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EFFECT OF THE TRIFLUOROACETYL GROUP ON THE DIRECTION OF THE RECYCLIZATION OF THE PYRAZINE RING IN 6-TRIFLUOROACETYL-PYRROLO[1,2-*a*]PYRAZINIUM SALTS

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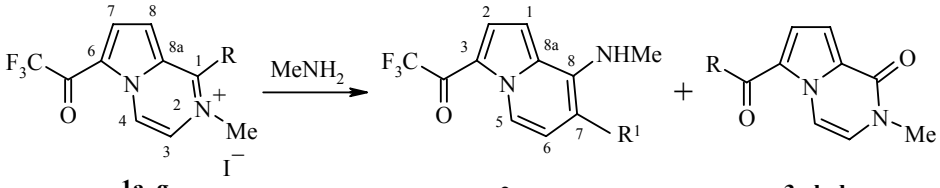
A cyclotransformation of 6-trifluoroacetylpyrrolo[1,2-a]pyrazinium salts involving the trifluoroacetyl group carbon atom was discovered and investigated.

Keywords: pyrrolo[1,2-*a*]pyrazine, pyrrolo[1,2-*a*]pyrazin-1-one, cyclotransformation.

The enamine rearrangement of the pyrazine ring has been demonstrated early for the bicyclic aromatic pyrrolo[1,2-*a*]pyrazine system [1]. It was established that 1-alkyl and 1-aralkyl derivatives recyclize by the action of ethanolic solutions of alkylamines to give 8-alkylaminoindolizines. The introduction of electron-withdrawing substituents into the starting aza ring is known to enhance the electrophilicity of this ring and, as a result, facilitate its opening by the action of a nucleophile [2].

In the present work, we show that 6-trifluoroacetylpyrrolo[1,2-*a*]pyrazinium salts **1a-c** containing a methylene group at $C_{(1)}$ are converted by the action of ethanolic methylamine into 3-trifluoroacetyl-8-methylaminoindolizines at lower temperature (70°C) than the 1-alkyl or 1-aralkyl analogs, which undergo a similar transformation at 140°C. 6-Acylpyrrolo[1,2-*a*]pyrazin-1-ones **3a,b,d-g** are formed in addition to the expected products of the Kost-Sagitullin rearrangement **2a-c**.



1a–g **2a–c** **3a,b,d–g**

1, 3 a R = Et, **b** R = *n*-Pr, **d** R = *i*-Pr, **e** R = *cyclo*-C_5H_9, **f** R = Ph, **g** R = 2-thienyl;
1 c R = $PhCH_2$; **2 a** R^1 = Me, **b** R^1 = Et, **c** R^1 = Ph

Salts **1a**,**b** containing a methylene group at $C_{(1)}$ participate in two parallel cyclotransformations leading to a mixture of 8-methylaminoindolizines **2a**,**b** and pyrrolo[1,2-*a*]pyrazin-1-ones **3a**,**b**.

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Change in the reaction conditions significantly affects the ratio of the recyclization products. Indolizines **2a,b** predominate in the reaction mixtures at 140°C, while 1,2-dihydropyrrolo-[1,2-*a*]pyrazin-1-ones **3a,b** predominate at 30°C. This discrepancy is evidently a function of the ratio of the rates of the two independent reactions, leading to products of fundamentally different cyclotransformations.

The opening of the pyrazine ring occurs by the action of aqueous solutions of a wide variety of nucleophiles such as NH_2NH_2, NH_2OH, $(CH_2NH_2)_2$, and $EtNH_2$ and is terminated, following the thin-layer chromatography results, in formation of 2-methyl-1,2-dihydropyrrolo[1,2-*a*]pyrazin-1-ones, which indicates an intramolecular mechanism of transformation of the aza ring.

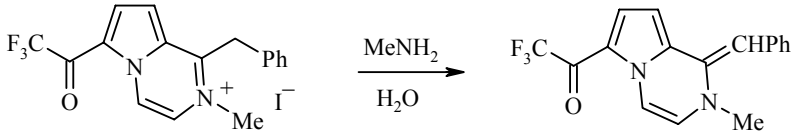
If aqueous methylamine is used as the reagent in the reaction with salts **1a,b,d-g**, only products of recyclization involving the carbonyl carbon atom of the trifluoroacetyl group are formed.

The rearrangement of salts **1d-g** without a methylene group at $C_{(1)}$ leads only to pyrrolo-[1,2-*a*]pyrazin-1-ones **3d-g** by the action of both aqueous and ethanolic methylamine.

The formation of the products of recyclization involving the methylene group was not observed in the reaction of N-methyl-1-isopropyl-6-trifluoroacetylpyrrolo[1,2-*a*]pyrazinium iodide (**1d**) or N-methyl-1-cyclopentylpyrrolo[1,2-*a*]pyrazinium iodide (**1c**) with methylamine [3]. This failure is probably the result of higher rate of cyclization to the trifluoroacetyl group in comparison with the possible competing reaction.

The reaction of N-methyl-1-benzyl-6-trifluoroacetylpyrrolo[1,2-*a*]pyrazinium iodide (**1c**) with ethanolic methylamine gives only 8-methylamino-7-phenyl-6-trifluoroacetylindolizine (**2c**) since the rate of formation of **2c** is higher than the rate of the competing cyclization involving the carbonyl carbon atom of the trifluoroacetyl group.

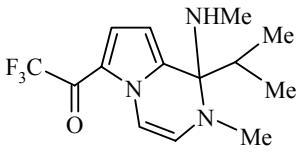
Salt **1c** reacts due to the enhanced CH-acidity of the methylene group with aqueous methylamine to give a stable base anhydride **4**, which does not undergo recyclization under conditions for the enamine rearrangement of the pyrrolo[1,2-*a*]pyrazinium salts even upon heating at 140°C for 20 h.



1c **4**

Stupnikova et al. [4] have described the formation of a base anhydride from N-methyl-1,2-dimethylbenzo[*b*]thieno[2,3-*c*]pyridinium iodide by the action of methanolic methylamine, which does not undergo the Kost-Sagitullin rearrangement upon heating at 100°C for 10 h.

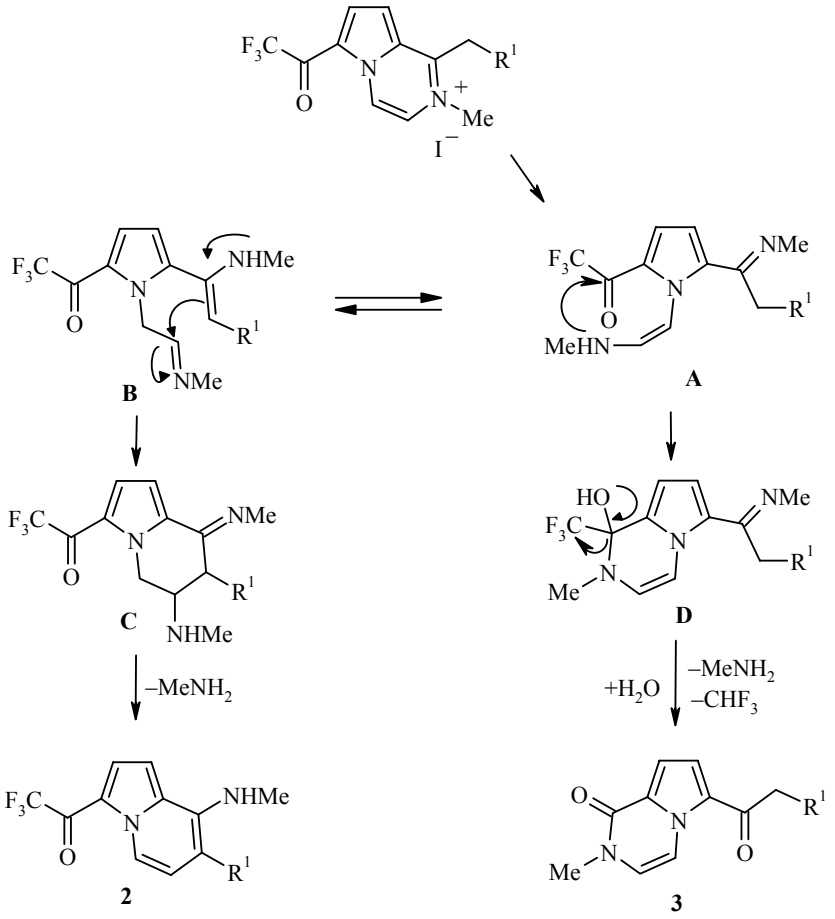
The mechanism of the reaction studied entails initial attack of the nucleophile at $C_{(1)}$ or $C_{(3)}$ of the pyrrolo[1,2-*a*]pyrazine system. The preference of the nucleophilic attack is not obvious but an unstable σ-adduct **5** was isolated in the reaction of aqueous methylamine with N-methyl-1-isopropyl-6-trifluoroacetyl-pyrrolo[1,2-*a*]pyrazinium iodide (**1d**) at room temperature.



5

The ^1H NMR spectrum of σ-adduct **5** shows signals for the pyrazine protons at higher field than for the signals of these protons in 1-isopropyl-6-trifluoroacetylpyrrolo[1,2-*a*]pyrazine, while the coupling constants are enhanced, indicating nonaromatic character of the aza ring. The upfield part of the spectrum shows signals for two diastereotopic methyl substituents belonging to the isopropyl group located next to an asymmetric site.

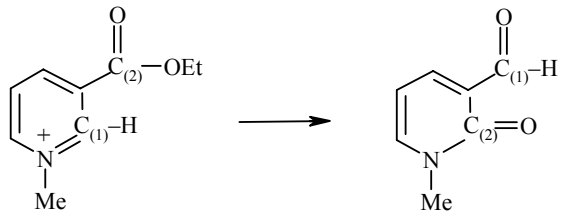
The opening of the pyrazine ring upon attack of the nucleophile both at $C_{(1)}$ and $C_{(3)}$ in the pyrazine ring leads to acyclic intermediates **A** and **B**, which participate in two parallel cyclotransformations. Intramolecular cyclization of intermediate **B** results in intermediate **C** and the subsequent restoration of aromaticity in **C** leads to indolizine **2**.



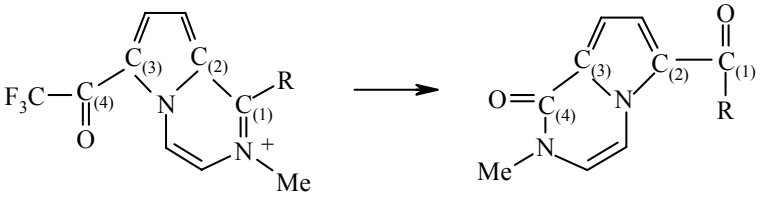
The second pathway involves attack of the enamine nitrogen in intermediate **A** at the carbonyl carbon atom of the trifluoroacetyl group to give intermediate **D**, which undergoes an unusual step with the loss of trifluoromethane to give pyrazinone **3**.

This scheme is in accord with the effect of the reaction medium on the rearrangement pathway. In aqueous solutions, the imine component in intermediate **A** is hydrolyzed to give the corresponding ketone. In this case, the formation of **B** or its enol analog is either impossible (when CH_2R = Ph or 2-thienyl) or proceeds much more slowly than the attack of the enamine component on the trifluoroacetyl group, leading to pyrazinone **3**.

A nucleophilic recyclization proceeding as the exchange of exocyclic carbon fragments by cyclic fragments has been observed for the ethyl ester of nicotinic acid [5] and involves the exchange of $C_{(1)}$ by $C_{(2)}$.



The cyclotransformation of pyrrolo[1,2-*a*]pyrazinium salts **1a,b,d-g** to give 6-acyl-2-methylpyrrolo-[1,2-*a*]pyrazin-1-ones **3a,b,d-g** proceeds as the exchange of two atoms $C_{(1)}$–$C_{(2)}$ in the ring by exocyclic atoms $C_{(3)}$–$C_{(4)}$.



Thus, this rearrangement belongs to a previously unknown structural type and is a new means to obtain 6-acylpyrrolo[1,2-*a*]pyrazin-1-ones.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Varian VXR-400 and Bruker Avance 400 spectrometers at 400 MHz in $CDCl_3$ at 28°C with TMS as the internal standard. The mass spectra were taken on a Kratos MS-90 spectrometer with 70 eV ionizing radiation. The IR spectra were taken on a UR-20 spectrometer for a film in CCl_4. The course of the reactions and purity of the products were monitored by thin-layer chromatography on Silufol plates with benzene and 1:1 benzene–ethyl acetate as the eluents.

Preparation of 2-Methyl-6-trifluoroacetylpyrrolo[1,2-*a*]pyrazinium Iodides (General Method). A mixture of corresponding 1-alkyl-, 1-aryl-, or 1-aralkyl-6-trifluoroacetylpyrrolo[1,2-*a*]pyrazine (3 mmol) and methyl iodide (5 ml) was heated for 5-7 h in a sealed ampule at 70°C until a precipitate formed. The precipitate was filtered off and washed several times with hot heptane.

Preparation of Indolizines 2a-c and Pyrazinones 3a,b,d-g (General Method). A. A mixture of quaternary salt **1a-g** (1 mmol) and 40% methylamine in absolute ethanol (5 ml) was heated in a sealed glass ampule for 3-5 h. The reaction mixture was evaporated. The residue was separated by chromatography on a column of silica gel 35/70 in benzene with increasing polarity of the eluent to 1:2 benzene–ethyl acetate.

Preparation of Pyrazinones 3a,b,d-g (General Method). B. A mixture of quaternary salt **1a-g** (1 mmol) and 40% aqueous methylamine (5 ml) was heated in a sealed glass ampule on a water bath for several minutes until the salt was completely dissolved. The reaction mixture was left for 24 h at room temperature until formation of a precipitate. The precipitate was filtered off, recrystallized from acetone, and dried on a glass filter. In the case of salt **1c**, base anhydride **4** was formed as dark-red precipitate, which was filtered off and recrystallized from heptane.

7-Methyl-8-methylamino-6-trifluoroacetylindolizine (2a). Mp 118-120°C (hexane). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.31 (3H, s, CH_3); 3.15 (3H, s, $NHCH_3$); 6.72 (1H, d, $J = 5.5$, H-1); 6.83 (1H, d, $J = 6.9$, H-6); 7.56 (2H, dq, $J = 5.5$, $J = 2.1$, H-2); 9.45 (1H, d, $J = 6.9$, H-5). Mass spectrum, *m/z* (I_{rel}, %): 256 $[M]^+$ (100), 187 $[M\text{-}CF_3]^+$ (57), 159 $[M\text{-}COCF_3]^+$ (46). Found, %: C 56.35; H 4.21; N 10.85. $C_{12}H_{11}F_3N_2O$. Calculated, %: C 56.25; H 4.29; N 10.93.

7-Ethyl-8-methylamino-6-trifluoroacetylindolizine (2b). Mp 112-114°C (hexane). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.27 (3H, t, $J = 7.6$, $CH_2C\underline{H}_3$); 2.66 (2H, q, $J = 7.6$, $C\underline{H}_2CH_3$); 3.12 (3H, s, $NHCH_3$); 6.73 (1H, dd, $J = 5.6$, $J = 0.5$, H-1); 6.87 (1H, d, $J = 6.9$, H-6); 7.56 (1H, dq, $J = 5.6$, $J = 2.3$, H-2); 9.50 (1H, d, $J = 6.9$, H-5). Mass spectrum, *m/z* (I_{rel}, %): 270 $[M]^+$ (100); 201 $[M\text{-}CF_3]^+$ (44); 158 $[M\text{-}COCF_3]^+$ (98). Found, %: C 57.41; H 4.81; N 10.21. $C_{13}H_{13}F_3N_2O$. Calculated, %: C 57.77; H 4.81; N 10.37.

8-Methylamino-7-phenyl-6-trifluoroacetylindolizine (2e). Mp 68-70°C (pentane). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.99 (3H, s, $NHCH_3$); 4.1 (1H, br. s, NH); 6.84 (1H, d, $J = 5.2$, H-1); 6.83 (1H, d, $J = 6.9$, H-6);

7.44-7.59 (5H, m, C_6H_5); 7.62 (1H, dq, J = 5.2, J = 2.3, H-2); 9.50 (1H, d, J = 6.9, H-5). ^{13}C NMR spectrum, δ, ppm (J, Hz): 34.9 ($NHCH_3$); 104.6 ($C_{(1)}$); 117.9 ($C_{(3)}$); 118.0 (q, J = 289, CF_3); 118.6 and 121.2 ($C_{(5)}$ and $C_{(6)}$); 124.5 (q, $J_{C\text{-}F}$ = 3.8, $C_{(2)}$); 124.9 ($C_{(8a)}$); 128.2 (*p*-C_6H_5); 128.8 and 129.2 (*m*-, *o*-C_6H_5); 135.4 (*ipso*-C_6H_5); 137.3 ($C_{(7)}$); 137.8 ($C_{(8)}$); 160.6 (q, $J_{C\text{-}F}$ = 36.0, C=O). Mass spectrum, *m/z* (I_{rel}, %): 318 $[M]^+$ (100); 249 $[M\text{-}CF_3]^+$ (41); 159 $[M\text{-}COCF_3]^+$ (33). Found, %: C 64.52; H 3.83; N 8.81. $C_{17}H_{13}F_3N_2O$. Calculated, %: C 64.15; H 4.08; N 8.80.

2-Methyl-6-propionylpyrrolo[1,2-*a*]pyrazinone (3a). Mp 223-225°C (acetone). IR spectrum, ν, cm^{-1}: 1640, 1660, 1680 (C=O, C=C). ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.25 (3H, t, J = 7.3, $C(O)CH_2C\underline{H}_3$); 2.94 (2H, q, $C(O)C\underline{H}_2CH_3$); 3.51 (3H, s, NCH_3); 6.55 (1H, d, J = 6.0, H-3); 7.11 (1H, d, J = 4.3, H-8); 7.26 (1H, d, J = 4.3, H-7); 8.55 (1H, d, J = 6.0, H-4). Mass spectrum, *m/z* (I_{rel}, %): 204 $[M]^+$ (64); 175 (100); 151 (57); 120 (80). Found: C 63.78; H 5.20; N 12.67%. $C_{11}H_{12}N_2O_2$. Calculated, %: C 63.70; H 5.92; N 12.63.

6-Butyryl-2-methylpyrrolo[1,2-*a*]pyrazinone (3b). Mp 198-200°C (acetone). IR spectrum, ν, cm^{-1}: 1640, 1680 (C=O, C=C). ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.03 (3H, t, J = 7.6, $C(O)CH_2CH_2C\underline{H}_3$); 1.77 (each 2H, m, $C(O)CH_2C\underline{H}_2CH_3$); 2.86 (2H, t, J = 7.6, $C_{(6)}(O)C\underline{H}_2CH_2CH_3$); 3.51 (3H, s, NCH_3); 6.54 (1H, d, J = 5.9, H-3); 7.10 (1H, d, J = 4.1, H-8); 7.24 (1H, d, J = 4.1, H-7); 8.57 (1H, d, J = 5.9, H-4). Mass spectrum, *m/z* (I_{rel}, %): 218 $[M]^+$ (77); 190 (37); 175 (100); 147 (40). Found, %: C 66.04; H 6.74; N 12.84. $C_{12}H_{14}N_2O_2$. Calculated, %: C 66.04; H 6.47; N 12.83.

6-Isobutyryl-2-methylpyrrolo[1,2-*a*]pyrazinone (3d). Mp 150-153°C (acetone). IR spectrum, ν, cm^{-1}: 1640, 1670 (C=O, C=C). ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.23 (6H, d, J = 6.9, $C(O)CH(C\underline{H}_3)_2$); 3.38 (1H, m, $C(O)C\underline{H}(CH_3)_2$); 3.55 (3H, s, NCH_3); 6.53 (1H, d, J = 6.4, H-3); 7.23 (1H, d, J = 4.0, H-8); 7.24 (1H, d, J = 4.0, H-7); 8.58 (1H, d, J = 6.4, H-4). Mass spectrum, *m/z* (I_{rel}, %): 218 $[M]^+$ (100); 175 (92); 147 (35). Found, %: C 66.25; H 6.41; N 13.09. $C_{12}H_{14}N_2O_2$. Calculated, %: C 66.04; H 6.47; N 12.83.

6-Cyclopentylcarbonyl-2-methylpyrrolo[1,2-*a*]pyrazinone (3e). Mp 93-94°C (acetone). IR spectrum, ν, cm^{-1}: 1630, 1670 (C=O, C=C). ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.10-1.25 (8H, m, $C(O)CH(C\underline{H}_2)_4$); 3.41 (1H, m, $C(O)C\underline{H}(CH_2)_4$); 3.53 (3H, s, NCH_3); 6.52 (1H, d, J = 6.2, H-3); 7.22 (1H, d, J = 4.0, H-8); 7.23 (1H, d, J = 4.0, H-7); 8.56 (1H, d, J = 6.2, H-4). Mass spectrum, *m/z* (I_{rel}, %): 244 $[M]^+$ (29); 175 (100); 147 (22); 124 (38). Found, %: C 63.40; H 6.60; N 10.95. $C_{14}H_{16}H_2O_2$. Calculated, %: C 63.83; H 6.60; N 11.46.

6-Benzoyl-2-methylpyrrolo[1,2-*a*]pyrazinone (3f). Mp 211-212°C (acetone). IR spectrum, ν, cm^{-1}: 1630, 1680 (C=O, C=C). ^{1}H NMR spectrum, δ, ppm (J, Hz): 3.55 (3H, s, NCH_3); 6.60 (2H, d, J = 6.1, H-3); 7.09 (1H, d, J = 3.9, H-8); 7.13 (1H, d, J = 3.9, H-7); 7.50 (2H, t, J = 7.4, H (*m*-C_6H_5)); 7.60 (1H, tt, J = 7.4, J = 1.2, H (*p*-C_6H_5)); 7.82 (2H, m, H (*o*-C_6H_5). Mass spectrum, *m/z* (I_{rel}, %): 252 $[M]^+$ (100); 175 (57); 105 (50). Found, %: C 71.21; H 4.74; N 10.90. $C_{15}H_{12}N_2O_2$. Calculated, %: C 71.42; H 4.79; N 11.11.

TABLE 1. Yields of Recyclization Products

Starting salt	Product	Yield, %				
		(sec., $MeNH_2$ ethanol) at T, °C			(sec, $MeNH_2$ aq.) at T, °C	
		30	70	140	30	70
1a	**2a**	10	49	45	—	—
	3a	39	11	6	35	49
1b	**2b**	15	40	44		
	3b	50	25	10	28	56
1c	**2c**	60	69	70	—	—
1d	**3d**	45	43	40	40	52
1e	**3e**	50	47	45	43	55
1f	**3f**	47	36	27	78	81
1g	**3g**	44	39	25	55	60

2-Methyl-6-thenoylpyrrolo[1,2-*a*]pyrazinone (3g). Mp 205-206°C (acetone). IR spectrum, ν, cm^{-1}: 1630, 1680 (C=O, C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.54 (3H, s, NCH_3); 6.58 (1H, d, *J* = 6.0, H-3); 7.17 (1H, d, *J* = 4.2, H-8); 7.17 (1H, d, *J* = 4.2, H-7); 7.20 (1H, dd, *J* = 4.0, *J* = 2.7, H (β'-Th)); 7.39 (1H, d, *J* = 4.2, H-7); 7.71 (1H, d, *J* = 4.0, H (α-Th)); 7.84 (1H, d, *J* = 2.7, H (β-Th)); 8.42 (1H, d, *J* = 6.0, H-4). Mass spectrum, *m/z* (I_{rel}, %): 260 $[M+2]^+$ (6), 258 $[M]^+$ (100), 175 (43), 120 (44), 111 (85). Found, %: C 60.38; H 3.86; N 9.25. $C_{13}H_{10}N_2O_2S$. Calculated, %: C 60.46; H 3.87; N 9.30.

1-Benzylidene-6-trifluoroacetyl-1,2-dihydropyrrolo[1,2-*a*]pyrazine (4) was obtained in 71% yield when the reaction was carried out at 30°C, mp 145-146°C (hexane). IR spectrum, ν, cm^{-1}: 1650 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.18 (3H, s, NCH_3); 5.50 (1H, s, $C_{(1)}$=CH); 5.71 (1H, d, *J* = 4.7, H-8); 6.20 (1H, d, *J* = 6.0, H-3); 7.00 (1H, dq, *J* = 4.7, J_{H-F} = 2.2, H-7); 7.20-7.40 (5H, m, H (C_6H_5)); 7.70 (1H, d, *J* = 6.0, H-4). Mass spectrum, *m/z* (I_{rel}, %): 318 $[M]^+$ (36), 205 (15), 91 (100). Found, %: C 64.12; H 4.01; N 8.75. $C_{17}J_{13}F_3N_2O$. Calculated, %: C 64.15; H 4.08; N 8.80.

1-Isopropyl-2-methyl-1-methylamino-1,2-dihydrotrifluoroacetylpyrrolo[1,2-*a*]pyrazine (5) was obtained in 67% yield, ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.87 and 0.98 (each 3H, both d, *J* = 6.9, $CH(C\underline{H}_3)_2$); 2.15 (1H, m, $C\underline{H}(CH_3)_2$); 2.20 (3H, s, $NHCH_3$); 2.83 (3H, s, NCH_3); 6.04 (1H, d, *J* = 6.0, H-3); 6.17 (1H, d, *J* = 4.4, H-8); 7.12 (1H, d, *J* = 6.0, H-4); 7.16 (1H, m, H-7).

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