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α-Aminoazoles in Synthesis of Heterocycles: IV.* Regiodirection of 3(5)-Amino-5(3)-methylpyrazole Reaction with Hexafluoroacetylacetone

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Abstract—The reaction of 3(5)-amino-5(3)-methylpyrazole with hexafluoroacetylacetone depending on the process conditions led to the formation either of pyrazolo[1,5-*a*]pyrimidine or pyrazolo[3,4-*b*]-pyridine. By means of 2D NMR spectroscopy the structure was established of a stable intermediate product, 2-methyl-5,7-bis(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]-pyrimidine-5,7-diol, whose dehydration yielded the above compounds.

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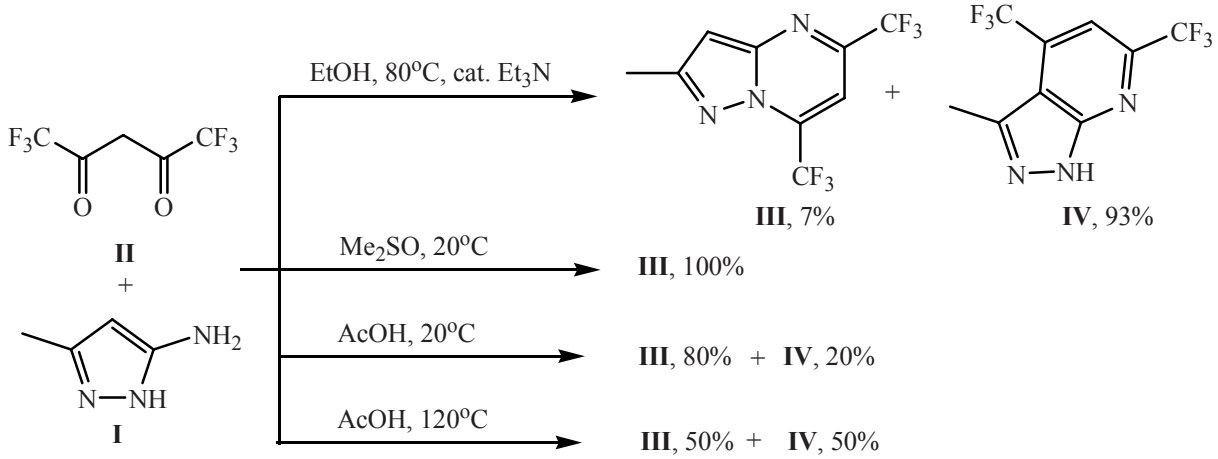
α-Aminopyrazoles find an extensive application in the synthesis of fused nitrogen heterocycles exhibiting a biological action [2–4]. The cyclocondensation of 5(3)-aminopyrazoles with 1,3-diketones containing a perfluoroalkyl group is one of the most common methods of building up perfluoroalkyl-containing heterocyclic systems [5–9]. Therewith the formation is possible of isomeric substances (pyrazolo[1,5-*a*]pyrimidines and pyrazolo[3,4-*b*]pyridines) resulting from the concurrent attack on the nucleophilic centers of the 5(3)-aminopyrazole (C^4, NH_2, N^1) by the carbon atoms of the carbonyl groups of the diketone. N-Unsubstituted 3(5)-aminopyrazoles usually react with 1,3-dicarbonyl compounds providing pyrazolo-[1,5-*a*]pyrimidines [2]. At the same time 3(5)-amino-5(3)-methylpyrazole and 3(5)-aminopyrazole reacted with trifluoromethyl-containing diketones giving pyrazolo[3,4-*b*]pyridine [10, 11] or its mixtures with pyrazolo[1,5-*a*]pyrimidine [9, 12].

The target of the present study was the investigation of the regiodirection of the reaction of 3(5)-amino-5(3)-methyl-NH-pyrazole (**I**) with hexafluoroacetylacetone depending on the conditions of the process, and also the establishment of the structure of intermediate compounds leading to the formation of pyrazolo[3,4-*b*]pyridine or pyrazolo[1,5-*a*]pyrimidine.

Scheme 1.



* For communication III, see [1].

The heating aminopyrazole **I** with hexafluoroacetylacetone in acetic acid led to the formation of a mixture of compounds **III** and **IV** (Scheme 1). At the use of DMSO pyrazolopyrimidine **III** formed as the only reaction product whereas at boiling the reagents in ethanol in the presence of triethylamine the predominant product was pyrazolopyridine **IV** (93%). Thus at 20°C the prevailing or the only reaction product was pyrazolopyrimidine **III**, and raising the temperature favored the increase in the fraction of pyrazolopyridine (Scheme 1).

At mixing aminopyrazole **I** with hexafluoroacetylacetone in CH_2Cl_2 at the temperature not higher than 20°C for 10 min a colorless crystalline precipitate formed that was 2-methyl-5,7-bis(trifluoromethyl)-4,5,6,7-tetrahydropyrasolo[1,5-*a*]pyrimidine-5,7-diol (**V**) (Scheme 2), whose composition and structure were established from elemental analysis and ^{1}H and ^{13}C NMR spectra. The same diol formed in the reaction carried out in ethanol.

The dehydration of diol **V** at room temperature in the presence of catalytical amounts of triethylamine or trifluoroacetic acid led to the formation of a single product, pyrazolopyrimidine **III**. At the same time the heating of the diol without solvent yielded nearly quantitatively pyrazolopyridine **IV** (Scheme 2). In DMSO at 20°C diol **V** is stable, the dehydration occurs only at heating giving a mixture of compounds **III** and **IV**. The reaction of aminopyrazole **I** with hexafluoroacetylacetone **II** in DMSO also proceeded through formation of diol **V** as an intermediate compound as showed the monitoring of the reaction mixture by ^{1}H NMR method. Probably the dehydration of diol to give pyrazolopyrimidine **III** in this case is caused by the catalysis of the reaction with a small excess of hexafluoroacetylacetone.

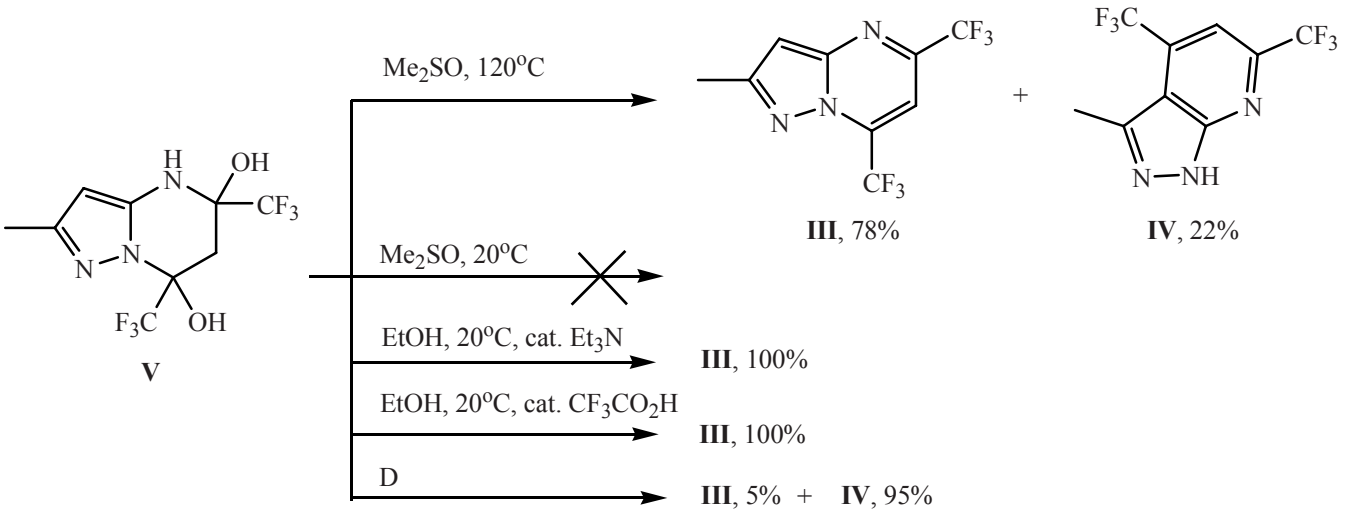
The results obtained show that at the dehydration of diol **V** and at the reaction of aminopyrazole with hexafluoroacetylacetone at 20°C the reaction product is nearly always only pyrazolopyrimidine **III**. A higher temperature and alkaline catalysis of these reactions favors the growing of the fraction of pyrazolopyridine **IV** in the reaction mixture. Considering that pyrazolopyrimidine **III** does not isomerize into pyrazolopyridine **IV** both under the reaction conditions or at heating without solvent to 140°C it is presumable that the latter forms through an intermediate form **A** (Scheme 3).

In the NMR spectrum of diol **V** in DMCO-d_6 two sets of signals were observed indicating that it existed as two diastereomers (**V**)**A** and (**V**)**B** in a ratio 7:3.

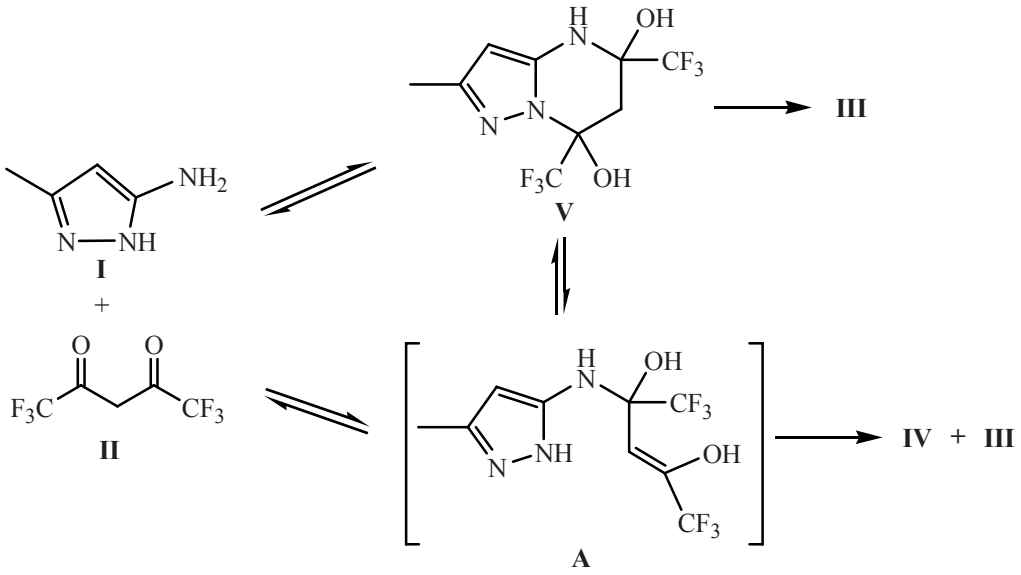
To prove the structure of diols (**V**)**A** and (**V**)**B** we used the data on indirect scalar interactions and direct dipole-dipole interactions between magnetic nuclei. These data were obtained as a result of the preliminary identification of all the signals in the ^{1}H NMR spectrum of these diol (see EXPERIMENTAL) by means of homo- and heteronuclear correlation procedures: DQF-COSY [13], J-COSY [14], NOESY [15], and HSQC [16] without decoupling from ^{13}C.

The most characteristic for the ^{1}H NMR spectra of diols (**V**)**A** and (**V**)**B** is the presence in the region 2.2–2.7 ppm of two pairs of doublet signals from protons of C^6H_2 group with the geminal constants $^2J_{H-H}$ –13.9 and

Scheme 2.



Scheme 3.



–14.8 Hz respectively. Therewith the peaks of each of the four doublet signals have different additional splitting due to the long-range scalar interactions. This fact makes it possible to establish the spatial orientation of the diastereotopic protons at the atom C^6. To distinguish the contribution into the lines broadening of homonuclear ($J_{H–H}$) and heteronuclear ($J_{F–H}$) scalar interactions and for the most precise estimation of the former values we used *J*-COSY method (Fig. 1) where the homo- and heteronuclear scalar interactions appear differently [17].

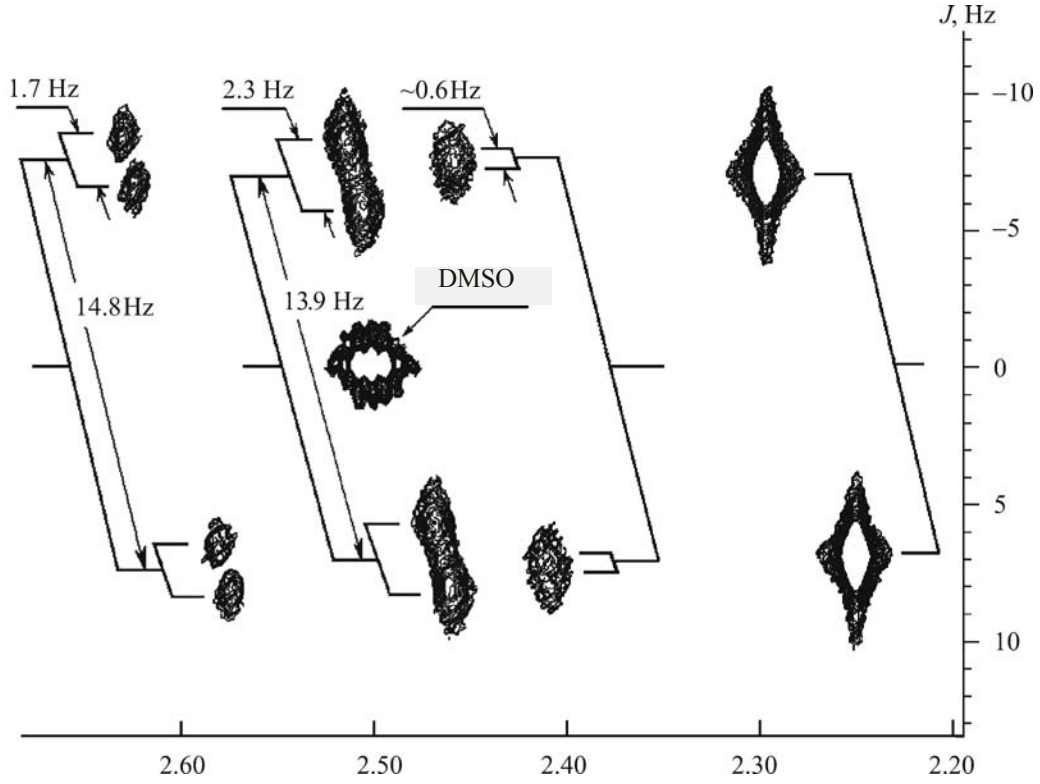


Fig. 1. Fragment of J-COSY spectrum of 2-methyl-5,7-bis(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-5,7-diol (**V**).

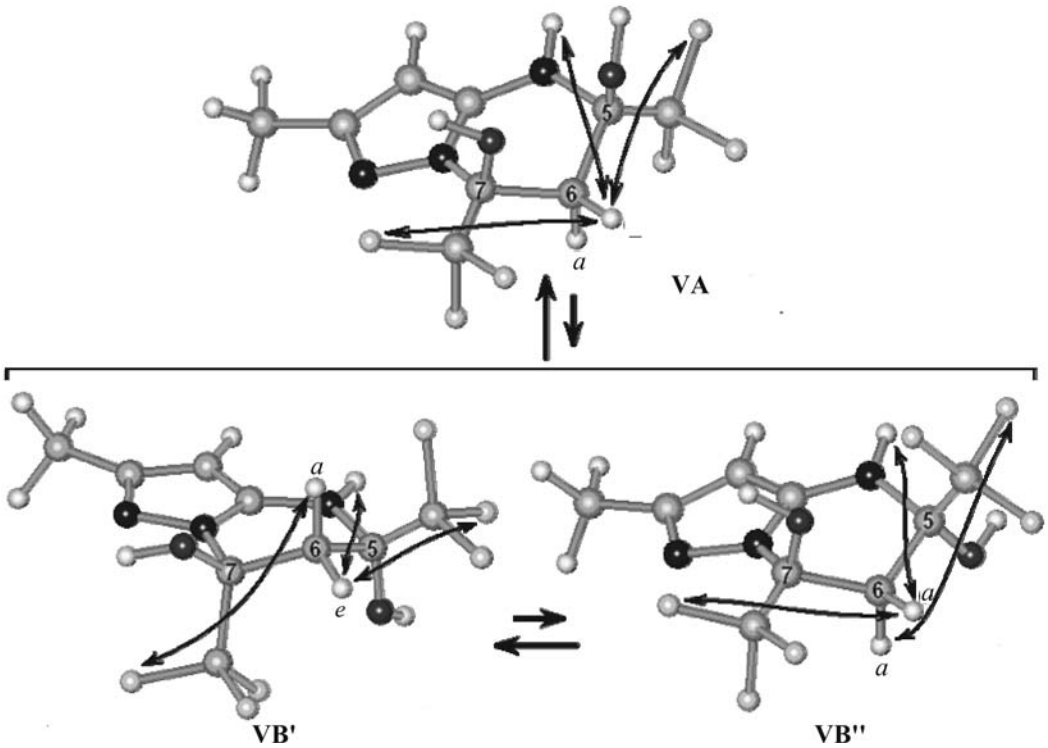


Fig. 2. Intramolecular dynamics and spatial structure of conformers of 2-methyl-5,7-bis(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo-[1,5-*a*]pyrimidine-5,7-diol (**V**).

Inasmuch as for the doublet signal at 2.29 ppm belonging to diol **VA** no long-range scalar interactions are observed, and for the signal at 2.49 ppm belonging to the same isomer exist both homonuclear ($^4J_{NH-H}$ 2.3 Hz) and heteronuclear ($^4J_{F-H} \leftrightarrow$ 0.3 Hz) scalar interactions of "W-type" [18] these findings on the one hand permit the assignment of the first signal to the pseudoaxial and the second signal to the pseudoequatorial protons of the C^6H_2 group of the prevailing diol **VA**, and on the other hand allow a conclusion on the pseudoequatorial orientation of the contiguous trifluoromethyl groups in this isomer. The equatorial conformation of trifluoromethyl substituents and axial conformation of hydroxy groups is consistent with a known fact that the conformational energy of the CF_3 group is significantly larger than that of OH (in substituted cyclohexanes 8.8 and 2.2 kJ mol^{-1} respectively) [19]. Hence isomer **VA** exists as *cis*-diastereomer.

A quite unlike set of long-range scalar interactions is observed in the signals of the methylene protons of the minor isomer **VB** located at 2.43 and 2.62 ppm. Each of these protons interacts both with the NH proton and at least with one of the two contiguous trifluoromethyl groups. Thus isomer **VB** exists as a diastereomer where OH and CF_3 groups are in the *trans*-position. The difference in the values of the homonuclear scalar constants $^4J_{NH-H}$ (~0.6 Hz for the first and 1.7 Hz for the second signal) and also a considerable difference of this constants from the corresponding values for isomer **VA** show that diol **VB** is present in the solution in a conformational equilibrium fast in the NMR time scale **VB'** $\leftrightarrow$ **VB''** related to the inversion of the six-membered ring (Fig. 2). Therefore the above values of constants $^4J_{NH-H}$ for methylene protons correspond to the values averaged in time. Consequently the signal at 2.62 ppm belongs to the proton whose lifetime in the pseudoequatorial orientation in one conformer is significantly longer than its lifetime in a pseudoaxial orientation in another conformer, and the signal at 2.43 ppm, respectively, belongs to the methylene proton that most of time is in the pseudoaxial orientation.

An independent proof of the existence of fast conformational exchange in diol **VB** is the small difference between the values of the heteronuclear scalar constants $^1J_{C-H}$ for the pseudoequatorial (H_e) and pseudoaxial (H_a) protons at the atom C^6 [20] that was measured by inverse HSQC method without decoupling from ^{13}C nuclei (Fig. 3). Whereas in diol **VA** that exists in the solution in a single conformation with the pseudoequatorial orientation of the trifluoromethyl groups this value

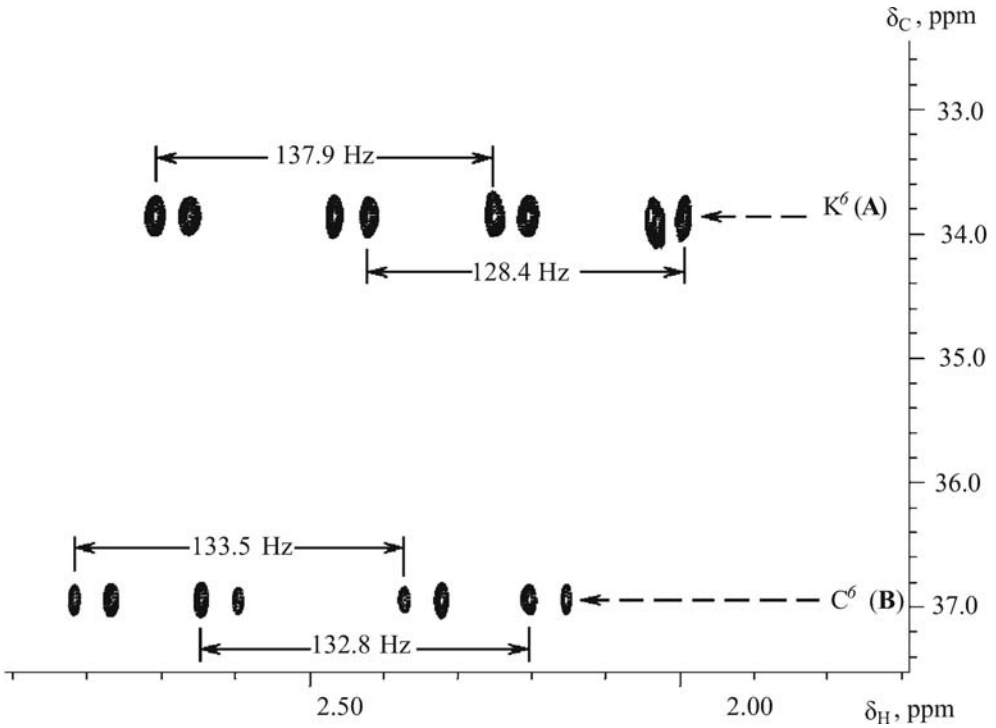


Fig. 3. Fragment of HSQC spectrum registered without decoupling from ^{13}C nuclei of 2-methyl-5,7-bis(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-5,7-diol (**V**).

($\Delta^1J_{C-H} = {}^1J_{C-He} - {}^1J_{C-Ha}$) amounts to 9.5 Hz, in diol (**V**)**B** due to the fast in the NMR time scale intramolecular mobility and the corresponding averaging in time of constants ${}^1J_{C-He}$ and ${}^1J_{C-Ha}$ for each of the methylene protons this value proved to be much smaller, 0.7 Hz.

According to quantum-chemical calculations (MM^+, PM3) conformer **VB'** where the CF_3 group at the atom C^5 is in a pseudoequatorial position, and the CF_3 group at the atom C^7 is in a pseudoaxial position proved to be thermodynamically more stable than conformer **VB''** with the reversed spatial orientation of the trifluoromethyl groups. However the accuracy of the experimental estimation of the constant of the equilibrium **VA'** ↔ **VA''** is considerably complicated both by the lack of reliable data on the values of long-range (${}^4J_{NH-H}$, ${}^4J_{F-H}$) and direct (${}^1J_{C-H}$) scalar constants for each conformer and by the complexity of precise calculation of these parameters because of the effect of electronegative sybstituents in the positions *5* and *7* of these diols. Taking for initial parameters the values of the long-range constants ${}^4J_{NH-H}$ in isomer **VA** (${}^4J_{NH-Ha}$ 0, ${}^4J_{NH-He}$ 2.3 Hz) then from the observed average value (1.7 Hz) in isomer **VB** the ratio of occupancy (*P*) of conformers **VA' : VA''** equals 74:26. If the analogous estimation of the conformational composition would be based on the difference of the direct constants Δ^1J_{C-H}, then the ratio $P_{\mathbf{VB'}} : P_{\mathbf{VB''}}$ would be 57:43. Hence only qualitative agreement is observed between the experimental and calculated estimations of the equilibrium constant: $P_{\mathbf{VB'}} > P_{\mathbf{VB''}}$.

Thus the reaction of the 3(5)-amino-5(3)-methylpyrazole with hexafluoroacetylacetone at 20°C led to the formation of pyrazolo[1,5-*a*]pyrimidine and increased reaction temperature favored the formation of pyrazolo[3,4-*b*]pyridine. By means of NMR spectroscopy a structure was established of a stable intermediate compound, 2-methyl-5,7-bis(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo-[1,5-*a*]pyrimidine-5,7-diol, whose dehydration at 20°C under alkaline and acid catalysis resulted in the formation of pyrazolo[1,5-*a*]pyrimidine, an at termolysis led to pyrazolo[3,4-*b*]pyridine.

EXPERIMENTAL

NMR spectra ^1H and ^{13}C, DQF-COSY, J-COSY, NOESY, and HSQC were registered on a spectrometer Bruker DPX-300 (300.13 and 75.47 MHz) at 22°C. Chemical shifts δ_H were measured from the residual proton signals of the deuterated solvents $CDCl_3$ (7.28 ppm) and DMSO-d_6 (2.50 ppm), and δ_C, from

signals of $CDCl_3$ (76.90 ppm) and DMSO-d_6 (39.50 ppm). 1,1,1,5,5,5-Hexafluoroacetylacetone and 5(3)-amino-3(5)-methylpyrazole used in the study were purchased from Acros Organics.

2-Methyl-5,7-bis(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-5,7-diol (V). A mixture of diastereomers **A** (70%) and **B** (30%). To a solution of 1 mmol of aminopyrazole **I** in 3 ml of CH_2Cl_2 was added dropwise an equiv amount (1 mmol) of hexafluoroacetylacetone in 3 ml of CH_2Cl_2. The mixture was maintained for 4 h at 10°C, the separated precipitate was filtered off, washed with cold CH_2Cl_2, and dried at 20°C.

Diastereomer A. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.07 s (3H, CH_3), 2.29 d.d (1H, H^a, J 13.9, $^4J_{NH-H}$ 2.3 Hz), 2.49 d.d (1H, H^e, J 13.9, $^4J_{NH-H}$ 2.3 Hz), 5.27 s (1H, C^{3}H), 7.00 s, 7.71 s (2H, 2OH), 7.71 d (1H, NH, ^4J 2.3 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 14.72 s (CH_3), 34.42 s (CH_2), 79.85 q (C^7, $^2J_{C-F}$ 31.0 Hz), 80.82 q (C^5, $^2J_{C-F}$ 31.5 Hz), 88.35 s (C^{3}H), 123.93 q (C$^5CF_3$, J_{C-F} 288.6 Hz), 124.44 q (C$^7CF_3$, J_{CF} 288.6 Hz), 144.69 s (C^3), 150.16 s (C^2).

Diastereomer B. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.07 s (3H, CH_3), 2.42 d.d (1H, H^a, J 14.8, $^4J_{NH-H}$ 1.7 Hz), 2.59 d.d (1H, H^e, J 14.8, $^4J_{NH-H}$ 1.7 Hz), 5.21 s (1H, C^{3}H), 7.08 s (H, OH), 7.66 d (1H, NH, J 1.7 Hz), 7.88 s (1H, OH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 14.72 s (CH_3), 35.50 s (CH_2), 79.85 q (C^7, $^2J_{C-F}$ 31.0 Hz), 80.73 q (C^5, $^2J_{C-F}$ 31.5 Hz), 87.20 s (CH), 123.93 q (C$^5CF_3$, J_{C-F} 288.6 Hz), 124.70 q (C$^7CF_3$, J_{C-F} 288.6 Hz), 145.34 s (C^3), 150.08 s (C^2). Found, %: C 35.21; H 3.28. $C_9H_9F_6N_3$. Calculated, %: C 35.42; H 2.97.

2-Methyl-5,7-bis(trifluoromethyl)pyrazolo[1,5-*a*]-pyrimidine (III). *a*. A solution of 1 mmol of diol **V** in 3 ml of ethanol in the presence of catalytic quantities of triethylamine or trifluoroacetic acid was left standing at 20°C for 24 h, the reaction mixture was poured into water (15 ml), extracted with CH_2Cl_2, the extract was dried with Na_2SO_4, the solvent was distilled off in a vacuum, and the residue was subjected to sublimation. Yield 40%.

b. A mixture of 1 mmol of aminopyrazole **I** and 1 mmol of hexafluoroacetylacetone in 1.5 ml of DMSO was left standing at 20°C for 24 h, the reaction mixture was poured into water (15 ml), extracted with CH_2Cl_2, the extract was dried with Na_2SO_4, the solvent was distilled off in a vacuum, and the residue was subjected to sublimation. Yield 42%, mp 49–49.5°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4, 1:2), δ, ppm: 2.56 s (3H, CH_3), 7.11 s (1H, C^{3}H), 7.94 s (1H, C^{6}H). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.65 d (3H, CH_3, $^4J_{H-H}$ 0.5 Hz), 6.89 m (1H, C^{6}H), 7.39 q (1H, C^{3}H, $^4J_{H-H}$ 0.5 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.75 s (CH_3), 99.87 s (C^3), 101.01 q.q [C^6, ^3J(C^6–C$^5CF_3$) 2.2, ^3J(C^6–C$^7CF_3$) 4.3 Hz], 118.94 q (C^7, J_{C-F} 274.9 Hz), 120.17 q (C^5, J_{C-F} 275.3 Hz), 134.72 q (C$^7CF_3$, $^2J_{C-F}$ 38.4 Hz), 145.21 q (C$^5CF_3$, $^2J_{C-F}$ 37.9 Hz), 148.84 s (C^{3a}), 158.73 C (C^2). Found, %: C 39.99; H 1.98. $C_9H_5F_6N_3$. Calculated, %: C 40.16; H 1.87.

3-Methyl-4,6-bis(trifluoromethyl)-1*H*-pyrazolo-[3,4-*b*]pyridine (IV). Diol **V** (1 mmol) was heated for 0.5 h at 100°C. The residue containing 95% of pyrazolo[3,4-*b*]pyridine **IV** and 5% of pyrazolo[1,5-*a*]-pyrimidine **III** (^{1}H NMR data) was recrystallized from acetonitrile. Yield 76%.

b. A mixture of 1 mmol of aminopyrazole **I** and 1 mmol of hexafluoroacetylacetone in 3 ml of ethanol in the presence of catalytic quantity of triethylamine was heated at 80°C for 1 h, and the solvent was distilled off in a vacuum. The residue containing 93% of pyrazolo-[3,4-*b*]pyridine **IV** and 7% of pyrazolo[1,5-*a*]-pyrimidine **III** (^{1}H NMR data) was recrystallized from acetonitrile. Yield 73%, mp 135°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.58 s (3H, CH_3), 7.92 s (1H, CH), 14.48 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 13.76 s (CH_3), 108.56 s (C^5), 109.90 s (C^{3a}), 121.07 q (CF_3, J_{C-F} 273.3 Hz), 122.09 q (CF_3, J_{C-F} 273.5 Hz), 131.42 q (C$^4CF_3$, $^2J_{C-F}$ 35.0 Hz), 139.63 s (C^3), 145.13 q (C$^6CF_3$, $^2J_{C-F}$ 35.0 Hz), 152.30 s (C^{7a}). Found, %: C 40.02; H 2.01. $C_9H_5F_6N_3$. Calculated, %: C 40.16; H 1.87.

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