One-pot synthesis of trifluoromethyl- and nitroso-substituted pyrazolines and pyrazoles and their tuberculostatic activity

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3-Trifluoromethyl-substituted 4-nitrosopyrazolines and 4-nitrosopyrazoles were prepared by a one-pot synthesis from trifluoromethyl-containing 1,3-diketones, sodium nitrite in acetic acid, and hydrazines (hydrazine hydrate, methylhydrazine). 3-Trifluoromethylpyrazolines can be converted to pyrazoles on heating. The use of phenylhydrazine in these reactions led to the formation of regioisomeric 4-hydroxyimino-5-(trifluoromethyl)pyrazoline. The structure of heterocycles synthesized was established using X-ray diffraction study, ^{1}H and ^{19}F NMR spectroscopy. The obtained products exhibited considerable tuberculostatic activity.

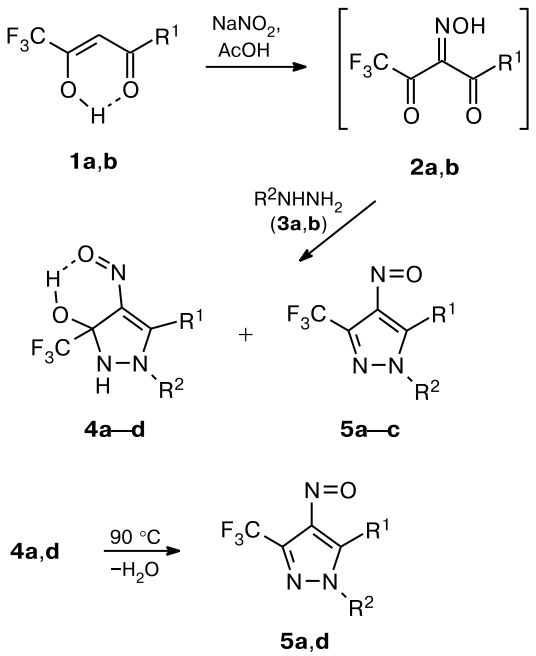
Key words: 4-nitrosopyrazoline, 4-nitrosopyrazole, 1,3-diketone, hydrazine, tuberculostatic activity.

Intensive development of drug resistance in the tuberculosis micobacteria,[1] as well as toxic and side effects of known antituberculosis medicines,[2] indicate a necessity to develop new efficient antituberculosis drugs, differing from the tuberculostatics used in practice in chemical structure and mechanism of action. 4-Nitrosopyrazoles are known[3] for their high fungicide and antibacterial activity, however, there is no information on their tuberculostatic activity.

A possibility to synthesize nonfluorinated 4-nitrosopyrazoles from acetylacetone, sodium nitrite, hydrochloric acid, and hydrazines in one step without isolation of the intermediate 3-hydroxyimino-substituted acetylacetone is shown in Ref. 4. The present work is devoted to a one-pot synthesis of trifluoromethyl-substituted derivatives of 4-nitrosopyrazole from 1,3-diketones and the study of their antituberculosis activity. Earlier,[5] 4-nitroso-5-phenyl-3-trifluoromethyl-1*H*-pyrazole has been obtained by us from 4,4,4-trifluoro-2-hydroxyimino-1-phenyl-1,3-butanedione by the reaction with hydrazine hydrate in ethanol. However, it has not been determined whether it had nitroso- or hydroxyimine structure.

It was found that trifluoromethyl-substituted 1,3-diketones **1a**,**b** upon treatment with sodium nitrite in acetic acid without isolation of the intermediate oxime **2** form with hydrazines **3a**,**b** mixtures of pyrazolines **4a**—**c** and pyrazoles **5a**—**c** (Scheme 1). The reaction of trifluoroacetylacetone **1a** with hydrazine hydrate **3a** predominantly furnishes pyrazoline **4a**, whereas in the reaction of 1,3-diketones **1a**,**b** with methylhydrazine **3b**, pyrazoles **5b**,**c** are the predominant products. Trifluoromethyl-substituted diketone **1b** reacts with sodium nitrite and hydrazine

Scheme 1



1, 2: R^1 = Me (**a**), Ph (**b**)
3: R^2 = H (**a**), Me (**b**)
4, 5: R^1 = Me, R^2 = H (**a**), R^1 = R^2 = Me (**b**), R^1 = Ph, R^2 = Me (**c**), R^1 = Ph, R^2 = H (**d**)

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hydrate **3a** to give only pyrazoline **4d**, which on heating at 90 °C virtually completely undergoes dehydration to form pyrazole **5d** in 98% yield (see Experimental). It turned out that 5-Me-substituted pyrazoline **4a** on heating at 90 °C undergoes dehydration with partial decomposition, therefore, pyrazole **5a** was obtained in moderate yield (62%) after additional purification by column chromatography.

Unlike convertions of trifluoromethyl-containing 1,3-diketones, reactions of acetylacetone with sodium nitrite and hydrazines led to the exclusive formation of pyrazoles.[4] A possibility of isolation of pyrazolines **4** is due to the presence of electron-withdrawing trifluoromethyl group in these compounds, which hinders easy elimination of the water molecule.

Apparently, under conditions of the one-pot synthesis nitrosation of 1,3-diketone **1a**,**b** takes place initially with the intermediate formation of the corresponding 2-hydroxyimino-1,3-diketone **2** (see Scheme 1) followed by cyclocondensation of oximes **2a**,**b** with hydrazines **3a**,**b** to yield pyrazole derivatives **4** and **5**.

Cyclocondensation of unsymmetric trifluoromethyl-containing 1,3-diketones with substituted hydrazines can lead to the formation of 3-CF_3- and 5-CF_3-regioisomeric pyrazoles or their mixture.

Regioisomeric and tautomeric structure of pyrazoles **5c**,**d** was established by X-ray diffraction study, according to which the crystal of compound **5d** is formed by two crystallographically independent molecules of 4-nitroso-3-trifluoromethylpyrazole with close geometrical parameters (Fig. 1). The independent molecules differ in the turning angle of the phenyl substituent with respect to the plane of heterocycle: the torsional angles C(2)—C(1)—C(7)—C(8) and C(6A)—C(1A)—C(7A)—C(8A) are −30.28° and 31.94°, respectively. The molecules are bound with each other by the system of intermolecular hydrogen bonds (IHB) between the nitroso group and the NH group of the heterocycle forming polymeric chains (Table 1).

The X-ray study also confirms 3-CF_3-regioisomeric structure of pyrazole **5c** (Fig. 2). The N(3)—O(1) bond distance is 1.245(2) Å, that is considerably shorter than the C(3)—N(3) bond (1.406(2) Å) and corresponds to the double N=O bond, therefore, pyrazole **5c** exists in the nitroso form. The nitroso group N(3)O(1) deviates from the plane of the pyrazole ring by only 7.26(2)°, whereas the turn of the phenyl substituent with respect to the pyrazole ring is significant and equal to 44.24(2)°. In the packing, molecules of **5c** are bound between each other by shortened contacts, which exist between the O(1) oxygen atom of the nitroso group and the hydrogen atom at position 6 (H(6A)) of the phenyl ring of neighboring molecule (see Table 1).

Pyrazoles **5a**,**b** are oily substances, therefore, to establish their regioisomeric structures we compared the ^1H and ^{19}F NMR spectroscopic data of these products and pyrazoles **5c**,**d**, whose structure was established by X-ray diffraction study.

Chemical shift of the signal for the pyrazole CF_3 group in the ^{19}F NMR spectrum is characteristic for determining its regioisomeric structure. Thus, in the ^{19}F NMR spectra of pyrazoles, the signals for the CF_3 substituents in the case of 3-CF_3 isomer are found at $\delta_F \approx 101$, whereas the 5-CF_3-pyrazoles have them at $\delta_F \approx 105$ (see Refs 6 and 7). Therefore, chemical shifts of the signals for the CF_3 groups (δ_F 98.79—100.6) in the ^{19}F NMR spectra of pyrazoles **5a**—**d** indicate the 3-CF_3 regioisomeric structure of these heterocyclic compounds.

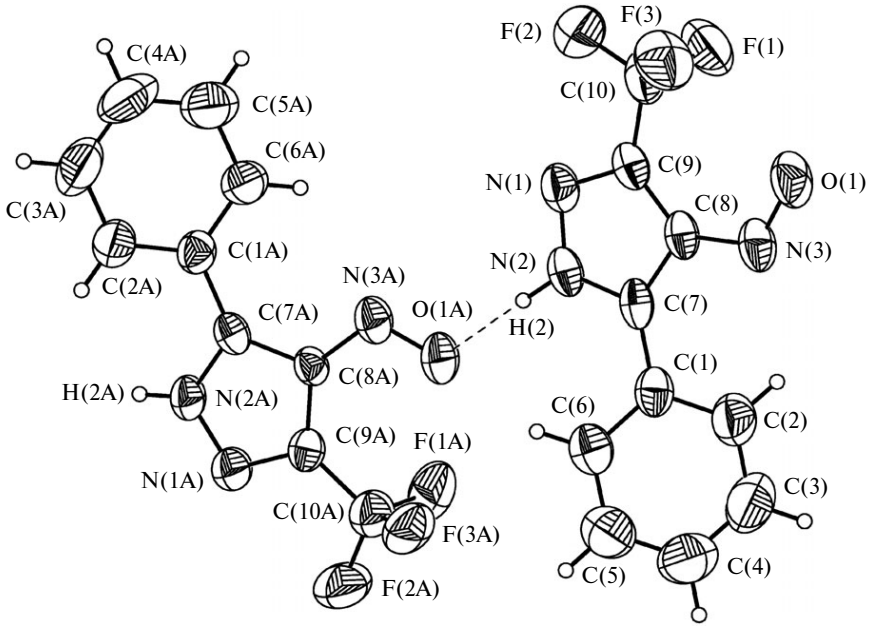


Fig. 1. Two crystallographically independent molecules in the structure of pyrazole **5d**. The dashed line shows the hydrogen bond.

Table 1. Characteristics of intermolecular hydrogen bonds (D—H...A) and short contacts (D...A) in the crystal structure of heterocyclic compounds **5c**,**d** and **6**

Compound	D—H...A	*d*(D—H)	*d*(H...A)	ω/deg	*d*(D...A)/Å
		Å			
5c	C(6A)—H(6A)...O(1)[a]	0.93	2.574	134.33	3.293(2)
5d	N(2)—H(2)...O(1A)	0.934(15)	1.861(15)	178.5(9)	2.795(2)
	N(2)—H(2)...N(3A)	0.934(15)	2.651(15)	155.4(9)	3.521(2)
	N(2A)—H(2A)...O(1)[b]	0.842(14)	1.998(14)	170(1)	2.831(2)
6	O(1)—H(1)...N(3)[c]	0.820	2.109	144.36	2.816(2)
	N(3)—H(3)...O(1)[c]	0.860	2.081	143.05	2.816(2)
	N(3)—H(3)...N(3)[c]	0.860	2.586	110.61	2.999(2)
	O(2)—H(2)...N(2)[d]	0.86(2)	2.02(2)	171(1)	2.871(2)

Note. The following signs are used: *d* is the bond lengths or interatomic distances, ω is the corresponding angles D—H...A. Operation of symmetry: [a] [$x + 1/2, -y + 1/2, z + 1/2$]; [b] [$x + 1, y, z + 1$]; [c] [$-x + 1, -y, -z + 2$]; [d] [$-x + 3/2, y + 1/2, -z + 3/2$].

In the ^{1}H and ^{19}F NMR spectra of 4-(het)arylazo-1-methyl-3,5-bis(trifluoromethyl)pyrazoles, the spin-spin coupling was observed between the fluorine atoms of the 5-CF_3 group and the protons of the NMe fragment with the spin-spin coupling constant 0.9—1.3 Hz and the fluorine atoms of the 3-CF_3 group with the protons of the NMe group with the spin-spin coupling constant 0—0.5 Hz.[8] The singlet signals of the NMe and CF_3 groups are observed in the ^{1}H and ^{19}F NMR spectra of pyrazoles **5b**,**c** that testifies in favor of 3-CF_3 isomer.

In addition, regioisomeric structure of pyrazoles can be inferred from the chemical shifts for the protons of the *C*-Me groups in the ^{1}H NMR spectra, since in 3-Me-pyrazoles they are observed more upfield (δ_H 2.3) as compared to the analogous signals in 5-Me-pyrazoles (δ_H 2.7).[9] In the ^{1}H NMR spectra of *C*-Me-containing pyrazoles **5a**,**b** synthesized by us, the singlet signals for the Me groups are found in the region δ_H 2.76—2.88, that indicates the presence of the Me group at position 5 of the heterocycle.

Thus, the ^{1}H and ^{19}F NMR spectroscopic data confirm the structure of 3-CF_3-pyrazole for heterocycles **5a**—**d**.

The structures of 3-hydroxy-4-nitrosopyrazoline **A**, 5-hydroxy-4-hydroxyiminopyrazoline **B**, and 3-hydrazono-substituted ketone **C** can be assigned to the precursors of pyrazoles **5a**—**d**, *i.e.*, pyrazolines **4a**—**d**, depending on how they were formed (Scheme 2).

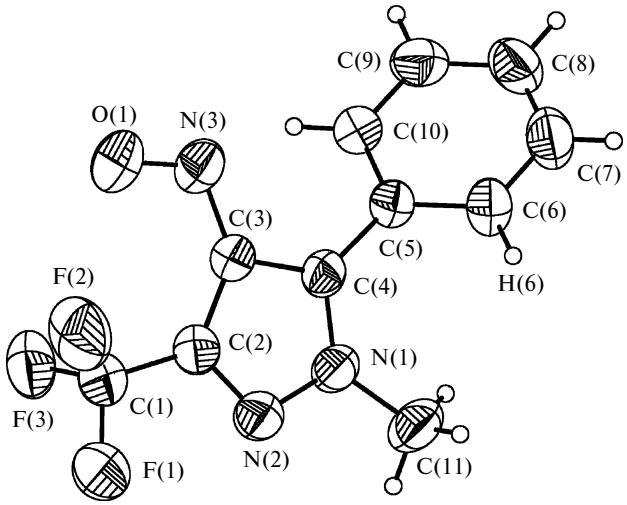
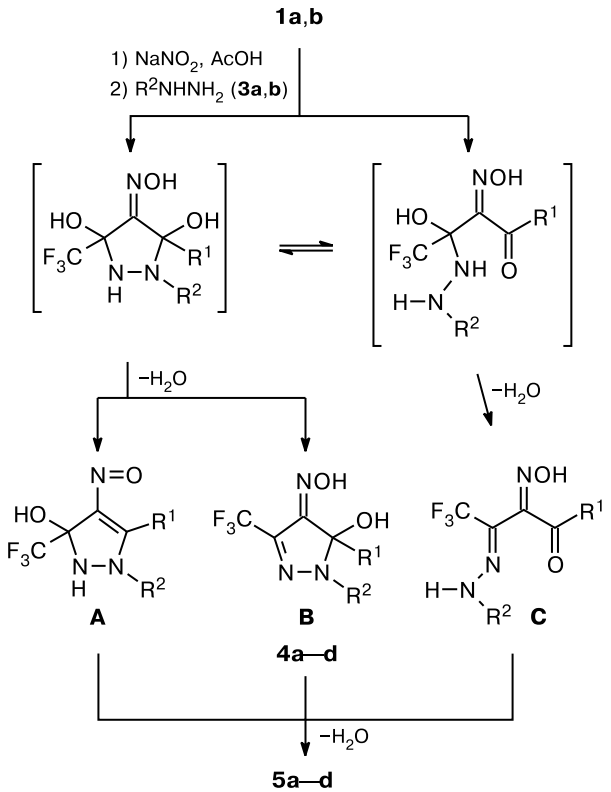


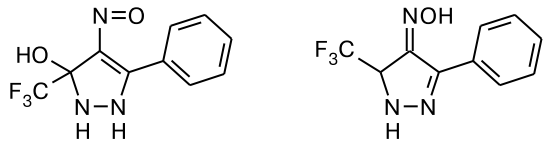
Fig. 2. Molecular structure of pyrazole **5c**.

Scheme 2



The absence of the absorption band for the carbonyl group in the IR spectra of pyrazolines **4a—d** allowed us to exclude the structure of 3-hydrazono-substituted ketone **C** from our consideration. The choice between pyrazolines **A** and **B** has been made based on the ^{19}F NMR spectroscopic data. Thus, the singlet signals for the fluorine atoms in the region δ_F 82.6—87.44 characteristic of the CF_3 group at the sp^3-hybridized carbon atom unambiguously confirm the structure **A** for pyrazolines **4a—d**.

Note that the NMR spectra of pyrazoline **4d** obtained from the phenyl-substituted 1,3-diketone **1b** and hydrazine hydrate **3a** exhibits two sets of signals in the ratio 74 : 26 (see Experimental). However, based on the available data, it is impossible to unambiguously establish whether **4d** is a mixture of hydroxyimino-imine **E** and nitroso-amine **D** tautomers or a mixture of *Z*- and *E*-isomers of the hydroxyimino-imine **E** tautomer.

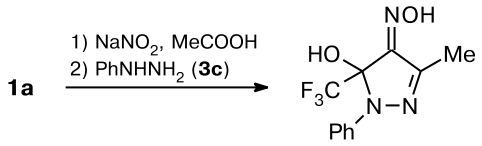


D **E**

4d

When phenylhydrazine **3c** is involved into the reaction with trifluoroacetylacetone **1a**, direction of the reaction changes (Scheme 3).

Scheme 3



6

The structure of product **6** obtained in this reaction was established by X-ray diffraction study, which indicates that it is 5-CF_3-pyrazoline existing in the hydroxyimine tautomeric form unlike 4-nitrosopyrazolines **4** (Fig. 3). In particular, the C(9)—N(3) bond (1.263(2) Å) is considerably shorter than the N(3)—O(1) bond (1.391(2) Å) and corresponds to the double C=N bond. Molecular packing of pyrazoline **6** has a number of IHB between hydroxyimine fragments, as well as between nitrogen N(2) of the pyrazoline ring and hydrogen of the hydroxy group O(2)H(2) (see Table 1). Since the proton of the hydroxyimine group cannot be unambiguously localized, it was used in the refinement with delocalization on the N(3) and O(1) atoms in the geometrically calculated positions with the population coefficients 0.5 with dependent thermal parameters.

It is obvious that upon the reaction of phenylhydrazine **3c** with trifluoroacetylacetone **1a**, the primary amino group

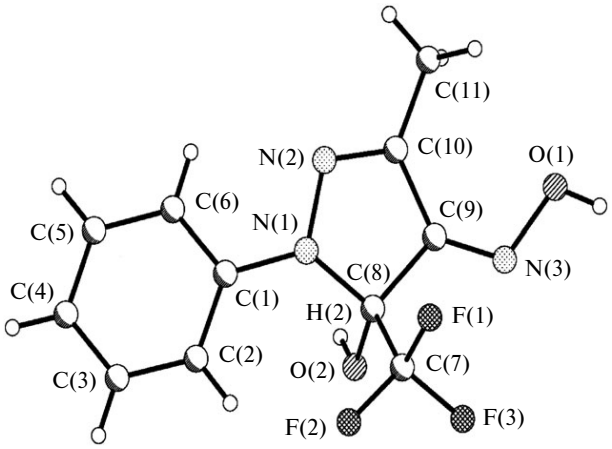


Fig. 3. Molecular structure of pyrazoline **6**.

of **3c** reacts regiospecifically at the less electrophilic acetyl group of **1a** giving 5-CF_3-pyrazoline **6** (see Scheme 3). Pyrazoline **6** upon heating to 130 °C does not undergo dehydration, heating to higher temperatures leads to its decomposition. Therefore, 5-CF_3-pyrazoline **6** is more stable to dehydration as compared to its regioisomeric analogs **4**.

We compared the results obtained by us with the reactions of methylhydrazine and phenylhydrazine with 2-unsubstituted trifluoromethyl-containing 1,3-diketones studied earlier.[6,10] The latter in ethanol give regioisomeric mixtures of *N*-methyl(phenyl)pyrazoles or mixtures of 3-CF_3-pyrazole and 5-CF_3-pyrazoline. To increase regioselectivity and purposefully obtain 3-CF_3-pyrazoles the authors in Ref. 10 used fluorinated alcohols. We found that the reaction of trifluoromethyl-substituted 1,3-diketones containing hydroxyimine or (het)arylhydrazone[8] substituent at position 2 with hydrazines proceeds regiospecifically. These reactions with methylhydrazine exclusively afford 3-CF_3-pyrazoles, whereas reactions with phenylhydrazine give 5-CF_3-pyrazoline. Regiospecificity of the reactions of such 2-substituted analogs of trifluoromethyl-containing 1,3-diketones with hydrazines, on our opinion, is explained by greater isolation of their reaction centers (carbonyl groups), for which the Pearson principle of hard and soft acids and bases (HSAB) becomes more applicable.[11]

The HSAB principle states that the more stable bond is formed when a hard acid reacts with a hard base or a soft acid with a soft base. At present, there is no strict qualitative evaluation of acid and base hardness and softness. They can be only approximately arranged in orders. For example, the hardness of bases decreases in the order: $NH_3 > RNH_2 \gg PhNH_2$ (see Ref. 11). This fact can be explained by the change in polarizability of bases. It is obvious that the hardness of bases used by us decreases in the order $NH_2NH_2 > MeNHNH_2 \gg PhNHNH_2$. To use the HSAB theory in the analysis of reactivity, an assumption is made that properties of electrophiles are analogous

to the properties of acids, whereas properties of nucleophiles to the properties of bases. Therefore, it is possible to talk about hard and soft electrophiles and nucleophiles. The hardness of the nucleophile acceptor atom depends on the nature of neighboring groups, for example, BF_3 is a hard electrophile, while BH_3 is a soft electrophile.[11] Similarly, the carbon atom of a carbonyl group bonded to a trifluoromethyl substituent is more hard electrophile as compared to the acceptor carbon atom of an acetyl and benzoyl groups. Therefore, hydrazine hydrate **3a** and methylhydrazine **3b**, as hard nucleophiles, attack a hard electrophile, *viz.*, trifluoroacetyl group of oxime **2**, giving rise to 3-CF_3-regioisomers **4** and **5**. Softer nucleophile, phenylhydrazine **3c**, reacts stronger with softer electrophile, *viz.*, the acetyl fragment leading to the formation of 5-CF_3-regioisomer **6**.

We have studied tuberculostatic activity of heterocycles **4b**, **5a**,**b**,**d**, and **6** *in vitro* experiments for the laboratory strain of tuberculosis micobacteria (TMB) $H_{37}Rv$. Isoniazide was used as a comparison sample, whose minimum concentration necessary for retarding the growth of TMB, is 0.15 μg mL^{-1}.

4-Nitrosopyrazole **5d** containing an NH group and a phenyl substituent at position 5 of the pyrazole ring possesses the highest tuberculostatic activity among compounds studied. This compound inhibits the growth of the TMB laboratory strain in the concentration 0.36 μg mL^{-1}. Replacement of the Ph group with the Me group in pyrazole **5d** leads to a decrease in tuberculostatic activity, since the minimum inhibiting concentration (MIC) of pyrazole **5a** is 1.62 μg mL^{-1}. Incorporation of the methyl substituent to the nitrogen atom N(1) of the ring still decreases antituberculosis activity, since the MIC of compound **5b** is 6.15 μg mL^{-1}.

Pyrazolines **4b** and **6** showed lower tuberculostatic activity. However, 5-CF_3-pyrazoline **6** are more active as compared to the 3-CF_3-pyrazoline **4b**. The MIC for heterocycle **6** is 3.12 μg mL^{-1}, whereas for compound **4b** it is the highest, *viz.*, 12.5 μg mL^{-1}.

We additionally studied tuberculostatic properties for the precursor of pyrazole **5d**, 2-hydroxyimino-4,4,4-trifluoro-1-phenylbutane-1,3-dione,[4] which exhibited moderate antituberculosis activity (the MIC of this compound against the TMB laboratory strain is 1.25 μg mL^{-1}).

In conclusion, the reaction of trifluoromethyl-containing 1,3-diketones with sodium nitrite and hydrazines (hydrazine hydrate, methylhydrazine) can be accomplished as a one-pot procedure giving 4-nitroso-3-trifluoromethylpyrazolines, which can be dehydrated to pyrazoles. The use of phenylhydrazine leads to the formation of more stable 4-hydroxyimino-5-(trifluoromethyl)pyrazoline. The study of tuberculostatic activity showed that it is promising to search antituberculosis drugs in the series of trifluoromethyl-substituted 4-nitrosopyrazoles and their precursors: pyrazolines and 2-hydroxyimino-1,3-diketones.

Experimental

^1H and ^{19}F NMR spectra were recorded on a Bruker DRX-400 spectrometer (400 and 75 MHz, respectively) in DMSO-d_6; using $SiMe_4$ (^1H) and C_6F_6 (^{19}F) as internal standards. Elemental analysis was performed on a Perkin—Elmer PE 2400 series II analyzer. IR spectra were recorded on a Perkin—Elmer Spectrum One FTIR-spectrometer in the region 4000—400 cm^{-1} in Nujol, for neat samples on KBr plates, or using the diffuse reflectance accessory (DRA). Melting points were measured in open capillaries on a Stuart SMP3 apparatus. Column chromatography was performed using L 100—250 μm silica gel.

Reaction of 1,3-diketones 1a,b with hydrazines 2a—c (general procedure). A solution of sodium nitrite (1 g) in water (5 mL) was added dropwise to a mixture of trifluoromethyl-substituted 1,3-diketone **1** (12.5 mmol) and glacial acetic acid (4 mL) at 8—12 °C with stirring. The reaction mixture was stirred for 20 min, cooled to 10 °C, followed by a slow dropwise addition of hydrazine (12.5 mmol) in water (5 mL). The reaction mixture was stirred for 3 h, extracted with diethyl ether. The extracts were treated with aqueous $NaHCO_3$ to pH 7, washed with water, dried with $MgSO_4$, the solvent was evaporated. For the isolation of pyrazolines **4a—d** and **6**, the solid substance formed was washed with hot chloroform (**4a**), reprecipitated with chloroform from the solution in ethyl acetate (**4b**), recrystallized from chloroform (**4d, 6**), purified by column chromatography (**4c**, eluent: $CHCl_3$—MeCN, 100 : 1). For the isolation of pyrazoles **5a**,**b**, the mother liquors obtained after isolation of pyrazolines **4a**,**b** were concentrated, the oily products **5a**,**b** were purified by column chromatography (eluent: $CHCl_3$—Et_2O, 10 : 1 (**5a**) or $CHCl_3$ (**5b**)). In the reaction of 1,3-diketone **1b** with methylhydrazine **2b**, pyrazole **5c** precipitated from aqueous alcoholic solution, it was filtered off and twice reprecipitated with hexane from the solution in chloroform.

3-Hydroxy-5-methyl-4-nitroso-3-trifluoromethyl-2,3-dihydro-1*H*-pyrazole (4a). The yield was 51%, m.p. 135—136 °C. IR (Nujol), ν/cm^{-1}: 3315, 3070, 2730, 1650 (2 NH, OH); 1650 (C=C); 1170—1200 (C—F). ^1H NMR, δ: 2.21 (s, 3 H, Me); 7.72, 8.14 (both s, 1 H each, NH); 12.23 (s, 1 H, OH). ^{19}F NMR, δ: 82.6 (s, CF_3). Found (%): C, 30.41; H, 3.05; F, 28.86; N, 21.39. $C_5H_6F_3N_3O_2$. Calculated (%): C, 30.47; H, 3.07; F, 28.91; N, 21.32.

3-Hydroxy-1,5-dimethyl-4-nitroso-3-trifluoromethyl-2,3-dihydro-1*H*-pyrazole (4b). The yield was 36%, m.p. 138—139 °C. IR (DRA), ν/cm^{-1}: 3330, 3120 (NH, OH); 1160—1200 (C—F). ^1H NMR, δ: 2.22 (s, 3 H, Me); 2.81 (s, 3 H, NMe); 8.01 (s, 1 H, NH); 12.38 (s, 1 H, OH). ^{19}F NMR, δ: 83.6 (s, CF_3). Found (%): C, 34.33; H, 3.66; F, 26.97; N, 20.06. $C_6H_8F_3N_3O_2$. Calculated (%): C, 34.13; H, 3.82; F, 26.99; N, 19.90.

3-Hydroxy-1-methyl-4-nitroso-5-phenyl-3-trifluoromethyl-2,3-dihydro-1*H*-pyrazole (4c). The yield was 13%, m.p. 117—118 °C. IR (DRA), ν/cm^{-1}: 3510, 3160, 3040, 1635 (NH, OH); 1600, 1490 (C=C); 1175—1200 (C—F). ^1H NMR, δ: 3.00 (s, 3 H, NMe); 7.34—7.55 (m, 5 H, Ph); 8.34, 12.50 (both s, 1 H each, NH, OH). ^{19}F NMR, δ: 84.54 (s, CF_3). Found (%): C, 48.59; H, 3.72; F, 21.12; N, 15.44. $C_{11}H_{10}F_3N_3O_2$. Calculated (%): C, 48.36; H, 3.69; F, 20.86; N, 15.38.

3-Hydroxy-4-nitroso-5-phenyl-3-trifluoromethyl-2,3-dihydro-1*H*-pyrazole (4d). The yield was 66%, m.p. 134—135 °C. IR (DRA), ν/cm^{-1}: 3290, 3190, 3070, 1640 (2 NH, OH); 1600, 1530, 1495 (C=C); 1160—1200 (C—F). ^1H NMR of major iso-

mer (74%), δ: 7.33—7.57 (m, 5 H, Ph); 8.06, 9.09, 12.40 (all s, 1 H each, NH, OH); of minor isomer (26%), δ: 7.35—7.94 (m, 5 H, Ph); 7.88, 8.89, 12.41 (all s, 1 H each, NH, OH). ^{19}F NMR of major isomer, δ: 83.25 (s, CF_3); of minor isomer, δ: 87.44 (s, CF_3). Found (%): C, 46.28; H, 3.15; F, 22.12; N, 16.28. $C_{10}H_8F_3N_3O_2$. Calculated (%): C, 46.34; H, 3.11; F, 21.99; N, 16.21.

5-Methyl-4-nitroso-3-trifluoromethyl-1*H*-pyrazole (5a). The yield was 23%. IR (KBr), ν/cm^{-1}: 3190 (NH); 1575, 1490 (C=N, C=C, N=O); 1130—1180 (C—F). ^{1}H NMR, δ: 2.76 (s, 3 H, Me); 14.53 (s, 1 H, NH). ^{19}F NMR, δ: 100.6 (s, CF_3). Found (%): C, 33.67; H, 2.44; F, 31.59; N, 23.31. $C_5H_4F_3N_3O$. Calculated (%): C, 33.53; H, 2.25; F, 31.82; N, 23.46.

1,5-Dimethyl-4-nitroso-3-trifluoromethylpyrazole (5b). The yield was 41%. IR (KBr), ν/cm^{-1}: 1570, 1500 (C=N, C=C, N=O); 1110—1180 (C—F). ^{1}H NMR, δ: 2.88 (s, 3 H, Me); 3.94 (s, 3 H, NMe). ^{19}F NMR, δ: 100.25 (s, CF_3). Found (%): C, 37.57; H, 3.43; F, 29.56; N, 22.08. $C_6H_6F_3N_3O$. Calculated (%): C, 37.31; H, 3.13; F, 29.51; N, 21.76.

1-Methyl-4-nitroso-5-phenyl-3-trifluoromethylpyrazole (5c). The yield was 63%, m.p. 97—98 °C. IR (DRA), ν/cm^{-1}: 1600, 1500 (C=N, C=C, N=O); 1140—1190 (C—F). ^{1}H NMR, δ: 3.98 (s, 3 H, Me); 7.66—7.96 (m, 5 H, Ph). ^{19}F NMR, δ: 99.3 (s, CF_3). Found (%): C, 51.93; H, 3.17; F, 22.37; N, 16.50. $C_{11}H_8F_3N_3O$. Calculated (%): C, 51.77; H, 3.16; F, 22.33; N, 16.47.

5-Hydroxy-4-hydroxyimino-3-methyl-1-phenyl-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazole (6). The yield was 56%, m.p. 135—136 °C. IR (Nujol), ν/cm^{-1}: 3260, 3100 (N=OH, OH); 1655, 1600, 1500 (C=N, C=C); 1180—1260 (C—F). ^{1}H NMR, δ: 2.36 (s, 3 H, Me); 6.97—7.41 (m, 5 H, Ph); 8.62, 12.69 (both s, 1 H each, OH). ^{19}F NMR, δ: 83.74 (s, CF_3). Found (%): C, 48.37; H, 3.7; F, 20.48; N, 15.41. $C_{11}H_{10}F_3N_3O_2$. Calculated (%): C, 48.36; H, 3.69; F, 20.86; N, 15.38.

Dehydration of pyrazolines 4a,d to pyrazoles 5a,d (general procedure). Pyrazoline **4** (5 mmol) was placed into a flask equipped with a reflux condenser and heated for 3 h in a water bath at 90 °C.

5-Methyl-4-nitroso-3-trifluoromethyl-1*H*-pyrazole (5a). The yield was 62%, the product was isolated by column chromatography, eluent: $CHCl_3$—Et_2O, 10 : 1. Physico-chemical characteristics were identical to those for the product obtained by the reaction of **1a** with **3a** (see above).

4-Nitroso-5-phenyl-3-trifluoromethyl-1*H*-pyrazole (5d). The yield was 98%, m.p. 125—126 °C (*cf.* Ref. 5: 124—126 °C). ^{19}F NMR, δ: 98.79 (s, CF_3).

X-ray study. Monocrystals of heterocycles **5d** and **6** were obtained by crystallization from chloroform, crystals of pyrazole **5c** were grown in dichloromethane. X-ray diffraction experiments were performed on a Xcalibur 3 CCD diffractometer (λ(Mo-Kα) = 0.71073 Å, graphite monochromator, ω-scanning, temperature 295(2) K). No allowance for absorption was made. Crystal structure was solved by the direct methods and subsequent Fourier-syntheses using the SHELXS-97 program.[12] The structure was refined by the least squares method in anisotropic full-matrix approximation for all the nonhydrogen atoms using the SHELXL-97 program.[13] The hydrogen atoms were placed in the geometrically calculated positions and included into the refinement using the riding model in isotropic approximation with dependent thermal parameters. The H(2) atom of the hydroxy group of compound **6** and atoms of the NH groups of compound **5d** were solved by the direct method and included into the refinement independently in isotropic approximation. The principal crystallographic data of compounds **5c**,**d** and **6** and some experimental characteristics are given in Table 2. Crystallographic data for compounds **5c**,**d** and **6** were deposited with the Cambridge Structural Database (CCDC 752784, CCDC 759260, and CCDC 752785, respectively) and are available at www.ccdc.cam.ac.uk/conts/retrieving.html.

Table 2. Principal crystallographic data and parameters of refinement for compounds **5c**,**d** and **6**

Parameter	**5c**	**5d**	**6**
Molecular formula	$C_{11}H_8F_3N_3O$	$C_{10}H_6F_3N_3O$	$C_{11}H_{10}F_3N_3O_2$
Molecular weight	255.2	241.18	273.22
Crystal system	Monoclinic	Triclinic	Monoclinic
Space group	$P2_1/n$	P-1	$P2_1/n$
a/Å	12.043(5)	7.8183(11)	10.9449(12)
b/Å	7.8048(16)	11.8(2)	7.3731(6)
c/Å	12.596(3)	12.239(18)	15.0971(13)
α/deg	90.00	95.055(17)	90.00
β/deg	98.08(3)	94.993(12)	95.760(8)
γ/deg	90.00	108.32(14)	90.00
V/Å^3	1172.3(6)	1059.8(3)	1212.2(2)
Z	4	4	4
d_{calc}/g cm^{-3}	1.446	1.512	1.497
μ/mm^{-1}	0.129	0.138	0.136
Angle of scanning θ/deg	3.08—26.5	2.76—28.28	3.08—26.37
Total number of reflections	5660	10517	5099
Number of independent reflections	2390	5041	2370
Number of reflections with $I > 2\sigma(I)$	1335	2049	1363
Number of refined parameters	164	315	177
R_1/wR_2 ($I > 2\sigma(I)$)	0.0421/0.1054	0.0357/0.0427	0.0445/0.1206
R_1/wR_2 ((on all the reflections)	0.0771/0.1161	0.1255/0.0467	0.0842/0.1324

Study of tuberculostatic activity. Tuberculostatic activity was determined by the method of serial dilutions with the use of the Novaya dense yolk medium or the Levenshtein—Yensen egg medium.[14] The $H_{37}Rv$ tuberculosis micobacteria culture was used as a laboratory strain.

The laboratory strain culture was weighted on a torsion balance, the sample (10 mg) was placed into a porselain mortar, thoroughly mulled, and a suspension of the culture was prepared using a bacterial standard turbidity 100 million of microbe bodies per 1 mL. A suspended matter obtained (0.2 mL in amount) was sown into the test-tubes containing a culture medium and a compound studied (5.0 mL) of each dilution, incubated for 7—10 days in a thermostat at 37 °C. The action of the substance on the tuberculosis micobacteria was studied simultaneously in three test-tubes for each concentrations.

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