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SYNTHESIS OF 5-TRIFLUOROMETHYLPYRAZOL-1-YL-SUBSTITUTED 1,2,4,5-TETRAZINES

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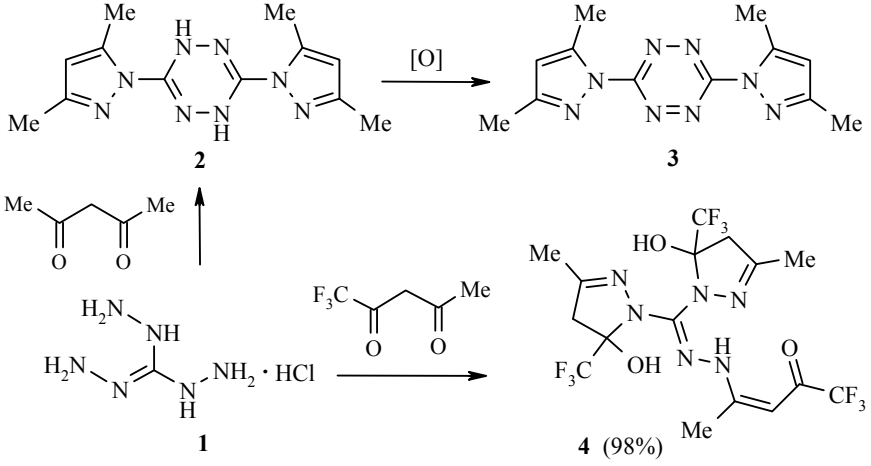
Previously unknown products of the cyclocondensation of 1,1,1-trifluoro-2,4-pentanedione with triaminoguanidine and hydrazine derivatives of 1,2,4,5-tetrazine have been obtained. 5-Hydroxy-5-trifluoromethylpyrazoline substituents formed on the tetrazine ring were dehydrated under the action of trifluoroacetic anhydride. A comparison has been carried out of the reactivity of 5-trifluoromethylpyrazolyl-substituted 1,2,4,5-tetrazines and their unfluorinated analogs in nucleophilic substitution and [4 + 2] cycloaddition reactions.

Keywords: 5-hydroxy-5-trifluoromethylpyrazolines, 3,6-di(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine, 3-methyl-5-trifluoromethylpyrazole, 1,2,4,5-tetrazines, triaminoguanidine, 1,1,1-trifluoro-2,4-pentanedione.

The interaction of triaminoguanidine (**1**) with acetylacetone [1] leads to 3,6-di(3,5-dimethylpyrazol-1-yl)-1,4-dihydro-1,2,4,5-tetrazine (**2**), on oxidation of which the aromatic tetrazine **3** is obtained, widely used for the modification of the tetrazine ring in nucleophilic substitution reactions [2-6]. Replacement of the



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methyl groups by acceptor trifluoromethyl substituents in compound **3** might be capable of increasing the activity of this substrate in nucleophilic substitution and [4+2] cycloaddition reactions with inverse electronic requirements. In addition, the introduction of fluorine atoms into the structure of the molecules significantly increases the lipophilicity of the compounds and enables the creation of new series of potentially biologically active compounds based on 1,2,4,5-tetrazine and pyridazine.

1,1,1-Trifluoro-2,4-pentanedione was used with the aim of synthesizing a trifluoromethyl-containing analogs of compound **3** in a cyclization reaction with triaminoguanidine. As a result of the interaction, in place of the expected dihydrotetrazine, compound **4** was formed, the structure of which was demonstrated unequivocally with the aid of X-ray structural analysis (Fig. 1).

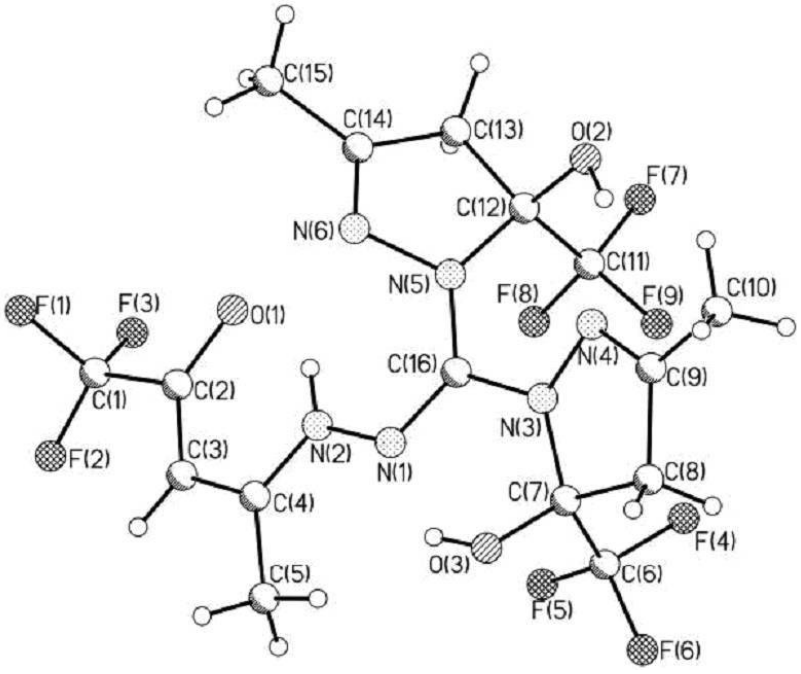


Fig. 1. Structure of compound **4**.

Condensation of trifluoroacetylacetone with triaminoquanidine occurs at the carbonyl groups of the unfluorinated portions of three molecules of the diketone with subsequent formation of two hydroxypyrazoline rings. The structure of compound **4** is characterized by the presence of a planar system of conjugated bonds of imino and aminovinyl ketone fragments with a deviation of atoms from mean square planarity within 0.075 Å.

TABLE 1. Parameters of Hydrogen Bonds in the Compound **4** Crystallosolvate

D–H	*d*(D–H), Å	*d*(H···A), Å	∠DHA, deg	*d*(D···A), Å	A
O(2S)–H(2SA)	0.82(2)	2.027	178.56	2.847(2)	O(1)
N(2)–H(2)	0.85(2)	1.953	138.19	2.645(2)	O(1)
N(2)–H(2)	0.85(2)	2.240	119.25	2.755(2)	N(6)
O(3)–H(3A)	0.77(3)	2.213	128.64	2.759(3)	N(1)
O(3)–H(3A)	0.77(3)	2.527	125.52	3.038(2)	N(6) [–*x*, –*y* + 1, –*z* + 1]
O(2)–H(2A)	0.90(4)	1.927	149.26	2.739(2)	N(4)

The pyrazoline fragments are bent away from the plane of conjugation by an angle of ~30-40° (torsion angle N(6)–N(5)–C(16)–N(1) is 39.9(3)°, N(4)–N(3)–C(16)–N(1) -149.46(19)°). On crystallization from ethanol compound **4** forms a crystallosolvate with molecules of alcohol in a 1:1 ratio. The solvate and the structure are mainly stabilized by a system of intermolecular and intramolecular hydrogen bonds, the main parameters of which are given in Table 1. In particular, the hydroxyl group of ethanol forms a hydrogen bond with the oxygen of the trifluoroacyl group O(2S)–H(2SA)···O(1) 2.027 Å, which probably aids the stabilization of the enamino ketone form. The bond lengths C(2)–C(3) at 1.375(2) and C(3)–C(4) at 1.391(2) Å of the enamino ketone fragment are trimmed, which indicates a strong delocalization of electron density.

The introduction of a fluorinated substituent into the diketone under the conditions of procedure [1] therefore inhibits cyclization into the corresponding tetrazine and leads to compound **4**, which may explain the stability towards dehydration of the resulting hydroxypyrazoline rings and stabilization of the structure of **4** by hydrogen bonds.

An alternative route to obtain the desired 1,2,4,5-tetrazines with trifluoromethylpyrazolyl substituents is the cyclocondensation of hydrazine derivatives of 1,2,4,5-tetrazines with fluorinated diketones. We showed that hydrazine groups in 6-(3,5-dimethylpyrazol-1-yl)-3-hydrazino-1,2,4,5-tetrazine (**5**) and 3,6-dihydrazino-1,2,4,5-tetrazine (**6**) are converted under the action of 1,1,1-trifluoro-2,4-pentanedione into 5-hydroxy-3-methyl-5-trifluoromethyl-4,5-dihydropyrazolyl substituents. The process of cyclization of hydrazinotetrazines **5, 6** with acetylacetone, on the other hand, leads to compound **3** with aromatic pyrazolyl groups.

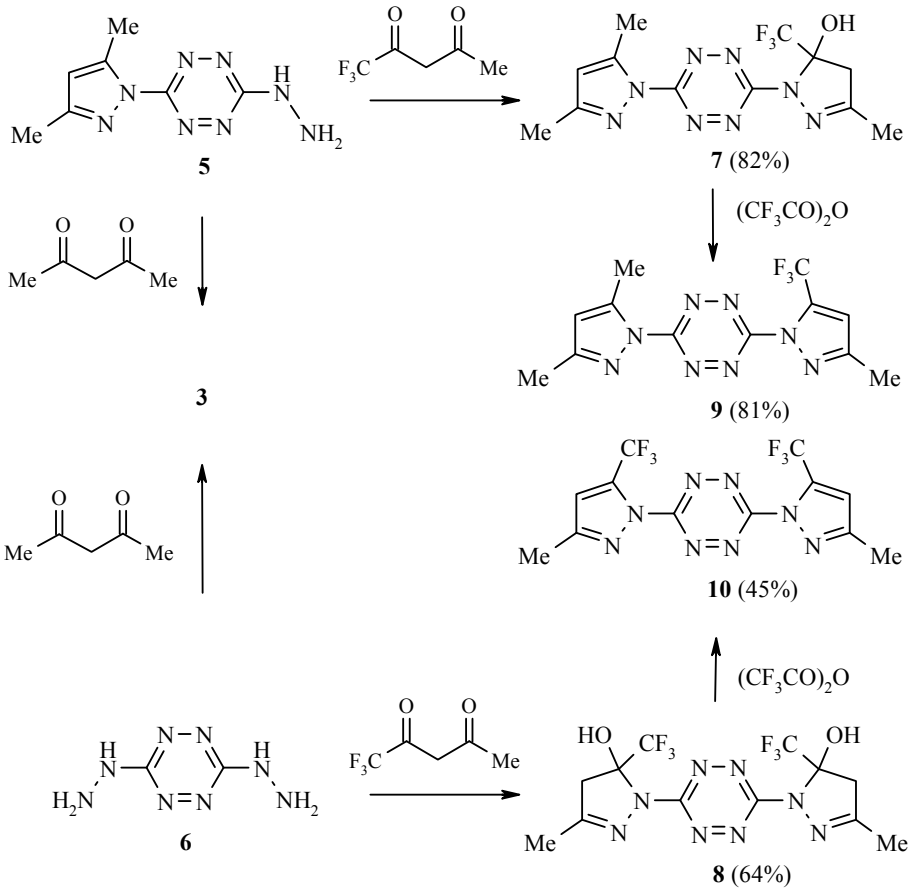
TABLE 2. Basic Parameters of X-ray structural analysis of Compound **4**

Empirical formula	$C_{16}H_{17}F_9N_6O_3 \cdot C_2H_6O$
Molecular mass	558.42
Temperature of the experiment, K	295(2)
System	Triclinic
Space group	$P\bar{1}$
a, Å	9.5890(16)
b, Å	10.5318(15)
c, Å	12.6545(13)
α, deg	73.996(11)
β, deg	86.911(11)
γ, deg	80.529(13)
V, Å^3	1211.6(3)
Z	2
d_{calc}, g/cm^3	1.531
Absorption coefficient, μ, mm^{-1}	0.154
Scanning region	$2.72 \le \theta \le 26.37$
Completeness of scanning for $\theta \le 26.37$, %	98.9
Amount of reflections measured*	4900
Number of reflections with $I > 2\sigma(I)$	2587
Number of refined parameters	404
S	1.000
*R*1 (at $I>2\sigma(I)$)	0.0507
*wR*2 at $I>2\sigma(I)$)	0.1274
*R*1 (on all reflections)	0.0972
*wR*2 (on all reflections)	0.1401
$\Delta\rho_{max}/\Delta\rho_{min}$, e Å^{-3}	0.444/–0.334

* When treating the set of intensities of reflections in the structural experiment the procedure for averaging all equivalent reflections was used (Merge all equivalents including Fridel opposites).

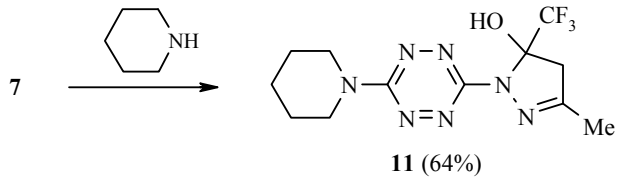
The ^{1}H NMR spectra of tetrazines **7, 8** are characterized by the presence of an AB system of diastereotopic protons of the methylene group of the hydroxypyrazoline ring in the range 3.3-3.5 ppm with a geminal coupling constant of 19 Hz, which corresponds to literature data for 5-hydroxypyrazolines [7].

The 5-hydroxypyrazoline substituents in compounds **7** and **8** were not successfully subjected to dehydration by the action of acetic anhydride or hydrochloric acid by the known methods of [8, 9]. The use of trifluoroacetic anhydride as a dehydrating agent enabled the desired compounds **9** and **10** to be obtained, containing respectively one and two 3-methyl-5-trifluoromethylpyrazolyl substituents in the tetrazine ring.

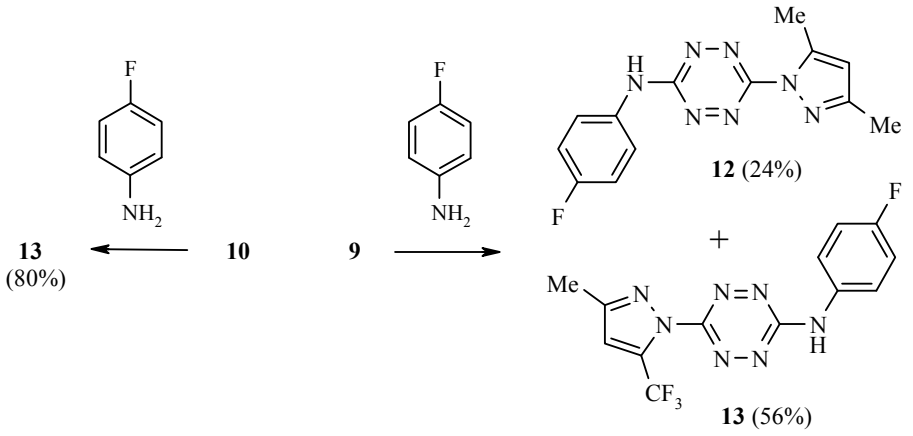


Nucleophilic substitution and [4+2] cycloaddition reactions of compounds **7-10** were investigated with the aim of clarifying the possibility of modifying the obtained fluorine-containing derivatives of 1,2,4,5-tetrazine and comparing their reactivity with nonfluorinated analogs.

In the example of the interaction with piperidine, which occurs completely in the course of 5 min at room temperature in acetonitrile, it was shown that the 3,5-dimethylpyrazolyl group in compound **5** is capable of being substituted by nucleopliles. However interaction with weak nucleophiles is difficult. For example, boiling tetrazine **7** with 4-fluoroaniline in acetonitrile for 8 h does not lead to the formation of any reaction products.

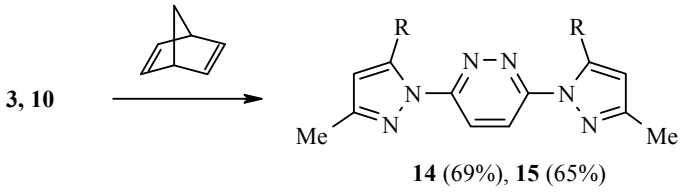


We showed previously that compound **3** forms a product of substitution of one of the 3,5-dimethylpyrazolyl groups with 4-fluoroaniline (**12**) at 50°C during 2 h [3]. Interaction of compound **9** with 4-fluoroaniline occurs after 1 h at room temperature with the formation of a mixture of compounds **12** and **13** in a ratio of ~ 1:2 in yields of 24 and 56% respectively.



Compound **13** may also be obtained from compound **10** in 80% yield. According to TLC data the interaction is complete after 5 min at room temperature. The introduction into the pyrazolyl substituents of a trifluoromethyl group therefore significantly accelerates the reaction of 1,2,4,5-tetrazines with weak nucleophiles. For the synthesis of substitution products it is more convenient to use symmetrically disubstituted tetrazine **10**.

The interaction of dipyrazolyl-1,2,4,5-tetrazines with dienophiles is also accelerated by introducing acceptor trifluoromethyl groups. The [4+2] cycloaddition reaction of norbornadiene with compounds **3** and **10** occurs on boiling in toluene for 3 h and 20 min respectively, with the formation of pyridazines **14** and **15**.



14 (69%), **15** (65%)

14 R = Me, **15** R = CF_3

The introduction of a trifluoromethyl group therefore leads to a change in the reactivity of pyrazolyl-1,2,4,5-tetrazines in comparison with the unfluorinated analogs and requires a change in the procedure for their synthesis. The increased reactivity of 1,2,4,5-tetrazines with trifluoromethylpyrazolyl substituents makes them promising starting materials for constructing new derivatives of 1,2,4,5-tetrazine and pyridazine.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker Avance DRX-400 (400 MHz) instrument in $CDCl_3$, internal standard was TMS. Melting points were determined on a Boetius hot stage. Elemental analysis was carried out on a Carlo Erba 1108 automatic analyzer. A check on the progress of reactions and the purity of the obtained compounds was carried out by TLC on plates with a bound layer of Sorbfil, eluent was benzene–acetonitrile, 1:1. Compounds **3**, **5**, **6**, **12**, and **14** were described previously in [1, 2, 10, 3, 11].

(*Z*)-4-[2-{bis(5-hydroxy-3-methyl-5-trifluoromethyl-4,5-dihydropyrazol-1-yl)methylidene}-1,1,1-trifluorohydrazinyl]pent-3-en-2-one (4). 1,1,1-Trifluoro-2,4-pentanedione (15.41 g, 100 mmol) was added to triaminoguanidine hydrochloride (7.08 g, 50 mmol) in water (48 ml) and the mixture stirred for 30 min, maintaining the temperature not above 30°C. The mixture was then heated for 3 h at 70°C. The solid which precipitated on cooling to room temperature was filtered off, and washed with methanol. Yield 17.1 g (98%); mp 143-144°C (methanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.12, 2.15, 2.23 (all 3H, s, $3CH_3$); 3.08, 3.52 (both 1H, both d, *J* = 18.5, CH_2); 3.13, 3.36 (2H, AB system, *J* = 19.0, CH_2); 5.33 (1H, s, CH); 7.20, 7.50 (both 1H, both br. s, 2OH); 13.50 (1H, br. s NH). Found, %: C 37.41; H 3.32; N 16.21. $C_{16}H_{17}F_9N_6O_3$. Calculated, %: C 37.51; H 3.35; N 16.40.

6-(3,5-Dimethylpyrazol-1-yl)-3-(5-hydroxy-3-methyl-5-trifluoromethyl-4,5-dihydropyrazol-1-yl)-1,2,4,5-tetrazine (7). Trifluoroacetylacetone (231 mg, 1.5 mmol) and acetic acid (0.05 ml) were added to a solution of 6-(3,5-dimethylpyrazol-1-yl)-3-hydrazino-1,2,4,5-tetrazine (**5**) (309 mg, 1.5 mmol) in methanol (10 ml). The reaction mixture was stirred for 1 h at room temperature. The resulting solid was filtered off, and recrystallized from methanol. Yield 419 mg (82%); mp 147-150°C (methanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.24, 2.37, 2.64 (all 3H, all s, $3CH_3$); 3.37, 3.51 (2H, AB system, *J* = 18.8, CH_2); 6.15 (1H, s, CH, pyrazolyl); 6.18 (1H, br. s, OH). Found, %: C 42.34; H 3.86; N 32.68. $C_{12}H_{13}F_3N_8O_2$. Calculated, %: C 42.11; H 3.83; N 32.74.

3,6-Di(5-hydroxy-3-methyl-5-trifluoromethyl-4,5-dihydropyrazol-1-yl)-1,2,4,5-tetrazine (8). Trifluoroacetylacetone (308 mg, 2 mmol) and acetic acid (0.05 ml) were added to a suspension of 3,6-dihydrazino-1,2,4,5-tetrazine (**6**) (142 mg, 1 mmol) in methanol (10 ml). The reaction mixture was stirred for 10 h at room temperature. The solvent was evaporated, and the residue washed with 2-propanol. Yield 264 mg (64%); mp 195-198°C (2-propanol). ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 2.21 (6H, s, $2CH_3$); 3.31 3.48 (4H, AB system, *J* = 19.0, $2CH_2$); 6.05 (2H, br. s, 2OH). Found, %: C 34.68; 3.04; N 26.99. $C_{12}H_{12}F_6N_8O_2$. Calculated, %: C 34.79; H 2.92; N 27.05.

3-R-6-(3-Methyl-5-trifluoromethylpyrazol-1-yl)-1,2,4,5-tetrazines 9, 10. Trifluoroacetic anhydride (1 ml, 2 ml for the synthesis of compound **10**) was added to a solution of 3-R-6-(5-hydroxy-3-methyl-5-trifluoromethyl-4,5-dihydropyrazol-1-yl)-1,2,4,5-tetrazine **7, 8** in dry toluene (10 ml). The reaction mixture was heated at 40°C for 1-6 h. The solvent was removed in vacuum, and the residue was washed with ether.

3-(3,5-Dimethylpyrazol-1-yl)-6-(3-methyl-5-trifluoromethylpyrazol-1-yl)-1,2,4,5-tetrazine (9). Yield 91%; mp 151-154°C (ether). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.41, 2.49, 2.75 (all 3H, all s, $3CH_3$); 6.23 (1H, s, CH, pyrazolyl); 6.90 (1H, s, CH, trifluoromethylpyrazolyl). Found, %: C 44.46; H 3.55; N 34.45. $C_{12}H_{11}F_3N_8$. Calculated, %: C 44.45; H 3.42; N 34.56.

3,6-Di(3-methyl-5-trifluoromethylpyrazol-1-yl)-1,2,4,5-tetrazine (10). Yield 45%; mp 152-155°C (ether). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.51 (6H, s, $2CH_3$); 6.94 (2H, s, 2CH). Found, %: C 38.05; H 1.94; N 29.54. $C_{12}H_8F_6N_8$. Calculated, %: C 38.11; H 2.13; N 29.63.

3-(5-Hydroxy-3-methyl-5-trifluoromethyl-4,5-dihydropyrazol-1-yl)-6-(N-piperidino)-1,2,4,5-tetrazine (11). Piperidine (43 mg, 0.5 mmol) was added to a solution of tetrazine **7** (171 mg, 0.5 mmol) in acetonitrile (6 ml) and the mixture was stirred for 10 min at room temperature. The solvent was removed in vacuum. The residue was recrystallized from pentane. Yield was 106 mg (64 %); mp 136-138°C (pentane). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.66-1.78 (6H, m, $3CH_2$); 2.16 (3H, s, CH_3); 3.21, 3.42 (2H, AB system, *J* = 18.8, CH_2); 3.87 (4H, t, *J* = 5.3, CH_2NCH_2); 6.41 (1H, br. s, OH). Found, %: C 43.55; H 4.81; N 29.51. $C_{12}H_{16}F_3N_7O$. Calculated, %: C 43.50; H 4.87; N 29.59.

6-(4-Fluorophenyl)amino-3-(3-methyl-5-trifluoromethylpyrazol-1-yl)-1,2,4,5-tetrazine (13). A. *p*-Fluoroaniline (67 mg, 0.6 mmol) was added to a solution of tetrazine **10** (207 mg, 0.5 mmol) in acetonitrile (10 ml) and the mixture stirred for 5 min at ~20°C. The solvent was removed, and the residue washed with pentane. Yield was 136 mg (80%); mp 161-162°C (pentane). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.46 (3H, s, CH_3); 6.82 (1H, s, CH, trifluoromethylpyrazolyl); 7.12-7.18 (2H, m, Ar); 7.65-7.69 (2H, m, Ar); 7.87 (1H, br. s, NH). Found, %: C 45.70; H 2.61; N 28.40. $C_{13}H_9F_4N_7$. Calculated, %: C 46.02; H 2.67; N 28.90.

B. *p*-Fluoroaniline (67 mg, 0.6 mmol) was added to a solution of tetrazine **9** (162 mg, 0.5 mmol) in acetonitrile (6 ml) and the mixture stirred for 1 h at ~20°C. The obtained mixture of compounds **12** and **13** was loaded onto a column of Lancaster silica gel 0.040-0.063 mm (230-400 mesh), eluent was ethyl acetate–hexane, 1:2 (R_f 0.83 (**13**), R_f 0.50 (**12**)). Yield of compound **12** 24%, and of compound **13**, 56%.

3,6-Di(3-methyl-5-R-pyrazol-1-yl)pyridazines 14, 15. Norbornadiene (92 mg, 1 mmol) was added to a solution of the appropriate tetrazine **3, 10** in toluene (10 ml) and the mixture boiled for 20 min – 3 h until decolorization of the reaction mixture. The solvent was removed in vacuum and the residue was dissolved in acetonitrile (5 ml). Water (2-5 ml) was added, and the resulting solid was filtered off.

3,6-Di(3-methyl-5-trifluoromethylpyrazol-1-yl)pyridazine (15). Yield 65%; mp 112-114°C (mixture H_2O–MeCN, 1:1). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.40 (6H, s, $2CH_3$); 6.77 (2H, s, 2CH, trifluoromethylpyrazolyl); 8.16 (2H, s, pyridazine). Found, %: C 44.73; H 2.67; N 22.05. $C_{14}H_{10}F_6N_6$. Calculated, %: C 44.69; H 2.68; N 22.34.

X-Ray Structural Investigation. Analysis of compound **4** was carried out for a fragment of a monocrystal of irregular shape (0.48 x 0.36 x 0.25 mm, colorless). Crystals were grown in ethanol. The investigation was carried out on a Xcalibur 3 diffractometer with a CCD detector (MoKα, graphite monochromator, ω-scanning) according to the standard procedure. Structures were solved by the direct method with the *SHELXS97* program and were refined with the *SHELXL97* program [12] by the method of least squares in an anisotropic approach for the non-hydrogen atoms. Hydrogen atoms were localized according to the peaks of spatial distribution of electron density. A portion of the hydrogen atoms participating in hydrogen bonds (see Table 1) were refined in an isotropic approximation, the remainder were included in the refinement in an isotropic approximation in a "rider" model. Corrections for absorption were not introduced in view of their small size.

The main structural parameters are given in Table 2.

The results of the X-ray structural investigation of compound **4** are registered at the Cambridge Crystallographic Data Center (CCDC 727102). These data are in free access and may be applied for at the address: www.ccdc.cam.ac.uk/data_request/cif

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REFERENCES

1. M. D. Coburn, G. A. Buntain, B. W. Harris, M. A. Hiskey, K.-Y. Lee, and D. G. Ott, *J. Heterocycl. Chem.*, **28**, 2049 (1991).
2. G. L. Rusinov, I. N. Ganebnykh, and O. N. Chupakhin, *Zh. Org. Khim.*, **35**, 1379 (1999).
3. G. L. Rusinov, N. I. Latosh, I. N. Ganebnykh, R. I. Ishmetova, N. K. Ignatenko, and O. N. Chupakhin, *Zh. Org. Khim.*, **42**, 772 (2006).
4. N. I. Latosh, G. L. Rusinov, I. N. Ganebnykh, and O. N. Chupakhin, *Zh. Org. Khim.*, **35**, 1392 (1999).
5. G. L. Rusinov, R. I. Ishmetova, I. N. Ganebnykh, and O. N. Chupakhin, *Heterocycl. Commun.*, **12**, 99 (2006).
6. Z. Novak, B. Bostai, M. Csekei, K. Lörincz, and A. Kotschy, *Heterocycles*, **60**, 2653 (2003).
7. K. N. Zelenin, A. R. Tugusheva, S. I. Yakimovich, V. V. Alekseev, and E. V. Zerova, *Khim. Geterotsikl. Soed.*, 762 (2002). [*Chem. Heterocycl. Comp.*, **38**, 668 (2002)].
8. A. B. Denisova, V. Ya. Sosnovskikh, W. Dehaen, S. Toppet, L. Van Meervelt, and V. A. Bakulev, *J. Fluorine Chem.*, **115**, 183 (2002).

9. S. Fustero, R. Román, J. F. Sanz-Cervera, A. Simón-Fuentes, A. C. Cuñat, S. Villanova, and M. Murguia, *J. Org. Chem.*, 73, 3523 (2008).
10. D. E. Chavez and M. A. Hiskey, *J. Heterocycl. Chem.*, **35**, 1329 (1998).
11. G. L. Rusinov, R. I. Ishmetova, N. I. Latosh, I. N. Ganebnych, O. N. Chupakhin, and V. A. Potemkin, *Russ. Chem. Bull.*, **49**, 355 (2000).
12. G. M. Sheldrick, *Acta Crystallogr.*, **A64**, 112 (2008).