Chemistry of Heterocyclic Compounds, Vol. 46, No. 10, 2011

1-(TRIFLUOROMETHYL)-3,4-DIHYDROPYRROLO-[1,2-*a*]PYRAZINES: SYNTHESIS AND REACTIONS WITH O- AND N-NUCLEOPHILES

V. I. Terenin[1]*, M. V. Galkin[1], E. V. Kabanova[1], and A. S. Ivanov[1]

The method of synthesis has been developed and reactions of 1-(trifluoromethyl)-3,4-dihydro-pyrrolo[1,2-a]pyrazines with O- and N-nucleophiles have been studied. It was found that reactions of nucleophiles with 1-(trifluoro-methyl)pyrrolo[1,2-a]pyrazines transforms the trifluoromethyl group to amide and amidine groups together with aromatization of the pyrrolo[1,2-a]pyrazine system as a result of the formal elimination of a molecule of hydrogen fluoride.

Keywords: 1-(trifluoromethyl)pyrrolo[1,2-*a*]pyrazine, nucleophilic reactions involving a trifluoromethyl group.

Pyrrolo[1,2-*a*]pyrazines are promising components in the composition of medicinal preparations, food additives, and optical materials [1-5]. One of the simplest and most convenient methods of preparing pyrrolo[1,2-*a*]pyrazines is based on the condensation of 2-acylfurans with ethylene diamine [6]. However, this synthetic method is only used for preparing 1,6-alkyl- and aryl-substituted pyrrolo[1,2-*a*]pyrazines, the difficultly obtainable pyrrolo[1,2-*a*]pyrazines with a functional group in position 1 not previously being available by this procedure.

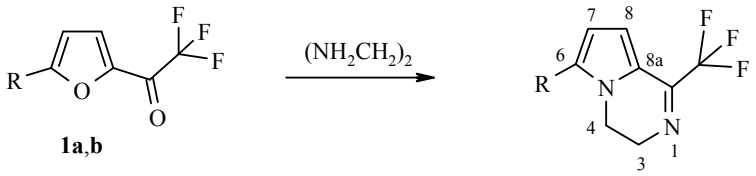
By condensation of ethylene diamine with the 2-(trifluoroacetyl)furans **1a,b** (prepared by method [7]) we were able to prepare the corresponding 1-trifluoromethyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine (**2a**) and 6-methyl-1-trifluoromethyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine (**2b**). It should be noted that the formation of a C=N bond by reaction with amines is not typical of carbonyl compounds with a trifluoromethyl group in the α-position, the reaction generally stopping at the stage of addition of the amine. Hence, for example, the loss of the water molecule and formation of an imino group in the reaction of amines with trifluoromethyl ketones generally needs a dehydrating agent like $POCl_3$ or $SOCl_2$ [8].

We have previously shown that a rearrangement involving the trifluoroacetyl group occurs in the reaction of methylamine with 6-trifluoroacetylpyrrolo[1,2-*a*]pyrazinium salts to yield pyrrolo[1,2-*a*]pyrazin-1-ones [9]. It might have been expected that treatment of compounds **2a**,**b** with nucleophiles would give rise to a similar conversion with elimination of the trifluoromethyl group and formation of pyrrolopyrazinones.

* To whom correspondence should be addressed, e-mail: vter@org.chem.msu.ru.

[1]M. V. Lomonosov State University, Moscow 119992, Russia.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1569-1578, October, 2010. Original article submitted January 21, 2010.

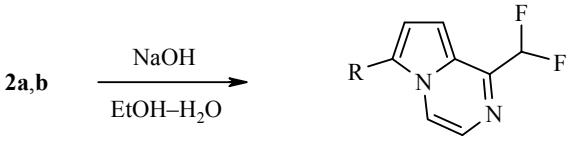


1a,**b**

2 a (27%), **b** (68%)

1, **2 a** R = H, **b** R = Me

However, treatment of the 1-trifluoromethyl-3,4-dihydropyrrolo[1,2-*a*]pyrazines **2a**,**b** with a 10% solution of sodium hydroxide in 80% ethanol unexpectedly gave the 1-(difluromethyl)pyrrolo[1,2-*a*]pyrazines **3a**,**b** as the only reaction products.

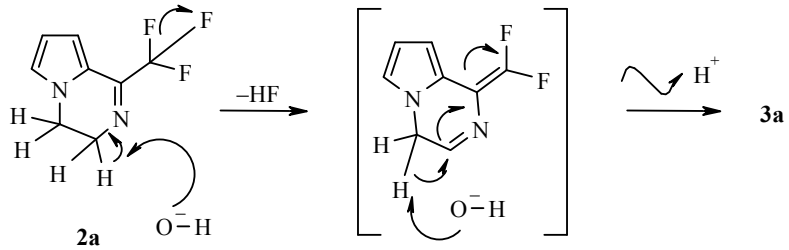


3a (90%), **b** (100%)

2,**3 a** R = H, **b** R = Me

Variation of the conditions did not cause a change in the results of the reaction. Optimal conditions proved to be when a mixture of compounds **3a**,**b** in alcoholic alkali solvent was held for 2 weeks at room temperature. Attempts to increase the rate of the reaction by heating led to a marked lowering in the yield and to a complex reaction mixture composition.

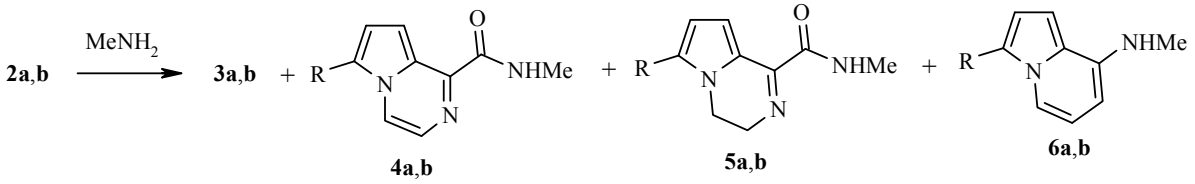
The following scheme can be proposed for this reaction. The action of base initially gives 1,4-elimination of a molecule of HF and then the migration of a proton from position 4 of the pyrazine ring of intermediate **A** to the carbon atom of the difluoromethyl group to give the 1-(difluoromethyl)pyrrolo[1,2-*a*]pyrazine (**3a**).



2a

A

Exchange of an O-nucleophile for a milder N-nucleophile led to a complex reaction mixture composition: treatment of compounds **2a**,**b** with a 33% solution of methylamine in ethanol gave compounds **3a**,**b** as well as the 3,4-dihydro- and aromatic N-methylpyrrolo[1,2-*a*]pyrazine-1-carboxamides **4a**,**b** and **5a**,**b** and also trace quantities of the products of cyclotransformation **6a**,**b**.



4a,**b**

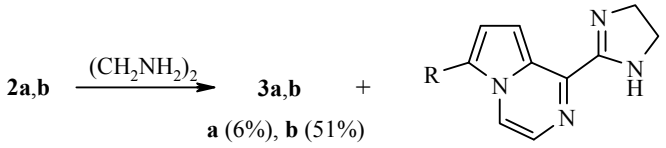
5a,**b**

6a,**b**

2-6 a R = H, **b** R = Me

In order to clarify whether the aromatic compounds **4** and **6** are the result of transformation of the initially formed compound **3** the 1-(difluoromethyl)pyrrolo[1,2-*a*]pyrazine (**3a**) was held for 5 h in a solution of methylamine in alcohol at 150ºC. Conversion of compound **3a** to amide **4a** and indolizine **6a** was not recorded and only the starting material was separated from the reaction mixture. On the basis of this experiment we can confirm that compound **3** does not act as an intermediate for the formation of compounds **4** and **6**, i.e. compounds **4** and **6** are formed directly from the trifluoromethyl derivatives **2**.

We have further studied the reaction of compound **2a** with ethylene diamine. With a twentyfold excess of the ethylene diamine the reaction mixture has a very complex composition and no kind of products could be separated. Decreasing the ratio of the starting materials to 1:1 and addition of propyl alcohol solvent made it possible to separate compound **3a** and also the 1-(4,5-dihydro-1H-imidazol-2-yl)pyrrolo[1,2-*a*]pyrazine (**7a**) in yields of 6 and 17% respectively.



2,**7** **a** R = H, **b** = Me

Under similar conditions for compound **2b** the process of forming the 1-(diflurомethyl)-6-methyl-pyrrolo[1,2-*a*]pyrazine (**3b**) predominated.

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	M^+ (I_{rel},%)	Yield, %
		C	H	N			
2a	$C_8H_7F_3N_2$	51.04 / 51.07	3.63 / 3.75	14.84 / 14.89	—*	188 (100)	27
2b	$C_9H_9F_3N_2$	53.54 / 53.47	4.31 / 4.49	13.86 / 13.86	49-51*[2]	202 (65)	68
3a	$C_8H_6F_2N_2$	57.01 / 57.14	3.51 / 3.60	16.50 / 16.66	—	168 (100)	90
3b	$C_9H_8F_2N_2$	59.38 / 59.34	4.30 / 4.43	15.23 / 15.38	48-50	182 (59)	100
4a	$C_9H_9N_3O$	61.92 / 61.70	5.29 / 5.18	23.80 / 23.99	94-96	175 (37)	27
4b	$C_{10}H_{11}N_3O$	63.48 / 63.48	5.64 / 5.86	21.99 / 22.21	110-112	189 (42)	16
5a	$C_9H_{11}N_3O$	61.15 / 61.00	6.15 / 6.26	23.75 / 23.71	—	177 (100)	47
5b	$C_{10}H_{13}N_3O$	62.99 / 62.81	6.89 / 6.85	21.82 / 21.97	61	191 (15)	33
7a	$C_{10}H_{10}N_4$	64.80 / 64.50	5.35 / 5.41	30.08 / 30.09	110	186 (100)	24
7b	$C_{11}H_{12}N_4$	66.00 / 65.98	6.18 / 6.04	27.80 / 27.98	114-116	200 (93)	21
8a	$C_{10}H_{12}N_4$	63.53 / 63.81	6.05 / 6.43	29.61 / 29.77	—	188 (90)	19
8b	$C_{11}H_{14}N_4$	65.29 / 65.32	7.12 / 6.98	27.61 / 27.70	108-109	202 (90)	24

* Bp 100ºC (9 mm Hg).

*[2] Bp 116-120ºC (7 mm Hg).

TABLE 2. ^{13}C NMR Spectra of the Compounds Synthesized

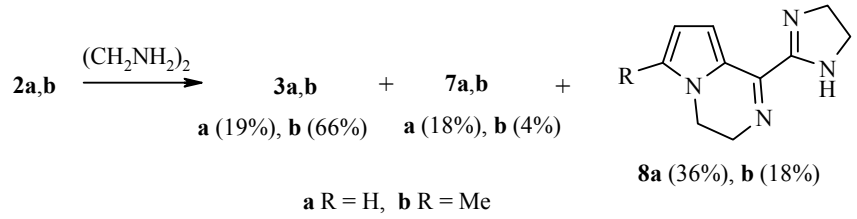
Compound	Chemical shifts, δ, ppm (*J*, Hz)									
	C(1)	C(3)	C(4)	C(6)	C(7)	C(8)	C(1a)	6-CH_3	Substituents	
2a	150.23 (q, $J_{1,F}$ = 35.1)	47.71	41.60	125.16	111.96	109.77	143.00 (d, $J_{8a,F}$ = 89.3)		119.82 (q, $J_{C,F}$ = 276.6, CF_3)	
2b	150.35 (q, $J_{1,F}$ = 35.1)	47.56	38.66	119.44	112.49	109.17	134.11	11.38	119.92 (q, $J_{C,F}$ = 276.6, CF_3)	
3a	147.03 (t, $J_{1,F}$ = 27.0)	125.73	115.96	119.67	115.66	103.94	123.94		115.30 (t, $J_{C,F}$ = 241.5, CHF_2)	
3b	146.65 (t, $J_{1,F}$ = 27.0)	125.74	115.73	123.73	116.15	103.7	123.73	11.19	115.38 (t, $J_{C,F}$ = 241.5, CHF_2)	
4a	144.09	124.93	115.13	120.2	116.73	107.05	125.97		164.61 (C=O)	25.93 ($NHCH_3$)
4b	156.78	124.95	116.53	122	116.74	106.81	126.23	11.37	174.21 (C=O)	25.93 ($NHCH_3$)
5a	153.15	47.43	41.93	122.42	114.8	109.59	124.19		163.85 (C=O)	25.78 ($NHCH_3$)
5b	153	47.25	38.73	122.1	115.26	109.06	132.95	11.52	164.08 (C=O)	25.77 ($NHCH_3$)
7a	142.96	115.14	119.41	125.57	106.68	116.13	125.8		50.58 (br. s, $\underline{C}H_2\underline{C}H_2$)	163.51 (NCNH)
7b	142.36	116.04	125.54	123.01	115.87	106.36	130.79	11.3	50.40 (br. s, $\underline{C}H_2\underline{C}H_2$)	163.67 (NCNH)
8a	151.24	47.65	41.61	122.64	113.86	108.87	123.65		50.23 (br. s, $\underline{C}H_2\underline{C}H_2$)	162.83 (NCNH)
8b	151.24	38.69	47.65	122.44	114.7	108.74	132.67	11.42	50.22 (br. s, $\underline{C}H_2\underline{C}H_2$)	162.89 (NCNH)

TABLE 3. ^{1}H NMR and IR Spectra* of the Compounds Synthesized

Compound	Chemical shifts, δ, ppm (*J*, Hz)						
	H-3	H-4	H-6	H-7	H-8	Substituents	
2a	3.98-4.07 (m)		6.67 (d, $J_{6,8}$ = 1.8)	6.28 (dd, $J_{7,8}$ = 3.7, $J_{7,6}$ = 2.6)	6.86 (br. s)		
2b	3.84 (t, $J_{3,4}$ = 6.7)	4.0 (t, $J_{4,3}$ = 6.7)	2.28 (br. s, CH_3)	6.02 (d, $J_{7,8}$ = 4.1)	6.62 (d, $J_{8,7}$ = 4.1)		
3a	7.52 (d, $J_{3,4}$ = 4.8)	7.89 (d, $J_{4,3}$ = 4.8)	7.55 (d, $J_{6,7}$ = 1.4)	7.00 (dd, $J_{7,8}$ = 4.0, $J_{7,6}$ = 2.6)	7.10 (d, $J_{8,7}$ = 1.4)	6.70 (t, $J_{H,F}$ = 54.4, C<u>H</u>F_2)	
3b	7.56 (d, $J_{3,4}$ = 4.8)	7.64 (d, $J_{4,3}$ = 4.8)	2.52 (s, CH_3)	6.78 (d, $J_{7,8}$ = 4.1)	7.05 (d, $J_{8,7}$ = 4.1)	6.68 (t, $J_{H,F}$ = 54.5, CHF_2)	
4a	7.47 (d, $J_{3,4}$ = 4.7)	7.94 (dd, $J_{4,3}$ = 4.7, $J_{4,8}$ = 1.0)	7.53 (dd, $J_{6,7}$ = 2.5, $J_{6,8}$ = 1.3)	7.03 (dd, $J_{7,8}$ = 4.1, $J_{7,6}$ = 2.5)	7.76 (d, $J_{8,7}$ = 4.1)	3.06 (d, $J_{H,NH}$ = 5.1, NHC<u>H</u>$_3$)	7.98 (br. s, NH)
4b	7.51 (d, $J_{3,4}$ = 4.7)	7.70 (d, $J_{4,3}$ = 4.7)	2.53 (s, CH_3)	6.83 (d, $J_{7,8}$ = 4.0)	7.73 (d, $J_{8,7}$ = 4.0)	3.05 (d, $J_{H,NH}$ = 4.8, NHC<u>H</u>$_3$)	8.01 (br. s, NH)
5a	3.95 (br. s)		6.79 (d, $J_{6,8}$ = 1.3)	6.26 (dd, $J_{7,8}$ = 3.9, $J_{7,6}$ = 2.5)	7.26 (dd, $J_{8,7}$ = 3.9, $J_{8,6}$ = 1.3)	2.95 (d, $J_{H,NH}$ = 5.0, NHC<u>H</u>$_3$)	7.47 (br. s, NH)
5b	3.80 (t, $J_{3,4}$ = 6.4)	3.92 (t, $J_{4,3}$ = 6.4)	2.26 (s, CH_3)	6.01 (d, $J_{7,8}$ = 3.7)	7.21 (d, $J_{8,7}$ = 3.7)	2.92 (d, $J_{H,NH}$ = 5.1, NHC<u>H</u>$_3$)	7.48 (br. s, NH)
10a	7.46 (d, $J_{3,4}$ = 4.7)	7.84 (dt, $J_{4,3}$ = 4.7, $J_{4,8}$ = 0.98)	7.45 (dd, $J_{6,7}$ = 2.5, $J_{6,8}$ = 1.1)	6.93 (dd, $J_{7,8}$ = 4.1, $J_{7,6}$ = 2.5)	7.61 (m)	3.89 (br. s, C<u>H</u>$_2$C<u>H</u>$_2$)	5.55 (br. s, NH)
10b	7.53 (d, $J_{3,4}$ = 4.7)	7.63 (d, $J_{4,3}$ = 4.7)	2.50 (s, CH_3)	6.75 (d, $J_{7,8}$ = 4.0)	7.60 (d, $J_{8,7}$ = 4.0)	3.87 (br. s, C<u>H</u>$_2$C<u>H</u>$_2$)	—
11a	3.65 (br. s)		6.51 (dd, $J_{6,7}$ = 2.5, $J_{6,8}$ = 1.5)	5.96 (dd, $J_{7,8}$ = 3.7, $J_{7,6}$ = 2.5)	6.91 (dd, $J_{8,7}$ = 3.7, $J_{8,6}$ = 1.5)	3.50 (br. s, C<u>H</u>$_2$C<u>H</u>$_2$)	5.66 (br. s, NH)
11b	3.80 (t, $J_{3,4}$ = 6.5)	3.94 (t, $J_{4,3}$ = 6.5)	2.25 (s, CH_3)	5.97 (d, $J_{7,8}$ = 3.5)	7.08 (d, $J_{8,7}$ = 3.5)	3.77 (br. s, C<u>H</u>$_2$C<u>H</u>$_2$)	4.32 (br. s, NH)

* IR spectra, ν, cm^{-1}: **4a** 1657 (amide C=O), 3334 (N–H); **4b** 1680 (amide C=O), 3379 (N–H); **5a** 1587, 1664 (C=N and amide C=O), 3323 (N–H); **5b** 1591, 1668 (C=N and amide C=O), 3224, 3327 (N–H).

Changing the ratio of ethylene diamine to starting compounds **2a**,**b** from 1:1 to 6:1 led to the formation of a still further reaction product. Column chromatography of the reaction mixture gave both the aromatic compounds **3a**,**b** and **7a**,**b** as well as the 1-(4,5-dihydro-1H-imidazol-2-yl)-3,4-dihydropyrrolo[1,2-*a*]pyrazines **8a**,**b**.



It was of interest to decrease the yield of compounds **3a**,**b** relative to compounds **7** and **8**. When the synthesis was carried out without solvent in a sealed ampul (140ºC) with a ratio of starting compounds **2a**,**b** to ethylene diamine of 1:1.5 the desired result was achieved. The yields of compounds **3a**, **7a**, and **8a** were 10, 24, and 19% and for the methyl-substituted compounds 30, 21, and 24% respectively.

Hence we have studied the reactions of 1-(trifluoromethyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazines with O- and N-nucleophiles and synthesized previously unknown 1-functionally substituted pyrrolo[1,2-*a*]pyrazines and dihydropyrrolo[1,2-*a*]pyrazines.

EXPERIMENTAL

IR spectra were obtained on UR-20 and IR-200 spectrometers. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-400 spectrometer (400 and 100 MHz respectively) using $CDCl_3$ at temperatures of 23 and 25ºC with TMS as internal standard. Mass spectra were taken on a Kratos MS-90 instrument with an ionization energy of 70 eV. Monitoring of the reaction course and purity of the compounds was performed by TLC on Silufol-254 (254 nm) and Alufol plates in the systems benzene–ethyl acetate (1:1) and methanol–chloroform (1:10).

2-(Trifluoroacetyl)furan (1a) was prepared by method [7]. Yield 52%; bp 40-41ºC (10 mm Hg) (bp 142ºC (765 mm Hg) [7]), n_D^{20} 1.4405. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.71 (1H, dd, $J_{4,3}$ = 3.8, $J_{4,5}$ = 1.7, H-4); 7.55 (1H, m, H-3); 7.85 (1H, dd, $J_{5,4}$ = 1.7, $J_{5,3}$ = 0.7, H-5).

2-(Trifluoroacetyl)-5-methylfuran (1b) was obtained by method [7]. Yield 67%; bp 55ºC (7 mm Hg) (bp 170ºC (756 mm Hg) [7]), n_D^{20} 1.4560. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.48 (3H, s, CH_3); 6.33 (1H, dq, $J_{4,3}$ = 2.0, J_{4,CH_3} = 0.8, H-4); 7.45 (1H, d, $J_{3,4}$ = 2.0, H-3).

1-(Trifluoromethyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazine (2a). A solution of ethylene diamine (42.5 ml, 630 mmol) in benzene (150 ml) was added dropwise over one hour to a solution of compound **1a** (29.4 g, 180 mmol) in benzene (50 ml). The reaction mixture was stirred for 1 h, refluxed for 1 h, water was added, and extracted with benzene. The benzene extracts were dried over $CaCl_2$ and the solvent was evaporated *in vacuo*. The residue was vacuum distilled. Yield 9.25 g (27%).

6-Methyl-1-(trifluoromethyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazine (2b) was prepared similarly to compound **2a** from compound **1b**. Yield 68%.

1-(Difluromethyl)pyrrolo[1,2-*a*]pyrazine (3a). A tenfold excess of 10% NaOH solution in 80% ethanol was added to compound **2a** (0.475 g, 2.5 mmol). The reaction mixture was held at room temperature for 2 weeks and the solvent was evaporated *in vacuo*. The residue was treated with water and extracted with benzene. The benzene extracts were dried over $CaCl_2$ and the solvent was evaporated. Compound **3a** was separated by column chromatography on 35/60 silica gel with eluent benzene–ethyl acetate (1:1). Yield 0.38 g (90%).

1-(Difluromethyl)-6-methylpyrrolo[1,2-*a*]pyrazine (3b) was prepared similarly to compound **3a** from compound **2b**. Yield 100%.

Reaction of 1-(Trifluoromethyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazine (2a) with Methylamine. A mixture of methylamine in absolute ethanol (5 ml, 33%) and the pyrrolopyrazine **2a** (0.377 g, 2 mmol) was heated at 140ºC for 12 h in a sealed glass ampul. Solvent and the residual reagent were evaporated *in vacuo* and the reaction product was separated by column chromatography on 35/60 silica gel using benzene as eluent and subsequently increasing the polarity of the eluent to a mixture of benzene–ethyl acetate (1:1) and finally to ethyl acetate and alcohol (1:1). Yield of reaction products: compound **3a** 0.085 g (25%); **N-methyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (5a)** 0.166 g (47%); **N-methylpyrrolo[1,2-*a*]pyrazine-1-carboxamide (4a)** 0.095 g (27%); and compound **6a** 0.004 g (1%).

8-(Methylamino)indolizine (6a). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.98 (3H, s, CH_3); 3.96 (1H, br. s, NH); 5.75 (1H, d, $J_{7,6}$ = 7.1, H-7); 6.30 (1H, d, $J_{1,2}$ = 2.7, H-1); 6.45 (1H, t, $J_{6,5\text{-}7}$ = 7.1, H-6); 6.69 (1H, d, $J_{2,1}$ = 2.7, H-2); 7.25 (1H, s, H-3); 7.50 (1H, d, $J_{5,6}$ = 7.1, H-5) [9].

Reaction of 6-Methyl-1-(trifluoromethyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazine (2b) with Methylamine. The conditions for carrying out the reaction are similar to those for the reaction of compound **2a** with methylamine compound **2b** (0.5 g, 2.5 mmol) gave compound **3b** (0.188 g, 42%); **N,6-dimethyl-3,4-dihydropyrrolo[1,2-*a*]-pyrazine-1-carboxamide (5b)** (0.156 g, 33%); **N,6-dimethylpyrrolo[1,2-*a*]pyrazine-1-carboxamide (4b)** (0.073 g, 16%), and compound **6b** (0.02 g, 6%).

3-Methyl-8-(methylamino)indolizine (6b). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.44 (3H, s, CH_3); 2.96 (3H, s, NHC$\underline{H}_3$); 3.95 (1H, br. s, NH); 5.75 (1H, d, $J_{7,6}$ = 7.0, H-7); 6.25 (1H, d, $J_{1,2}$ = 3.7, H-1); 6.43 (1H, d, $J_{1,2}$ = 3.7, H-2); 6.51 (1H, t, $J_{6,5\text{-}7}$ = 7.1, H-6); 7.24 (1H, d, *J* = 7.1, H-5) [10].

Reaction of 1-(Trifluoromethyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazine (2a) with Ethylene Diamine. A. A mixture of compound **2a** (0.79 g, 4.2 mmol) and ethylene diamine (0.31 ml, 4.2 mmol) was heated for 4 h. Solvent and reagent residue were evaporated *in vacuo*. The residue was treated with water and extracted with benzene. The benzene extracts were dried over $CaCl_2$ and the solvent was evaporated. The reaction products were separated by column chromatography on 35/60 silica gel eluting with benzene–ethyl acetate (1:1) and increasing the polarity to a mixture of ethyl acetate and alcohol (1:1) and then eluting with alcohol. Yield of reaction products: compound **3a** (0.096 g, 6%) and **1-(4,5-Dihydro-1H-imidazol-2-yl)pyrrolo[1,2-*a*]pyrazine** (**7a**) (0.14 g, 17%).

B. A mixture of the pyrrolopyrazine **2a** (1 g, 5.3 mmol) and ethylene diamine (2 ml, 30 mmol) in propyl alcohol (2 ml) was heated for 4 h. Solvent and excess reagent were evaporated *in vacuo*. The reaction products were separated by column chromatography on 35/60 silica gel eluting with benzene–ethyl acetate (1:1) and increasing the polarity to a mixture of ethyl acetate and alcohol (1:1) and then eluting with alcohol. Yield of reaction products: compound **3a** (0.171 g, 19%); **1-(4,5-Dihydro-1H-imidazol-2-yl)-3,4-dihydropyrrolo-[1,2-*a*]pyrazine (8a)** (0.355 g, 36%) as an oily liquid; and compound **7a** (0.174 g, 18%).

Reaction of 6-Methyl-1-(trifluoromethyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazine (2b) with Ethylene Diamine. A. The conditions for carrying out the reaction are similar to those for the reaction of compound **2a** with ethylene diamine. Reaction of compound **2b** (0.4 g, 1.74 mmol) and ethylene diamine (0.12 ml, 1.74 mmol) gave: compound **3b** (0.161 g, 51%) and **1-(4,5-dihydro-1H-imdazol-2-yl)-6-methylpyrrolo[1,2-*a*]-pyrazine (7b)** (0.01 g, 3%).

B. A mixture of compound **2b** (0.86 g, 3.74 mmol) and ethylene diamine (1.5 ml, 22 mmol) in propyl alcohol (2 ml) was heated for 4 h. Solvent and excess reagent were evaporated *in vacuo*. The reaction products were separated by column chromatography on 35/60 silica gel eluting with benzene–ethyl acetate (1:1) and increasing the polarity to a mixture of ethyl acetate and alcohol (1:1) and then eluting with alcohol. Yield of reaction products: compound **3b** (0.449 g, 66%); **1-(4,5-dihydro-1H-imidazol-2-yl)-6-methyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine (8b)** (0.134 g, 18%); and compound **7b** (0.031 g, 4%).

REFERENCES

1. I. Flament, P. Sonnay, and G. Ohloff, *Helv. Chim. Acta*, **60**, 1872 (1977).
2. J. R. Kim and Y. Won, *Bull. Korean Chem. Soc.*, **25**, 1874 (2004).
3. F. Micheli, B. Bertani, A. Bozzoli, L. Crippa, P. Cavanni, R. Di Fabio, D. Donati, P. Marzorati, G. Merlo, A. Paio, L. Perugini, and P. Zarantonello, *Bioorg. Med. Chem. Lett.*, **18**, 1804 (2008).
4. Shionogi and Co Limited, US Pat. 6756376 B1 (2004); http://v3.espacenet.com
5. E. Wong Ho Fong, L. A. Cortes-Burgos, and B. N. Rogers, Pharmacia and UpJohn Company Limited, WO Pat. 039815 (2004); http://www.wipo.int
6. A. M. Likhosherstov, V. P. Peresada, V. G. Vinokurov, and A. P. Skoldinov, *Zh. Org. Khim.*, **22**, 2610 (1986).
7. V. G. Glukhovtsev, Yu. V. Il'in, A. V. Ignatenko and L. Yu. Brezhnev, *Izv. Akad. Nauk SSSR Ser. Khim.*, 2834 (1987).
8. I. L. Knunyants and G. G. Yakobson (editors), *Synthesis of Fluoroorganic Compounds* [in Russian], Khimiya, Moscow (1973), p. 312.
9. V. I. Terenin and A. S. Ivanov, *Khim. Geterotsikl. Soedin.*, 1714 (2007). [*Chem. Heterocycl. Comp.*, **43**, 1460 (2007)].
10. V. I. Terenin and A. S. Ivanov, *Khim. Geterotsikl. Soedin.*, 1267 (2006). [*Chem. Heterocycl. Comp.*, **42**, 1101 (2006)].