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NEW FUNCTIONALIZED PYRAZOLINES FROM 1-AROYL-2-PHENYLACETYLENES AND THIOCARBONOHYDRAZIDES

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The reaction of 1-aroyl-2-phenylacetylenes with thiocarbonohydrazide and benzaldehyde thiocarbohydrazone in acetic acid–water or ethanol–water systems with the reagents in an equimolar ratio leads to the selective formation of 1-carbothiohydrazinoyl-5-hydroxy-3-phenyl-5-R-2-pyrazolines. Ring–chain tautomerism involving the enamine and hydrazone forms was detected for solutions of the pyrazolines (with R = 2-thienyl) in DMSO.

Keywords: 1-aroyl-2-phenylacetylenes, 1-carbothiohydrazinoyl-5-hydroxy-3-phenyl-5-R-2-pyrazolines, thiocarbonohydrazides, heterocyclization, ring–chain tautomerization, nucleophilic addition.

The reaction of α-alkynyl ketones with sulfur- and nitrogen-containing polydentate nucleophiles allows the possibility of alternative reaction paths, the direction of which can be changed by the choice of conditions and substituents in the reacting partners.

Earlier we demonstrated the synthetic possibilities of the "N,S-polydentate nucleophile–α-acetylenic ketone" system for the construction of heterocycles with various structures by changing the reaction conditions and introducing substituents into the structure of the initial components [1-4].

In order to study the generality of this approach for the controlled formation of the reaction products in the present work we investigated the reaction of 1-aroyl-2-phenylacetylenes with thiocarbonohydrazide and benzaldehyde thiocarbohydrazone.

Thiocarbonohydrazide is the closest structural analog of thiosemicarbazide, derivatives of which are recommended as effective antitubercular [5, 6] and antiviral [7] preparations. Derivatives of thiocarbazides of the aromatic series also exhibit high antiviral [8] and antimicrobial [9] activity. Macrocycles synthesized in the reactions of thiocarbonohydrazide with polycarbonyl compounds and their complexes with the salts of divalent metals are effective fungistatic agents [10], while the cytotoxicity of the carbohydrazones and thiocarbohydrazones of some ketones is commensurable with or even exceeds the cytotoxicity of the well-known product melphalan [11].

* Dedicated to Academician M. G. Voronkov on his 85th birthday.

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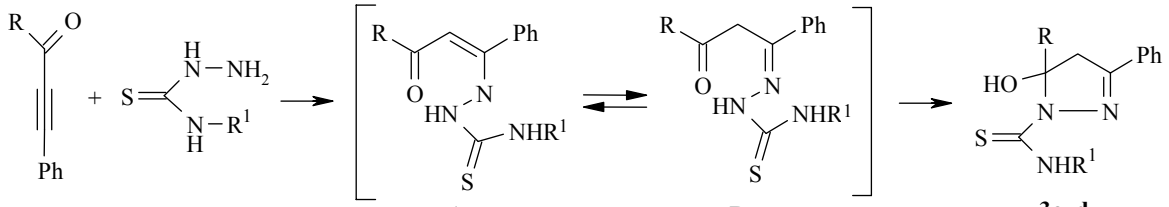
Terminal α-acetylenic ketones and methyl propiolate react with thiocarbonohydrazide when heated in water–ethanol solution with the formation of 6-acylmethylhexahydro-1,2,4,5-tetrazine-3-thiones [12]. With unsubstituted acylacetylenes in methanol or acetonitrile at 20°C, depending on the ratio of the reagents, thiocarbonohydrazides of the aromatic series form 2-(2-acylvinyl)thiocarbohydrazones or 2,2-bis(2-acylvinyl)thiocarbohydrazones, but with thiocarbodihydrazone the reaction takes place at the sulfur atom with the formation of S-(acylvinyl)isothiocarbodihydrazone [13].

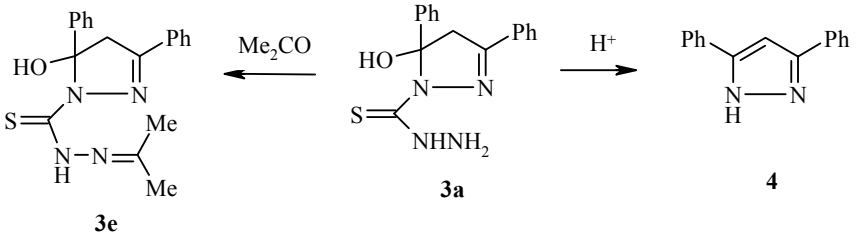
We found that the reaction of 1-benzoyl-2-phenylacetylene (**1a**) and 1-(2-thenoyl)-2-phenylacetylene (**1b**) with thiocarbonohydrazide (**2a**) and benzaldehyde thiocarbohydrazone (**2b**) in acetic acid–water or ethanol–water with the reagents in an equimolar ratio leads to the formation of the corresponding 1-carbothiohydrazinoyl-5-hydroxy-3-phenyl-5-R-2-pyrazolines **3a-d** with yields of 60-88%.



1 a R = Ph; **b** R = C_4H_3S; **2 a** $R^1 = NH_2$; **b** R = N=CHPh; **3 a** R = Ph, $R^1 = NH_2$; **b** R = C_4H_3S, $R^1 = NH_2$; **c** R = Ph, R^1 = N=CHPh; **d** R = C_4H_3S, R^1 = N=CHPh

One method for the synthesis of pyrazoles involves the reaction of α-acetylenic ketones with hydrazines, which may take place by a 1,2- and/or 1,4-addition mechanism [14, 15]. The structure of the compounds **3a-d** that we obtained demonstrates that the process takes place selectively through the intermediate formation of the enamine **A**, which is in tautomeric equilibrium with the hydrazone form **B**; at the second stage of the reaction attack by the amide nitrogen atom on the electron-deficient carbonyl carbon atom is accompanied by closure of the pyrazoline ring.

Compounds **3a-d** are stable products under the conditions of their recrystallization from ethanol. When heated with acetone the pyrazoline **3a** readily forms the corresponding hydrazone derivative **3e** (yield 91%), but during recrystallization from a mixture of acetic acid and water it undergoes dehydration and hydrolysis with the formation of 3,4-diphenylpyrazole (**4**).



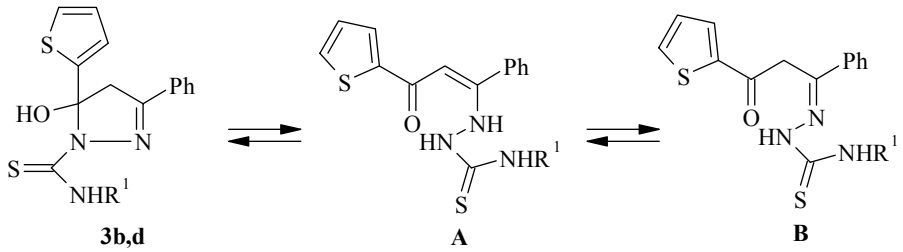
The structure of the pyrazolines **3a-e** was proved conclusively by data from the ^1H, ^{13}C, and ^{15}N NMR spectra. The ^1H NMR spectra of these compounds contain an AB system corresponding to the signals for the absorption of the prochiral hydrogen atoms of the CH_2 group in the region of δ 3.46-3.92 ppm (J_{AB} = 17.9-18.7 Hz), a signal for the protons of the OH group, and signals for the protons of the thioamide group and the protons of the primary amino group for compounds **3a**,**b** (δ 4.22-4.84 ppm). The cyclic structure of the obtained compounds is supported by the data from the ^{13}C NMR spectra, which contain a signal for the asymmetric $C_{(5)}$ atom in the region of 94.08-95.50 ppm. In order to identify the compounds unambiguously the

2D HMBC spectrum (^{15}N–^{1}H) of compound **3a** was recorded. The presence of cross peaks, due to long-range spin–spin coupling of the methylene protons both with the imine (δ_N 315.7 ppm, standard NH_3) and with the amine (δ_N 196.4 ppm) nitrogen atoms, indicates the five-membered pyrazoline structure.

After analyzing the ^{1}H and ^{13}C NMR spectra of the carbohydrazinoyl-5-dihydropyrazolines produced by the condensation of carbonohydrazide with 1,3-dicarbonyl compounds, the authors of [16] concluded that these compounds are present in the reaction mixtures in the form of two conformers with intramolecular hydrogen bonds of the O–H···O=C and N–H···OH types. The presence of only single signals in the ^{1}H and ^{13}C NMR spectra of the pyrazolines **3a-e** that we obtained makes it possible to suppose that the reaction under the selected conditions takes place stereoselectively with the formation of only one type of conformer. In the case of compound **3a** and the hydrazone derivative **3e** obtained from it the conformer is probably stabilized by an O–H···S=C intramolecular hydrogen bond. This is consistent with the presence of bands for the stretching vibrations of the OH group (~3330 cm^{-1}), the intensity of which does not depend on the concentration, in the IR spectra of their solutions in carbon tetrachloride (c = 10^{-2}-10^{-3} M). A narrow intense ν_{OH} band at ~3310 cm^{-1} is also observed in the spectra of the crystalline compounds **3a**,**e** (tablets with potassium bromide), characterizing as in the solutions a hydroxyl group participating in the formation of an intramolecular hydrogen bond. The NH groups in these compounds form intermolecular hydrogen bonds; bands for the stretching vibrations of the free NH groups at 3411 cm^{-1}, with a simultaneous decrease in the intensity of the low-frequency bands (3280 cm^{-1}) for the vibrations of the associated NH groups, appear in the spectra of the solutions as a result of dissociation. The participation of the proton of the hydroxyl group in the formation of the intramolecular hydrogen bond in compounds **3a** and **3e** is also confirmed by its downfield shift in the ^{1}H NMR spectra (solutions in DMSO-d_6) to the regions with δ 10.06 and 10.50 ppm respectively. At the same time there is probably an intramolecular hydrogen bond of the NH···N type in compound **3c**. In the IR spectrum of a dilute solution of this compound there is a band for the stretching vibrations of only a combined NH group (3300 cm^{-1}), close in value to the band in the spectrum of the solid compound. Here a band at 3620 cm^{-1} characterizes the free OH group of its molecule, while the band at 3340 cm^{-1} (the intensity of which decreases with dilution of the solution) corresponds to the hydroxyl group participating in the formation of the self-associate. The participation of the NH group in the formation of the intramolecular hydrogen bond is confirmed by the downfield shift of the signal for the proton (δ 11.84), which in the HMBC spectrum (^{1}H–^{13}C) gives two cross peaks, due to coupling of the NH proton with the carbon atoms of the thiocarbonyl and azomethine groups. Detailed investigation of the conformation of the pyrazolines that are formed and its dependence on the nature of the substituent is of separate interest and is not an aim of the present work.

It is known that thiocarbohydrazones exhibit a tendency to ring–chain and ring–linear–ring tautomerism [17]. This effect is of undoubted interest in view not only of its direct bearing on the synthesis of heterocyclic structures but also, possibly, of a direct connection with the biological activity [18].

We established that compounds **3a**,**c**,**e** are individual cyclic products in solutions in deuterochloroform and DMSO-d_6. At the same time the pyrazolines **3b** and **3d** are also represented by the linear forms **A** and/or **B** in solutions in DMSO-d_6, while the pyrazoline **3b** is in equilibrium only with the hydrazone form **B** and the pyrazoline **3d** is in equilibrium with the enamine **A** and hydrazone **B** forms.



3b,d **A** **B**

The state of the equilibrium and the ratio of the isomers were determined by means of the ^{1}H and ^{13}C NMR spectra of samples that had been kept in DMSO-d_6 for 2 h. In the ^{1}H NMR spectrum of the pyrazoline **3b**, together with the signals for the cyclic form, there are a singlet for the methylene protons (δ 4.80) and additional signals for the protons of the NH groups (δ 10.76 and 9.83 ppm), demonstrating the presence of the tautomeric form **B**; in the ^{13}C NMR spectrum there are a signal for the carbonyl carbon (δ 187.58), a signal for the carbon of the methylene group (δ 38.00), and two signals for the thiocarbonyl groups from the cyclic and linear forms (δ 173.47 and 176.12 ppm respectively). According to the data from the ^{1}H NMR spectra, the ratio of the cyclic and hydrazone **B** forms amounts to 3:2.

In the ^{1}H NMR spectrum of the pyrazoline **3d**, apart from the signals of the cyclic form, there is a set of new signals from the tautomeric forms **A** and **B**, i.e., a singlet for the methylene protons of form **B** (δ 4.88) and a signal for the proton of the vinyl group in form **A** (δ 6.00), and additional signals for the protons from the azomethine groups (δ 8.12 and 8.29) and the NH groups in the form of broad singlets (δ 11.13 and 11.90 ppm). In the 13C NMR spectrum there are additional signals from the α-carbon of the vinyl group of form **A** (δ 94.12), the methylene carbon of form **B** (δ 39.27), signals for the carbon atoms of the conjugated (δ 180.73) and unconjugated (δ 188.46) carbonyl groups of forms **A** and **B**, and signals for the carbon atoms of the thiocarbonyl groups in forms **A** and **B** (δ 178.63 and 175.40 ppm). According to the data from the ^{1}H NMR spectra, the ratio of the cyclic and chain forms **A** and **B** is 2:3:3.

It is notable that adducts indicating the participation of the S-nucleophilic center in the reaction process were not detected in any of the experiments. This fact indicates higher nucleophilicity for both the hydrazine and the thioamide nitrogen atoms, due probably to the α effect – coupling of the unshared electron pairs of the adjacent nitrogen atoms [19].

The new functionally substituted pyrazolines obtained in the present work are of interest as potential biologically active compounds combining the pharmacophoric effects of pyrazoles [20] and thiocarbohydrazones. They may also find application as ligands for complex formation and as synthons in fine organic synthesis.

EXPERIMENTAL

The IR spectra were recorded on a Specord IR-75 instrument. The ^{1}H and ^{13}C NMR spectra were obtained on Bruker DPX-400 and AV-400 spectrometers (400 and 100 MHz respectively) in DMSO-d_6 (compounds **3a**,**c**,**e**) or deuterochloroform (compounds **3b**,**d**) with the solvent signal as internal standard.

1-Carbothiohydrazinoyl-5-hydroxy-3,5-diphenyl-2-pyrazoline (3a). To a solution of (1.03 g, 5 mmol) of 1-benzoyl-2-phenylacetylene **1a** in 15 ml of acetic acid we added in one portion thiocarbonohydrazide **2a** (0.53 g, 5 mmol). The reaction mixture was stirred at room temperature for 4 h, water (25 ml) was added, and the mixture was stirred for 1 h. The precipitate was filtered off, washed with water, and dried over calcium chloride in a vacuum. Yield 1.25 g (80%), and the product formed lemon-yellow crystals; mp 147-149°C (ethanol). IR spectrum (potassium bromide), ν, cm^{-1}: IR spectrum (potassium bromide), ν, cm^{-1}: 3200-3340 (NH, NH_2, OH), 1410-1520 (C=N, C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.46, 3.71 (2H, q, J_{AB} = 18.7, CH_2); 4.84 (2H, s, NH_2); 6.68 (1H, s, NH); 7.25-7.93 (10H, m, $2C_6H_5$); 10.06 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 51.05 (CH_2); 95.50 ($C_{(5)}$); 124.38 (C_m, Ph–C=N); 127.08 (C, $PhC_{(5)}$); 127.28 (C_p, $PhC_{(5)}$); 128.22 (C_m, $PhC_{(5)}$); 128.67 (C_o, Ph–C=N); 130.85 (C_i, Ph–C=N); 130.45 (C_p, Ph–C=N); 144.89 (C_i, $PhC_{(5)}$); 151.11 (C=N); 173.55 (C=S). Found, %: C 61.33; H 5.31; N 17.84; S 10.58. $C_{16}H_{16}N_4OS$. Calculated, %: C 61.54; H 5.13; N 17.95; S 10.26.

During the crystallization of compound **3a** from a 1:2 mixture of acetic acid and water 3,5-diphenylpyrazole **4** was obtained in the form of colorless crystals; mp 199-201°C (mp 199-200°C [21]). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 99.62 ($C_{(4)}$); 115.61, 116.54, 125.13, 127.45, 128.12, 128.63, 129.00, 133.69 ($2C_6H_5$); 143.38 ($C_{(5)}$); 151.34 ($C_{(3)}$).

1-Carbothiohydrazinoyl-5-hydroxy-3-phenyl-5-(2-thienyl)-2-pyrazoline (3b). This compound was obtained similarly to compound **3a** from 2-phenyl-1-(2-thenoyl)acetylene **1b** (1.06 g, 5 mmol) and compound **2a** (0.53 g, 5 mmol). Yield 1.39 g (88%), and the product formed yellow crystals; mp 143-144°C (ethanol). IR spectrum (potassium bromide), ν, cm^{-1}: 3210-3360 (NH, NH_2, OH), 1400-1500 (C=N, C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.58, 3.84 (2H, q, J_{AB} = 18.2, CH_2); 4.22 (2H, s, NH_2); 6.74 (1H, s, NH); 6.93-7.68 (8H, m, C_4H_3S, C_6H_5); 8.56 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 51.12 (CH_2); 94.08 ($C_{(5)}$); 123.32, 125.26, 126.73, 127.07, 128.84, 130.23, 131.04, 148.45 (C_4H_3S, C_6H_5); 152.58 (C=N); 177.19 (C=S). Found, %: C 53.26; H 4.58; N 17.48; S 20.38. $C_{14}H_{14}N_4OS_2$. Calculated, %: C 52.81; H 4.43; N 17.60; S 20.14.

1-[N'-(Phenylmethylene)carbothiohydrazinoyl]-5-hydroxy-3,5-diphenyl-2-pyrazoline (3c). A suspension of benzaldehyde thiocarbazone **2b** (0.97 g, 5 mmol) in a mixture of ethanol (10 ml) and water (5 ml) was heated at 60°C, and a solution of compound **1a** (1.03 g, 5 mmol) in ethanol (5 ml) was added dropwise with stirring. The reaction mixture was stirred at 60°C for 2.5 h, cooled to room temperature, and stirred for 1 h. The precipitate was filtered off, washed with water, and dried over calcium chloride in a vacuum. Yield 1.28 g (64%), and the product was a light-yellow powder; mp 123-124°C. IR spectrum (potassium bromide), ν, cm^{-1}: 3150-3340 (NH, OH), 1415-1515 (C=N, C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.53, 3.78 (2H, q, J_{AB} = 18.5, CH_2); 6.93 (1H, s, OH); 7.32-7.95 (15H, m, $3C_6H_5$); 8.59 (1H, c, N=C<u>H</u>Ph); 11.84 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 50.79 (CH_2); 95.08 ($C_{(5)}$); 124.13, 125.08, 127.08, 127.34, 128.32, 128.69, 128.81, 130.04, 130.39, 130.88, 134.29, 144.34 ($3C_6H_5$); 148.62 (N=<u>C</u>HPh); 152.37 (C=N); 171.86 (C=S). Found, %: C 68.86; H 5.38; N 14.18; S 8.31. $C_{23}H_{20}N_4OS$. Calculated, %: C 69.00; H 5.00; N 14.00; S 8.00.

1-[N'-(Phenylmethylene)carbothiohydrazinoyl]-5-hydroxy-3-phenyl-5-(2-thienyl)-2-pyrazoline (3d). This compound was obtained similarly to compound **3c** from compound **1b** (1.06 g, 5 mmol) and compound **2b** (0.97 g, 5 mmol). Yield 1.22 g (60%), and the product formed a light-yellow powder; mp 143-145°C. IR spectrum (potassium bromide), ν, cm^{-1}: 3160-3290 (NH, OH), 1410-1510 (C=N, C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.66, 3.92 (2H, q, J_{AB} = 18.3, CH_2); 6.94 (1H, s, OH); 7.01-7.77 (13H, m, C_4H_3S, $2C_6H_5$); 8.17 (1H, s, N=C<u>H</u>Ph); 10.48 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 51.35 (CH_2); 94.64 ($C_{(5)}$); 123.53, 125.37, 127.05, 127.20, 127.94, 127.79, 129.06, 130.64, 131.43, 133.57, 148.21 (C_4H_3S, $2C_6H_5$); 148.10 (N=C<u>H</u>Ph); 152.94 (C=N); 172.18 (C=S). Found, %: C 62.26; H 4.68; N 13.98; S 15.51. $C_{21}H_{18}N_4OS_2$. Calculated, %: C 62.07; H 4.43; N 13.79; S 15.76.

1-[N'-(1-Methylethylene)carbothiohydrazinoyl]-5-hydroxy-3,5-diphenyl-2-pyrazoline (3e). A solution of compound **3a** (0.72 g, 2.3 mmol) in dry acetone (20 ml) was boiled for 2 h and was then kept at 5-8°C for two days. The precipitate was filtered off and dried under vacuum. Yield 0.74 g (91%), and the product formed colorless needles; mp 136-137°C. IR spectrum (potassium bromide), ν, cm^{-1}: 3190-3330 (NH, OH), 1410-1510 (C=N, C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.97 (6H, br. s, $2CH_3$); 3.52, 3.77 (2H, q, J_{AB} = 17.9, CH_2); 6.96 (1H, s, NH); 7.25-7.85 (10H, m, $2C_6H_5$); 10.50 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm: 17.94 (CH_3); 25.30 (CH_3); 51.39 (CH_2); 96.02 ($C_{(5)}$); 124.57, 127.45, 127.81, 128.72, 128.89, 129.20, 130.78, 131.21, 144.81 ($2C_6H_5$); 152.26 (C=N); 159.33 (<u>C</u>Me_2); 172.01 (C=S). Found, %: C 65.06; H 5.58; N 15.78; S 9.23. $C_{19}H_{20}N_4OS$. Calculated, %: C 64.75; H 5.72; N 15.90; S 9.10.

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