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Synthesis of 4-Thioacetyl-1,2,3-thiadiazoles. Reversible Rearrangement of N-Substituted 5-Methyl-1,2,3-thiadiazole-4-carbothioamides

P. E. Prokhorova, T. A. Kalinina, T. V. Glukhareva, and Yu. Yu. Morzherin

Yeltsin Ural Federal University, ul. Mira 19, Yekaterinburg, 620002 Russia
e-mail: yu.yu.morzherin@ustu.ru

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Abstract—The equilibrium in the reversible rearrangement of 5-methyl-1,2,3-thiadiazole-4-carbothioamides into 5-amino-4-thioacetyl-1,2,3-thiadiazoles is displaced toward the former, and polar solvents favor increased fraction of the thioketone.

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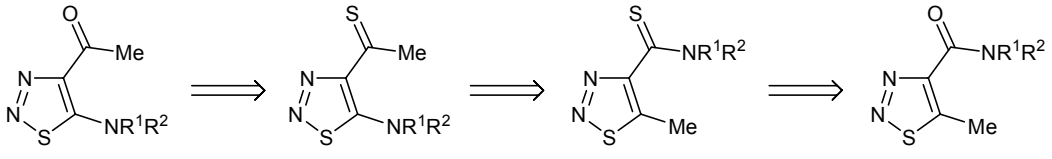
1,2,3-Thiadiazoles containing an acetyl group in the 4-position have been poorly studied [1]. Such compounds are generally synthesized according to Wolff [2], which determines a limited set of substituents and hence a limited number of available 4-acetyl-1,2,3-thiadiazole derivatives. With a view to synthesize new derivatives of 4-acyl-1,2,3-thiadiazoles **I** we propose a retrosynthetic scheme based on transformations of 5-methyl-1,2,3-thiadiazole-4-carboxamides **IV**. The scheme includes rearrangement of 1,2,3-thiadiazole-4-carbothioamides **III** into isomeric 4-thioacetyl-1,2,3-tiadiazoles **II** and subsequent hydrolysis of the thioketone group (Scheme 1).

Analogous reversible rearrangement was reported by us previously [3]. Unlike the results obtained in [3], thionation of N-substituted 5-methyl-1,2,3-thiadiazole-4-carboxamides **IV** gave individual thioamides **IIIa**–**IIId** rather than isomer mixtures (Scheme 2), and the structure of **IIIa**–**IIId** was determined by spectral methods and X-ray analysis of a single crystal of **IIIa** (see figure). Isomers **II** were detected only by TLC, but we failed to isolate them.

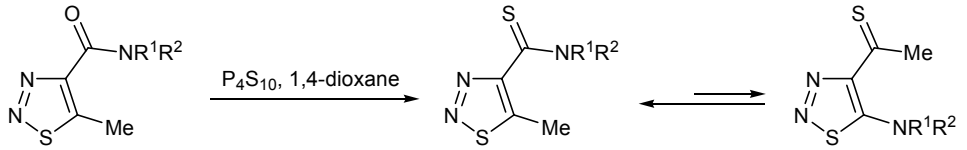
In order to identify isomeric thioketones **II** we examined effects of the solvent and temperature on the isomer ratio. The ratio of isomers **II** and **III** depended on the solvent (Table 1), but did not depend on the temperature or reaction time. We therefore concluded that the formation of 4-thioacetyl-1,2,3-thiadiazole **II** is an equilibrium process; the fraction of **II** increased with rise in the polarity of the medium.

Scheme 1.



I **II** **III** **IV**

Scheme 2.



IVa–IVd **IIIa–IIId** **IIa–IId**

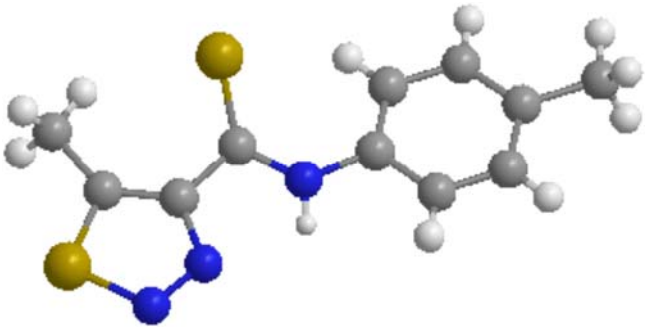
R^1 = H, R^2 = 4-MeC_6H_4 (**a**), Ph (**b**); $R^1R^2 = (CH_2)_5$ (**c**), R^1R^2N = morpholin-4-yl (**d**).

Table 1. Solvent effect on the ratio of isomers **IIa** and **IIIa**

Solvent	Dipole moment μ , D [4]	δ(H_{arom}), ppm		δ(CH_3), ppm		Mole fraction, %	
		IIa	**IIIa**	**IIa**	**IIIa**	**IIa**	**IIIa**
C_6D_6	0.0	7.35, 6.96	7.63, 6.90	2.34, 2.05	2.45, 2.02	2.4	97.6
$CDCl_3$	3.8	–	7.71, 7.27	–	3.09, 2.39	2.9	97.1
CD_3OD	5.7	7.01, 6.72	7.74, 7.25	2.95, 2.33	2.93, 2.37	3.4	96.6
Acetone-d_6	9.0	7.04, 6.83	7.89, 7.29	3.00, 2.33	2.99, 2.37	3.5	96.5
DMSO-d_6	13.5	6.95, 6.67	7.77, 7.21	2.94, 2.23	2.87, 2.37	4.4	95.6

We have found a good correlation between the composition of equilibrium mixture **IIa**/**IIIa** and dipole moment of the solvent: ν = (0.142±0.015)μ + (2.4±0.1), r = 0.98, s = 0.14, n = 5; ν is the mole fraction of **II** (%), and μ is the dipole moment of the solvent (D). However, solvent effect on the equilibrium is insignificant: considerable increase of the dipole moment is accompanied by change of the fraction of **II** from 2.4 to 4.6%.

We estimated the stabilities of isomeric thiadiazoles **II** and **III** by quantum-chemical calculations. As subjects for the study we selected 5-methyl-1,2,3-thiadiazole-4-carbothioamides having different substituents on the amide nitrogen atom. The calculations were performed in terms of AM1 and PM3 semiempirical approximations, as well as at the DFT level [B3LYP/6-31G(d)], using GAUSSIAN 03W software package [5]; the results are collected in Table 2. It is seen that electron-donor substituents in the aromatic ring on the amide nitrogen atom stabilize thioamide structure **III** and that electron-withdrawing groups favor thioketone isomer **II**. Aliphatic substituents on the nitrogen stabilize carbothioamide **III**. For instance, the enthalpy of formation of thiadiazole **IIIc** considerably exceeds that found for the corresponding thioketone **IIc**. On the other hand, the difference in ΔH_f values for thioamide **IIIg** and amine **IIg** is as small as 0.6 kcal/mol. Thus the results of quantum-chemical calculations suggest that the proposed scheme for the preparation of 5-amino-4-acetyl-1,2,3-thiadiazoles is applicable only to derivatives containing electron-withdrawing groups in the carbothioamide fragment.



Structure of the molecule of 5-methyl-*N*-(4-methylphenyl)-1,2,3-thiadiazole-4-carbothioamide (**IIIa**) according to the X-ray diffraction data.

To conclude, we have shown that thiadiazoles **III** are formed as equilibrium mixtures with isomeric thioketones **II**, the former prevailing. The fraction of thioketones **II** in a polar solvent (DMSO) is higher than in weakly polar chloroform. Thioamides **III** turned out to be stable on heating in boiling water, and we failed to isolate targeted 4-acetyl-1,2,3-thiadiazoles **I**.

EXPERIMENTAL

The progress of reactions and the purity of products were monitored by TLC on Kieselgel 60 F254 plates. The IR spectra were recorded on a Bruker Alpha-E spectrometer. The ^{1}H and ^{13}C NMR spectra were run on a Bruker DRX-400 instrument at 400 and 100 MHz, respectively, using TMS as internal reference.

The X-ray diffraction data for compound **IIIa** were acquired at 295 K on an Xcalibur 3 diffractometer [CCD detector, MoK_α irradiation, λ = 0.71073, ω/θ-scanning, $2\theta_{max}$ = 143.0°, μ(CuK_α) = 0.424 mm^{-1}] from a 0.50×0.34×0.11-mm single crystal (orange plate). Monoclinic crystal system, space group $P2_1/n$; $C_{11}H_{11}N_3S_2$; unit cell parameters: a = 7.2598(10), b = 23.649(4), c = 7.4688(6) Å; β = 112.299(11)°; V = 1186.4(3) Å^3; Z = 4; d_{calc} = 1.396 g/cm^3. Total of 6318 reflection intensities were measured (2798 independent reflections); R_1 = 0.0389 [for 1230 reflections with $I > 2\sigma(I)$], wR_2 = 0.0843.

5-Methyl-1,2,3-thiadiazole-4-carbothioamides III and 1-(5-arylamino-1,2,3-thiadiazol-4-yl)ethanethiones II (*general procedure*). 5-Methyl-1,2,3-thiadiazole-4-carboxamide **IVa**–**IVd**, 1.0 g (3.6 mmol), was

dissolved in 10 ml of anhydrous 1,4-dioxane, 0.5 mmol of P_4S_{10} was added at a temperature not exceeding 60°C, and the mixture was heated for 2 h under reflux. The mixture was evaporated, the residue was treated with water, the mixture was heated to the boiling point and left to stand for crystallization, and the precipitate was filtered off, washed with water, and dried. The product was a mixture of compounds **III** and **II**, the former prevailing.

5-Methyl-*N*-(4-methylphenyl)-1,2,3-thiadiazole-4-carbothioamide (IIIa). Yield 0.705 g (63%), mp 80°C, R_f 0.58 (chloroform–hexane, 9:1). IR spectrum, ν, cm^{-1}: 3258 (N–H), 1110 (C=S). ^1H NMR spectrum, δ, ppm (s, 1H, NH): 11.08 ($CDCl_3$), 12.10 (DMSO-d_6), 10.95 (C_6D_6), 11.50 (acetone-d_6), 11.62 (CD_3OD). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 21.18, 119.91, 123.68, 129.55, 135.48, 137.05, 154.30, 158.72, 183.61. Found, %: C 53.12; H 4.40; N 16.57; S 25.95. $C_{11}H_{11}N_3S_2$. Calculated, %: C 52.98; H 4.45; N 16.85; S 25.72.

1-[5-(4-Methylphenylamino)-1,2,3-thiadiazol-4-yl]ethanethione (IIa). R_f 0.56 (chloroform–hexane, 9:1). ^1H NMR spectrum, δ, ppm (s, 1H, NH): 9.39 (DMSO-d_6), 9.22 (C_6D_6), 9.92 (acetone-d_6), 9.69 (CD_3OD) (for other signals, see Table 1).

5-Methyl-*N*-phenyl-1,2,3-thiadiazole-4-carbothioamide (IIIb). Yield 0.6 g (53%), mp 62°C, R_f 0.58 (chloroform–hexane, 9:1). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.94 s (3H, CH_3), 7.06 t (1H, H_{arom}, J = 8.4 Hz), 7.20 t (2H, H_{arom}, J = 8.4 Hz), 7.77 d (2H, H_{arom}, J = 8.4 Hz), 12.10 s (1H, NH). Found, %: C 50.95; H 3.67; N 17.98; S 27.49. $C_{10}H_9N_3S_2$. Calculated, %: C 51.04; H 3.85; N 17.86; S 27.25.

1-(5-Phenylamino-1,2,3-thiadiazol-4-yl)ethanethione (IIb). R_f 0.57 (chloroform–hexane, 9:1). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.87 s (3H, CH_3), 7.04 t (1H, H_{arom}, J = 8.4 Hz), 7.11 t (2H, H_{arom}, J = 8.4 Hz), 7.71 d (2H, H_{arom}, J = 8.4 Hz), 10.50 s (1H, NH).

(5-Methyl-1,2,3-thiadiazol-4-yl)(piperidin-1-yl)-methanethione (IIIc). Yield 0.46 g (56%), mp 73°C, R_f 0.47 (ethyl acetate–hexane, 1:1). ^1H NMR spectrum (DMSO-d_6–CCl_4), δ, ppm: 1.52–1.63 m (2H, CH_2), 1.76–1.84 m (4H, CH_2), 2.53 s (3H, CH_3), 3.35–3.43 m (2H, NCH_2), 4.30–4.40 m (2H, NCH_2). Found, %: C 47.67; H 5.93; N 18.29; S 28.11. $C_9H_{13}N_3S_2$. Calculated, %: C 47.55; H 5.76; N 18.48; S 28.21.

1-[5-(Piperidin-1-yl)-1,2,3-thiadiazol-4-yl]-ethanethione (IIc). R_f 0.46 (ethyl acetate–hexane, 1:1). ^1H NMR spectrum (DMSO-d_6–CCl_4), δ, ppm: 1.52–1.63 m (2H, CH_2), 1.76–1.84 m (4H, CH_2), 2.83 s (3H, CH_3), 3.54–3.60 m (2H, NCH_2), 4.20–4.10 m (2H, NCH_2).

Table 2. Calculated enthalpies of formation of compounds **II** and **III**

Compound no.	ΔH_f, kcal/mol		
	AM1	PM3	B3LYP/6-31G(*d*)
IIb	1.88	0.38	4.00
IIIb	0.00	0.00	0.00
IIc	16.79	3.73	13.83
IIIc	0.00	0.00	0.00
IIe[a]	1.50	0.15	20.16
IIIe[a]	0.00	0.00	0.00
IIf[a]	0.91	–0.21	–4.49
IIIf[a]	0.00	0.00	0.00
IIg[a]	8.55	0.01	0.64
IIIg[a]	0.00	0.00	0.00

[a] R^1 = H, R^2 = 4-$MeOC_6H_4$ (**e**), 4-$MeOC(O)C_6H_4$ (**f**), Me (**g**).

(5-Methyl-1,2,3-thiadiazol-4-yl)(morpholin-4-yl)-methanethione (IIId). Yield 0.45 g (56%), mp 85°C, R_f 0.44 (ethyl acetate–hexane, 1:2). IR spectrum: ν 1107 cm^{-1} (C=S). ^1H NMR spectrum (DMSO-d_6–CCl_4), δ, ppm: 2.63 s (3H, CH_3), 3.46–3.49 m (2H, OCH_2), 3.62–3.65 m (2H, OCH_2), 3.83–3.86 m (2H, NCH_2), 4.38–4.41 m (2H, NCH_2). ^{13}C NMR spectrum (DMSO-d_6–CCl_4), δ_C, ppm: 9.81, 48.72, 52.18, 65.65, 66.26, 150.08, 158.62, 186.31. Found, %: C 41.97; H 4.83; N 18.25; S 27.91. $C_8H_{11}N_3OS_2$. Calculated, %: C 41.90; H 4.83; N 18.32; S 27.96.

1-[5-(Morpholin-4-yl)-1,2,3-thiadiazol-4-yl]-ethanethione (IId). R_f 0.43 (ethyl acetate–hexane, 1:2). ^1H NMR spectrum (DMSO-d_6–CCl_4), δ, ppm: 2.88 s (3H, CH_3), 3.60–3.65 m (4H, OCH_2), 4.10–4.20 m (4H, NCH_2).

5-Methyl-1,2,3-thiadiazole-4-carboxamides IVa–IVd (*general procedure*). 5-Methyl-1,2,3-thiadiazole-4-carboxylic acid, 2.0 g (10 mmol), was dissolved in 15 ml of toluene, 1 mol of phosphorus(V) chloride was added, and the mixture was heated for 3 h under reflux. The corresponding amine, 10 mmol, was then added, the mixture was heated for 2 h under reflux and washed with three portions of water, the organic phase was separated, dried over Na_2SO_4, and evaporated under reduced pressure, and the residue was recrystallized from ethanol.

5-Methyl-*N*-(4-methylphenyl)-1,2,3-thiadiazole-4-carboxamide (IVa). Yield 1.51 g (65%), mp 143°C, R_f 0.65 (chloroform). IR spectrum, ν, cm^{-1}: 3344 (N–H), 1677 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.35 s (3H, 5-CH_3), 3.01 s (3H, 4′-CH_3), 7.19 d (2H, H_{arom}, J = 8.4 Hz), 7.59 d (2H, H_{arom}, J = 8.4 Hz), 9.39 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 10.60, 20.43, 120.58, 129.06, 129.83, 158.6. Found, %: N 18.09; S 13.81. $C_{11}H_{11}N_3OS$. Calculated, %: N 18.01; S 13.74.

5-Methyl-*N*-phenyl-1,2,3-thiadiazole-4-carboxamide (IVb). Yield 1.38 g (63%), mp 147°C, R_f 0.65 (chloroform). IR spectrum, ν, cm^{-1}: 3390 (N–H), 1655 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.02 s (3H, CH_3), 7.18 t (1H, H_{arom}, J = 7.4 Hz), 7.42–7.36 m (2H, H_{arom}), 7.71 d (2H, H_{arom}, J = 7.6 Hz), 9.64 s (1H, NH). Found, %: C 53.55; H 4.20; N 20.47; S 13.98. $C_{10}H_9N_3OS$. Calculated, %: C 54.78; H 4.14; N 19.16; S 14.62.

(5-Methyl-1,2,3-thiadiazol-4-yl)(piperidin-1-yl)-methanone (IVc). Yield 0.85 (43%), mp 107°C, R_f 0.68 (chloroform–ethanol, 9:1). IR spectrum (KBr): ν 1675 cm^{-1} (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.45–1.68 m (6H, CH_2), 2.66 s (3H, CH_3), 3.34–3.39 m (2H, NCH_2), 3.68–3.73 m (2H, NCH_2). Found, %: C 50.92; H 6.16; N 19.99; S 15.32. $C_9H_{13}N_3OS$. Calculated, %: C 51.16; H 6.20; N 19.89; S 15.18.

(5-Methyl-1,2,3-thiadiazol-4-yl)(morpholin-4-yl)-methanone (IVd). Yield 0.64 (35%), mp 75°C, R_f 0.69 (chloroform–ethanol, 30:1). IR spectrum: ν 1625 cm^{-1} (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.66 s (3H, CH_3), 3.39–3.43 m (2H, NCH_2), 3.56–3.60 m (2H, OCH_2), 3.67–3.74 m (4H, NCH_2, OCH_2). Found, %: C 44.87; H 5.13; N 19.96; S 15.21. $C_8H_{11}N_3O_2S$. Calculated, %: C 45.06; H 5.20; N 19.70; S 15.04.

REFERENCES

1. Bakulev, V.A. and Dehaen, W., *The Chemistry of 1,2,3-Thiadiazoles*, Hoboken, NJ: Wiley, 2004.
2. Regitz, M. and Liedhegener, A., *Justus Liebigs Ann. Chem*., 1967, vol. 710, p. 118.
3. Morzherin, Yu.Yu., Bakulev, V.A., Dankova, E.F., and Mokrushin, V.S., *Khim. Geterotsikl. Soedin*., 1994, p. 548.
4. Reichardt, C., *Solvents and Solvent Effects in Organic Chemistry*, Weinheim: VCH, 1988, 2nd ed.
5. Frisch, M.J., Trucks, G.W., Schlegel, H.B., Scuseria, G.E., Robb, M.A., Cheeseman, J.R., Montgomery, J.A., Jr.,, Vreven, T., Kudin, K.N., Burant, J.C., Millam, J.M., Iyengar, S.S., Tomasi, J., Barone, V., Mennucci, B., Cossi, M., Scalmani, G., Rega, N., Petersson, G.A., Nakatsuji, H., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Klene, M., Li, X., Knox, J.E., Hratchian, H.P., Cross, J.B., Bakken, V., Adamo, C., Jaramillo, J., Gomperts, R., Stratmann, R.E., Yazyev, O., Austin, A.J., Cammi, R., Pomelli, C., Ochterski, J.W., Ayala, P.Y., Morokuma, K., Voth, G.A., Salvador, P., Dannenberg, J.J., Zakrzewski, V.G., Dapprich, S., Daniels, A.D., Strain, M.C., Farkas, O., Malick, D.K., Rabuck, A.D., Raghavachari, K., Foresman, J.B., Ortiz, J.V., Cui, Q., Baboul, A.G., Clifford, S., Cioslowski, J., Stefanov, B.B., Liu, G., Liashenko, A., Piskorz, P., Komaromi, I., Martin, R.L., Fox, D.J., Keith, T., Al-Laham, M.A., Peng, C.Y., Nanayakkara, A., Challacombe, M., Gill, P.M.W., Johnson, B., Chen, W., Wong, M.W., Gonzalez, C., and Pople, J.A., *Gaussian 03, Revision A.1*, Wallingford CT: Gaussian, 2004.