Synthesis of di(2-bromoalkyl) disulfides by electrophilic addition of dithiobisamines to olefins

N. V. Zyk, E. K. Beloglazkina, and N. S. Zefirov*

Department of Chemistry, M. V. Lomonosov Moscow State University, Vorob'evy Gory, 119899 Moscow, Russian Federation. Fax: 007 (095) 939 0290

A new method for the synthesis of di(2-haloalkyl) disulfides and β,β′-dibromothiacyclanes was proposed based on reactions of dithiobisamines with olefins in the presence of PBr_3, PBr_5, or $POBr_3$. Reactions with alkenes lead to di(2-bromoalkyl) disulfides. Analogous products and heterocyclic dibromosulfides, *i.e.*, the products of addition of one dithiobisamine molecule to both double bonds of a diene, are obtained in reactions with alkadienes.

Key words: phosphorus bromides, phosphorus oxobromide, dithiobisamines, di(2-bromoalkyl) disulfides, alkenes, electrophilic addition.

It is known that organic compounds of the X—S—S—X type (X = Ar, Alk, OR, NR_2, *etc.*) enter into both electrophilic and nucleophilic reactions with difficulty. The exception is sulfur halides, S_2Hal_2, which form, without any additional activation, addition products at multiple bonds and electrophilic aromatic substitution products, *viz.*, di-β-haloalkyl or diaryl disulfides, respectively.[1—3] Even if compounds of the disulfide series could be introduced into organic reactions, these reactions involve, as a rule, homolytic cleavage of the S—S bond,[4,5] and comparatively few reactions occurring with cleavage of the S—X bond are known.

Dithiobisamines were chosen as the object of study. They significantly differ from thiobisamines $(R_2N)_2S$, their closest analogs, in the ease of heterolytic cleavage of the S—N bond, even with activation. For example, free or complex-bound sulfur trioxide transforms thiobisamines into electrophilic sulfenylating agents.[6,7] Methods for enhancement of the electrophilic reactivity of thiobisamines using catalysis with different Lewis acids have also been developed,[8—10] whereas only two methods for activation with Lewis acids are known for dithiobisamines in reactions of electrophilic sulfenylation of alkenes: with boron trifluoride etherate or $ZnCl_2$.[11] In the first case, di(2-dialkylaminoethyl) disulfides form, and in the second case, only monoaddition products, dialkylamino (2-dialkylaminoethyl) disulfides. Electrophilic ring-opening of cyclopropanes was also activated with $ZnCl_2$.[12] Other examples of the use of dithiobisamines as sulfenylating agents are not documented.

We found that phosphorus halides and oxohalides ($PHal_3$, $PHal_5$ and $POHal_3$, Hal = Cl, Br) can activate electrophilic sulfenylation, which involves compounds containing S—N bonds.[13,14] Strictly speaking, these reactions are not typical catalysis with Lewis acids, because phosphoric or phosphorous acid halide participates in the second stage of electrophilic addition as a nucleophile to give the corresponding β-thiosubstituted alkyl halides.

According to our studies, dithiobismorpholine reacts with olefins in the presence of PBr_3, PBr_5 or $POBr_3$ to form di(2-haloalkyl) disulfides in high yields. An alternative method for the synthesis of these substances can also be addition of sulfur monobromide to alkenes and alkadienes, but the use of this compound appears to be significantly less convenient in synthetic practice than the use of stable non-volatile dithiobisamines devoid of unpleasant odor.

We studied the reactions of two dithiobisamines: dithiobismorpholine (**1a**) and dithiobispiperidine (**1b**), with different phosphorus bromides. Both dithiobisamines studied react vigorously with phosphorus halides at −40 °C to give reactive complexes of the type **2**, which were not isolated due to their low thermostability and hygroscopicity. When an alkene was added to a solution of these complexes, the main, if not the sole, reaction products were the corresponding dihaloalkyl disulfides (**3**—**9**) (Scheme 1).

The reaction of dithiobisamines **1a**,**b** with cyclohexene leads to the formation of di(2-bromocyclohexyl) disulfide (**3**). Data on the yields of the target disulfide are given in Table 1. The slight decrease in the product yield when PBr_3 was used can be explained by its lower strength as a Lewis acid compared to phosphorus(v) bromide and oxobromide.

The stereospecificity of the process leading to a product with *trans*-arrangement of substituents was shown

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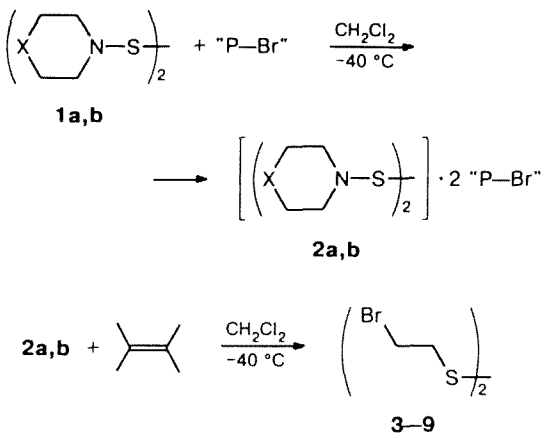
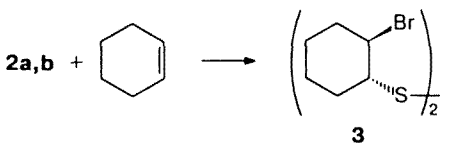
Scheme 1



1, 2: X = O (**a**), CH_2 (**b**)
"P—Br" = $POBr_3$, PBr_5, PBr_3

with cyclohexene as an example. The stereochemistry of the product was proved based on the data from the ^1H NMR spectrum where the signals for the α-protons of the substituents form multiplets of 19—21 Hz width (ω-parameter[15]).



It is known that di(2-chlorocyclohexyl) sulfide, the addition product of sulfur dichloride to cyclohexene, has two asymmetric centers in each cyclohexane fragment and forms as a mixture of two diastereomers. In our case, taking into account that the torsion angle C—S—S—C in dialkyl disulfides is usually equal to 85—90°[16] and that free rotation around the S—S bond is hampered by the presence of two bromine atoms at the β-position of the cyclohexane rings, one could expect the formation of four diastereomeric products. The data from the high-resolution ^1H NMR spectrum confirm this suggestion. Indeed, four multiplets with a similar set of coupling constants are observed in the region of both the HCS protons (3.39—3.05 ppm) and the HCBr protons (4.30—4.10 ppm).

Table 1. Yield of *trans*-di(2-bromocyclohexyl) disulfide **3** depending on reaction conditions

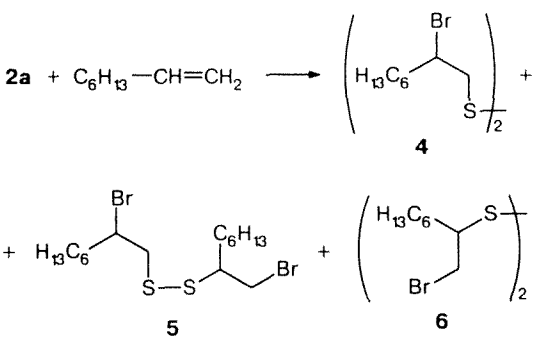
Dithiobisamine	"P—Br"	Ratio of **1** : "P—Br", mol/mol	Yield of **3** (%)
1a	$POBr_3$	1 : 1	45
1a	$POBr_3$	1 : 2	90
1a	PBr_5	1 : 2	82
1a	PBr_3	1 : 2	54
1b	$POBr_3$	1 : 2	78

It should be noted that attempts to activate only one of the two S—N bonds of dithiobisamine by introducing dithiobismorpholine **1a** and $POBr_3$ in the reaction in the ratio of 1 : 1 did not result in formation of the expected product of monoaddition, 2-bromocyclohexyldithiomorpholine. As before, the product of this reaction was disulfide **3** (45% yield).

The best results (as regards the yield of the target product) for the reaction with cyclohexene were obtained using of dithiobismorpholine **1a** as the sulfenylating agent and $POBr_3$ as the activator of the reaction. The reactions with other olefins were carried out with these reagents.

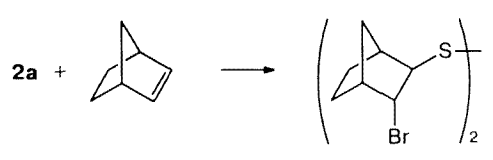
The result of the reaction of dithiobismorpholine **1a** with a terminal olefin, oct-1-ene, attests to the low regioselectivity of this addition, which is typical of sulfenylation. All three possible disulfides **4**, **5**, and **6** are formed (Scheme 2).

Scheme 2

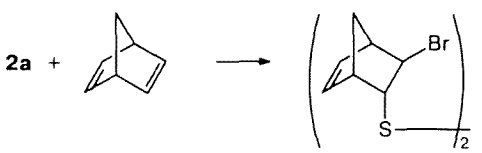


The sulfenylation of olefins of bicyclo[2.2.1]heptane series is of interest from two viewpoints. First, in the case of formation of 1,2-adducts, it allows judging the stereochemistry of addition on the basis of NMR criteria. In addition, the ratio between rearranged and nonrearranged products formed is an index of the electrophilic strength of the reagent.

Diastereomeric dibromodisulfides (**7**) were isolated as the products of the reaction of complex **2a** with norbornene. The *trans*-stereospecificity of the addition, which is proved by the values of the coupling constants of the α-protons of the substituents (4.1 Hz), confirms the electrophilic nature of the reagent formed. At the same time, the absence of products of skeleton rearrangements among the disulfides obtained suggests the low effective electrophilicity of the sulfenylating complex.



The orientation of the entering electrophile is of interest in the reaction with norbornadiene. For norbornene, an electrophile enters the product as an *exo*-substituent in nearly all known cases, while the published data are quite contradictory for norbornadiene. Examples of both the *exo*- and *endo*-orientation of a thio-fragment in the reaction product were described even for different methods of electrophilic sulfenylation.[17,18] The steric arrangement of substituents in product **8** was determined by a ^{1}H NMR study of the diastereomers obtained, *viz.*, {^{1}H}-^{1}H double resonance from the absence of spin coupling between the HCBr (4.03 ppm) and H(1) (3.20—2.92 ppm) protons.



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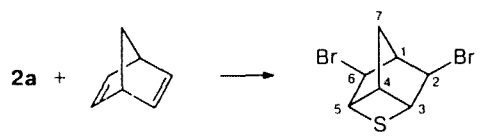
In reactions with dienes, the molecule of dithiobisamine as a rule can be added intramolecularly to both double bonds of the same olefin molecule. In this case, heterocyclic disulfides must be the reaction products. We carried out the reaction of dithiobismorpholine with norbornadiene in a molar ratio of 1 : 1 under conditions of high dilution, and the corresponding sulfide **9**, the product of addition followed by elimination of a sulfur atom, was isolated as the sole reaction product. An anomalously low coupling constant between the HCS—HCBr *trans*-protons (~1 Hz, the normal value of J is 2.5—5 Hz) is observed in the ^{1}H NMR spectrum of compound **9**. Such a significant change in the coupling constant is likely due to deformation of the norbornane skeleton of the molecule in formation of a four-membered sulfur-containing ring. (A value of 95.22—97.48° was obtained for the torsion angle H—C(Br)—C(S)—H as a result of quantum-chemical calculations using different semi-empirical procedures (AM1, MNDO, and ZINDO) performed to optimize the geometry of the sulfide **9** molecule.)



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Thus, the reaction of dithiobisamines with olefins in the presence of phosphorus bromides and phosphorus oxobromide is a convenient method for the synthesis of β,β'-dibromo-substituted dialkyl disulfides or β,β'-dibromo-substituted thiacyclanes, depending on the type of the unsaturated compound and the ratio between the initial reagents.

Experimental

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian-400XR instrument (the working frequency was 400 MHz for ^{1}H and 25 MHz for ^{13}C) in deuteriochloroform. The chemical shifts are given in the δ scale with respect to Me_4Si as the internal standard. The course of the reactions was monitored by TLC on Silufol plates (ethyl acetate—heptane, 1 : 3). The isolation of the reaction products was performed by preparative TLC on Silufol plates using the same solvent system.

Dithiobisamines were obtained according to the known procedure[20] from the corresponding amines and sulfur monochloride in ether.

The interaction of dithiobisamines with olefins in the presence of phosphorus bromide or oxobromide. General procedure. A solution of phosphorus bromide or oxobromide in anhydrous dichloromethane was added with stirring to a solution of dithiobisamine in the same solvent at −40 °C, and then a solution of an olefin was added immediately. After 0.5 h, the temperature of the reaction mixture was gradually raised to −20 °C, and the mixture was passed through a short column with silica gel (h = 5 cm). The solvent was then removed *in vacuo*, and the residue was chromatographed.

***trans*-Di(2-bromocyclohexyl) disulfide (3).** Disulfide **3** was obtained in the reaction of dithiobismorpholine or dithiobispiperidine (0.24 g, 1 mmol) with $POBr_3$ (0.60 g, 2 mmol) or PBr_5 (0.86 g, 2 mmol) or PBr_3 (0.54 g, 2 mmol). The yields are given in Table 1. R_f 0.85. ^{1}H NMR, δ: 2.6—1.3 (16 H); 3.05, 3.12, 3.24, and 3.39 (all m, 2 H, HCS); 4.12, 4.15, 4.23, and 4.30 (all m, 2 H, HCBr). Found (%): C, 37.37; H, 5.15. $C_{12}H_{20}Br_2S_2$. Calculated (%): C, 37.12; H, 5.19.

Di(2-bromooctyl) disulfide (4), [(1-bromomethyl)heptyl] 2-bromooctyl disulfide (5), and di(1-bromomethyl)heptyl disulfide (6). A mixture of disulfides **4**, **5**, and **6** (0.22 g, 50%) was obtained in the reaction of dithiobismorpholine (0.24 g, 1 mmol) with $POBr_3$ (0.60 g, 2 mmol) and oct-1-ene (0.21 g, 2.5 mmol). R_f 0.71. ^{1}H NMR, δ: 0.95 (t, CH_3, J = 7.5 Hz); 1.25—2.10 (m, 20 H, CH_2); 2.83—3.51 (m, HCS); 3.52—4.35 (m, HCBr). Found (%): C, 42.93; H, 7.19. $C_{16}H_{32}Br_2S_2$. Calculated (%): C, 42.87; H, 7.19.

Di(*endo*-3-bromonorborn-2-yl) *exo,exo*-disulfide (7). Diastereomeric disulfides **7** (0.19 g, 78%) were obtained in the reaction of dithiobismorpholine (0.24 g, 1 mmol) with $POBr_3$ (0.60 g, 2 mmol) and norbornene (0.24 g, 2.5 mmol). R_f 0.80. ^{1}H NMR, δ: 1.45—2.02 (m, 6 H, HC(5), HC(6), HC(7)); 2.22, 2.29, 2.31, and 2.33 (all d, 2 H, HC(4), J = 3.8 Hz); 2.47, 2.52, 2.54, and 2.55 (all t, 2 H, HC(1), J = 4.1 Hz); 2.78, 2.90, 3.02, and 3.04 (all dd, 2 H, HCS, J_1 = 2.7 Hz, J_2 = 4.1 Hz); 3.95, 4.00, 4.17, and 4.23 (all d.t, 2 H, HCBr, J_1 = 2.0 Hz, J_2 = 4.1 Hz). ^{13}C NMR, δ: 24.80, 24.91, 25.12, and 25.18 (2 C, C(5)); 29.78, 29.80, 29.92, and 29.95 (2 C, C(6)); 36.33, 36.38, 36.48, and 36.59 (2 C, C(7)); 44.08, 44.31, 44.38, and 45.29 (2 C, C(4)); 45.60, 45.91, 45.97, and 46.03 (2 C, C(1)); 56.61, 59.00, 59.10, and 59.65 (2 C, CS); 60.97, 61.37, 62.50, and 63.02 (2 C, CBr). Found (%): C, 40.59; H, 4.94. $C_{14}H_{20}Br_2S_2$. Calculated (%): C, 40.79; H, 4.89.

Di(*exo*-3-bromonorborn-5-ene-2-yl) *endo,endo*-disulfide (8). A mixture of diastereomeric disulfides **8** (0.17 g, 70%) was obtained in the reaction of dithiobismorpholine (0.24 g, 1 mmol) with $POBr_3$ (0.60 g, 2 mmol) and norbornadiene (0.23 g, 2.5 mmol). R_f 0.80. ^{1}H NMR, δ: 1.38—2.05 (m, 4 H, HC(7)); 2.92—3.20 (m, 4 H, HC(1) and HC(4)); 3.53, 3.60, 3.67, and 3.73 (all dd, 2 H, HCS, J_1 = 2.5 Hz, J_2 = 4.9 Hz);

4.03 and 4.14 (both m, 2 H, HCBr). Found (%): C, 40.59; H, 4.94. $C_{14}H_{18}Br_2S_2$. Calculated (%): C, 40.99; H, 4.42.

4,8-Di-*exo*-bromo-2-thiatricyclo[3.2.1.0^{3,7}]octane (9). Compound **9** (0.18 g, 63%) was obtained in the reaction of dithiobismorpholine (0.24 g, 1 mmol) with $POBr_3$ (0.60 g, 2 mmol) and norbornadiene (0.10 g, 1 mmol). M.p. 80—81 °C (*cf.* Ref. 21: m.p. 81—83 °C). ^{1}H NMR, δ: 2.28 (s, 2 H, HC(6)); 3.34 (br.s, 1 H, HC(5)); 3.42 (dd, 2 H, HCS, J_1 = 4.2 Hz, J_2 = 1.0 Hz); 4.01 (m, 1 H, HC(7)); 4.70 (s, 2 H, HCBr). The ^{1}H NMR spectrum corresponds to the published data.[21]

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