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SHORT COMMUNICATIONS

α-Aminoazoles in the Synthesis of Heterocycles. Intermediates of Reaction between 3(5)-Aminopyrazoles and Trifluoroacetylacetone

E. E. Emelina, A. A. Petrov, and A. V. Firsov

St. Petersburg State University, St. Petersburg, 198504 Russia

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3(5)-Aminopyrazoles are widely used in the syntheses of various polycyclic heterocycles [1–5]. In reactions of 3(5)-aminopyrazoles with unsymmetrical CH-electrophiles usually a mixture of two regioisomers is obtained [2, 3]. Therewith they react regiospecifically in acetic acid with trifluoromethyl-containing diketones affording pyrazolo[1,5-*a*]pyrimidines with a CF_3 group in position *7* [1].

We demonstrated in this study that in reaction of substituted 3(5)-aminopyrazoles **Ia–c** with 1,1,1-trifluoropentane-2,4-dione (**II**) in dichloromethane at a temperature not higher than 10°C formed 5,7-dihydroxy-5-methyl-7-trifluoromethyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidines (**IVa–c**) (Scheme 1).

Diols **IVa–c** are colorless crystalline compounds, sparingly soluble in solvents of low polarity, well soluble in alcohols, DMSO. They readily are converted by heating into the corresponding pyrazolo[1,5-*a*]-pyrimidines **IIIa–c** containing a C^7F_3 group. Previously such diols were detected only by spectral methods as intermediates in reactions of symmetric diketones with nitrogen-containing binucleophiles [6]. The formation of stable condensation products from aminopyrazoles with trifluoroacetylacetone is an unusual phenomenon.

Monitoring of the reaction by ^1H NMR spectroscopy showed that in $CDCl_3$ the reaction takes several minutes, and the only observed primary reaction product is diol **IVa–c**. Within some minutes in the spectrum of the solution appear signals of the final product **IIIa–c**. The spectral characteristics of the compounds are given in Tables 1, 2. The proofs of the regiostructure

Scheme 1.

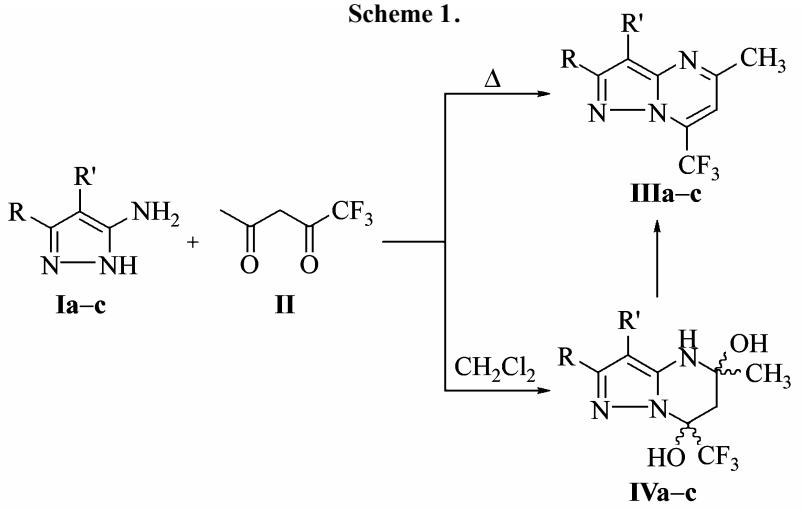

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Table 1. ^{1}H NMR spectra of compounds **IIIa–c** in $CDCl_3$ and **IVa–c, Va–c** in DMSO-d_6

Compd. no.	R	R′	C^5CH_3	C^6H	C^3H (C^2CH_3)	NH, C^5OH, C^7OH	Ar (CH_3)
IIIa [1]	C_6H_5	H	2.64	6.97	6.97	–	7.48–8.05
IIIb [1]	4-ClC_6H_4	H	2.68	7.01	6.94	–	7.42–7.96
IIIc [1]	CH_3	C_6H_5	2.67	7.00	(2.67)	–	7.36–7.71
IVa	C_6H_5	H	1.87	2.25, 2.42[a]	5.73	7.56,6.75, 6.69	7.16–7.68
Va	C_6H_5	H	1.78	[b]	5.69	6.96, 6.59, 6.33	7.16–7.68
Ivb	4-ClC_6H_4	H	1.87	2.29, 2.43[a]	5.77	7.61, 6.70, 6,80	7.30–7.73
Vb	4-ClC_6H_4	H	1.74	[b]	5.72	7.19, 6.54[c]	7.30–7.73
IVc	CH_3	C_6H_5	1.83	2.34, 2.45[a]	(2.18)	6.87, 6.35, 6.05	7.37–7.17
Vc	CH_3	C_6H_5	1.73	[b]	(2.20)	6.55, 6.60, 5.55	7.37–7.17

[a] *AB*-system, *J* 13.7 Hz.
[b] Center of *AB*-system 2.30–2.40 ppm., the signals are overlapped by stronger signals of the other isomer.
[c] Overlapped by other signals.

Table 2. ^{13}C NMR spectra of compounds **IIIa–c** in $CDCl_3$ and **IVa–c** in DMSO-d_6

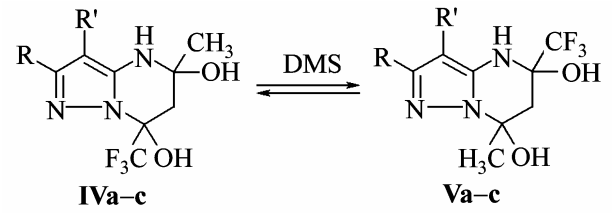
Compd. no.	C^2	C^3	C^{3a}	C^5	C^6	C^7	5-CH_3	7-CF_3
IIIa [1]	156.90	93.40	150.10	157.70	106.40	133.08[a]	24.60	119.15[a]
IIIb [1]	156.36	94.09	150.94	158.66	107.32[a]	133.88[a]	25.32	119.82[a]
IIIc [1]	154.29	110.35	147.12	158.37	106.87	133.47[a]	25.43[b]	119.97[a]
IVa	150.55	85.63	143.15	81.57	39.49	80.70[c]	27.65	124.10c[c]
	150.55	85.08	143.61	82.00	41.44	81.34[c]	29.52	124.50[c]
IVb	149.32	85.62	143.39	81.60	39.52	80.64[c]	27.69	124.10[c]
	149.32	85.07	143.82	82.05	41.43	81.80[c]	29.61	124.50[c]
IVc	146.17	103.26	138.33	81.15	39.09	81.12[c]	27.75	124.00[c]
	145.92	102.69	138.70	81.76	[d]	81.82[c]	29.49[e]	124.46[c]

[a] Coupling constants, ^1J(C–F) 274.2–274.8 Hz, ^2J(C–CF_3) 37.1–37.6 Hz, ^3J(C–CCF_3) 2.8 Hz.
[b] δ (C^2CH_3) 14.71 ppm.
[c] Coupling constants, ^1J(C–F) 287 Hz, ^2J(C–F_3) 30.5–31.5 Hz.
[d] Overlapped by solvent signals.
[e] δ (C^2CH_3) 14.03 ppm.

of compounds **IIIa–c** were presented in [1] and were based on characteristic chemical shifts in ^{1}H and ^{13}C NMR spectra of both C^5 and C^7 and the substituents attached thereto.

The structure of compounds **IVa–c** was proved by ^{1}H and ^{13}C NMR spectra. In the spectra of compounds **IVa–c** registered immediately after dissolving in DMSO-d_6 was observed a single set of signals containing a characteristic unsymmetrical doublet of an *AB*-sytem belonging to diastereotopic methylene protons of the ring, the signals from labile protons of NH group and two OH groups (whose intensity gradually decreased on addition of D_2O). In the ^{13}C NMR spectra of compounds **IVa–c** appear signals from methyl and methylene carbons, characteristic signals from C^5 and C^7 atoms; the latter signal is a quartet due to spin-spin coupling with the adjacent trifluoro-methyl group. It is presumable that the isolated diols are the primary products of reaction between aminopyrazoles and trifluoroacetylacetone, and their regiostructure governs the regiostructure of the final products. Consequently, when the final product contains groups C^5CH_3 and C^7CF_3 [1], then the diol also has been of the same structure (Scheme 1).

Scheme 2.



IVa–c **Va–c**

In the ^{I}H and ^{13}C NMR spectra of compounds **IVa–c** in DMSO-d_6 registered in 24 h after dissolution appears a second set of signals with the close values of chemical shifts (Table 1, 2); in 2-3 days the equilibrium is established, and the isomer ratio **IV : V** in solution becomes ~2:1 (Scheme 2). Apparently in the solution arises a regioisomeric diol **Va–c** containing groups $C^{7}CH_3$ and $C^{5}CF_3$ (Scheme 2).

Pyrazolo[1,5-*a*]pyrimidines **IIIa–c** were prepared as in [1].

Procedure for synthesis of diols IVa-c. To a solution of 1 mmol of aminopyrazole **Ia–c** [7, 8] in 3 ml of dichloromethane at cooling to –15°C was added dropwise an equivalent amount (1 mmol) of trifluoroacetylacetone in 3 ml of dichloromethane. The mixture was left standing at the same temperature for 3–24 h, the precipitate formed was filtered off and washed with cold dichloromethane.

On heating diols **IVa–c** over 50°C (or at prolonged standing at room temperature) water is liberated to furnish pyrazolopyrimidines **IIIa–c**. The data of ^{1}H NMR spectra and melting points of compounds **IIIa–c** obtained are identical to those previously published [1].

5,7-Dihydroxy-5-methyl-7-trifluoeomethyl-2-phenyl-4.5.6.7-tetrahydropyrazolo[1,5-*a*]pyrimidine (IVa). Yield 48%. Found, %: C 53.60; H 4.62. $C_{14}H_{14}F_3N_3O_2$. Calculated, %: C 53.67; H 4.50.

5,7-Dihydroxy-5-methyl-7-trifluoeomethyl-2-(4-chlorophenyl-4.5.6.7-tetrahydropyrazolo[1,5-*a*]-pyr-imidine (IVb). Yield 44%. Found, %: C 48.30; H 3.85. $C_{14}H_{13}ClF_3N_3O_2$. Calculated, %: C 48.36; H 3.71.

5,7-Dihydroxy-2,5-dimethyl-7-trifluoeomethyl-3-phenyl-4.5.6.7-tetrahydropyrazolo[1,5-*a*]pyrimidine (IVa). Yield 38%. Found, %: C 54.92; H 5.03. $C_{15}H_{16}F_3N_3O_2$. Calculated, %: C 55.04; H 4.93.

^{1}H and ^{13}C NMR spectra were registered on spectrometer Bruker DPX-300 (300.13 and 75.47 MHz respectively). As solvents were applied $CDCl_3$ and DMSO-d_6.

REFERENCES

1. Emelina, E.E., Petrov, A.A, and Firsov, A.V., *Zh. Org. Khim.,* 2001, vol. 37, p. 899.
2. Elnagdi, M.H., Elmoghayar, M.R.H., and Elgemeie, G.E.H., *Adv. Heterocycl. Chem.*, Katritzky, A.R., Ed., New York: Academic Press, 1987, vol. 41, 319.
3. Elnagdi, M.H., Abdel-Galid, F.M., and Riad, B.Y., *Heterocycles*, 1983, vol. 20, p. 2437.
4. Holland, G.F. and Pereira, J.N., *J. Med. Chem.,* 1967, vol. 10, p. 149.
5. Maquestiau, A., Target, H., and Vanden Eyden, J.-J., *Bull. Soc. Chim. Belg.,* 1992, vol. 101, p. 131.
6. Selivanov, S.I., Bogatkin, R.A., Ershov, B.A., *Zh. Org. Khim.*, 1982, vol. 28, p. 908.
7. German Patent 145750, 1981; *Chem. Abstr.,* 1981, vol. 95, 80952m.
8. Grandberg, I.I., Din, Vei-Py, and Kost, A.N. *Zh. Obshch. Khim.,* 1961., vol. 31, p. 2311.