DMSO-HCl system as an efficient oxidant of thioamides and selenoamides

Victor V. Dotsenko*, Konstantin A. Frolov and Sergey G. Krivokolysko

ChemEx Laboratory, Vladimir Dal' East Ukrainian National University, kv Molodezhny 20-A 7/309, 91034 Lugansk

(2*E*,2'*E*)-2,2'-(1,2,4-Thiadiazole-3,5-diyl)*bis*(3-arylacrylonitriles) were obtained by short-time heating of 3-aryl-2-cyanoprop-2-enethioamides with DMSO–HCl system. Under the same conditions, cyclic thioamides (2-thioxo-1,2-dihydropyridine-3-carbonitriles and quinoxaline-2(1*H*)-thione) reacted to form *bis*(hetaryl)disulfides in good yields (65-91%). When treated with DMSO–HCl, ethyl 4-(4-chlorophenyl)-5-cyano-2-phenyl-6-thioxo-1,4,5,6-tetrahydropyridine-3-carboxylate afforded a mixture of products of oxidation at sulfur atom and hetero ring. The oxidation of *N*-aryl-4,6-dimethyl-2-thioxo-1,2-dihydropyridine-3-carboxamides leads to isothiazolo[5,4-b]pyridines. 3-Aryl-2-cyanoprop-2-eneselenoamides reacted with DMSO–HCl to give (2*E*,2'*E*)-2,2'-(1,2,4-selenadiazole-3,5-diyl)*bis*(3-arylacrylonitriles).

Keywords: cyanothioacetamide, dimethyl sulfoxide, disulfides, isothiazolo[5,4-b]pyridines, pyridine-2(1*H*)-thiones, 1,2,4-selenadiazoles, selenoamides, 1,2,4-thiadiazoles, thioamides, oxidation, oxidative dimerization.

Introduction

Dimethylsulfoxide activated by various electrophilic agents have been recognized as an effective and versatile oxidant widely used in modern practice of organic synthesis [1-5]. One of the most common and available reagents of this type is DMSO dopped with HCl. DMSO-HX (X = Cl, Br) system have been successfully used for oxidation of acetophenones to arylglyoxals [6], halogenation of aromatic compounds [7], as well as for the oxidative dimerization of primary thioamides and thioureas to 3,5-disubstituted 1,2,4-thiadiazoles [8, 9]. The mechanism of the latter reaction is discussed [9-11]. Noteworthy that in the presence of acetone or its homologs, thiourea derivatives react with DMSO-HCl system to afford 2-aminothiazoles and 2-iminothiazolines [11]. This method represents an alternative to the classical Hantzsch thiazole synthesis and allows thiazole derivatives without using α-halocarbonyl compounds.

In continuation of our studies in the field of chemistry of cyanothioacetamide, cyanoselenoacetamide and their cyclic derivatives, we decided to study the behavior of a number of linear and cyclic thioamides **1**–**5** and selenoamides **6** in the reactions with DMSO-HCl and DMSO-HCl-acetone systems.

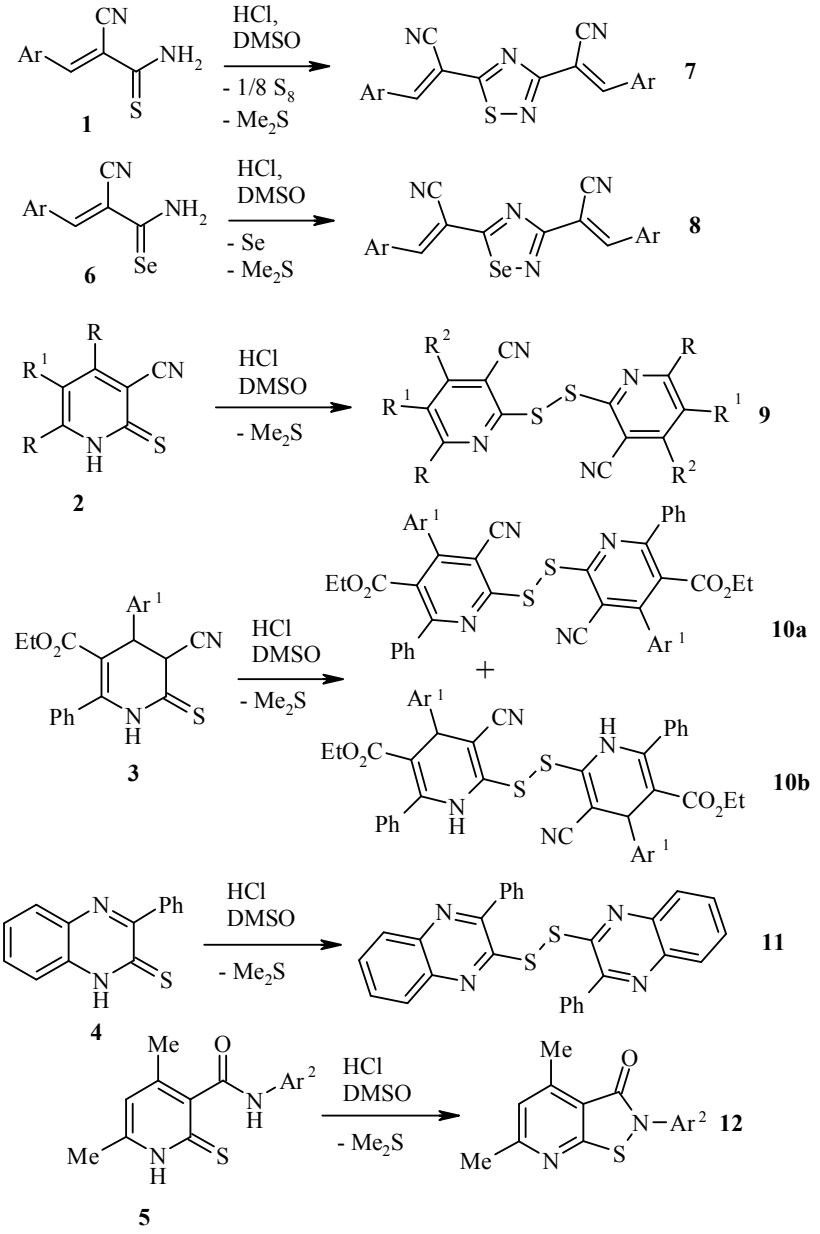
When a solution of 3-aryl-2-cyanoprop-2-enethioamides **1** in DMSO was treated with 30% HCl at 25 °C, a rapid reaction accompanied by formation of dimethyl sulfide and elemental sulfur was observed. The main products were identified as 1,2,4-thiadiazoles **7** (Scheme 1). Structure of thiadiazoles **7** was confirmed by the spectral data (LC/MS, ^{1}H NMR, ^{13}C NMR, IR) and results of microanalysis.

By analogy with thioamides, 3-aryl-2-cyanoprop-2-eneselenoamides **6** reacted with DMSO-HCl to give 1,2,4-selenadiazoles **8**, which are derivatives of a relatively rare heterocyclic system. The reaction is accompanied by elimination of elemental Se and Me_2S, and proceeds smoothly in acetone solution.

The reaction of thioamides **1** with DMSO-HCl-acetone system under similar conditions gave the same products of the oxidative dimerization, namely, thiadiazoles **7**. No products of reactions involving acetone were observed or isolated, even when a large excess of acetone used. Moreover, acetone was found to be a suitable solvent for oxidation of thioamides **1** and selenoamides **6**. The use of excessive amounts of DMSO or HCl provides more rapid and

* Author to whom correspondence should be addressed

complete conversion of a substrate and does not affect the yields of the target products. (*E*)-3-(4-Hydroxy-3-methoxyphenyl)-2-cyanoprop-2-enethioamide (**1a**) was also subjected to oxidation in the presence of hexanone-2, cyclohexanone, ethyl acetoacetate and acetylacetone. In all cases only thiadiazole **7a** (Ar = 4-HO-3-MeOC_6H_3) has been isolated.



The only products obtained from the oxidation of 2-thioxo-1,2-dihydropyridine-3-carbonitriles **2** with DMSO-HCl and DMSO-HCl-acetone systems were bis(pyrid-2-yl)disulfides **9**. The yields of disulfides **9** are good to excellent. It should be noted that oxidation of tetrahydropyridines **3** (Ar^1 = 4-ClC_6H_4) leads to a mixture of disulfide **10a** and 1,4-dihydro analog **10b** in ~3:1 ratio. The addition of DMSO and HCl to a boiling suspension of 3-phenylquinoxaline-2(1*H*)-thione **4** in acetone leads to the formation of the corresponding disulfide **11** in 88% yield. In contrast, the oxidation of 2-thioxonicotinamides **5** gives only isothiazolopyridines **12**. In this case, the neighborhood of C=S and carbamoyl fragments favors the oxidative cyclization to form isothiazole ring.

In summary, the DMSO-HCl system can be successfully used for the oxidation of various thioamides and selenoamides. The structures of end products are strongly dependent on the structures of substrates. The proposed methods for synthesis of 1,2,4-thiadiazoles, isothiazolopyridines and bis(hetaryl)disulfides are highly effective and allow high yields,

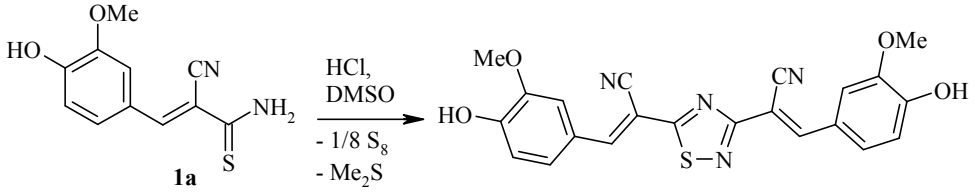
simplicity and clean-processing. It should be noted that DMSO and HCl are exceptionally available and low cost reagents.

Experimental

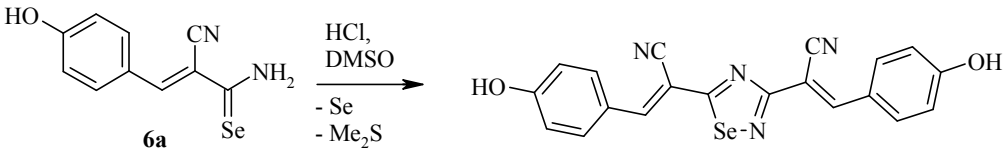
^{1}H NMR spectra were recorded on Brucker Avance DPX 300 (300.16 MHz), Varian Unian Plus (400.40 MHz) and Bruker DRX-500 (500.07 MHz) instruments in DMSO-d_6, with TMS as an internal standard. ^{13}C NMR spectra were recorded on Bruker DRX-500 spectrometer in DMSO-d_6 (125.76 MHz). IR spectra were recorded on an IKS-29 Spectrometer (nujol mulls). HPLC-MS analysis was performed on liquid chromatograph Shimadzu LC-10AD with detectors Shimadzu SP D-10A UV-Vis (254 nm) and Sedex 75 ELSD, combined with a PE SCIEX API 150EX mass spectrometer, ionization method ES-API. Elemental analysis was performed on Carlo-Erba 1106 elemental analyser. The purity of all obtained compounds was checked by TLC on Silufol UV-254 plates with acetone–hexane (1:1) as eluent; spots were visualized with iodine vapors and UV light. Melting points were determined on a Koefler apparatus and are uncorrected.

(2*E*,2'*E*)-2,2'-(1,2,4-Thiadiazol-3,5-diyl)bis(3-arylacrilonitriles) 7 and (2*E*,2'*E*)-2,2'-(1,2,4-selenadiazol-3,5-diyl)bis(3-arylacrilonitriles) 8. **General procedure**. A 10 ml beaker was charged with 1.50 mmol of the appropriate thioacrylamide **1** or selenoamide **6**, then 5-8 ml of acetone and 0.6 ml (8.45 mmol) of DMSO were added in succession. The mixture was gently heated to dissolve thio(seleno)amide (if appropriate). To the solution formed, 0.5 mL (4.7 mmol) of 30% HCl (d = 1.15 g/cm^3) was added dropwise under vigorous stirring. For a moment the reaction mixture turned red, then discoloration and turbidity (formation of colloidal sulfur) or red/black precipitate formation (elemental Se) were observed. (*Caution! Dimethylsulfide evolved!*). The mixture was quickly filtered through a large pore paper filter to separate sulfur/selenium. The resulting solution was stirred at reflux temperature for 1-2 minutes with a partial evaporation of acetone, then allowed to cool, diluted with 5 mL of EtOH and kept for 24-48 h at 20 °C. The precipitate was filtered off, washed with EtOH. The reaction can also be carried out in the absence of acetone in pure DMSO, following by precipitation of the end products with EtOH and/or water and recrystallization from an appropriate solvent to remove S/Se impuruties. In this case, the yields of thiadiazoles/selenadiazoles are somewhat lower, probably because of their good solubility in DMSO.

Representative examples:



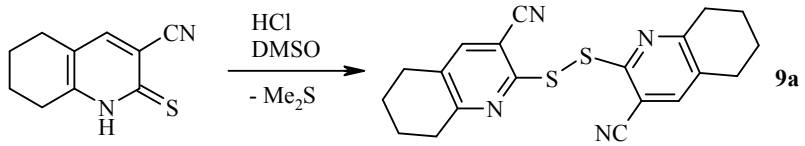
(2*E*,2'*E*)-2,2'-(1,2,4-Thiadiazol-3,5-diyl)*bis*[3-(4-hydroxy-3-methoxyphenyl)-acrylonitrile] (7a). Yield 69%, dark yellow crystalline powder, mp 255-257 °C (acetone: EtOH), R_f = 0.46 (acetone:hexane). IR (nujol), ν, cm^{-1}: 2216 (C≡N). ^{1}H NMR spectrum (500 MHz, DMSO-d$_6$), δ, ppm (J, Hz): 3.87 (6H, s, 2 MeO); 6.96 (1H, d, ^{3}J = 8.3, H Ar); 6.99 (1H, d, ^{3}J = 8.3, H Ar); 7.56 (1H, d.d, ^{3}J = 8.3, ^{4}J = 1.5, H Ar); 7.66 (1H, d.d, ^{3}J = 8.3, ^{4}J = 1.5, H Ar), 7.74 (1H, d, ^{4}J = 1.5, H Ar); 7.76 (1H, d, ^{4}J = 1.5, H Ar); 8.37 (1H, s, CH=), 8.41 (1H, s, CH =), 10.29 (1H, br.s, OH), 10.59 (1H, br.s, OH). Mass spectrum, *m/z* (ESI): 433.0 $[M+H]^+$. Found, %: C 60.86; H 6.48; N 13.09. $C_{22}H_{16}N_4O_4S$ (M 432.45). Calculated, %: C 61.10; H 3.73; N 12.96. In the reaction of (E)-3-(4-hydroxy-3-methoxyphenyl)-2-cyanoprop-2-enethioamide (**1a**) (300 mg, 1.28 mmol) with DMSO (0.3 mL, 4.22 mmol) and 30% HCl (0.35 ml, 3.31 mmol) in 2 ml of the appropriate carbonyl compound (2-hexanone, cyclohexanone, ethyl acetoacetate and acetylacetone) as solvent much in the same way as described above, thiadiazole **6a** was obtained in 69%, 43%, 57% and 64% yields, respectively.



(2*E*,2'*E*)-2,2'-(1,2,4-Selenadiazol-3,5-diyl)*bis*[3-(4-hydroxyphenyl)acrylonitrile] (8a). Yield 17%, green-yellow crystalline powder, mp > 200 °C (EtOH), R_f = 0.41 (acetone:hexane). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (J, Hz): 6.96 (2H, d, ^{3}J = 8.5, H Ar); 6.99 (2H, d, ^{3}J = 8.1, H Ar); 7.96 (2H, d, ^{3}J = 8.5, H Ar); 8.06 (2H, d, ^{3}J = 8.1, H Ar), 8.45 (1H, s, CH=), 8.48 (1H, s, CH =), 10.57 (1H, br.s, OH), 10.88 (1H, br.s, OH). Found, %: C 57.36; H 2.98; N 13.49. $C_{20}H_{12}N_4O_4Se$ (M 419.3). Calculated, %: C 57.29; H 2.88; N 13.36.

***Bis*(hetaryl)disulfides 9-11. General procedure**. A 10 ml beaker was charged with 2.0 mmol of the appropriate cyclic thioamide **2-4** and 4-5 ml of acetone, then the mixture was brought to a a boil. To the stirred hot suspension, 0.4 mL (5.6 mmol) of DMSO and 0.6 ml (5.7 mmol) of 30% HCl (d = 1.15 g/cm^3) were added dropwise in succession. The mixture was stirred at reflux temperature for 2-3 minutes (*Caution! Dimethylsulfide evolved!*). A beige or yellow crystalline solid precipitated during the heating. The reaction mixture was allowed to cool, diluted with 5 ml of EtOH, and left to stand for 24-48 h at 20 °C. The solid was filtered off, washed with EtOH, and recrystallized from a suitable solvent (if appropriate).

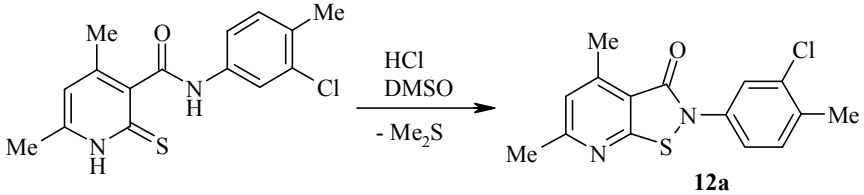
Representative example:



2,2'-Dithio-*bis*(5,6,7,8-tetrahydroquinoline-3-carbonitrile) (9a). Yield 91%, light yellow crystalline powder, mp 159-161 °C (AcOH), R_f = 0.85 (acetone:hexane). IR (nujol mulls), ν, cm^{-1}: 2217 (C≡N). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.73-1.79 (4H, m, 2 CH_2), 1.81-1.87 (4H, m, 2 CH_2), 2.75-2.78 (4H, m, 2 CH_2), 2.81-2.85 (4H, m, 2 CH_2), 7.92 (2H, s, H-4, H-4'). Mass spectrum, *m/z* (ESI): 379.1 $[M+H]^+$. Found, %: C 63.32; H 4.85; N 14.98. $C_{20}H_{18}N_4S_2$ (M 378.52). Calculated, %: C 63.46; H 4.79; N 14.80.

Isothiazolo[5,4-b]pyridines 12. General procedure. A 10 ml beaker was charged with 2.5 mmol of 2-thioxonicotinamide **5**, 2 mL of DMSO, the mixture was stirred and gently heated until complete dissolution. To the solution formed, 0.4 mL (3.8 mmol) of 30% HCl (d = 1.15 g/cm^3) was added dropwise (*Caution! Dimethylsulfide evolved!*). The mixture was stirred at reflux temperature for 1 min, then allowed to cool, left for 24 h at 20 ° C. The suspension was diluted with 5 mL of EtOH, the crystalline product was filtered off, washed with EtOH to give pure isothiazolopyridines **12**.

Representative example:



2-(3-Chloro-4-methylphenyl)-4,6-dimethylisothiazolo[5,4-b]pyridin-3(2*H*)-one (12a). Yield 81%, heavy sand-colored crystals, mp 168-170 °C. IR (nujol), ν, cm^{-1}: 1672 (C=O). ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 2.39 (3H, s, Me); 2.60 (3H, s, Me); 2.70 (3H, s, Me); 7.27 (1H, s, H-5), 7.51 (1H, d, ^{3}J = 8.3, H Ar); 7.53 (1H, d.d, ^{3}J = 8.3, ^{4}J = 1.0, H Ar); 7.86

(1H, br.s, H Ar). Mass spectrum, *m/z* (ESI): 305.0 $[M+H]^+$. Found,%: C 58.92; H 4.40; N 9.30. $C_{15}H_{13}ClN_2OS$ (M 304.80). Calculated, %: C 59.11; H 4.30; N 9.19.

References

1. W. W. Epstein, F. W. Sweat, *Chem. Rev*., 1967, **67**, 247 (1967).
2. R. Oda, Y. Hayashi, *Bull. Inst. Chem. Res., Kyoto Univ*., **47**, 480 (1969).
3. A. J. Mancuso, D. Swern, *Synthesis*, 165 (1981).
4. T. T. Tidwell, *Synthesis*, 857 (1990).
5. Dimethylsulfoxide (DMSO). Technical Bulletin. Gaylord Chemical Corp. Avail. URL: http://www.gaylordchemical.com/bulletins/Bulletin105B/Bulletin105B.pdf
6. M. B. Floyd, M. T. Du, P. F. Fabio, L. A. Jacob, B. D. Johnson, *J. Org. Chem*., **50**, 5022 (1985).
7. G. Majetich, R. Hicks, S. Reister, *J. Org. Chem*., **62**, 4321 (1997).
8. Y. Takikawa, K. Shimada, K. Sato, S. Sato, S. Takizawa, *Bull. Chem. Soc. Jpn*., **58**, 995 (1985).
9. L. Forlani, A. Lugli, C. Boga, A. B. Corradi, P. Sgarabotto, *J. Heterocycl. Chem*., **37**, 63 (2000).
10. L. Forlani, C. Boga, *J. Chem. Soc., Perkin Trans. 2*, 768 (2002).
11. C. Boga, L. Forlani, C. Silvestroni, A. B. Corradi, P. Sgarabotto, *J. Chem. Soc., Perkin Trans. 1*, 1363 (1999).