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Synthesis of sulfur-containing sydnones

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A method for the synthesis of 4-alkylthio- and 4-arylthiosydnones from 4-lithiosydnones and elementary sulfur was proposed.

Key words: sydnones, metalation, sulfur.

Sydnones, which are representatives of mesoionic heterocyclic compounds, possess a broad spectrum of pharmacological activities.[1,2] It is known that sulfur-containing substituents significantly influence the biological activity of heterocyclic compounds. However, only a few number of sydnone derivatives bearing thioalkyl substituents have been described in the literature.

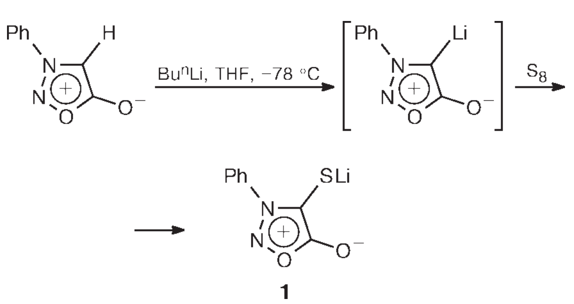
Earlier, sulfur-containing sydnones have been obtained by the reactions of 4-lithiosydnone with disulfides[3] or by the reactions of sulfoxides with 4-non-substituted sydnones in the presence of AcCl.[4] However, these methods are of limited utility.

The goal of the present study was to investigate the method of introduction of alkyl- and arylthio substituents in position 4 of the sydnone ring based on the reactions of 4-lithiosydnones with elementary sulfur.

Results and Discussion

We found that elementary sulfur is inserted into the C—Li bond in the reaction with 4-lithiosydnone to give lithium thiolate **1** (Scheme 1).

Scheme 1



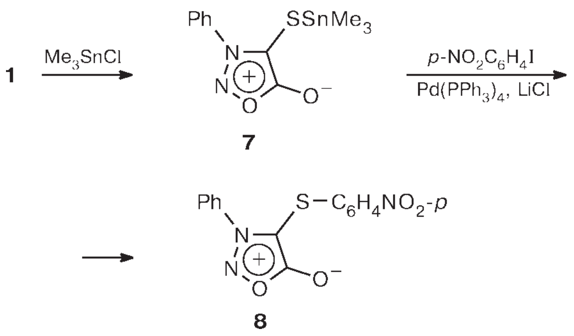
Compound **1** shows properties inherent in common alkali-metal alkane- and arenethiolates. Thus its treatment with water affords 4-mercapto-3-phenylsydnone **2**, which reacts with organic halides such as methyl iodide, propargyl bromide, and ethyl bromoacetate to give the corresponding sulfides **3**—**5** and with pivaloyl chloride to form thioester **6** (Scheme 2).

Scheme 2

Compound	RX	R
2	H_2O	H
3	MeI	Me
4	$HC{\equiv}CCH_2Br$	$HC{\equiv}CCH_2$
5	$BrCH_2CO_2Et$	CH_2CO_2Et
6	Bu^tCOCl	Bu^tCO
7	Me_3SnCl	Me_3Sn

Of special note is that thiolate **1** reacts with Me_3SnCl to give product **7** with an S—Sn bond; the Stille reaction of the latter with *p*-iodonitrobenzene yields sulfide **8** (Scheme 3).

Scheme 3



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Experimental

^{1}H NMR spectra were recorded on a Bruker WM-400 spectrometer with Me_4Si as the internal standard. IR spectra were recorded on a Specord M-80 spectrometer (solutions in $CHCl_3$). Melting points were determined in glass capillaries in a metallic block. All reactions involving organometallic compounds were carried out in an atmosphere of dry argon in anhydrous solvents.

3-Phenylsydnone was prepared from *N*-phenylglycine according to the known procedure.[5]

4-Mercapto-3-phenylsydnone (2). A 1.75 *M* solution of Bu^nLi (1.9 mL, 3.4 mmol) in hexane was added at −78 °C to a solution of 3-phenylsydnone (0.5 g, 3.1 mmol) in 50 mL of THF. The reaction mixture was stirred at −78 °C for 5 min and, after addition of elementary sulfur (0.1 g), at the same temperature for 10 min. Then the reaction mixture was warmed to ~20 °C, and 2 *M* HCl (2 mL) was added. The solvent was removed *in vacuo*, and the residue was dissolved in $CHCl_3$ and filtered through a layer of Al_2O_3 (2×3 cm) with $CHCl_3$ as the eluent. The eluate was concentrated *in vacuo*, and the product was isolated by preparative TLC on silica gel in ether—chloroform (1 : 1) and recrystallized from a chloroform—ether mixture. The yield of compound **2** was 0.24 g (40%), m.p. 148—149 °C. Found (%): C, 49.53; H, 2.84; N, 14.38; S, 16.6. $C_8H_6N_2SO_2$. Calculated (%): C, 49.48; H, 3.11; N, 14.42; S, 16.51. ^{1}H NMR ($CDCl_3$), δ: 1.60 (s, 1 H, SH); 7.60—7.80 (m, 5 H, Ph). IR, ν/cm^{-1}: 1762, 1784 (CO).

4-Methylthio-3-phenylsydnone (3). 3-Phenylsydnone (3.1 mmol) was converted into thiolate **1** as described above. Methyl iodide (0.23 mL, 3.7 mmol) was added at ~20 °C, and the reaction mixture was stirred for 30 min. Water (1 mL) was added, and THF was removed *in vacuo*. The residue was dissolved in $CHCl_3$ and filtered through a layer of Al_2O_3 (2×3 cm) with $CHCl_3$ as the eluent; the eluate was concentrated *in vacuo*. The product was isolated by preparative TLC and recrystallized from a chloroform—ether mixture. The yield of compound **3** was 0.4 g (63%), m.p. 101—102 °C (*cf.* Refs.: m.p. 101—102 °C [3] and 101.5—102 °C [4]). Found (%): C, 51.82; H, 3.96; N, 13.46; S, 15.45. $C_9H_8N_2SO_2$. Calculated (%): C, 51.99; H, 3.87; N, 13.45; S, 15.40. ^{1}H NMR ($CDCl_3$), δ: 2.20 (s, 3 H, Me); 7.60—7.80 (m, 5 H, Ph). IR, ν/cm^{-1}: 1752 (CO).

Compounds **4**—**7** were synthesized analogously.

3-Phenyl-4-propargylthiosydnone (4), yield 71%, m.p. 75—76 °C. Found (%): C, 56.64; H, 3.48; N, 11.91; S, 13.91. $C_{11}H_8N_2SO_2$. Calculated (%): C, 56.89; H, 3.47; N, 12.06; S, 13.80. ^{1}H NMR (DMSO-d_6), δ: 3.20 (t, 1 H, CH, J = 2.67 Hz); 3.53 (d, 2 H, CH_2); 7.59—7.85 (m, 5 H, Ph). IR, ν/cm^{-1}: 1760 (CO).

4-Ethoxycarbonylmethylthio-3-phenylsydnone (5), yield 64%, oil. Found (%): C, 51.65; H, 4.58; N, 9.28; S, 10.86. $C_{12}H_{12}N_2SO_4$. Calculated (%): C, 51.42; H, 4.32; N, 9.99; S, 11.44. ^{1}H NMR ($CDCl_3$), δ: 1.10 (t, 3 H, Me); 3.30 (s, 2 H, SCH_2); 4.00 (q, 2 H, OCH_2); 7.50—7.70 (m, 5 H, Ph). IR, ν/cm^{-1}: 1758 (CO); 1736 (CO).

3-Phenyl-4-pivaloylthiosydnone (6), yield 76%, oil. Found (%): C, 56.24; H, 5.22; N, 9.28; S, 11.63. $C_{13}H_{14}N_2SO_3$. Calculated (%): C, 56.10; H, 5.07; N, 10.06; S, 11.52. ^{1}H NMR ($CDCl_3$), δ: 1.00 (s, 9 H, Bu^t); 7.60—7.80 (m, 5 H, Ph). IR, ν/cm^{-1}: 1750 (CO); 1736 (CO).

3-Phenyl-4-trimethylstannylthiosydnone (7), yield 67%, m.p. 125—127 °C. Found (%): C, 36.53; H, 5.70; N, 7.21; S, 8.36; Sn, 32.11. $C_{11}H_{14}N_2SSnO_2$. Calculated (%): C, 36.39; H, 5.55; N, 7.72; S, 8.83; Sn, 32.69. ^{1}H NMR ($CDCl_3$), δ: 0.55 (s, 9 H, $SnMe_3$); 7.55—7.80 (m, 5 H, Ph). IR, ν/cm^{-1}: 1748 (CO).

4-(4-Nitrophenylthio)-3-phenylsydnone (8). A mixture of compound **7** (0.3 g, 0.84 mmol), *p*-iodonitrobenzene (0.2 g, 0.84 mmol), LiCl (0.14 g, 3.36 mmol), and $Pd(PPh_3)_4$ (0.05 g, 0.042 mmol) in 25 mL of anhydrous benzene was refluxed for 3 h. The reaction mixture was cooled to ~20 °C, and a saturated solution of KF (10 mL) was added. The organic layer was decanted, dried with potassium carbonate, and filtered through a layer of Al_2O_3 (2×3 cm) with $CHCl_3$ as the eluent. The eluate was concentrated *in vacuo*, and the residue was recrystallized from a chloroform—hexane mixture. The yield of compound **8** was 0.21 g (80%), m.p. 115 °C. Found (%): C, 53.42; H, 2.91; N, 13.30; S, 9.96. $C_{14}H_9N_3SO_4$. Calculated (%): C, 53.33; H, 2.88; N, 13.33; S, 10.17. ^{1}H NMR ($CDCl_3$), δ: 7.30, 8.15 (dd, 4 H, C_6H_4, AB system, J = 12 Hz); 7.40—7.76 (m, 5 H, Ph). IR, ν/cm^{-1}: 1764 (CO).

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