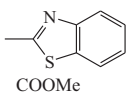
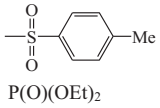
3. Conclusions

In summary, based on cycloaddition of readily accessible trifluoropyruvate imines with diazomethane, we have developed a simple and efficient synthesis of N-substituted 2-(trifluoromethyl)aziridine-2-carboxylates and respective carboxylic acids.

4. Experimental

IR spectra were obtained with an UR-20 instrument. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker Avance DRX 500 (operating frequency 500.068 and 125.76 MHz respectively), ^{19}F NMR and ^{31}P spectra – on Gemini 200 Varian instrument operating at 188.14 and 80.95 MHz, respectively. Chemical shifts are reported relative to internal TMS (^1H) or $CFCl_3$ (^{19}F) and external 85%-H_3PO_4 (^{31}P) standards. Melting points are uncorrected. Solvents were dried before use according to standard methods. Atmospheric pressure chemical ionization mass spectra (APCI MS) were recorded on Agilent 1100/LC/MSD spectrometer. Starting compounds **1a** [6], **1b** [7], **1c** [8], **1f** [9], **1h** [10] were prepared as described in the literature.

Table 1
Synthesis of compounds **3** and **4**.

Compound	X	The ratio of **3**/**4** (see exptl.)	Solvent and reaction time (h) for **3** → **4** conversion	Yield of **4** (%)	Molecular formula of **4**	MS (*m*/*z*) of **4** (M+1)	Analysis of **4** found (calcd.)
a		>20	Toluene, 7	70	$C_{11}H_{10}F_3NO_2$ (245.2)	245.8	C, 53.35 (53.88); H, 4.15 (4.11); N, 5.65 (5.71)
b		10:1	Toluene, 4	90	$C_{10}H_9F_3N_2O_2$ (246.2)	246.8	C, 48.35 (48.79); H, 3.62 (3.68); N, 11.30 (11.38)
c		10:1	Toluene; 31	67	$C_{10}H_{10}F_3N_3O_2$ (261.2)	262.0	C, 45.75 (45.98); H, 3.89 (3.86); N, 16.1 (16.09)
d		10:1	Toluene; 35	62	$C_9H_9F_3N_2O_3$ (250.2)	251.0	C, 43.18 (43.21); H, 3.59 (3.63); N, 11.15 (11.20)
e		2:1	Benzene; 6	70	$C_{12}H_9F_3N_2O_2S$ (302.3)	303.0	C, 47.63 (47.68); H, 2.98 (3.00); N, 9.25 (9.27); S, 10.55 (10.61)
f	COOMe	10:1	$CHCl_3$, 3	95	$C_7H_8F_3NO_4$ (227.1)	227.8	C, 36.89 (37.01); H, 3.59 (3.55); N, 6.11 (6.17)
g		--[a]	--	75	--	--	--
h	$P(O)(OEt)_2$	>20	$CHCl_3$, 5	77	$C_9H_{15}F_3NO_5P$ (305.2)	306.2	C, 35.37 (35.42); H, 4.90 (4.95); N, 4.54 (4.59)

[a] 3 g was not detected.

Table 2
Characteristics of compounds **3** and **4**.

Compound	Melting point (°C)	IR ν (cm^{-1}) (C=O)	^{19}F NMR ($CDCl_3$), δ (ppm)	^1H NMR ($CDCl_3$), δ (ppm), J (Hz); ^{13}C NMR ($CDCl_3$), δ (ppm), J (Hz)
3a	Oil	1760	−74.5	^1H NMR: 3.75 (s, 3H, MeO), 4.93 (d, $^2J_{HH}$ = 17.6 Hz, 1H, NCH_A), 5.03 (d, $^2J_{HH}$ = 17.6 Hz, 1H, NCH_B), 7.19 (t, $^3J_{HH}$ = 7.5 Hz, 1H, Ph), 7.27 (d, $^3J_{HH}$ = 7.5 Hz, 2H, Ph), 7.36 (t, $^3J_{HH}$ = 7.5 Hz, 2H, Ph) ^{13}C NMR: 53.77 (MeO), 68.00 (q, $^2J_{CF}$ = 30.2 Hz, $\underline{C}CF_3$), 76.52 (CH_2), 119.68, 125.70, 129.28, 138.93 (Ph), 123.13 (q, $^1J_{CF}$ = 289 Hz, CF_3), 166.08 (C=O)
3b	–-[a]	1760	−75.2	^1H NMR: 3.77 (s, 3H, MeO), 4.82 (d, $^2J_{HH}$ = 17.6 Hz, 1H, NCH_A), 5.02 (d, $^2J_{HH}$ = 17.6 Hz, 1H, NCH_B), 7.00 (m, 1H, Ht), 7.70 (m, 2H, Ht), 8.21 (m, 1H, Ht)
3c	–-[a]	1765	−75.2	^1H NMR: 2.50 (s, 3H, MeC), 3.78 (s, 3H, MeO), 4.89 (d, $^2J_{HH}$ = 17.8 Hz, 1H, NCH_A), 5.1 (d, $^2J_{HH}$ = 17.8 Hz, 1H, NCH_B), 6.91 (d, $^3J_{HH}$ = 4.9 Hz, 1H, Ht), 8.44 (d, $^3J_{HH}$ = 4.9 Hz, 1H, Ht)
3d	–-[a]	1755	−74.4	^1H NMR: 2.41 (s, 3H, MeC), 3.85 (s, 3H, MeO), 4.94 (d, $^2J_{HH}$ = 18 Hz, 1H, NCH_A), 5.08 (d, $^2J_{HH}$ = 18 Hz, 1H, NCH_B), 6.34 (s, 1H, Ht)
3e	–-[a]	–-	−74.3	–-
3f	–-[a]	1765	−76.2	^1H NMR: 3.85 (s, 3H, MeO), 3.96 (s, 3H, MeO), 4.83 (d, $^2J_{HH}$ = 18.3 Hz, 1H, NCH_A), 5.00 (d, $^2J_{HH}$ = 18.3 Hz, 1H, NCH_B)
3h[b]	–-[a]	1765	−77.4	^1H NMR: 1.37 (m, 6H, $\underline{Me}CH_2$), 3.87 (s, 3H, MeO), 4.24 (m, 4H, CH_2O), 4.76 (dd, $^2J_{HH}$ = 18.0 Hz, $^4J_{HP}$ = 0.9 Hz, 1H, NCH_A), 5.00 (dd, $^2J_{HH}$ = 18.0 Hz, $^4J_{HP}$ = 1.8 Hz, 1H, NCH_B) ^{13}C NMR: 15.85 (d, $^3J_{CP}$ = 6.3 Hz, $\underline{Me}CH_2$), 54.01 (MeO), 64.66 (d, $^2J_{CP}$ = 7.5 Hz, CH_2O), 64.73 (d, $^2J_{CP}$ = 5 Hz, CH_2O), 65.76 (qd, $^2J_{CF}$ = 31.4 Hz, $^2J_{CP}$ = 7.5 Hz, $\underline{C}CF_3$), 76.39 (d, $^2J_{CP}$ = 7.5 Hz, CH_2N), 122.87 (q, $^1J_{CF}$ = 284 Hz, CF_3), 166.37 (C=O)
4a	Oil	1750	−72.9	^1H NMR: 2.87 (d, $^2J_{HH}$ = 1.3 Hz, 1H, NCH_A), 3.03 (m, 1H, NCH_B) 3.55 (s, 3H, CH_3O), 6.9 (d, $^3J_{HH}$ = 7.5 Hz, 2H, Ph), 7.05 (t, $^3J_{HH}$ = 7.5 Hz, 1H, Ph), 7.26 (t, $^3J_{HH}$ = 7.5 Hz, 2H, Ph) ^{13}C NMR: 35.01 (CH_2), 45.98 (q, $^2J_{CF}$ = 36.5 Hz, $\underline{C}CF_3$), 52.82 (CH_3O), 122.46 (q, $^1J_{CF}$ = 275 Hz, CF_3), 119.58, 123.96, 129.11, 146.79 (Ph), 163.21 (C=O)
4b	Oil	1750	−72.9	^1H NMR: 2.94 (d, $^2J_{HH}$ = 0.9 Hz, 1H, NCH_A), 3.23 (m, 1H, NCH_B), 3.60 (s, 3H, CH_3O), 6.86 (d, $^3J_{HH}$ = 8 Hz, 1H, 3-H_{Py}), 6.99 (m, $^3J_{H\text{-}5,H\text{-}4}$ = 7.3 Hz, $^3J_{H\text{-}5,H\text{-}6}$ = 5 Hz, 1H, 5-H_{Py}), 7.60 (m, $^3J_{H\text{-}4,H\text{-}3}$ = 8 Hz, $^3J_{H\text{-}4,H\text{-}5}$ = 7.3 Hz, 1H, 4-H_{Py}), 8.27 (d, $^3J_{HH}$ = 5.0 Hz, 1H, 6-H_{Py})
4c	70–72	1745	−73.1	^1H NMR: 2.43 (s, 3H, MeC), 2.98 (d, $^2J_{HH}$ = 1 Hz 1H, NCH_A), 3.21 (m, 1H, NCH_B), 3.68 (s, 3H, MeO), 6.82 (d, $^3J_{HH}$ = 5 Hz, 1H, Ht), 8.34 (d, $^3J_{HH}$ = 5 Hz, 1H, Ht)
4d	30–31	1750	−72.9	2.32(s, 3H, MeC), 2.89 (br, 1H, NCH_A), 3.16 (m, 1H, NCH_B), 3.71 (s, 3H, MeO), 5.71 (s, 1H, Ht)
4e	80–83	1760	−73.0	^1H NMR: 3.09 (d, $^3J_{HH}$ = 0.6 Hz, 1H, NCH_A), 3.46 (m, 1H, NCH_B), 3.70 (s, 3H, CH_3O), 7.29 (t, $^3J_{HH}$ = 7.9 Hz, 1H, Ht), 7.40 (t, $^3J_{HH}$ = 7.9 Hz, 1H, Ht), 7.69 (d, $^3J_{HH}$ = 7.9 Hz, 1H, Ht), 7.79 (d, $^3J_{HH}$ = 7.9 Hz, 1H, Ht); ^{13}C NMR: 37.20 (CH_2), 46.88 (q, $^2J_{CF}$ = 37.7 Hz, $\underline{C}CF_3$), 53.60 (CH_3O), 121.74 (q, $^1J_{CF}$ = 276 Hz, CF_3), 121.44, 121.99, 124.55, 126.42, 133.42, 150.62, 167.82, (Ht), 162.40 (C=O)
4f	Liquid	1765	−73.6 (d, $^4J_{FH}$ 1 Hz)	^1H NMR: 2.70 ($^2J_{HH}$ = 1.1 Hz 1H, NCH_A), 2.99 (quintet, $^2J_{HH}$ = $^4J_{HF}$ = 1.1 Hz 1H, NCH_B), 3.77 (s, 3H, CH_3O), 3.88 (s, 3H, CH_3O); ^{13}C NMR: 34.41 (CH_2), 43.05 (q, $^2J_{CF}$ = 37.7 Hz, $\underline{C}CF_3$), 53.71 (CH_3O), 54.02 (CH_3O), 121.33 (q, $^1J_{CF}$ = 276 Hz, CF_3), 158.55 (C=O), 163.64 (C=O)
4g	78–80[c] (petroleum ether)	1755	−73.4 (d, $^4J_{FH}$ = 1.5 Hz)	^1H NMR: 2.46 (s, 3H, CH_3), 2.79 (s, 1H, NCH_A), 3.54 (q, $^4J_{HF}$ = 1.6 Hz, 1H, NCH_B), 3.93 (s, 3H, CH_3O), 7.37 (d, $^3J_{HH}$ = 8.2 Hz, 2H, Ar), 7.85 (d, $^3J_{HH}$ = 8.2 Hz, 2H, Ar)
4h[d]	Oil	1765	−74.3	^1H NMR: 1.36 (m, 6H, $\underline{Me}CH_2$, 2.63 (dd, $^3J_{HP}$ = 11.4 Hz, $^2J_{HH}$ 2 Hz, 1H, NCH_A), 3.02 (m, $^3J_{HP}$ = 15.3 Hz, $^2J_{HH} \sim {}^4J_{HF} \sim$ 2 Hz, 1H, NCH_B), 3.85 (s, 3H, MeO), 4.20 (m, 4H, CH_2O); ^{13}C NMR: 15.95 (d, $^3J_{CP}$ = 6 Hz, $\underline{Me}CH_2$), 16.04 (d, $^3J_{CP}$ = 7 $\underline{Me}CH_2$), 32.90 (dq, $^2J_{CP}$ = 6 Hz, $^3J_{CF}$ = 2 Hz, CH_2N), 44.60 (qd, $^2J_{CF}$ = 37.7 Hz, $^2J_{CP}$ = 6.3 Hz, $\underline{C}CF_3$), 53.51(CH_3O), 64.22 (d, $^2J_{CP}$ = 7 Hz, CH_2O), 64.35 (d, $^2J_{PC}$ = 6 Hz, CH_2O), 121.78 (qd, $^1J_{CF}$ = 277 Hz, $^3J_{CP}$ = 6 Hz, CF_3), 163.22 (d, $^3J_{CP}$ = 7 Hz, C=O)

[a] Identified in mixture with respective aziridine **4** (see Table 1).
[b] δ_P −6.4 ppm ($CDCl_3$).
[c] lit. **4b** m.p. 80–82 °C.
[d] δ_P 5.7 ppm ($CDCl_3$).

Table 3
Characteristics of compounds **5**.

Compound	Melting point (°C)	Yield (%)	IR, ν (cm^{-1}) (C=O)	^{19}F NMR, δ (ppm)	Molecular formula	MS (m/z)	Analysis found (calcd.)
5a	122–125	65	1740	−73.0 ($CDCl_3$)	$C_{10}H_8F_3NO_2$ (231.2)	232.2 (M+1)	C, 51.89 (51.96); H, 3.44 (3.49); N, 6.01 (6.06)
5b	133–135	60	1735	−72.7 (D_2O)	$C_9H_7F_3N_2O_2$ (232.2)	233.0 (M+1)	C, 46.49 (46.56); H, 3.07 (3.04); N, 12.03 (12.07)
5c	168–170	63	1735	−72.3 (acetone=d_6)	$C_9H_8F_3N_3O_2$ (247.2)	248.2 (M+1)	C, 43.67 (43.73); H, 3.23 (3.26); N, 16.97 (17.00)
5d	70–73	90	1740	−72.9 ($CDCl_3$)	$C_8H_7F_3N_2O_3$ (236.1)	235.0 (M-1)	C, 40.65 (40.69); H, 3.01 (2.99); N, 11.83 (11.86)
5e	180–182	78	1725	−73.0 (acetone-d_6)	$C_{11}H_7F_3N_2O_2S$(288.2)	289.2 (M+1)	C, 45.77 (45.84); H, 2.41 (2.45); N, 9.70 (9.72); S, 11.09 (11.12)
5f	213–215	75	1760	−72.1 (acetone-d_6)	$C_6H_6F_3NO_4$ (213.1)	214.1 (M+1)	C, 33.73 (33.82); H, 2.81 (2.84); N, 6.52 (6.57)
5g	100–113	67	1770	−71.5 (DMSO-d_6)	$C_{11}H_{10}F_3NO_4S$(309.3)	310.3 (M+1)	C, 42.65 (42.72); H, 3.22 (3.26); N, 4.51 (4.53); S, 10.32 (10.37)

Table 4
^1H, ^{13}C NMR spectra of compounds **5**.

Compound	^1H NMR, δ (ppm), J (Hz); ^{13}C NMR, δ (ppm), J (Hz)
5a	^1H NMR ($CDCl_3$): 2.89 (br, 1H, NCH_A), 2.98 (br, 1H, NCH_B), 6.89 (d, $^3J_{HH}$ = 7.5 Hz, 2H, Ph), 7.05 (t, $^3J_{HH}$ = 7.5 Hz, 1H, Ph), 7.24 (t, $^3J_{HH}$ = 7.5 Hz, 2H, Ph)
5b	^1H NMR (D_2O): 2.93 (br, 1H, NCH_A), 3.02 (br, 1H, NCH_B) 7.23 (d, $^3J_{HH}$ = 8.7 Hz, 1H, 3-H_{Py}), 7.32 (m, 1H, 5-H_{Py}), 8.1 (m, 2H, 4-H_{Py}, 6-H_{Py})
5c	^1H NMR (acetone-d_6): 2.25 (s, 3H, Me), 2.81 (d, $^3J_{HH}$ = 0.6 Hz, 1H, NCH_A), 3.16 (br m, 1H, NCH_B), 6.84 (d, $^3J_{HH}$ = 5 Hz, 1H, Ht), 8.22 (d, $^3J_{HH}$ = 5 Hz, 1H, Ht)
5d	^1H NMR ($CDCl_3$): 2.31 (s, 3H, Me), 2.86 br, 1H, NCH_A), 3.06 br, 1H, NCH_B), 5.77 (s, 1H, Ht)
5e	^1H NMR (DMSO-d_6): 3.25 (d, $^3J_{HH}$ = 1.5 Hz, 1H, NCH_A), 3.32 (br, 1H, NCH_B), 7.32 (m, 1H, Ht), 7.43 (m, 1H, Ht), 7.77 (d, $^3J_{HH}$ = 7.9 Hz, 1H, Ht), 7.94 (d, $^3J_{HH}$ = 7.6 Hz, 1H, Ht); ^{13}C NMR (DMSO-d_6): 37.56 (CH_2), 46.92 (q, $^2J_{CF}$ = 35.2 Hz, $\underline{C}CF_3$), 122.70 (q, $^1J_{CF}$ = 276 Hz, CF_3), 121.83, 122.58, 124.76, 126.85, 133.46, 150.94, 169.02 (Ht), 163.17 (C=O),
5f	^1H NMR (acetone-d_6): 2.27 (d, $^3J_{HH}$ = 0.9 Hz, 1H, NCH_A), 2.67 (br m, 1H, NCH_B), 3.51 (s, 3H, CH_3O); ^{13}C NMR (acetone-d_6): 32.62 (CH_2), 44.60 (q, $^2J_{CF}$ = 35.6 Hz, $\underline{C}CF_3$), 53.15 (CH_3O), 123.31 (q, $^1J_{CF}$ = 276 Hz, CF_3), 161.44 (C=O), 166.20 (C=O)
5g	^1H NMR (DMSO-d_6): 2.39 (s, 3H, Me), 2.58 (d, $^3J_{HH}$ = 0.7 Hz, 1H, NCH_A), 3.05 (br m, 1H, NCH_B), 7.39 (d, $^3J_{HH}$ = 8 Hz, 2H, Ar), 7.82 (d, $^3J_{HH}$ = 8 Hz, 2H, Ar)

*4.1. Compounds **1d**, **e**, **g**: general procedure [8]*

The methyl trifluoropyruvate (20 mmol) was added dropwise to a stirred suspension of appropriate amine (20 mmol) in benzene (20 ml) at r.t. The reaction mixture is spontaneously warmed and became homogeneous. The mixture was left for 1 h at r.t., and then thionyl chloride (20 mmol) was added. After 15 minutes pyridine (40 mmol) was added dropwise to stirred and cooled to 0 °C mixture and allowed to warm to room temperature. Pyridine hydrochloride was filtered off, the solvent was evaporated under reduced pressure and the residue was distilled to give iminotrifluoropropanoate **1**.

*4.1.1. Methyl 3,3,3-trifluoro-2-[(5-methylisoxazol-3-yl)imino]propanoate **1d***

Yield 88%, bp 53 °C (0.07 mm Hg), m.p. 35–37 °C. IR (KBr): 1640 (C=N), 1790 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.45 (s, 3H, CH_3C), 3.89 (s, 3H, CH_3O), 6.07 (s, 1H, Ht). ^{19}F NMR (188 MHz, $CDCl_3$): δ −71.07. Anal. calcd. for $C_8H_7F_3N_2O_3$: C, 40.69; H, 2.99; N, 11.86. Found: C, 40.65; H, 2.96; N, 11.85.

*4.1.2. Methyl 3,3,3-trifluoro-2-[(1,3-benzothiazol-2-yl)imino]propanoate **1e***

Yield 90%, bp 101 °C (0.07 mm Hg). ^1H NMR data of compound **1e** are in agreement with the literature data [11].

*4.1.3. Methyl 3,3,3-trifluoro-2-(tosylimino)propanoate **1 g***

Yield 80%, m.p. 47–48 °C. IR (KBr): 1690 (C=N), 1770 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.47 (s, 3H, CH_3C), 4.04 (s, 3H, CH_3O), 7.40 (d, 2H, $^3J_{HH}$ 8.3 Hz, Ar), 7.88 (d, 2H, $^3J_{HH}$ 8.3 Hz, Ar). ^{19}F NMR ($CDCl_3$): δ = −71.5. Anal. calcd for $C_{11}H_{10}F_3NO_4S$: C, 42.72; H, 3.26; N, 4.53, S, 10.37. Found: C, 42.39; H, 3.35; N, 4.41, S, 10.23.

*4.2. Methyl 1-X-5-trifluoromethyl-1H-4,5-dihydro-1,2,3-triazole-5-carboxylates **3** and methyl 1-X-2-trifluoromethylaziridine-2-carboxylates **4**: general procedure*

A solution of diazomethane **2** (1.3 mmol) in diethyl ether (15 ml) was added to imine **1** (0.13 mmol) at 5 °C and stirred at room temperature overnight. The solvent was evaporated in vacuum to give the mixture of triazoline **3** and aziridine **4**, the ratio is indicated in Table 1. The mixture was dissolved in respective solvent (in case of compounds **3a**, **b**, **h** 1–2 drops of CF_3COOH were added to the solution) and refluxed. The solvent and reaction time are indicated in Table 1. After reaction was complete the solvent was evaporated in vacuum and the residue was extracted with petroleum ether (3× 5 mL). The combine extracts were evaporated under reduced pressure to give target compound **4** (Tables 1 and 2).

*4.3. Preparation of 1-X-2-trifluoromethylaziridine-2-carboxylic acids **5**: general procedure*

To a stirred and cooled solution of respective ester **4** (0.81 mmol) in THF (2 mL), 1 M aq NaOH (1 mL) was slowly added dropwise at 0 °C. The resulting reaction mixture was left at 15–20 °C overnight. The organic solvent was removed in vacuo, resulting water solution was washed with chloroform (5 ml) and acidified to pH 4 with 10% aq citric acid at 0 °C. Water was evaporated in vacuo, the residue was extracted with ethyl acetate (3× 10 ml). The solvent was removed in vacuo and the residue was triturated with diethyl ether to give acid **5** (Tables 3 and 4).

In case of compound **5e**, acidification is accompanied by precipitation. The precipitate formed was separated and washed with diethyl ether to afford pure acid **5e**.

References

[1] X.-L. Qiu, F.-L. Qing., Eur. J. Org. Chem (2011) 3261–3278.
[2] (a) R. Filler, Y. Kobayashi, L.M. Yagupolskii (Eds.), Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications, Elsevier, Amsterdam, 1993;
(b) R. Smits, C.D. Cadicamo, K. Burger, B. Koksch, Chem. Soc. Rev 37 (2008) 1727–1739.
[3] P. Zhou, B.-C. Chen, F.D. Davis, in: K.A. Yudin (Ed.), Aziridines and Epoxides in Organic Synthesis, Wiley-VCH, Weinheim, 2006, pp. 73–116.
[4] (a) S.N. Osipov, A.F. Kolomiets, A.V. Fokin, Russ. Chem. Bull. 37 (1988) 122–126;
(b) E. Yamauchi, T. Kawate, T. Katagiri, K. Uneyama, Tetrahedron Lett. 44 (2003) 6319–6322;
(c) E. Yamauchi, T. Kawate, H. Itahashi, T. Katagiri, K. Uneyama, Tetrahedron 59 (2003) 9839–9847;
(d) D. Colantoni, S. Fioravanti, L. Pellacani, P.A. Tardella, Org. Lett. 6 (2004) 197–200.
[5] Y.V. Zeifman, N.P. Gambaryan, L.A. Simonyan, R.B. Minasyan, I.L. Knunyants, Zhurn. Obshch. Khim. 37 (1967) 2476–2486; Russ. J. Gen. Chem. [Engl.] 37 (1967) 2355–2363.
[6] V.A. Soloshonok, I.I.Yu. Gerus, L. Yagupol'skii, V.P. Kukhar, Zhurn. Org. Khim. 23 (1987) 2308–2313; Russ. J. Org. Chem. [Engl.] 23 (1987) 2034–2038.
[7] V.B.A. Sokolov, Yu. Aksinenko, I.V. Martynov, Russ. Chem. Bull. 54 (2005) 470–471.
[8] Y.V. Rassukana, Y.Y. Khomutnyk, Onys'ko, P.P.; Sinitsa, A.D.; Gakh A. A. J., Fluor. Chem. 131 (2010) 1044–1048.
[9] V.A. Soloshonok, I.I. Gerus, L. Yu., Yagupol'skii, Zhurn. Org. Khim. 22 (1986) 1335–1337; Russ. J. Org. Chem. [Engl.]). 22 (1986) 1204–1205.
[10] P.P. Onys'ko, Yu.V. Rassukanaya, A.D. Sinitsa, Zhurn. Obshch. Khim. 72 (2002) 1802–1806; Russ. J. Gen. Chem. [Engl.] 72 (2002) 1699–1702.
[11] Yu. Aksinenko, T.V. Goreva, T.A. Epishina, A.N. Pushin, V.B. Sokolov, Russ. Chem. Bull. 55 (2006) 1052–1055.