Journal of Fluorine Chemistry 132 (2011) 175–180

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

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

Formation and reactivity of *gem*-difluoro-substituted pyridinium ylides: Experimental and DFT investigation

Ilia J. Kobylianskii, Mikhail S. Novikov *, Alexander F. Khlebnikov

Department of Chemistry, Saint-Petersburg State University, Universitetskii pr. 26, 198504 St. Petersburg, Petrodvorets, Russia

ARTICLE INFO

Article history:
Received 28 October 2010
Received in revised form 11 December 2010
Accepted 21 December 2010
Available online 28 December 2010

Keywords:
Indolizines
Pyridines
Carbenes
Ylides
Dipolar cycloaddition

ABSTRACT

According to DFT B3LYP/6-31G* calculations the reaction of difluorocarbene with pyridines proceeds reversibly with the formation of thermodynamically unstable intermediates, difluoro-substituted pyridinium ylides, which dissociate to carbene and pyridine with low activation barrier. The equilibrium constant of the reaction increases with increasing electron-withdrawing ability of substituents in the pyridine ring. Difluoroylides were generated from 4-cyano, 4-benzoyl- and 4-ethoxycarbonyl-substituted pyridines under difluorocarbene generation conditions (CF_2Br_2/Pb/Bu_4NBr/CH_2Cl_2/ultrasound) and trapped with dimethyl maleate or fumaronitrile. 3-Fluoroindolizines were isolated as final products of the reaction which involves dehydrofluorination of the primary cycloadducts followed by dehydrogenation by active MnO_2.

1. Introduction

Fluorine substituents have a unique and often profound impact on the structure and chemical reactivity of organic compounds. This is especially true for reactive intermediates that are formed in different reactions of fluorinated compounds. Thus a successive replacement of hydrogens by fluorines results in increased pyramidalization of carbon-centered radicals [1,2]. Attachment of fluorine onto the divalent carbon of a carbene stabilizes the singlet state relative to the triplet because of π-donating ability of fluorine [3,4]. Besides, fluorine directly attached to a carbene center thermodynamically stabilizes the carbene and, as a result, difluorocarbene is more highly stabilized and less reactive than other halo- and dihalocarbenes [5].

Recently using quantum-chemical calculations (B3LYP/6-31G*) we revealed a fundamental difference in the formation of difluoro- and other dihalogeno-substituted azomethine ylides. Dichlorocarbene, for example, adds to imines in irreversible mode without an activation barrier, whereas analogous reactions of difluorocarbene are reversible [6]. The reversibility of the formation of *gem*-difluorosubstituted iminium ylides is the origin of some peculiarities of its reactivity. In particular they do not cyclize to aziridines in contrast to monofluoro- [7] and *gem*-dichloro-substituted analogues [8].

Ylides, generated by addition of dichlorocarbene to azines, diazines and its fused derivatives, are well studied [8–15]. These species have been used as synthetic blocks in the preparation of chlorosubstituted indolizines, its heteroatomic and fused derivatives via 1,3-dipolar cycloaddition to various dipolarophiles. Recently the UV detection of pyridinium and isoquinolinium difluoroylides in the reactions of pyridine and isoquinoline with difluorocarbene, generated by FVP of difluorodiazirine, was reported [16]. Fluorinated pyridinium ylides also were supposed to have been intermediates in the reactions of *N*-bromodifluoromethylated pyridine salts but have never been trapped by dipolarophiles [17,18].

In this paper we report a new method of generation and the first example of cycloadditions of *gem*-difluorosubstituted pyridinium ylides, which give rise to a new class of fluoro-containing heterocycles, 3-fluoroindolizines, as well as the calculation results for the formation and reactivity of these dipolar intermediates.

2. Computational details

Geometry optimizations of reactants, products, intermediates and transition states in the gas phase were performed at the B3LYP/6-31G* [19–21] level using Gaussian 03 [22]. Stationary points on the respective potential-energy surfaces were characterized at the same level of theory by evaluating the corresponding Hessian indices. Careful verification of the unique imaginary frequencies for transition states was carried out to check whether the frequency indeed pertains to the desired reaction coordinate.

* Corresponding author. Fax: +7 812 4286939.
E-mail address: m.s.novikov@chem.spbu.ru (M.S. Novikov).

0022-1139/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2010.12.013

Intrinsic reaction coordinates (IRC) were calculated to authenticate all transition states [23].

3. Results and discussion

3.1. Quantum-chemical study

Earlier we have shown that difluorocarbene adds to imines and 3-aryl-2*H*-azirines to form corresponding difluoroylides with $\Delta G^{\neq}$ = 42–46 kJ/mol [6,24]. The reverse reaction has an activation barrier 8–13 kJ/mol lower. Iminiodifluoromethanides and aziriniodifluoromethanides are, therefore, thermodynamically unstable compounds which are formed in reaction mixtures in relatively low concentrations. Nevertheless, it was experimentally proven that they can be effectively trapped by active dipolarophiles [8]. In contrast to these species the onium nitrogen of pyridinium difluoroylides is a part of an aromatic system that can influence profoundly its stability and reactivity.

To elucidate the thermodynamic stability of pyridinium ylides and the electronic influence of substituents in the pyridine ring on life-time, as well as rates of formation and degradation of these species, the activation free energies of formation of ylides **2**, from difluorocarbene and pyridines **1a–j**, and their dissociation were computed at the B3LYP/6-31G* level (Table 1).

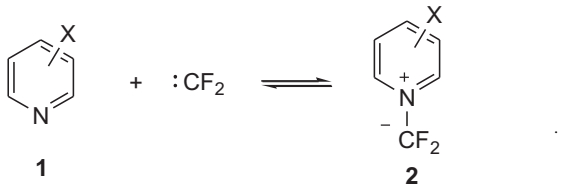
Reaction profiles for the formation of 4-substituted pyridinium ylides are depicted in Fig. 1.

It follows from the presented data (Table 1 and Fig. 1) that the influence of the *p*-substitutent on the activation free energy of difluorocarbene addition to pyridines has rather a complicated character. The most rapid reaction proceeds with 4-aminopyridine, the most slow with 4-nitropyridine, whereas 4-hydroxy-, 4-benzoyl-, 4-carbamoyl-substituted and nonsubstituted pyridines have comparable $\Delta G^{\neq}$ values. The least active substrate was shown to be 2-cyanopyridine, which is probably due to some steric hindrance to the approach of carbene to the pyridine nitrogen.

In contrast, $\Delta G^{\neq}$ of the reverse process, ylide dissociation to pyridine and difluorocarbene, dramatically depends on the polar effect of the *p*-substituent. In general, ylides with electron-donating substituents (4-OH, 4-NH_2) dissociate more rapidly than the acceptor-substituted ones. Significant stabilization of pyridiniodifluoromethanide by π-electron-withdrawing substituents at C^4 can be explained by the delocalization of negative charge of the 1,3-dipolar fragment, due to direct polar conjugation effect (significant contribution of resonance structure **2f″** of compound **2f**) (Scheme 1). On the contrary, increased electron density on the carbon atom of the 1,3-dipole caused by the direct polar conjugation effect of π-electron-donating *p*-substituents destabilizes the ylide due to the I_{π}-effect of the two fluorine atoms (insignificant conribution of resonance structure **2h″**). The shortening of the F_2C–N bond in optimized structures **2** (4-NH_2 1.497, 4-OH 1.475, H 1.475, 4-$CONH_2$ 1.387, 4-COPh 1.376, 4-CN 1.373, 4-NO_2 1.354 Å) also confirm a tendency of increase of stability and life-times of pyridiniodifluoromethanides with π-electron-withdrawing substituents.

No correlation however was found between the calculated $\Delta G^{\neq}$ of formation of the ylide and the *p*-substituent constants. The free

Table 1
Activation free energies ($\Delta G^{\neq}$) of formation and dissociation of substituted pyridinium ylides $XC_5H_4N^+$–C^-F_2 **2a–j** and free energies (ΔG_r) of reaction of pyridines **1a–j** with difluorocarbene in kJ/mol.



1 **2**

X = PhCO (**a**), CO_2Me (**b**), 4-CN (**c**), 3-CN (**d**), 2-CN (**e**), H (**f**), 4-$CONH_2$ (**g**), 4-NO_2 (**h**), 4-NH_2 (**i**), 4-OH (**j**)

Substituent X (ylide)	$\Delta G^{\neq}$		ΔG_r
	Formation	Dissociation	
4-PhCO (**2a**)	39.86	30.69	9.2
4-CO_2Me (**2b**)	31.53	19.55	12.0
4-CN (**2c**)	44.96	31.36	13.6
3-CN (**2d**)	34.30	15.84	18.5
2-CN (**2e**)	62.18	22.01	40.2
H (**2f**)	36.67	12.68	24.0
4-$CONH_2$ (**2g**)	40.17	25.48	14.7
4-NO_2 (**2h**)	45.89	40.40	5.5
4-NH_2 (**2i**)	27.99	-0.12	28.1
4-OH (**2j**)	36.52	3.71	32.8

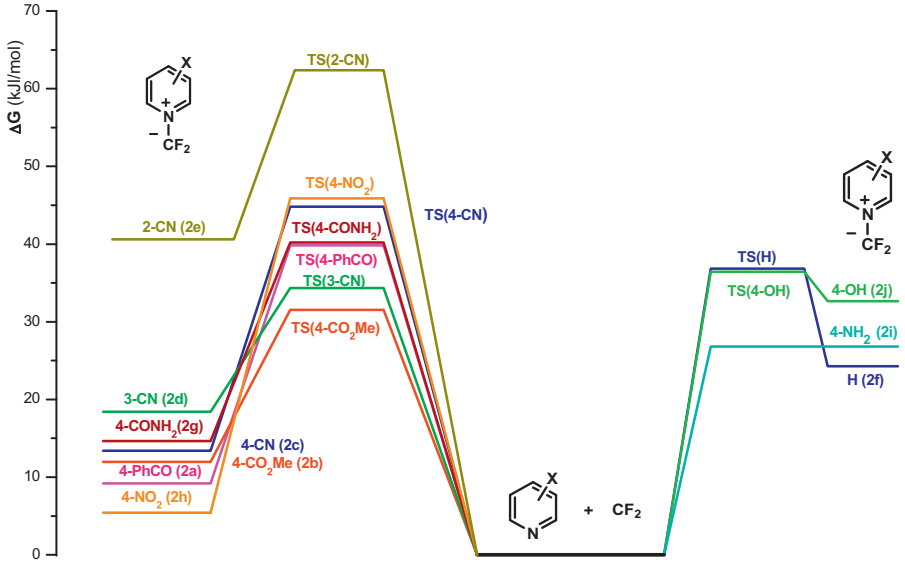
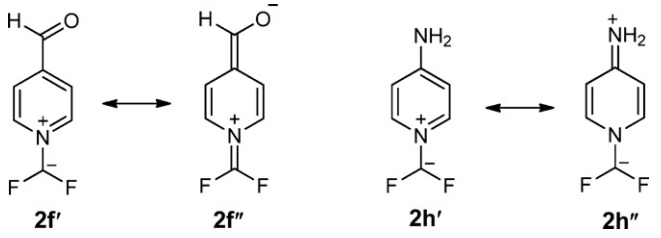


Fig. 1. Free energy profile of formation and dissociation of pyridiniodifluoromethanides **2a–j**. Energies ($\Delta G^{\neq}$, kJ/mol) are reported relative to the system "substituted pyridine + :CF_2".



Scheme 1. Resonance structures of ylides **2f**,**h**.

energies of the reaction of pyridines with difluorocarbene ΔG_r regularly decrease on going from electron-donating to electron-withdrawing substituents and a satisfactory correlation between computed values of ΔG_r and σ^--constants [25,26] of substituents in 4-R-substituted ylides **2** (R = OH, NH_2, H, $CONH_2$, CO_2Me, COPh, CN, NO_2) is observed ($\Delta G_r = -16.41\sigma^- + 25.34$, $R^2 = 0.97$) (Fig. 2).

To elucidate the influence of the position of π-electron-withdrawing substituent in the pyridine ring on thermodynamic stability of the ylide, the thermodynamic parameters for formation and dissociation of 3-cyano- and 2-cyano-substituted ylides were also calculated. Of the 4-CN, 3-CN and 2-CN-substituted ylides the 3-cyano-isomer has the least activation barrier both of formation (44.96, 34.30, and 62.18 kJ/mol) and dissociation (31.36, 15.84, and 22.01 kJ/mol) (Fig. 1 and Table 1). In other words, 3-cyanopyridiniodifluoromethanide **2d** is both more rapidly formed and more rapidly dissociated than its **2c**,**e** isomers. However the values of free energy of the reaction ΔG_r regularly decrease in this row of cyano-substituted pyridines and consequently the highest concentration of ylide can be achieved in with the 4-cyano-substituted derivative.

The calculation results show that the addition of difluorocarbene to pyridines have nonzero activation free energies and positive values of ΔG_r. This led to the assumption that pyridiniodifluoromethanides **2** are thermodynamically unstable species with a very short life-time, easily dissociating to starting pyridine and difluorocarbene. At the same time π-acceptor substituents in the 4-position of the pyridine ring displace the equilibrium towards ylide. The ylides of this type should have a sufficiently more prolonged life-time with the chance to be trapped by active dipolarophiles strongly increased.

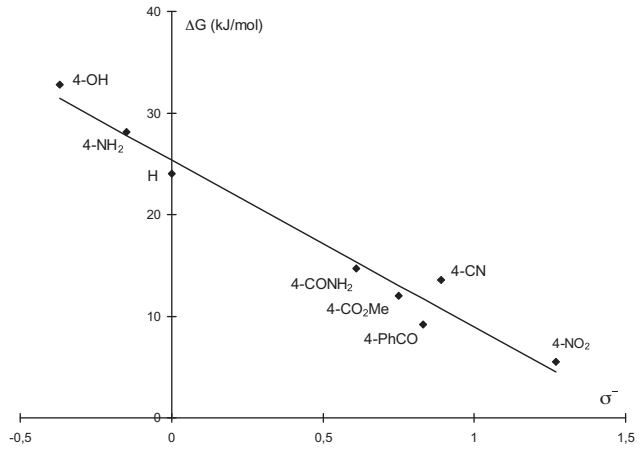
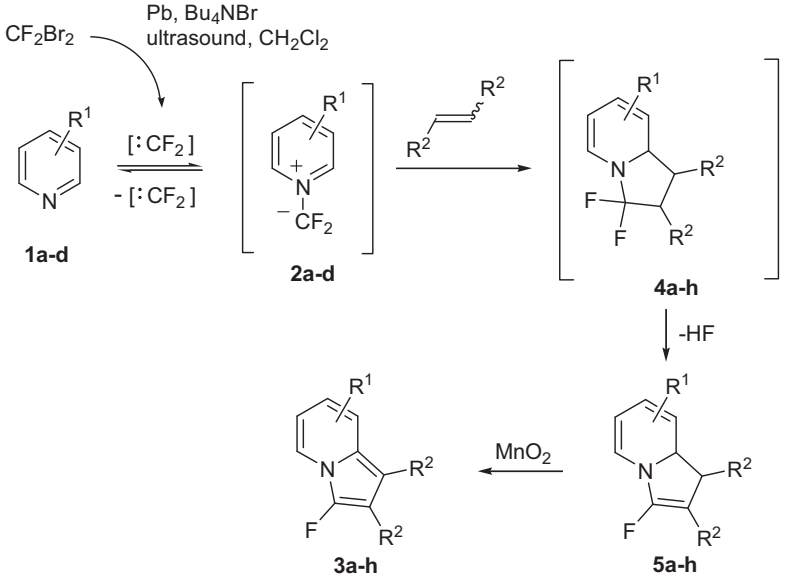


Fig. 2. Correlation between the calculated free energies of ylides **2** formation (ΔG_r, kJ/mol) and σ^--constants.

3.2. Experimental study

The reactions of pyridines with difluorocarbene, generated by reduction of dibromodifluoromethane with lead filings in the presence of tetrabutylammonium bromide [23] were carried out in anhydrous dichloromethane at 35–40 °C. Pyridine **1f**, phenyl(pyridin-4-yl)methanone **1a**, quinoline and isoquinoline under difluorocarbene generation conditions gave a dark tar as a main product. The same result was observed when the reactions of pyridine **1f**, quinoline and isoquinoline were carried out in the presence of dimethyl maleate or maleonitrile as dipolar traps. The reaction mixture obtained from 4-benzoyl-substituted pyridine **1a** with the addition of three equivalents of dimethyl maleate contained, according to TLC, two products: a luminescent compound, the structure of which was attributed to 3-fluoroindolizine **3a**, and a yellow-coloured compound, which under exposure to air in solution interconverts to indolizine **3a** (Scheme 2). Obviously, the labile yellow compound is dihydroindolizine **5a**, the product of dehydrofluorination of primary adduct **4a** of 1,3-dipolar cycloaddition of pyridinium ylide **2a** to dimethyl maleate. Dehydrofluorination of the primary cycloadduct **4a** readily proceeds under the reaction conditions in the same way as in the reactions of difluorocarbene with Schiff bases [6,27,28].



Scheme 2. Reaction of pyridines **1a**–**d** with CF_2 in the presence of dipolarophiles.

Table 2
Preparation of indolizines **3a**–**h**.

Pyridine	Dipolarophile	R^1	R^2	Yield, % (indolizine)
1a	Dimethyl maleate	4-COPh	CO_2Me	18 (**3a**)
1a	Fumaronitrile	4-COPh	CN	31 (**3b**)
1b	Dimethyl maleate	4-CO_2Et	CO_2Me	23 (**3c**)
1b	Fumaronitrile	4-CO_2Et	CN	28 (**3d**)
1c	Dimethyl maleate	4-CN	CO_2Me	48 (**3e**)
1c	Fumaronitrile	4-CN	CN	43 (**3f**)
1d	Dimethyl maleate	3-CN	CO_2Me	16 (**3g**:**3h**) (1:1)

Compound **3a** was isolated only in poor yield (4%) that may partly be due to unselective oxidation of dihydroindolizine **5a** by air oxygen during chromatographic purification. When the reaction mixture was oxidized by active manganese dioxide before chromatographic work-up the yield of indolizine **3a** was improved to 18%. In all the experiments full conversion of the starting pyridine **1a** and tar formation was observed.

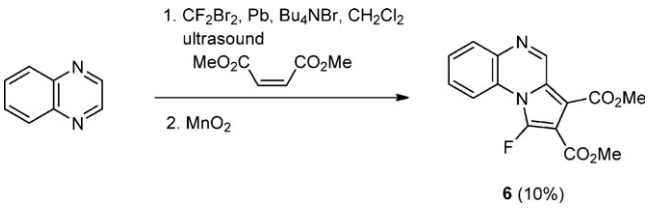
Carrying out of the reaction with a 2-fold excess of pyridine **1a** afforded compound **3a** in 40%, based on CF_2Br_2.

When ultrasound irradiation of the reaction mixture was changed to ordinary stirring, a drastic increase of the reaction time and incomplete consumption of lead filings was observed. The use of zinc dust in THF instead of the reduction system Pb/Bu_4NBr/CH_2Cl_2 in the reaction of pyridine **1a** with dimethyl maleate gave only traces of indolizine **3a**.

By varying the ratio of the reagents optimal reaction conditions were found: pyridine **1a**, dipolarophile, Bu_4NBr, CF_2Br_2, CH_2Cl_2 in mole ratio 1:2:3:8:50 under ultrasound irradiation at 30–40 °C followed by oxidation with active MnO_2. Reactions of substituted pyridines **1b**–**h** were carried out according to this protocol (Table 2).

The reaction of pyridine-3-carbonitrile **1d** with difluorocarbene in the presence of dimethyl maleate gave rise to a mixture of isomeric indolizines **3g** and **3h** in 1:1 ratio. All the attempts to obtain the corresponding fluoroindolizine from pyridine-2-carbonitrile were unsuccessful. The influence of the position of the cyano-group in the pyridine ring on the yield of indolizine **3** is in good agreement with calculation predictions. The yields decrease in the order **1c** > **1d** > **1e** and that corresponds to the order of the decrease in ylide life-time (**2c** > **2d** > **2e**). Thus the total yield of isomeric indolizines **3g**,**h** derived from nicotine acid nitrile **1d** is sufficiently lower than the yield of indolizine **3d** synthesized from isonicotine acid nitrile **1c**. In the case with picolinic acid nitrile no products were observed at all under these conditions.

Quinoxaline should afford a difluoro-substituted ylide in which the negative charge of the 1,3-dipolar fragment is delocalized by the direct polar conjugation effect of the second nitrogen atom to a greater extent than in ylides, generated from quinoline and isoquinoline. These gave no products in the reaction with difluorocarbene in the presence of dipolar traps. Ultrasound irradiation of a mixture of quinoxaline, CF_2Br_2, lead, Bu_4NBr and dimethyl maleate in dichloromethane followed by oxidation with active MnO_2 and chromatographic purification afforded compound **6** in 10% yield (Scheme 3).



6 (10%)

Scheme 3. Reaction of quinoxaline with CF_2 in the presence of dimethyl maleate.

4. Conclusion

According to DFT-calculations the addition of difluorocarbene to pyridines proceeds with nonzero activation free energy and positive reaction free energy to give thermodynamically unstable pyridiniodifluoromethanides. The latter easily dissociate back to pyridine and difluorocarbene with a low activation barrier. A π-acceptor substituent in the 4-position of the pyridine ring displaces the equilibrium towards the ylide, thus increasing the chances of trapping them by active dipolarophiles. The ylides derived from 4-cyano, 4-benzoyl- or 4-ethoxycarbonyl-substituted pyridines react with dimethyl maleate or fumaronitrile to give unstable 3-fluorodihydroindolizines, which after oxidation with active MnO_2 give rise to a new class of fluorinated heterocycles – 3-fluoroindolizines.

5. Experimental

5.1. General

Melting points were determined on a hot stage microscope (Boetius) and are uncorrected. IR spectra were recorded on a Carl-Zeiss UR 20 spectrometer. ^1H NMR spectra were recorded on a Bruker DPX 300 spectrometer at 300 MHz with internal standard TMS (δ = 0), ^{13}C NMR spectra at 75 MHz with internal standard $CDCl_3$ (δ = 77.0). ^{19}F NMR spectra were recorded on a Brucker AM-500 at 470 MHz; chemical shifts are reported in ppm from $CFCl_3$ as an internal standard. Elemental analysis was performed on a Hewlett-Packard 185B CHN-analyser. Dichloromethane was dried by distillation over phosphorus pentoxide. Silica gel Merck 60 was used for column chromatography. 4-Benzoylpyridine, pyridine-2-carbonitrile, pyridine-3-carbonitrile, pyridine-4-carbonitrile, dibromodifluoromethane, tetrabutylammonium bromide, fumaronitrile and dimethyl maleate were obtained commercially. Active MnO_2 was prepared according to published procedure [29].

5.2. Dimethyl 7-benzoyl-3-fluoroindolizine-1,2-dicarboxylate (3a) (typical procedure)

A flask containing anhydrous dichloromethane (7 ml) was charged with freshly prepared lead filings (0.848 g, 4.1 mmol), Bu_4NBr (1.32 g, 4.1 mmol), phenyl(pyridin-4-yl)methanone **1a** (0.25 g, 1.365 mmol), dimethyl maleate (0.591 g, 4.1 mmol) and CBr_2F_2 (2.2 g, 10.6 mmol). The flask was tightly stoppered, immersed in a sonic cleaner (160 W) and irradiated with ultrasound at 30–40 °C until the lead was consumed completely (reaction time 30–40 h). Active MnO_2 (1.78 g, 20.5 mmol) was added at room temperature to the reaction mixture and stirred for 2 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent hexane – $CHCl_3$, 3:1) to afford after recrystallization from ethyl acetate 0.088 g (18%) of indolizine **3a** as a yellow solid: mp 114–116 °C. ^1H NMR ($CDCl_3$): δ 3.85 (3H, s, CH_3), 3.96 (3H, s, CH_3), 7.39 (1H, d, J = 7.3 Hz, H-6), 7.51–7.56 (2H, m, Ph), 7.61–7.66 (1H, m, Ph), 7.81–7.83 (2H, m, Ph), 7.94 (1H, d, J = 7.3 Hz, H-5), 8.52 (1H, s, H-8). ^{13}C NMR ($CDCl_3$): δ 51.7 (CH_3), 52.5 (CH_3), 102.7 (C-2, d, J = 6.0 Hz), 104.0 (C-1), 113.2, 119.6, 124.9, 125.5 (d, J = 2.0 Hz), 128.5, 129.7, 130.5 (d, J = 2.0 Hz), 132.8, 136.7, 140.5 (d, J = 276.3 Hz, C-3), 162.0 (d, J = 5.0 Hz, CO_2Me), 163.2 (d, J = 3.0 Hz, CO_2Me), 193.7 (COPh). ^{19}F NMR (DMF): δ −137.4. IR ($CHCl_3$); ν 1750, 1725 cm^{-1} (C=O). Anal. Calcd. for $C_{19}H_{14}FNO_5$: C, 64.2; H, 4.0; N, 3.9. Found: C, 64.5; H, 4.1; N, 3.9.

5.3. 7-Benzoyl-3-fluoroindolizine-1,2-dicarbonitrile (3b)

Indolizine **3b** (0.198 g, 31%) was obtained from phenyl(pyridin-4-yl)methanone (0.4 g, 2.18 mmol) and fumaronitrile (0.34 g,

4.36 mmol). The product was isolated by column chromatography (eluent hexane – Et_2O, 3:1) followed by recrystallization from CH_2Cl_2–hexane: a yellow solid, mp 232–234 °C. ^1H NMR (DMSO-d_6): δ 7.39 (1H, d, J = 7.3 Hz, H-6), 7.59 (2H, t, J = 7.3 Hz, Ph), 7.74 (1H, t, J = 7.3 Hz, Ph), 7.82 (2H, d, J = 7.3 Hz, Ph), 7.97 (1H, s, H-8), 8.53 (1H, d, J = 7.3 Hz, H-5). ^{13}C NMR (DMSO-d_6): δ 81.7 (d, J = 7.7 Hz, C-2), 82.9 (d, J = 3.1 Hz, C-1), 110.1 (J = 4.6 Hz, CN), 112.6 (J = 2.0 Hz, CN), 114.1, 120.6, 122.7, 128.72, 128.73, 128.8, 129.6, 132.6, 133.3, 135.9, 142.9 (d, J = 279.3 Hz, C-3), 192.9 (COPh). ^{19}F NMR (DMF): δ −129.7. IR ($CHCl_3$); ν 2260, 2240 (CN), 1720 (C=O) cm^{-1}. Anal. Calcd. for $C_{17}H_8FN_3O$: C, 70.6; H, 2.8; N, 14.5. Found: C, 70.4; H, 2.7; N, 14.5.

5.4. 7-Ethyl-1,2-dimethyl 3-fluoroindolizine-1,2,7-tricarboxylate (3c)

Indolizine **3c** (0.196 g, 23%) was obtained from ethyl pyridine-4-carboxylate (0.4 g, 2.65 mmol) and dimethyl maleate (0.763 g, 5.3 mmol). The product was isolated by column chromatography (eluent hexane – EtOAc, 5:1) followed by recrystallization from Et_2O–hexane: a yellow solid, mp 91–93 °C. ^1H NMR ($CDCl_3$): δ 1.42 (3H, t, J = 7.3 Hz, CH_3), 3.94 (3H, s, CH_3O), 3.96 (3H, s, CH_3O), 4.41 (2H, q, J = 7.3 Hz, CH_2), 7.38 (1H, d, J = 7.3 Hz, H-6), 7.86 (1H, d, J = 7.3 Hz, H-5), 8.79 (1H, s, H-8). ^{13}C NMR ($CDCl_3$): δ 14.2 (CH_3), 51.8 (CH_3O), 52.5 (CH_3O), 61.6 (CH_2), 102.5 (d, J = 5.5 Hz, C-2), 103.4 (C-1), 112.8, 119.1 (d, J = 1.5 Hz), 123.4, 124.2 (d, J = 2.0 Hz), 125.9 (d, J = 2.5 Hz), 140.3 (d, J = 275.8 Hz, C-3), 162.2 (d, J = 4.0 Hz, CO_2Me), 163.3 (d, J = 3.0 Hz, CO_2Me), 164.7 (CO_2Et). ^{19}F NMR (DMF): δ −137.6. IR ($CHCl_3$); ν 1720 (C=O) cm^{-1}. Anal. Calcd. for $C_{15}H_{14}FNO_6$: C, 55.7; H, 4.4; N, 4.3. Found: C, 55.8; H, 4.3; N, 4.3.

5.5. Ethyl 1,2-dicyano-3-fluoroindolizine-7-carboxylate (3d)

Indolizine **3d** (0.190 g, 28%) was obtained from ethyl 4-pyridine-4-carboxylate (0.4 g, 2.65 mmol) and fumaronitrile (0.41 g, 5.28 mmol). The product was isolated by column chromatography (eluent hexane – Et_2O, 3:1) followed by recrystallization from CH_2Cl_2–hexane: a cream-coloured solid, mp 139–141 °C. ^1H NMR ($CDCl_3$): δ 1.45 (3H, t, J = 7.3 Hz, CH_3), 4.45 (2H, q, J = 7.3 Hz, CH_2), 7.56 (1H, dd, J = 7.3, 1.5 Hz, H-6), 7.99 (1H, d, J = 7.3 Hz, H-5), 8.37 (1H, br s, H-8). ^{13}C NMR ($CDCl_3$): δ 14.2 (CH_3), 62.3 (CH_2), 83.3 (d, J = 7.8 Hz, C-2), 85.0 (d, J = 2.6 Hz, C-1), 109.0 (d, J = 4.5 Hz, CN), 111.8 (CN), 114.6, 120.0, 120.9, 126.5 (d, J = 4.5 Hz), 129.1 (d, J = 3.6 Hz), 142.4 (d, J = 281.5 Hz, C-3), 163.5 (C=O). ^{19}F NMR (DMF): δ −127.6. IR ($CHCl_3$); ν 2260, 2240 (CN), 1730 (C=O) cm^{-1}. Anal. Calcd. for $C_{13}H_8FN_3O_2$: C, 60.7; H, 3.1; N, 16.3. Found: C, 60.8; H, 3.2; N, 16.3.

5.6. Dimethyl 7-cyano-3-fluoroindolizine-1,2-dicarboxylate (3e)

Indolizine **3e** (0.378 g, 48%) was obtained from pyridine-4-carbonitrile (0.3 g, 2.88 mmol) and dimethyl maleate (0.83 g, 5.76 mmol). The product was isolated by column chromatography (eluent hexane – Et_2O, 3:1) followed by recrystallization from Et_2O–hexane: a yellow solid, mp 174–176 °C. ^1H NMR ($CDCl_3$): δ 3.94 (3H, s, CH_3), 3.97 (3H, s, CH_3), 6.91 (1H, dd, J = 7.3, 1.5 Hz, H-6), 7.92 (1H, d, J = 7.3 Hz, H-5), 8.51 (1H, br s, H-8). ^{13}C NMR ($CDCl_3$): δ 52.0 (CH_3), 52.7 (CH_3), 103.4 (d, J = 6.0 Hz, C-2), 104.1 (CN), 105.2 (d, J = 2.0 Hz, C-1), 113.2, 117.3, 120.3, 124.6 (d, J = 2.0 Hz), 127.5, 140.5 (d, J = 276.3 Hz, C-3), 161.6 (d, J = 4.0 Hz, C=O), 162.6 (d, J = 3.0 Hz, C=O). ^{19}F NMR (DMF): δ −132.8. IR ($CHCl_3$); ν 1730 (C=O) cm^{-1}. Anal. Calcd. for $C_{13}H_9FN_2O_4$: C, 56.5; H, 3.3; N, 10.1. Found: C, 56.5; H, 3.3; N, 10.0.

5.7. 3-Fluoroindolizine-1,2,7-tricarbonitrile (3f)

Indolizine **3f** (0.260 g, 43%) was obtained from pyridine-4-carbonitrile (0.3 g, 2.88 mmol) and fumaronitrile (0.45 g, 5.80 mmol). The product was isolated by column chromatography (eluent hexane – Et_2O, 3:1) followed by recrystallization from CH_2Cl_2–hexane: a yellow solid, mp 119–121 °C. ^1H NMR (DMSO-d_6): δ 7.31 (1H, dd, J = 7.4, 1.1 Hz, H-6), 8.51 (1H, d, J = 7.4 Hz, H-5), 8.53 (1H, br s, H-8). ^{13}C NMR (DMSO-d_6): δ 82.6 (d, J = 8.0 Hz, C-2), 83.7 (d, J = 3.0 Hz, C-1), 107.5 (CN), 109.3 (d, J = 4.0 Hz, CN), 111.6 (d, J = 2.0 Hz, CN), 114.5, 116.4, 122.9, 125.0, 127.7 (d, J = 4.0 Hz), 142.8 (d, J = 280.7 Hz, C-3). ^{19}F NMR (DMF): δ −128.5. IR ($CHCl_3$); ν 2250 (CN) cm^{-1}. Anal. Calcd. for $C_{11}H_3FN_4$: C, 62.9; H, 1.4; N, 26.7. Found: C, 62.8; H, 1.4; N, 26.8.

5.8. Dimethyl 6-cyano-3-fluoroindolizine-1,2-dicarboxylate (3g) and dimethyl 8-cyano-3-fluoroindolizine-1,2-dicarboxylate (3h)

A 1:1 mixture of indolizines **3g** and **3h** (0.125 g, 16%) was obtained from pyridine-3-carbonitrile (0.3 g, 2.88 mmol) and dimethyl maleate (0.83 g, 5.76 mmol). The mixture was isolated by column chromatography (eluent hexane – Et_2O, 3:1). After additional separation by column chromatography (eluent hexane – EtOAc, 5:1) followed by recrystallization from CH_2Cl_2–hexane analytically pure samples of indolizines **3g** and **3h** were obtained. Compound **3g**: a yellow solid, mp 119–121 °C. ^1H NMR ($CDCl_3$): δ 3.94 (3H, s, CH_3), 3.98 (3H, s, CH_3), 7.07 (1H, d, J = 9.8, H-8), 8.20 (1H, d, J = 9.8 Hz, H-7), 8.31 (1H, s, H-5). ^{13}C NMR ($CDCl_3$): δ 51.9 (CH_3), 52.8 (CH_3), 100.5, 102.2, 102.8 (d, J = 4.5 Hz, C-1), 104.8, 115.8, 121.1 (d, J = 2.0 Hz), 121.2, 126.3 (d, J = 6.0 Hz), 139.8 (d, J = 277.3 Hz, C-3), 161.7 (d, J = 4.0 Hz, C=O), 163.0 (d, J = 3.0 Hz, C=O). ^{19}F NMR (DMF): δ −134.6. Anal. Calcd. for $C_{13}H_9FN_2O_4$: C, 56.5; H, 3.3; N, 10.1. Found: C, 56.3; H, 3.3; N, 10.0.

Compound **3h**: a yellow solid, mp 152–154 °C. ^1H NMR ($CDCl_3$): δ 3.95 (3H, s, CH_3), 4.01 (3H, s, CH_3), 6.83 (1H, dd, J = 7.3, 6.5 Hz, H-6), 7.44 (1H, d, J = 6.9 Hz, H-7), 8.03 (1H, d, J = 7.3 Hz, H-5). ^{13}C NMR ($CDCl_3$): δ 52.0 (CH_3), 52.5 (CH_3), 101.0 (d, J = 4.5 Hz, C-2), 104.6, 104.8, 111.9, 115.1, 119.4, 123.6 (d, J = 2.0 Hz), 131.0 (d, J = 1.5 Hz), 140.2 (d, J = 277.3 Hz, C-3), 161.5 (d, J = 4.5 Hz, C=O), 162.9 (d, J = 2.5 Hz, C=O). ^{19}F NMR (DMF): δ −132.5. Anal. Calcd. for $C_{13}H_9FN_2O_4$: C, 56.5; H, 3.3; N, 10.1. Found: C, 56.5; H, 3.3; N, 10.1.

5.9. Dimethyl 1-fluoropyrrolo[1,2-a]quinoxaline-2,3-dicarboxylate (6)

Compound **3j** (0.090 g, 10%) was obtained from quinoxaline (0.386 g, 2.97 mmol) and dimethyl maleate (0.887 g, 6.16 mmol). The product was isolated by column chromatography (eluent hexane – Et_2O, 3:1) followed by recrystallization from Et_2O–hexane: a yellow-red solid, mp 160–162 °C. ^1H NMR ($CDCl_3$): δ 3.98 (6H, s, $2CH_3$), 7.56–7.63 (2H, m), 8.00–8.03 (1H, m), 8.20–8.24 (1H, m), 9.32 (1H, d, J = 2.9 Hz). ^{13}C NMR ($CDCl_3$): δ 52.2 (CH_3), 52.5 (CH_3), 101.5 (d, J = 8.0 Hz, C-2), 107.3 (C-3), 116.3, 116.4, 124.8 (d, J = 3.0 Hz), 127.4, 129.0 (d, J = 4.0 Hz), 130.4, 136.5, 144.5 (d, J = 282.7 Hz, C-1), 145.2, 161.8 (d, J = 4.0 Hz, C=O), 162.7 (d, J = 3.0 Hz, C=O). ^{19}F NMR ($CDCl_3$): δ −121.5. IR ($CHCl_3$); ν 1720 (C=O) cm^{-1}. Anal. Calcd. for $C_{15}H_{11}FN_2O_4$: C, 59.6; H, 3. 7; N, 9.3. Found: C, 59.6; H, 3.8; N, 9.1.

Acknowledgements

We gratefully acknowledge Federal Targeted Programme "Scientific and Scientific-Pedagogical Personnel of the Innovative Russia in 2009–2013" (contract no. 16.740.11.0442) and the Russian Foundation for Basic Research (project no. 11-03-00186) for support of this research.

References

[1] R.W. Fessenden, R.H. Schuler, J. Chem. Phys. 43 (1965) 2704–2712.

[2] K.S. Chen, P.J. Krusic, P. Meakin, J. Kochi, J. Phys. Chem. 78 (1974) 2014–2030.
[3] D.A. Dixon, J. Phys. Chem. 90 (1986) 54–56.
[4] E.A. Carter, W.A. Goddard III, J. Chem. Phys. 92 (1988) 1752–1763.
[5] D.L.S. Brahms, W.P. Dailey, Chem. Rev. 96 (1996) 1585–1635.
[6] A.F. Khlebnikov, M.S. Novikov, S.A. Dolgikh, J. Magull, ARKIVOC ix (2008) 94–115.
[7] A.S. Konev, M.S. Novikov, A.F. Khlebnikov, Tetrahedron Lett. 46 (2005) 8337–8340.
[8] A.F. Khlebnikov, M.S. Novikov, R.R. Kostikov, Russ. Chem. Rev. 74 (2005) 171–192.
[9] A.F. Khlebnikov, R.R. Kostikov, Chem. Heterocycl. Comp. 23 (1987) 708–709.
[10] A.F. Khlebnikov, E.I. Kostik, R.R. Kostikov, V.Ya. Bespalov, Chem. Heterocycl. Comp. (1990) 304–311.
[11] A.F. Khlebnikov, E.I. Kostik, J. Kopf, E.V. Aleksandrov, R.R. Kostikov, Russ. J. Org. Chem. 34 (1998) 712–724.
[12] A.F. Khlebnikov, E.I. Kostik, R.R. Kostikov, Synthesis 25 (1993) 568–570.
[13] B. Bachowska, Monatsh. Chem. 126 (1995) 227–231.
[14] K. Berg-Nielson, Acta Chem. Scand., Ser. B B31 (1977) 224–226.
[15] A.F. Khlebnikov, E.I. Kostik, R.R. Kostikov, Chem. Heterocycl. Comp. (1991) 636–642.
[16] R.A. Moss, L. Wang, K. Krogh-Jespersen, J. Am. Chem. Soc. 131 (2009) 2128–2130.
[17] G. Bissky, V.I. Staninets, A.A. Kolomeitsev, G.-V. Röschenthaler, Synlett 12 (2001) 374–378.
[18] G. Bissky, G.-V. Röschenthaler, E. Lork, J. Barten, M. Mádebielle, V. Staninets, A.A. Kolomeitsev, J. Fluorine Chem. 109 (2001) 173–181.
[19] A.D. Becke, J. Chem. Phys. 98 (1993) 5648–5652.
[20] A.D. Becke, Phys. Rev. A 38 (1998) 3098–3100.
[21] C. Lee, W. Yang, R.G. Parr, Phys. Rev. B 37 (1998) 785–789.
[22] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery Jr., T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. Hratchian, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, S. Dapprich, A.D. Daniels, M.C. Strain, O. Farkas, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J.V. Ortiz, Q. Cui, A.G. Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez, J.A. Pople, Gaussian 03, Revision B.05, Gaussian Inc., Wallingford, CT, 2004.
[23] C. Gonzalez, H.B. Schlegel, J. Chem. Phys. 90 (1989) 2154–2161.
[24] A.F. Khlebnikov, M.S. Novikov, Russ. J. Gen. Chem. 80 (2010) 1341–1354.
[25] C. Hansch, A. Leo, R.W. Taft, Chem. Rev. 91 (1991) 165–195.
[26] A. Fisher, G.J. Leary, R.D. Topsom, J. Vaughan, J. Chem. Soc. (1966) 782–785.
[27] M.S. Novikov, A.F. Khlebnikov, M.V. Shevchenko, J. Fluorine Chem. 123 (2003) 177–181.
[28] M.S. Novikov, A.F. Khlebnikov, E.S. Sidorina, R.R. Kostikov, J. Chem. Soc., Perkin Trans. 1 (2000) 231–237.
[29] J. Attenburrow, A.F.B. Cameron, J.H. Chapman, R.M. Evans, B.A. Hems, A.B.A. Jansen, T. Walker, J. Chem. Soc. (1952) 1094–1112.