Reaction of 4-aryl-2-methylbut-3-yn-2-ols with thiourea as a new approach to the synthesis of 4-arylmethylidene-5,5-dimethyl-4,5-dihydrothiazole-2-amines

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A reaction of thiourea with 4-aryl-2-methylbut-3-yn-2-ols in refluxing pyridine led to the synthesis of 4-arylmethylidene-5,5-dimethyl-4,5-dihydrothiazole-2-amines.

Key words: alkynes, heterocyclization, thiourea, 2-thiazolines.

Synthetic potential of acetylenes significantly broadens in the presence of acceptor substituents, especially, when functional groups are placed close to the triple bond. Activated alkynes in the reactions with nucleophilic agents can undergo various and unusual transformations. In fact, we have observed such nontrivial rearrangements and heterocyclizations earlier in the reactions of *peri*-R-ethynyl-9,10-anthraquinones with guanidine,[1,2] including acetylenic alcohols.[3]

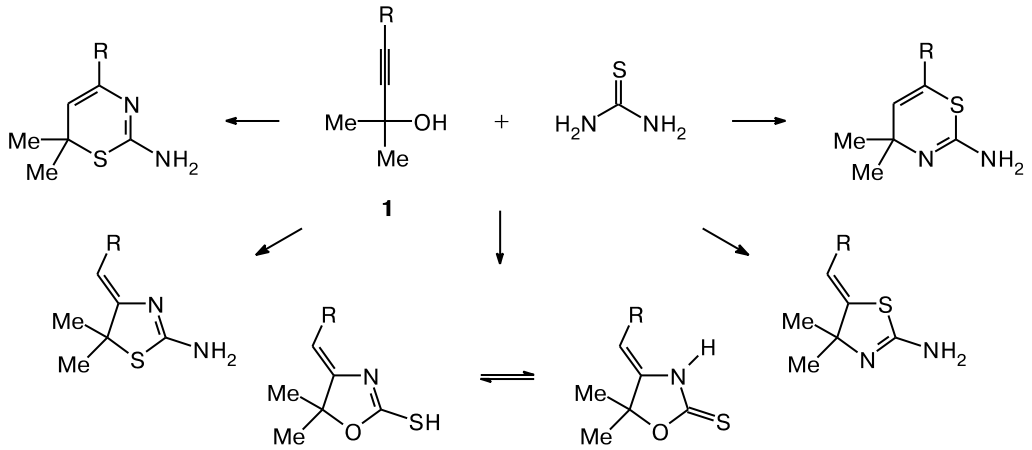
In continuation of our studies on the reactivity of activated alkynes with polyfunctional nucleophilic agents, we investigated a reaction of tertiary acetylenic alcohols with thiourea.

It should be pointed out that when addition reactions of nucleophiles at triple bonds are studied, a question always arises on the regioselectivity of the process. In the case of the reaction of alcohols **1** with thiourea, several pathways of cycloaddition could have been expected (Scheme 1).

The reaction of alcohols **1a**,**b** with thiourea led to 4-arylmethylidene-5,5-dimethyl-4,5-dihydrothiazole-2-amines **2a**,**b** in 31 and 38% yields, respectively. In the case of **1c**, thiazoline **2c** (37%) and 5,5-dimethyl-4-(2,5-dimethyl-4-nitrobenzylidene)thiazolidine-2-thione (**3**) (10%) were formed (Scheme 2).

The X-ray diffraction data not only unambiguously indicated the structure of **2a** as 5,5-dimethyl-4-(4-nitrobenzylidene)-4,5-dihydrothiazole-2-amine, but also its *Z*-configuration (Fig. 1).

Scheme 1



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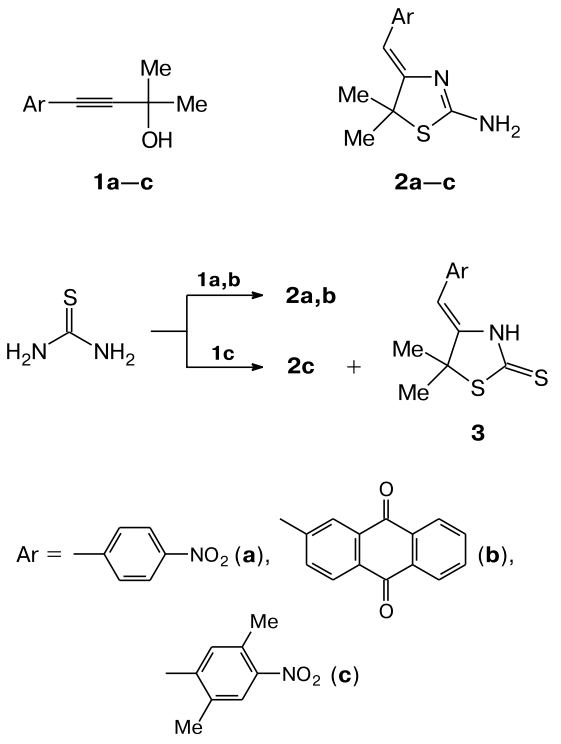
Scheme 2



The X-ray diffraction analysis of the crystalline sample of **2a** showed that the ethylidenedihydrothiazole fragment is planar within ±0.038 Å (see Fig.. 1). The plane of the nitrophenyl group forms with the indicated plane the angle of 15.97(8)°. The bond distances in the dihydrothiazole ring are close to the analogous values in 2-amino-4-(1,2,2,2-tetrafluoroethylidene)-5,5-bis(trifluoromethyl)-4,5-dihydrothiazole[4] and 1-[4-(1,2,2,2-tetrafluoroethylidene)-5,5-bis(trifluoromethyl)-4,5-dihydrothiazole-2-yl]-1*H*-pyridin-2-one.[5] A 3D architecture in the crystal was formed by the hydrogen bonds N(1)—H...O(1) (H...O 2.12(3), 2.33(2) Å, N—H...O 164(2), 161(2)°). Note also the interactions C(9)—H...π(thiazole) and C(11)—H...π-(phenyl) with the distances H—centroid of 2.87 and 2.89 Å.

It should be noted that for the medicinal chemistry, compounds containing a thiazoline fragment are of significant interest, since many of them are antibiotics.[6]

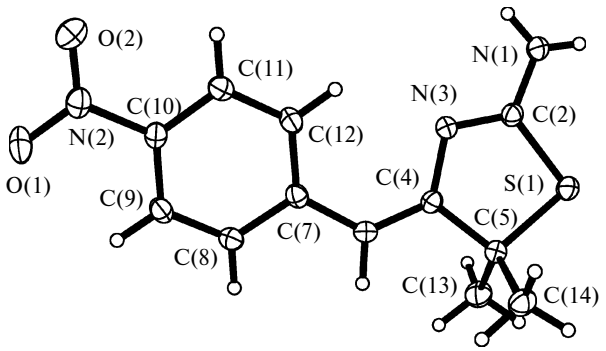


Fig. 1. Molecular structure of **2a** with 50% thermal ellipsoids of nonhydrogen atoms.

The reaction is accompanied by the formation of large amounts of poorly separable by-products, which made purification problematic and led to additional losses of the final heterocycles **2a—c** and **3**. It is possible that the predominance of the secondary processes is caused by the involvement of alkyne **1** in the reactions with numerous products of thiourea destruction, which inevitably are formed upon its prolonged heating.

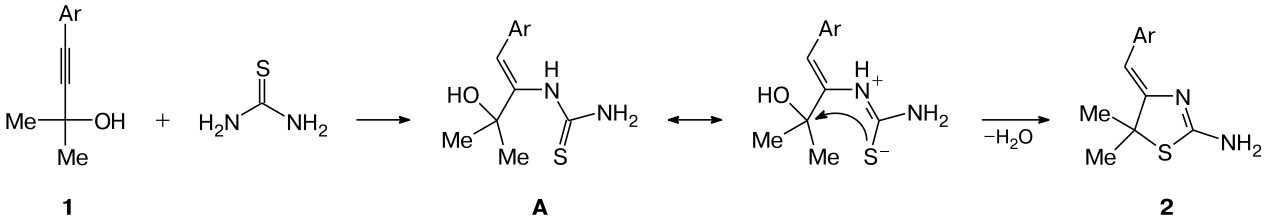
The low solubility of thiourea in many organic solvents limited their use, meanwhile, it is extremely necessary to use excess of thiocarbamide. In this case, pyridine turned out to be more appropriate medium than, for example, aliphatic alcohols (MeOH, EtOH, BuOH).

The formation of the thiazoline ring can be represented by the addition of the NH_2 group of thiourea at the triple bond with subsequent cyclization of enamine **A** and elimination of water (Scheme 3).

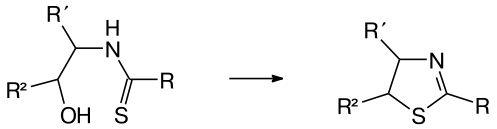
The intramolecular cyclization of the enamine intermediate **A** (Scheme 4) resembles the transformations of *N*-(β-hydroxyethyl)thioamides, in the course of which, as it is known, a thiazoline ring is also closed.[6]

As it was previously mentioned, the thiazoline structure **2a** was reliably confirmed by X-ray crystallography. Comparison of the spectral data (^{1}H and ^{13}C NMR) of compounds **2a** and **2b,c** allowed us to state that these compounds belonged to thiazolines. The signals for the protons of the *exo*-=CH—Ar moieties for all three thiazolines **2a—c** lie in the narrow range: 5.56 (**2a**), 5.66 (**2b**), and 5.55 ppm (**2c**).

Scheme 3



Scheme 4



We also noted that the values of all the corresponding chemical shifts for carbon atoms of thiazolines **2a**—**c** fell in the very narrow range in their ^{13}C NMR spectra. Special attention was drawn by the closeness of chemical shifts for the key α- and β-carbon atoms at the double bond, though this is the case when chemical shifts for the carbon atoms at *exo*- and *endo*-double bond should differ considerably: 166.83 (=C<), 105.29 (=CH) for **2a**, 166.76 (=C<), 105.68 (=CH) for **2b**, and 166.12 (=C<), 102.40 (=CH) for **2c**. As it is seen, the differences for δ(=C<) are maximum of 0.7 ppm, that is insignificant for the ^{13}C NMR spectra. The difference in the δ(=CH) values between **2a** and **2b** is 0.39 ppm. A slightly larger Δδ (~2 ppm) value for **2c** was anticipated: this upfield shift of the signal can be explained by the presence of two donor methyl groups on the aromatic ring. Such a difference excludes an alternative thiazine structure in going from the five-membered thiazoline with the *exo*-methine fragment to the six-membered thiazine with the *endo*-methine fragment. The δ value for the =CH-fragment would have been downfield shifted by 25—30 ppm as compared to the observed values. As to the recording of 2D NMR spectra, the 2D-correlations on the remote C—H constants for the double bond often are ambiguous because of complicated dependence of the constant values through the double bond.

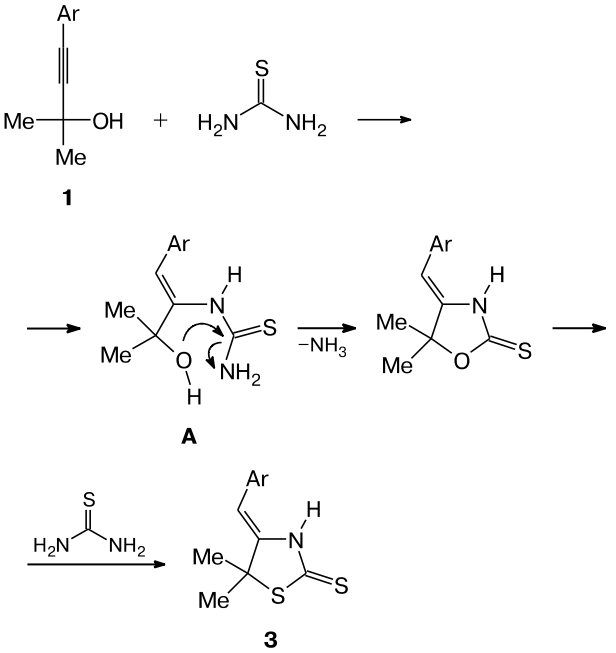
Moreover, all three alcohols **1a**—**c** contain strong accepting substituents, they uniformly cause such a polarization when the deficiency of the electron density is formed on the β-carbon atom of the triple bond (relative to the aryl substituent), which facilitates attack of the nucleophile on this carbon atom. In going from compound **1a** to acetylenic alcohols **1b**,**c** with more bulky substituents, the steric hindrance from the side of this bulky substituent makes the attack of nucleophile on the α-carbon atom (*i.e.*, formation of thiazine) still less probable.

Thus, a combination of ^{1}H and ^{13}C NMR spectral data for all the compounds and X-ray analysis for the most representative compound **2a** reliably confirms the structure of products **2a**—**c** as 4-arylmethylidene-5,5-dimethyl-4,5-dihydrothiazole-2-amines.

The IR spectra of **2a**—**c** contain bands of stretching vibrations of the NH_2 group (3479—3303 cm^{-1}), as well as strong bands of stretching vibrations of the C=N-bond of the thiazoline ring (1533—1492 cm^{-1}).

In the reaction of alcohol **1c** with thiourea, besides a predominant thiazoline **2c** (37%), a minor product, thiazolidinethione **3** (10%), was also formed. It is possible that the closure of the heterocycles **2** and **3** is effected by the transformation of the common enamine intermediate **A** by different pathways. Product **3** can be formed as a result of cyclization of **A** to oxazolidinethione, which upon the action of excess thiourea undergoes thiolation (Scheme 5).

Scheme 5



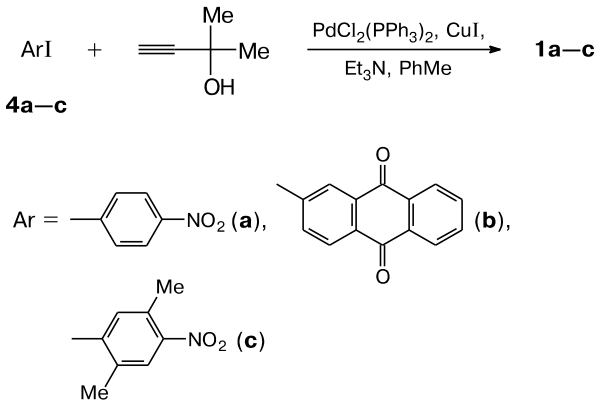
The step of the oxazolidine ring closure can be considered as a type of cyclization described in the works,[7,8] since the intermediate **A** structurally resembles 1-(2-hydroxyethyl)guanidine and 1-(2-hydroxyethyl)-3-nitroguanidine.

The structure of compound **3** was confirmed by a combination of analytical and spectral data (IR, mass spectra, and ^{1}H, ^{13}C NMR spectra). Heterocycles of the type **3** can exist as two tautomeric forms, thiol and thione.[9] The presence in the ^{13}C NMR spectra of the signal for the carbon atom of the C=S group at δ 193.17 confirms its thione structure, that also agrees with the presence in the ^{1}H NMR spectra of compound **3** of the signal for the proton of the NH group as a broad singlet at δ 8.18.

The starting alcohols **1a**—**c** were obtained by the cross-coupling of 2-methylbut-3-yn-2-ol with iodides **4a**—**c** under standard conditions of the Sonogashira reaction[10] in 91—96% yields (Scheme 6).

Thus, cyclocondensation of thiourea with 4-aryl-2-methylbut-3-yn-2-ols **1a**—**c** in refluxing pyridine leads to yield 4-arylmethylidene-5,5-dimethyl-4,5-dihydrothiazole-2-amines **2a**—**c**. The discovered reaction opens a new approach to the synthesis of substituted 2-amino-2-thiazolines.

Scheme 6



Experimental

Elemental analysis was performed on a Carlo Ebra 1106 CHN-analyzer (Italy). IR spectra were recorded on a Bruker Vector 22 spectrometer in KBr pellets. NMR spectra were recorded on a Bruker AV 400 spectrometer in $CDCl_3$ (400.13 (^{1}H) and 100.61 MHz (^{13}C)). Mass spectra were obtained on a Thermo Electron Corporation DFS mass spectrometer (70 eV), using direct injection, the temperature of the ionization chamber was 220—270 °C. Alumina (50—150 μm, TU 6-09-3916-75) was used for column chromatography, TLC monitoring was carried out on Silufol 60 F254 plates.

2-Methyl-4-(4-nitrophenyl)but-3-yn-2-ol (1a). A mixture of 1-iodo-4-nitrobenzene (**4a**) (2.2 g, 9 mmol), 2-methylbut-3-yn-2-ol (0.8 g, 9 mmol), $PdCl_2(PPh_3)_2$ (20 mg, 0.028 mmol), CuI (10 mg, 0.052 mmol), and Et_3N (7 mL, 38.6 mmol) in toluene (60 mL) was stirred for 1.5 h at 60 °C under argon. The reaction mixture was cooled and filtered through Al_2O_3 (d = 25 mm, h = 20 mm), eluted with toluene. The solvent was evaporated *in vacuo*. The compound **1a** (1.77 g, 96%) was isolated by subsequent recrystallization from a mixture of toluene with hexane, m.p. 104—105 °C (see Ref. 11: m.p. 104.5—105 °C (CCl_4)).

The alcohol **1b** was obtained similarly. The yield was 92%, m.p. 133—134 °C (toluene—hexane; see Ref. 12: m.p. 134—135 °C (benzene)).

4-(2,5-Dimethyl-4-nitrophenyl)-2-methylbut-3-yn-2-ol (1c) was obtained similarly. The yield was 91%, yellow crystals, m.p. 52—53 °C (hexane—toluene). Found (%): C, 67.02; H, 6.44; N, 5.82. $C_{13}H_{15}NO_3$. Calculated (%): C, 66.94; H, 6.48; N, 6.00. ^{1}H NMR ($CDCl_3$), δ: 1.64 (s, 6 H, 2 Me); 2.15 (s, 1 H, OH); 2.42 (s, 3 H, *m*-Me); 2.52 (s, 3 H, *o*-Me); 7.32 (s, 1 H, H_m); 7.82 (s, 1 H, H_o). ^{13}C NMR ($CDCl_3$), δ: 20.09 (*m*-Me); 20.13 (*o*-Me); 31.53 (2 Me); 65.86 ($\underline{C}Me_2$); 79.52 (—C≡); 101.89 (≡C—); 125.50 (C_m); 128.03 (C_p); 130.97 ($\underline{C}_m$—Me); 135.94 (C_o); 139.16 ($\underline{C}_o$—Me); 147.99 (C—NO_2). IR, ν/cm^{-1}: 3460 (OH); 2980, 2931, 2868 (Me); 2226 (C≡C); 1512, 1335 (NO_2).

***Z*-5,5-Dimethyl-4-(4-nitrobenzylidene)-4,5-dihydrothiazole-2-amine (2a).** A mixture of **1a** (1 g, 4.8 mmol) and thiourea (3.6 g, 48 mmol) in pyridine (24 mL) was refluxed for 9 h. A cooled reaction mixture was diluted with CH_2Cl_2 (200 mL) and washed with H_2O (2×250 mL). The organic layer was separated, dried with Na_2SO_4, the solvent was evaporated *in vacuo*, a precipitate formed was subjected to chromatography on Al_2O_3 in toluene. The yield was 31%, red crystals, m.p. 212—213 °C (toluene). Found (%): C, 54.89; H, 4.86; N, 15.78; S, 12.21. $C_{12}H_{13}N_3O_2S$. Calculated (%): C, 54.74; H, 4.98; N, 15.96; S, 12.18. ^{1}H NMR ($CDCl_3$), δ: 1.73 (s, 6 H, 2 Me); 5.33 (br.s, 2 H, NH_2); 5.56 (s, 1 H, CH=); 7.95 (td, 2 H, H_m, J = 1.80 Hz, J = 2.45 Hz, J = 8.90 Hz); 8.13 (td, 2 H, H_o, J = 1.80 Hz, J = 2.45 Hz, J = 8.90 Hz). ^{13}C NMR ($CDCl_3$), δ: 31.74 (2 Me); 66.72 ($\underline{C}Me_2$); 105.29 (CH=); 123.74 (C_m); 128.38 (C_o); 144.64, 145.02 (C_{arom}); 166.83 (=C<); 167.37 (CNH_2). HRMS, found: m/z 263.0722 [M]$^+$. $C_{12}H_{13}N_3O_2S$. Calculated: M = 263.0723. IR, ν/cm^{-1}: 3479, 3329 (NH_2); 1317, 1516 (NO_2); 1492 (C=N).

The reactions of acetylenic alcohols **1b** and **1c** were performed similarly, in the second case, thione **3** was isolated by chromatography together with amine **2c**.

4-[(9,10-Anthraquinon-2-yl)methylidene]-5,5-dimethyl-4,5-dihydrothiazole-2-amine (2b). The yield was 38%, red crystals, m.p. 207—208 °C (toluene). Found (%): C, 68.98; H, 4.91; N, 7.65; S, 9.25. $C_{20}H_{16}N_2O_2S$. Calculated (%): C, 68.94; H, 4.63; N, 8.04; S, 9.20. ^{1}H NMR ($CDCl_3$), δ: 1.75 (s, 6 H, 2 Me); 5.47 (br.s, 2 H, NH_2); 5.66 (s, 1 H, CH=); 7.77 (m, 2 H, H(3), H(4)); 8.27 (m, 4 H, H(5), H(6), H(7), H(8)); 8.67 (s, 1 H, H(1)). ^{13}C NMR ($CDCl_3$), δ: 31.79 (2 Me); 66.70 ($\underline{C}Me_2$); 105.68 (CH=); 126.67, 127.21, 127.23, 127.60, 129.98, 133.31, 133.61, 133.76, 133.94, 134.08, 134.20, 144.50 (C_{arom}); 166.76 (=C<); 167.40 (CNH_2); 182.93, 184.15 (2 C=O). HRMS, found: m/z 348.0930 [M]$^+$. $C_{20}H_{16}N_2O_2S$. Calculated: M = 348.0927. IR, ν/cm^{-1}: 3344, 3169 (NH_2); 1666 (C=O); 1533 (C=N).

4-(2,5-Dimethyl-4-nitrobenzylidene)-5,5-dimethyl-4,5-dihydrothiazole-2-amine (2c). The yield was 37%, yellow crystals, m.p. 210—211 °C (toluene). Found (%): C, 57.91; H, 5.87; N, 14.07; S, 11.07. $C_{14}H_{17}N_3O_2S$. Calculated (%): C, 57.71; H, 5.88; N, 14.42; S, 11.00. ^{1}H NMR ($CDCl_3$), δ: 1.74 (s, 6 H, 2 Me); 2.34 (s, 3 H, *m*-Me); 2.60 (s, 3 H, *o*-Me); 5.40 (br.s, 2 H, NH_2); 5.55 (s, 1 H, CH=); 7.84 (s, 1 H, H_m); 8.20 (s, 1 H, H_o). ^{13}C NMR ($CDCl_3$), δ: 19.81 (*m*-Me); 21.17 (*o*-Me); 32.09 (2 Me); 66.13 ($\underline{C}Me_2$); 102.40 (CH=); 126.23 (C_m); 131.57 ($\underline{C}_m$—Me); 132.69 (C_o); 133.71 ($\underline{C}_o$—Me); 142.13 (C_p); 145.37 (CNO_2); 166.12 (=C<); 166.39 (CNH_2). IR, ν/cm^{-1}: 3420, 3303 (NH_2); 2927, 2920, 2858 (Me); 1537, 1325, (NO_2); 1492 (C=N).

4-(2,5-Dimethyl-4-nitrobenzylidene)-5,5-dimethylthiazolidine-2-thione (3). The yield was 10%, white crystals, m.p. 228—230 °C (toluene—ethyl acetate). Found (%): C, 54.80; H, 5.31; N, 8.91; S, 20.85. $C_{14}H_{16}N_2O_2S_2$. Calculated (%): C, 54.52; H, 5.23; N, 9.08; S, 20.79. ^{1}H NMR ($CDCl_3$), δ: 1.69 (s, 6 H, 2 Me); 2.31 (s, 3 H, *m*-Me); 2.59 (s, 3 H, *o*-Me); 6.40 (s, 1 H, CH=); 7.22 (s, 1 H, H_m); 7.85 (s, 1 H, H_o), 8.18 (br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 19.31 (*m*-Me); 20.47 (*o*-Me); 29.68 (2 Me); 72.41 ($\underline{C}Me_2$); 115.15 (CH=); 126.51 (C_m); 131.35 (C_o); 131.91 ($\underline{C}_m$—Me); 135.27 ($\underline{C}_o$—Me); 140.00 (C_p); 147.68 (CNO_2); 147.96 (=C<); 193.17 (C=S). HRMS, found: m/z 308.0645 [M]$^+$. $C_{14}H_{16}N_2O_2S_2$. Calculated: M = 308.0653. IR, ν/cm^{-1}: 3443, 3126 (NH); 2982, 2930, 2851 (Me); 1516, 1338 (NO_2); 1034 (C—N).

X-ray diffraction experiment was performed on a Bruker KAPPA APEX II CCD diffractometer (graphite monochromator, λ(Mo-Kα) = 0.71073 Å, temperature 150(2) K, φ,ω-scan technique). Monoclinic crystal system, $C_{12}H_{13}N_3O_2S$, M = 263.31, space group $P2_12_12_1$, a = 6.8897(5) Å, b = 7.6734(5) Å, c = 23.5513(17) Å, V = 1245.10(15) Å^3, Z = 4, d_{calc} = 1.405 g cm^{-3}, μ = 0.258 mm^{-1}. Intensities of 24568 reflections (2θ < 60°) were

measured for the sample of 0.06×0.12×0.20 mm in size, from them 3644 were independent reflections (R_{int} = 0.0407) and 3169 reflections with $I > 2\sigma(I)$, number of refined parameters 173, $R_1(I > 2\sigma(I)) = 0.0328$, $wR_2 = 0.0796$ and GOOF = 1.038 (on all the reflections). Allowance for absorption was made using the SADABS program (T_{min}/T_{max} = 0.8985/0.9703). The structure was solved by direct method. Positions and temperature parameters of nonhydrogen atoms were refined in isotropic and then in anisotropic approximation by full-matrix least squares method. The hydrogen atoms of the amino group were localized from the differential syntheses and refined in isotropic approximation, other H atoms were refined using the riding model. All the calculations were performed using the SHELXTL software. Atomic coordinates and their temperature parameters were deposited with the Cambridge Structural Database (CCDC 854823).

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