Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2009, **19**, 84–86
Mendeleev Communications

Synthesis of 1,2,5-thiadiazole-3(2*H*)-thiones and 1,2,5-thiadiazol-3(2*H*)-ones from 1,2,3-dithiazoles

Lidia S. Konstantinova,[a] Oleg A. Bol'shakov,[a] Natalia V. Obruchnikova,[a] Svetlana P. Golova,[a] Yulia V. Nelyubina,[b] Konstantin A. Lyssenko[b] and Oleg A. Rakitin*[a]

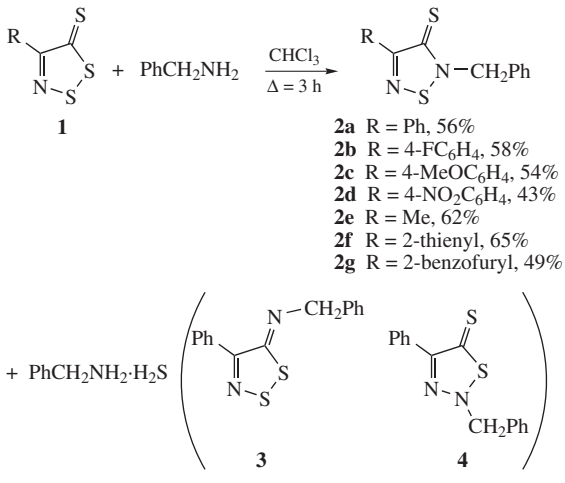
[a] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 5328; e-mail: orakitin@ioc.ac.ru*
[b] *A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119991 Moscow, Russian Federation*

DOI: 10.1016/j.mencom.2009.03.010

5*H*-1,2,3-Dithiazole-5-thiones and 5*H*-1,2,3-dithiazol-5-ones undergo a new transformation into 1,2,5-thiadiazole-3(2*H*)-thiones and 1,2,5-thiadiazol-3(2*H*)-ones, respectively, upon treatment with primary amines; the structure of thiadiazolethione was confirmed by X-ray diffraction.

During the last two decades, much attention in the chemistry of 1,2,3-dithiazol-5-ones and their derivatives has been focused on exploring reactions with nucleophiles (most frequently, alkylamines). Nucleophilic attack can proceed at the ring carbon atom C-2 with extrusion of diatomic sulfur, S_2, and a chloride anion, destruction of the heterocyclic ring and formation of various functionalized derivatives such as *N*′-aryl-*N*-alkylcyanoformamidines,[1] *N*-alkyl- and *N*,*N*-dialkylcyanothioformamides,[2] N,N′-disubstituted ureas[3] and (alkylamino)cyanomethylidenes.[4] But surprisingly other than 4-chloro-1,2,3-dithiazoles are hardly available.[5] Recently, we have found that 4-substituted 1,2,3-dithiazol-5-ones and 1,2,3-dithiazole-5-thiones can be selectively obtained in a one-pot reaction of various ethanoneoximes with S_2Cl_2 and pyridine in MeCN with subsequent addition of the corresponding reagent (formic acid or thioacetamide) in the last stage of the reaction.[6] In search of new materials, we studied the reaction of these 1,2,3-dithiazoles with primary alkylamines.

4-Phenyl-5*H*-1,2,3-dithiazole-5-thione **1a** was found inert towards primary arylamines (aniline). Treatment of thione **1a** with 4 equiv. of more basic benzylamine in chloroform by reflux for 2 h afforded new product **2a**.[†] Compound **2a** (56% yield), a yellow solid with $C_{15}H_{12}N_2S_2$ according to its mass spectra, elemental analysis and ^{1}H and ^{13}C NMR spectra is formally a product of addition of benzylamine and extrusion of H_2S the formation of which was confirmed by isolation of benzylammonium hydrogen sulfide from the reaction mixture in practically quantitative yield (Scheme 1).



1

2a R = Ph, 56%
2b R = 4-FC_6H_4, 58%
2c R = 4-$MeOC_6H_4$, 54%
2d R = 4-$NO_2C_6H_4$, 43%
2e R = Me, 62%
2f R = 2-thienyl, 65%
2g R = 2-benzofuryl, 49%

3 **4**

Scheme 1

Three isomeric structures can be proposed for this product: 1,2,5-thiadiazolone **2a**, imino-1,2,3-dithiazole **3**, and 1,2,3-thiadiazole **4**. Analysis of the spectral data obtained and calculated NMR spectra of these structures did not give a strong preference

[†] *General procedure for the preparation of 1,2,5-thiadiazole-3(2*H*)-thiones* **2** *and 1,2,5-thiadiazol-3(2*H*)-ones* **8**. A mixture of primary amine (1.8 mmol) and **1** or **7** (1 mmol) in acetonitrile (10 ml) or THF (10 ml) was stirred at room temperature up to disappearance of **1** or **7**. Solvents were evaporated, and the residue was dissolved in DCM, washed with H_2O, dried with $MgSO_4$ and evaporated. The residue was separated by column chromatography (Silica gel Merck 60, light petroleum–CH_2Cl_2 mixtures) or crystallized from hot hexane.

New compounds were characterised by elemental analysis, ^{1}H and ^{13}C NMR, and mass spectra. The spectral data of selected thiadiazolethiones and thiadiazolones are given below.

2a: yield 56%, yellow crystals, mp 95–97 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.31 (s, 2H, CH_2), 7.49 (m, 8H, Ar), 8.42 (m, 2H, Ar). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 53.8 (CH_2), 128.1, 129.1, 129.5, 129.86, 129.92, 130.5 (10CH, Ar), 133.0, 133.2 , 160.5, 177.45 (4sp^2 tertiary C). Found (%): C, 63.45; H, 4.39; N, 10.05. Calc. for $C_{15}H_{12}N_2S_2$ (%): C, 63.35; H, 4.25; N, 9.85. MS (EI, 70 eV) *m*/*z* (%): 284 (M^+, 25), 251 (13).

2b: yield 58%, yellow crystals, mp 140–143 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.30 (s, 2H, CH_2), 7.17 (d, 2H, Ar, *J* 8.80 Hz), 7.48 (m, 5H, Ar), 8.49 (d, 2H, Ar, *J* 8.80 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 53.8 (CH_2), 115.2, 129.6, 130.0, 131.2, 131.3 (9CH, Ar), 129.2, 133.0, 160.9, 165.7, 177.2 (5sp^2 tertiary C). Found (%): C, 59.70; H, 3.92; N, 9.32. Calc. for $C_{15}H_{11}FN_2S_2$ (%): C, 59.58; H, 3.67; N, 9.26. MS (EI, 70 eV) *m*/*z* (%): 302 (M^+, 17), 269 (7), 121 (22).

2c: yield 54%, yellow crystals, mp 86–88 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.87 (s, 3H, Me), 5.29 (s, 2H, CH_2), 6.97 (d, 2H, Ar, *J* 8.80 Hz), 7.46 (s, 5H, Ar), 8.48 (d, 2H, Ar, *J* 8.80 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 53.6 (CH_2), 55.4 (OMe), 113.4, 129.4, 129.8, 129.9, 130.7 (9CH, Ar), 125.8, 133.2, 159.9, 161.3, 177.2 (5sp^2 tertiary C). Found (%): C, 61.20; H, 4.63; N, 8.97. Calc. for $C_{16}H_{14}N_2OS_2$ (%): C, 61.12; H, 4.49; N, 8.91. MS (EI, 70 eV) *m*/*z* (%): 314 (M^+, 8), 133 (15).

8a: yield 94%, colourless crystals, mp 87–90 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.05 (s, 2H, CH_2), 7.40 (m, 5H, Ph), 7.48 (m, 3H, Ph), 8.48 (m, 2H, Ph). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 47.9 (CH_2), 126.9, 128.0, 128.6, 128.7, 129.22, 130.5 (10CH, Ar), 128.8, 137.2, 149.6, 161.3 (4sp^2 tertiary C). MS (EI, 70 eV) *m*/*z* (%): 268 (M^+, 12), 135 (10). Found (%): C, 67.28; H, 4.39; N, 10.50. Calc. for $C_{15}H_{12}N_2OS$ (%): C, 67.14; H, 4.51; N, 10.44.

for one of them. The structure of **2a** was finally proved by X-ray analysis of closely related analogue **2f** (see below).

We extended the reaction with benzylamine to other 1,2,3-dithiazole-5-thiones **1**. 1,2,5-Thiadiazolothiones **2** were obtained in all reactions in moderate yields† (Scheme 1).

The structure of thieno derivative **2f** was confirmed by X-ray diffraction analysis‡ (Figure 1). The bond lengths and angles of the thiadiazole ring, except for S(1)–N(1) and N(1)–C(2) bonds, fall into the range typical of such a type of heterocyclic compounds. Close investigation of the molecular geometry of **2f** revealed the significant contribution of a betaine-like resonance form with formal single N(1)–C(2) and double N(1)–S(1) bonds. Moreover, when the standard dataset with 2θ below 60° was used, in the crystal of **2f** the unexpected elongation [up to 1.543(4) Å] of presumably double C(3)–C(13) bond was observed. The addition of high-angle data ($2\theta < 90°$) resulted in the molecule of **2f** being the superposition (80:20) of two isomers with cisoid and transoid dispositions of S(2) and S(3) atoms (Figure 1). The *cis* form (*cis*-**2f**) appears to be stabilized by the extremely short intermolecular contact between sulfur of the C=S group and one of the thiophene ring [S···S 3.1812(7) Å, C(4)–S(3)–S(2) 171.33(6)°], accompanied by charge transfer from the lone pair (Lp) of the S(2) atom to the σ* orbital of the C–S bond. In turn, S(3′) of the minor component (*trans*-**2f**) presumably binds to the N(1) thiadiazole atom [S···N 2.9342(8) Å, S(1)–N(1)–S(4) 175.95(6) Å] through charge transfer from one of the sulfur Lps to the σ* orbital of S(1)–N(1) bond. Quantum chemical calculations (B3LYP/6-311+G*)§ and subsequent topological analysis of theoretical electron density functions[7] for two isomers have shown that the cisoid-form is stabilized by the S···S interaction, which contributes 2.9 kcal mol^{-1}, as estimated by Espinosa's correlation scheme.[8,9] In the second isomer instead of S···N–C interaction the weaker (1.8 kcal mol^{-1}) C(13′)–H···S(2) binding is observed. On the other hand, *trans*-**2f** was found to be a little more stable (0.63 kcal mol^{-1}) than *cis*-**2f**, apparently, owing to conjugation between thiadiazole and thiophene cycles that is more pronounced in the case of the transoid-form.

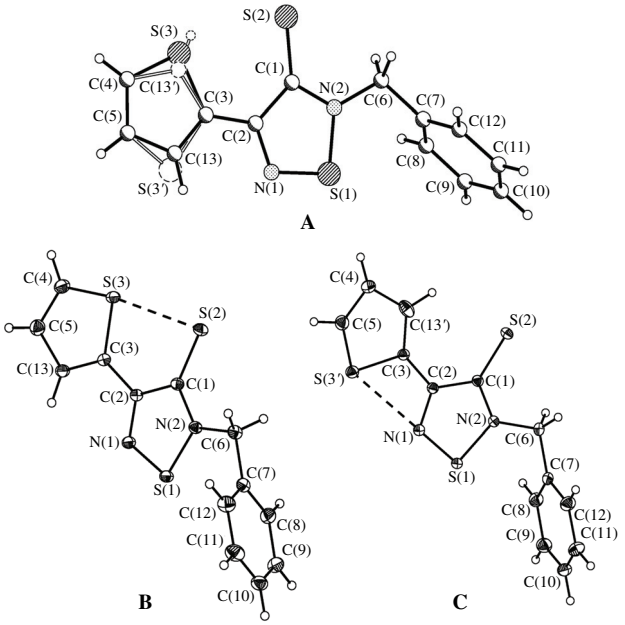


Figure 1 General view of compound **2f** (**A**), which is a superposition of two isomers: *cis*-**2f** (**B**) and *trans*-**2f** (**C**) in a ratio of 4:1, with representation of atoms *via* thermal ellipsoids at 50% probability level. Selected bond lengths (Å): C(1)–S(2) 1.6799(7), S(1)–N(1) 1.6222(6), S(1)–N(2) 1.6887(6), N(1)–C(2) 1.3228(9), C(1)–C(2) 1.4614(10), C(1)–N(2) 1.3526(9), C(2)–C(3) 1.4521(10), N(2)–C(6) 1.4675(9); selected bond angles (°): C(2)–C(1)–N(2) 106.73(6), C(1)–C(2)–N(1) 114.65(6), C(2)–N(1)–S(1) 112.07(5), N(1)–S(1)–N(2) 93.14(3), C(1)–N(2)–S(1) 113.36(5), C(1)–C(2)–C(3) 126.23(6).

The N(1) atom of both isomers participates in the formation of the N···S–N interaction [S···N 2.9045(8) Å, N(1′)–S(1)–N(2) 168.56(7) Å] with the charge being transferred from the nitrogen Lp to the σ* orbital of the latter bond that leads to the dimerization of the neighbouring molecules. These supramolecular associates are assembled into a 3D framework by a number of weak S···H, π···π and S···S contacts.

It was envisaged that 1,2,3-dithiazole-5-thiones **7** on reaction with primary amines should give ketones **8**. We checked this possibility by treatment of dithiazolone **7a** with benzylamine, but it turned out that the formation of 1,2,5-dithiazolone **8a** is complicated by formation of a by-product, N-substituted 2-oxoacetamide **9a** (Scheme 2).

To obtain thiadiazolone **8a** selectively, the reaction between **7a** (R = Ph) and benzylamine was investigated in detail; the nature of the solvent appeared crucial for successful reaction. If the reaction was carried out in an inert solvent such as chloroform, starting dithiazolone **7a** was isolated in a practically quantitative yield. Attempts to employ strong aprotic dipolar solvents such as DMF or acetonitrile at room temperature led to formation of the mixtures of **8** and **9** in a ratio of 1:1 or 1:2, respectively. Treatment of benzylamine with **7a** in absolute THF gave selectively 1,2,5-thiadiazolone **8a** in quantitative yield. We then extended these conditions to other ketones **7**. 1,2,5-Thiadiazolones **8** were obtained in high yields in practically all

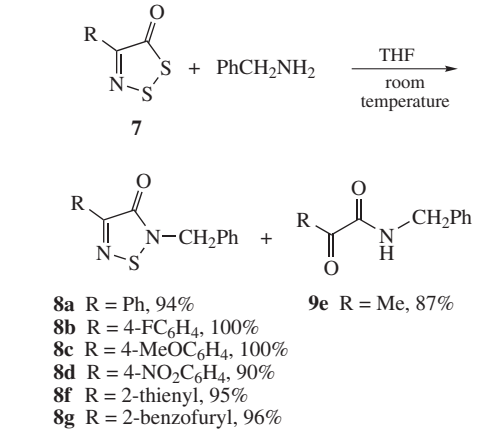
8b: yield 100%, colourless crystals, mp 72–74 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.03 (s, 2H, CH_2), 6.99 (d, 2H, Ar, J 8.80 Hz), 7.39 (m, 5H, Ar), 8.46 (d, 2H, Ar, J 8.80 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 47.8 (CH_2), 115.4, 115.7, 126.7, 128.7, 129.1 (9CH, Ar), 125.8, 134.7, 148.4, 161.1, 165.7 (5sp^2 tertiary C). MS (EI, 70 eV) *m/z* (%): 286 (M^+, 100), 256 (20), 173 (5), 121 (87). Found (%): C, 63.08; H, 3.92; N, 9.55. Calc. for $C_{15}H_{11}FN_2OS$ (%): C, 62.92; H, 3.87; N, 9.78.

8c: yield 100%, colourless crystals, mp 68–72 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.87 (s, 3H, Me), 5.03 (s, 2H, CH_2), 7.14 (m, 2H, Ar), 7.39 (m, 5H, Ar), 8.49 (m, 2H, Ar). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 47.9 (CH_2), 113.9, 128.6, 128.7, 128.9, 129.2 (9CH, Ar), 125.2, 134.9, 149.2, 161.3, 161.4 (5sp^2 tertiary C). MS (EI, 70 eV) *m/z* (%): 298 (M^+, 43), 256 (– S, 12), 160 (5), 133 (45). Found (%): C, 64.65; H, 4.92; N, 9.55. Calc. for $C_{16}H_{14}N_2O_2S$ (%): C, 64.41; H, 4.73; N, 9.39.

‡ *Crystallographic data*. Crystals of **2f** ($C_{13}H_{10}N_2S_3$, M = 290.41) are monoclinic, space group $P2_1/c$, at 100 K: a = 12.6684(3), b = 13.9186(7) and c = 7.4243(5) Å, β = 104.972(5)°, V = 1264.66(11) Å^3, Z = 4 (Z' = 1), d_{calc} = 1.525 g cm^{-3}, μ(MoKα) = 5.66 cm^{-1}, F(000) = 600. Intensities of 50901 reflections were measured with a Bruker SMART APEX2 CCD diffractometer [λ(MoKα) = 0.71072 Å, ω-scans, $2\theta < 90°$] and 10363 independent reflections [R_{int} = 0.0458] were used in further refinement. The structure was solved by direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic-isotropic approximation. The positions of hydrogen atoms were calculated, and they were refined in an isotropic approximation in riding model. The molecule is disordered by two positions with the 80:20 ratio. For **2f**, the refinement converged to wR_2 = 0.0927 and GOF = 1.003 for all independent reflections [R_1 = 0.0355 was calculated against F for 7426 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0.

CCDC 723464 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2009.

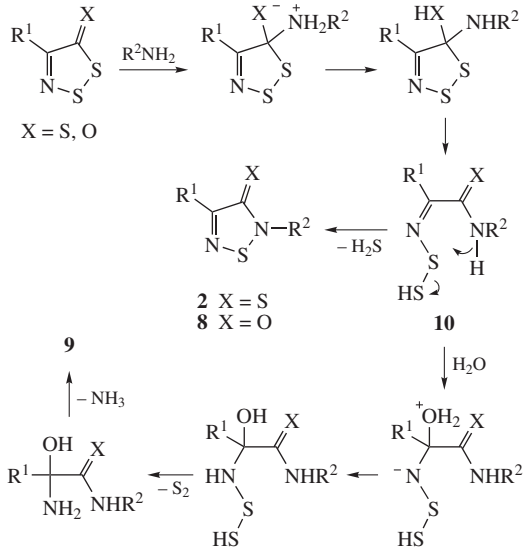
§ DFT calculations of the isolated *cis*-**2f** and *trans*-**2f** were performed with the Gaussian03[10] program package using the B3LYP functional. Full optimization of the molecules was carried out with the 6-311+G* basis set starting from the X-ray structural data. As convergence criteria, the standard threshold limits of 4.5×10^{-4} and 1.8×10^{-3} a.u. were applied for the maximum force and displacement, respectively. The topological analysis of computed electron densities was performed using the AIM2000 program packages.[11]



Scheme 2

cases except for the methyl derivative where oxoacetamide **9e** was formed selectively in a yield of 87% (Scheme 2).

The reactions described are the conversions of 1,2,3-dithiazole to 1,2,5-thiadiazole ring systems through insertion of nucleophilic amine and elimination of H_2S. The most plausible pathway (Scheme 3) includes a nucleophilic attack of amine onto the C-5 position of the dithiazole ring followed by opening of



Scheme 3

the heterocyclic ring and the formation of key intermediate **10**. The formation of the 1,2,5-dithiazole ring occurs probably through an intramolecular attack of amide (thioamide) nitrogen onto the S-2 sulfur atom with extrusion of hydrogen sulfide. The formation of oxamide **9** could be suggested *via* the hydrolysis of intermediate **10** with extrusion of S_2 and NH_3.

This work was supported by the Russian Foundation for Basic Research (grant no. 08-03-00003a).

References

1 H. Lee and K. Kim, *J. Org. Chem*., 1993, **58**, 7001.
2 H.-S. Lee and K. Kim, *Tetrahedron Lett*., 1996, **37**, 3709.
3 Y.-G. Chang, H.-S. Lee and K. Kim, *Tetrahedron Lett*., 2001, **42**, 8197.
4 M.-K. Jeon and K. Kim, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3107.
5 (*a*) M. A. Gray, C. W. Rees and D. J. Williams, *Heterocycles*, 1994, **37**, 1827; (*b*) K. Emayan and C. W. Rees, *Bull. Soc. Chim. Belg*., 1997, **106**, 605.
6 L. S. Konstantinova, O. I. Bol'shakov, N. V. Obruchnikova, H. Laborie, A. Tanga, V. Sopéna, I. Lanneluc, L. Picot, S. Sablé, V. Thiéry and O. A. Rakitin, *Bioorg. Med. Chem. Lett*., 2009, **19**, 136.
7 R. F. W. Bader, *Atoms in Molecules. A Quantum Theory*, Clarendon Press, Oxford, 1990.
8 E. Espinosa, E. Molins and C. Lecomte, *Chem. Phys. Lett.*, 1998, **285**, 170.
9 E. Espinosa, I. Alkorta, I. Rozas, J. Elguero and E. Molins, *Chem. Phys. Lett.*, 2001, **336**, 457.
10 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. A. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle and J. A. Pople, *Gaussian 98, Revision A.9*, 1998, Gaussian, Inc., Pittsburgh PA.
11 AIM2000 designed by Friedrich Biegler-König, University of Applied Sciences, Bielefeld, Germany.

Received: 15th September 2008; Com. 08/3216