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# 4-Thio derivatives of sydnone imines

**Ilya A. Cherepanov, Sergey N. Lebedev, Alina S. Samarskaya,**
**Ivan A. Godovikov, Yulia V. Nelyubina and Valery N. Kalinin***

*A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 6549; e-mail: vkalin@ineos.ac.ru*

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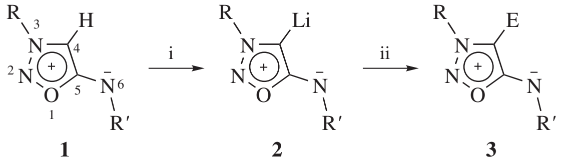
**4-Thio derivatives of sydnone imines were obtained by the reaction of 4-lithiosydnone imines with elemental sulfur and subsequent treatment of the reaction mixture with electrophiles.**

Sydnone imines (5-amino-1,2,3-oxadiazolium betaine) are the most studied substances among mesoionic heterocyclic compounds.[1,2] Their synthesis and characterization are of great interest because of the broad spectrum of sydnone imine pharmacological activity.[2] Recently, it was shown that sydnone imines are effective exogenous donors of nitrogen oxide (NO), which is a unique intracellular regulator of the metabolism in living organisms.[3–5]

Unfortunately, sydnone imines with a heteroatom (S, P, N, *etc.*) as a substituent at the 4-position are unknown. Introduction of a sulfur atom as a substituent at the 4-position of the sydnone imine ring can significantly change the pharmacological activity of these promising heterocyclic compounds. The aim of this study was to develop a synthetic approach to previously unknown 4-mercapto derivatives of sydnone imines and to investigate their reactivity.

We have already mentioned that $N_6$-derivatives of sydnone imines **1**, which bear no substituent at the $C_4$-position, are smoothly metalated by the action of *n*-BuLi giving corresponding 4-lithio derivatives[6] **2** whose interaction with electrophiles yields sydnone imines **3** functionalized at the 4-position (Scheme 1).

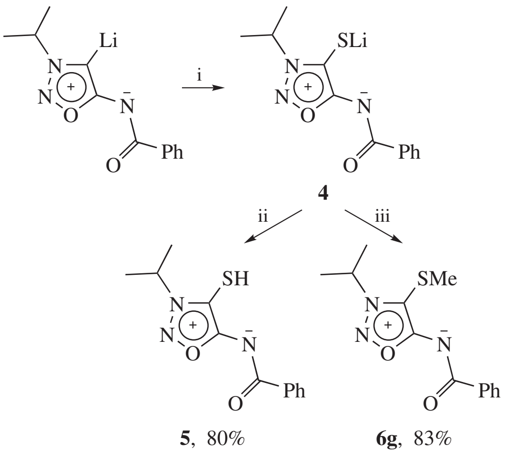


**Scheme 1** *Reagents and conditions*: i, *n*-BuLi, THF, –90 °C, 30 min; ii, E$^+$, THF, –90 °C, 2 h.

We supposed that, as in the case of sydnones whose 4-lithio derivatives easily react with elemental sulfur,[7] 4-lithio derivatives of sydnone imines should also undergo this reaction.

The treatment of the 4-lithio derivative of 3-isopropyl-$N_6$-benzoylsydnone imine with elemental sulfur gives lithium thiolate **4**, whereas the consequent acidification of the reaction mixture gives free thiol **5** in high yield (Scheme 2).

The treatment of lithium thiolate **4** formed in the reaction with methyl iodide gives heteryl methyl sulfide **6g** in a high yield. The structure of the product was confirmed by X-ray diffraction analysis[†] (Figure 1), which showed that sulfide **6** crystallizes with four independent molecules in an asymmetric unit. Their geometrical parameters are typical of the compounds of this type and close to each other with the main difference being observed for the phenyl group which rotates around the C(7)–C(9) bond by up to 11.6°. There is a pseudo-inversion center relating the independent species in such a way that there are two pseudosymmetric pairs of molecules; it is displaced from the exact symmetry element[8] by 0.42 Å. Supramolecular organization in the crystal of **6g** follows exactly the same trend; *i.e.*, the species within these pairs form nearly the same intermolecular contacts while the chemical patterns of those belonging to the different pairs markedly vary.



**Scheme 2** *Reagents and conditions*: i, $S_8$, THF, –90 °C → room temperature, 30 min; ii, $H_2O$; iii, MeI, THF, 20 °C, 2 h.

Other 4-mercapto derivatives of sydnone imines were obtained by an analogous way. However, these derivatives are unstable,

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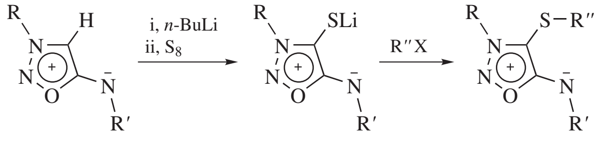
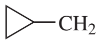
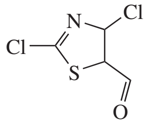
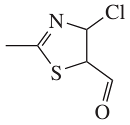
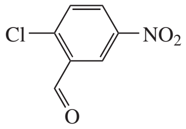
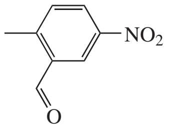
[†] Crystals of **6g** ($C_{13}H_{15}N_3O_2S$, $M = 277.34$) are triclinic, space group $P\bar{1}$, at 100 K: $a = 10.2520(4)$, $b = 11.2447(4)$ and $c = 23.8900(8)$ Å, $\alpha = 103.240(5)°$, $\beta = 91.368(5)°$, $\gamma = 90.574(5)°$, $V = 2679.75(17)$ Å$^3$, $Z = 8$ ($Z' = 4$), $d_{calc} = 1.375$ g cm$^{-3}$, (MoK$\alpha$) = 2.43 cm$^{-1}$, $F(000) = 1168$. Intensities of 384485 reflections were measured with a Bruker SMART APEX2 CCD diffractometer [$\lambda$(MoK$\alpha$) = 0.71072 Å, $\omega$-scans, $2\theta < 90°$] and 43867 independent reflections ($R_{int} = 0.0354$) were used in the further refinement. The structure was solved by a direct method and refined by the full-matrix least-squares technique against $F^2$ in the anisotropic-isotropic approximation. Hydrogen atoms were located from the Fourier synthesis of the electron density and refined in the isotropic approximation. For **6g** the refinement converged to $wR_2 = 0.1239$ and GOF = 1.004 for all independent reflections [$R_1 = 0.0396$ was calculated against $F$ for 35309 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0.[9]

CCDC 737013 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.

**Table 1** Synthesis of 4-thio derivatives of sydnone imines.



**1** **6**

| Product | R | R′ | R″X | R″ | Yield (%) | mp/°C |
|---|---|---|---|---|---|---|
| **6a** | Bu$^n$ | C(O)Ph | MeI | Me | 68 | 78–79 |
| **6b** | Bu$^n$ | C(O)CF$_3$ | MeI | Me | 58 | 50–51 |
| **6c** | Bu$^n$ | C(O)Bu$^t$ | MeI | Me | 70 | 48–49 |
| **6d** | NMe$_2$ | C(O)Me | MeI | Me | 83 | 75–76 |
| **6e** | NMe$_2$ | C(O)Ph | MeI | Me | 68 | 79–80 |
| **6f** | Pr$^i$ | C(O)Me | MeI | Me | 54 | 108–109 |
| **6g** | Pr$^i$ | C(O)Ph | MeI | Me | 83 | 73–74 |
| **6h** | Pr$^i$ | C(O)Ph | PhCH$_2$Br | PhCH$_2$ | 75 | 81–82 |
| **6i** | Pr$^i$ | C(O)Ph |  CH$_2$Br |  CH$_2$ | 89 | Oil |
| **6j** | Pr$^i$ | C(O)Ph |  |  | 83 | 135–136 |
| **6k** | Pr$^i$ | C(O)Ph |  |  | 76 | 179–180 |

and they quickly decomposed on isolation and storage. Thus, the further isolation of their pure forms was not carried out. Lithium thiolate **4** formed in the reaction was *in situ* treated with organohalides and corresponding sulfide **6** was isolated as a reaction product. The results are given in Table 1.[‡]

According to these data, the properties of the intermediate 4-lithiothiolates of sydnone imines are typical of such a type of compounds. They are smoothly alkylated with alkyl halides giving 4-thioalkyl-substituted sydnone imines. On the interaction with aryl or heteroaryl halides, the active halogen atom is substituted giving corresponding sulfides **6k**, **6j**. Note that both chlorine atoms can be replaced in the case of 2,4-dichloro-5-formylthiazole. However, the reverse addition, *i.e.*, the addition of a lithium thiolate solution to organic halide, allowed monosubstituted substance **6j** to be obtained in a high yield.

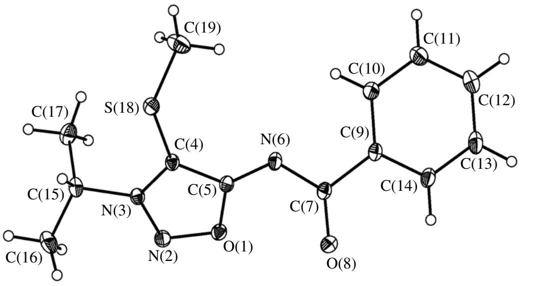


**Figure 1** General view of compound **6g** in representation of atoms *via* thermal ellipsoids at 50% probability level.

The presence of an aldehyde function in sulfides **6j** and **6k** or that of the replaceable chlorine atom in **6j** gives additional possibilities for the functionalization of the 4-thio derivatives of sydnone imines thus obtained. This is significant for a search for new physiologically active derivatives among mesoionic heterocyclic compounds.

Thus, preparative methods for the synthesis of previously unknown 4-mercapto-, 4-thioalkyl-, 4-thioaryl- and 4-thioheteryl derivatives of sydnone imines were elaborated.

### *Online Supplementary Materials*

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2009.11.009.

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[‡] *Standard procedure*: 2.1 mmol of *n*-BuLi solution in hexane was added to 2.0 mmol of sydnone imine in 50 ml of dry THF at –85 °C. The solution was stirred at –85 °C for 15 min; then, 2.2 mmol of powdered sulfur was added. The resulting mixture was stirred at –85 °C for 15 min and heated to room temperature in a bath; then, 3 mmol of organohalide were added. The reaction mixture was stirred for additional 2–24 h for completing the reaction (control by TLC) and quenched with 1 ml of water. The solvent was evaporated at reduced pressure, the residue was dissolved in 50 ml of methylene chloride, and the solution was filtered through a layer of Al$_2$O$_3$. The solvent was evaporated, the residue was purified by chromatography on a SiO$_2$ column (chloroform–ethyl acetate, 5:1). The product was crystallized from isopropanol–hexane. Satisfactory data of elemental analysis, $^1$H and $^{13}$C NMR spectroscopy were obtained for all of the new substances (see Online Supplementary Materials).