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Preparation and properties of nitrogen-substituted thiosulfinyl compounds and related new heterocycles

Sanae Yoshida, Yoshiaki Sugihara and Juzo Nakayama*

Department of Chemistry, Graduate School of Science and Engineering, Saitama University, Sakura-ku, Saitama, Saitama 338-8570, Japan

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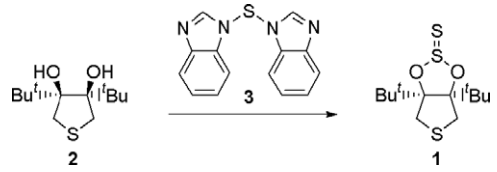
Abstract—The reaction of dilithiated *N*,*N*′-dimethyl-1,2-diphenylethylenediamine with disulfur dichloride (S_2Cl_2) gave a thiosulfinyl compound $(R_2N)_2S{=}S$, 2,5-dimethyl-3,4-diphenyl-1,2,5-thiadiazolidine 1-sulfide, whereas the treatment of dilithiated *N*,*N*′-bis(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine with S_2Cl_2 furnished a new heterocycle, 3,6-bis(*p*-toluenesulfonyl)-4,5-diphenyl-4*H*,5*H*-1,2,3,6-dithiadiazine.

The chemistry of the thiosulfinyl (>S=S) group has been attracting considerable attention. Compounds that possess this highly reactive functional group become stable to be isolated, only when both substituents on the sulfur atom are heteroatom. Thus, $F_2S{=}S$ is a long-known compound[1] and the first synthesis of thionosulfites $(RO)_2S{=}S$ was reported in 1965.[2] Recently, new thionosulfites have been synthesized and characterized in detail by Harpp et al.[3] We have also reported the preparation of stable, crystalline thionosulfite **1** and the full characterization of its chemical properties; it was obtained by the treatment of cyclic diol **2** with **3** (Scheme 1).[4]

As an extension of the above work, we have now investigated the preparation of nitrogen-substituted thiosulfinyl compounds $(R_2N)_2S{=}S$. Reportedly, **4** and **5**, easily obtainable from commercially available starting materials, are more reactive sulfuration reagents than **3** is.[5] Thus, initially we have examined the reactions of 1,2-diamine **6**[6] with **4** and **5** with the expectation of obtaining 1,2,5-thiadiazolidine 1-sulfide **7a**. However, disappointingly, the reaction did not give the expected **7a**, but gave sulfoxide **8** instead in 35% yield by the use of **4** and in 93% yield by the use of **5** (Scheme 2). The formation of **8** might involve the initial formation of **9**, which further reacts with **4** or **5** to give **7a** whose oxidation or hydrolysis leads to **8**. Direct oxidation of **9** may also explain the formation of **8**. Structure of **8** was established by independent synthesis; the reaction of **6** with thionyl chloride gave **8** quantitatively.



Scheme 1.

We then examined the reaction of dilithiated **6** with disulfur dichloride (ClSSCl), where the formation of **7a** (via paths **a** and **b** in Scheme 3) and also the formation of a new heterocycle, 1,2-dithiadiazine **7b** (path **c**) were expected. Thus, **6** was dilithiated by *n*-BuLi (2 equiv) in Et_2O and then treated with ClSSCl. The reaction gave a mixture of **7a**, **8**, and the starting material **6** in the ratio 43:23:33, which was estimated by the analysis of ^1H NMR of the crude reaction mixture. Dithiadiazine **7b** was not formed. The reaction in THF gave the same compounds in the ratio 54:13:33. Incidentally, neither **7a** nor **8** was formed by the use of triethylamine as the base. Density functional theory (DFT) calculations (B3LYP/6-31G* level)[7] predicted that **7a** is more stable than **7b** by 3.3 kcal/mol.

Compound **7a** is unstable both thermally and kinetically, and could not be isolated in pure form despite many efforts. It turned to **8** partially by hydrolysis or

Keywords: Thiosulfinyl compound; New heterocycle; Ethylenediamine; Disulfur dichloride.
* Corresponding author. Tel.: +81 48 858 3390; fax: +81 48 858 3700; e-mail: nakaj@post.saitama-u.ac.jp

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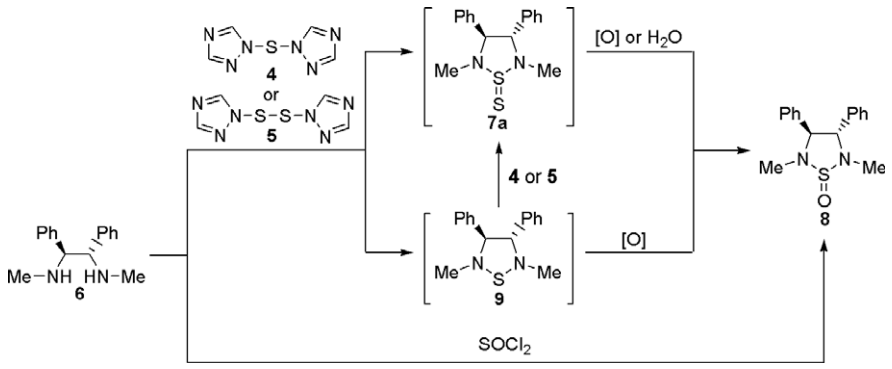
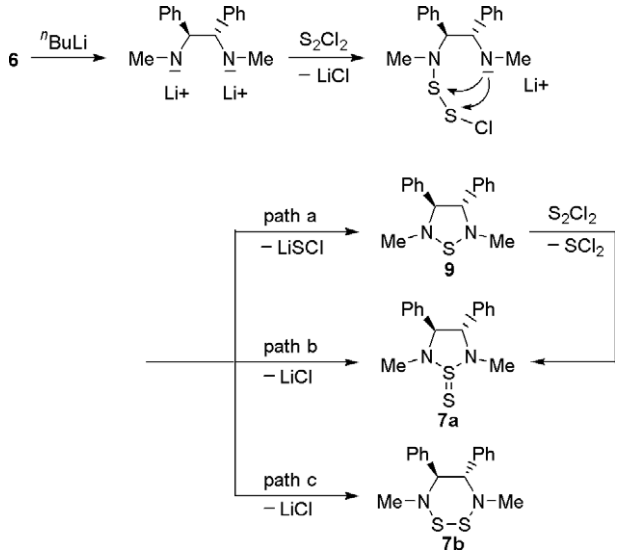


Scheme 2.



Scheme 3.

oxidation during purification processes. It also reacted with CH_2Cl_2 to give **10**[8] when its solution in CH_2Cl_2 was allowed to stand (Scheme 3). Thus, the ^1H and ^{13}C NMR spectra of **7a** were determined by using the sample freshly purified by silica gel column chromatography and containing small amounts of compounds **8** and **10** as the impurity. The two methine protons of **8** appear as two doublets at δ 4.14 and 4.44 with $J = 9.7$ Hz. The signal at δ 4.14 is assigned to the *trans* proton to the >S=O group, and the latter to the *cis* one (Fig. 1). The difference of the observed chemical shifts is due to the diamagnetic anisotropy of the >S=O group. The ^1H NMR data of **7a** are expected to be similar to those of **8** since the diamagnetic anisotropy of the >S=S group is similar to that of the >S=O group as previously reported by us.[4] Indeed, the two methine protons of **7a** appeared as two doublets at δ 4.19 and 4.45 with $J = 9.6$ Hz. For the ^{13}C NMR spectra, the methine carbons of **7a** appeared at δ 76.1 and 79.4, chemical shifts similar to those of **8**, δ 75.0 and 78.7.

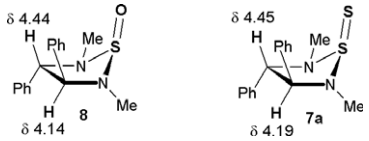
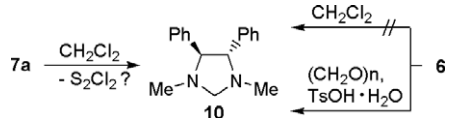


Figure 1. ^1H NMR chemical shifts of **7a** and **8**.

Although **7a** quickly reacted with CH_2Cl_2 to give **10**, 1,2-diamine **6** did not react with CH_2Cl_2 even when a solution of **6** in CH_2Cl_2 was allowed to stand for more than one month (Scheme 4). The terminal sulfur atom of the >S=S group of **7a** is negatively charged as predicted by Mulliken population analysis (Fig. 2),[7] and thus the initial process of the above conversion might involve the nucleophilic attack of the sulfur atom on the carbon atom of CH_2Cl_2. Compound **10** was alternatively prepared by acid-catalyzed condensation of **6** with paraformaldehyde in CH_2Cl_2 for 19 h at room temperature, which gave a mixture of **6** and **10** in the ratio 69:31.

Next, the reaction of 1,2-ethylenediamine **11**,[9] which has an electron-withdrawing group on the nitrogen atoms, with ClSSCl was examined. Thus, **11** was treated with *n*-BuLi (2 equiv) in Et_2O at 0 °C and then with ClSSCl, which furnished compound **12b** with a new heterocyclic system in 57% isolated yield with the recovery of **11** in 39% (Scheme 5). The reaction used THF as the solvent gave sulfoxide **13** in 27% yield with recovery of **11** in 72%. The structure of **12b** was determined based on ^1H NMR, ^{13}C NMR, Raman, and IR spectral data and X-ray crystallographic analysis. Molecular structure of **12b** is shown in Figure 3. The six-membered ring of



Scheme 4.

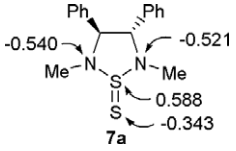
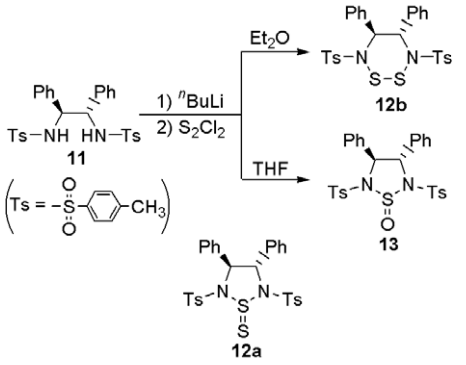


Figure 2. Mulliken population analysis of **7a** at the B3LYP/6-31G* level.



Scheme 5.

12b exists in a chair conformation. The two S–N bond lengths of **12b** are not equal to each other and are 1.699 and 1.691 Å, and are shorter than the usual S–N(sp^3) bond length (1.765 Å);[10] a literature survey revealed that the S–N bond lengths of compounds >N–S–S–N< are generally shorter than the usual S–N(sp^3) bond lengths.[11] The S–S bond length (2.034 Å) of **12b** is a usual one, although, reportedly, the S–S bond lengths of X–S–S–X (X = O, 1.972 Å; F, 1.888 Å) are shorter than the usual S–S bond lengths.[1,3d,12]

DFT calculations (B3LYP/6-31G** level)[7] predicted, on the contrary to the case of **7**, that **12b** is more stable than **12a** by 3.7 kcal/mol. No thermal isomerization of **12b** to **12a** was observed even when **12b** was heated in toluene-d_8 at 120 °C for 48 h in a sealed NMR tube. When **12b** was heated in boiling *o*-dichlorobenzene for 24 h, decomposition took place to give **11** in a yield of less than 33%. Compound **12b** was hydrolyzed to **11** in 98% yield by treatment with $NaHCO_3$ in aqueous THF for 24 h at room temperature.

Finally, 1,8-diaminonaphthalene **14**[13] was treated with *n*-BuLi at 0 °C and then with ClSSCl in THF. A ^{1}H NMR analysis of the crude reaction mixture revealed that the reaction gave a 35:18:47 mixture of **15**, **16**, and **14** (Scheme 6). Compound **15** is susceptible to oxidation and was converted to **16** partially during isolation procedure. Thus the isolated yield of **15** became 10%, while the yield of **16** increased to 27% and the yield of **14** remained unchanged. The reaction gave neither **17a** nor **17b**.

As described, DFT calculations predicted that methyl group on the nitrogen atoms stabilizes the >S=S form, whereas *p*-toluenesulfonyl group stabilizes the isomeric –S–S– form. We therefore carried out DFT calculations on compounds **18**–**23** to show that the relative stability of the >S=S form **A** and –S–S– form **B** depends upon the electronic properties of the substituent on the nitrogen atoms (Table 1). However, although they provided expected results for the combinations of **18** and **19** and of **22** and **23**, they did not for a combination of **20** and **21**. Thus, both for compounds **18** and **19**, which

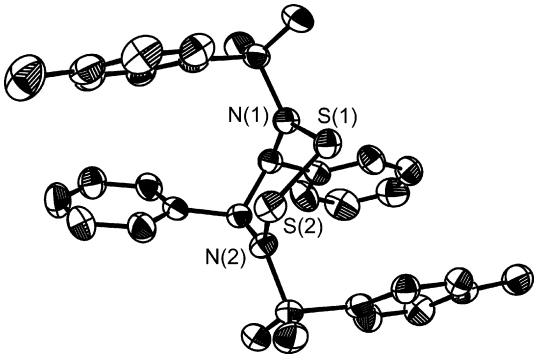
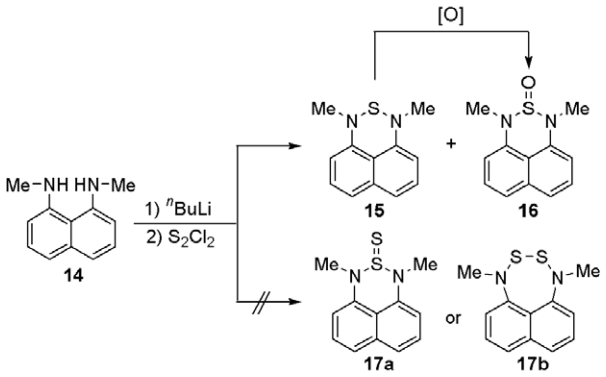
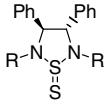
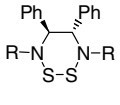
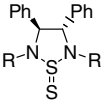
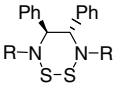
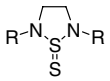
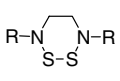
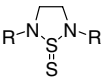
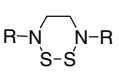


Figure 3. ORTEP plot of the molecular structure of **12b**. Relevant bond lengths [Å]: S(1)–N(1), 1.699; S(1)–S(2), 2.034; S(2)–N(2), 1.691.



Scheme 6.

Table 1. DFT calculations on the relative stability of the >S=S form **A** and the –S–S– form **B**[7]

Electron-donating groups	A	B	Electron-withdrawing groups	A	B
					
18: R = *p*-$Me_2NC_6H_4$	0 kcal/mol	+2.0 kcal/mol	**19**: R = *p*-$O_2NC_6H_4$	0 kcal/mol	+1.4 kcal/mol
					
20: R = *p*-$Me_2NC_6H_4$	0 kcal/mol	−7.9 kcal/mol	**21**: R = *p*-$O_2NC_6H_4$	0 kcal/mol	−5.3 kcal/mol
22: R = Me	0 kcal/mol	−1.7 kcal/mol	**23**: R = MeCO	0 kcal/mol	−14.0 kcal/mol

DFT calculations (BLYP/6-31G** level).

have electron-donating *p*-$Me_2NC_6H_4$ group and electron-withdrawing *p*-$O_2NC_6H_4$ group on the nitrogen atoms, respectively, form **A** is more stable than form **B**, although the relative stability difference is slightly larger for **18** than for **19**. Meanwhile, both for compounds **20** and **21**, form **B** is more stable than form **A** and, in addition, the relative stability difference is greater for **20** than for **21**. For compound **22**, which has methyl group on the nitrogen atom, form **A** is less stable only by 1.7 kcal/mol, whereas for **23**, which carries electron-withdrawing acetyl group, form **A** is less stable than form **B** by 14.0 kcal/mol.

In conclusion, we have succeeded in the preparation of nitrogen-substituted thiosulfinyl compound **7a** and new heterocycles such as **12b** and **15**.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.09.127.

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