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A convenient preparation of mixed allylic and allenic thiosulfinates

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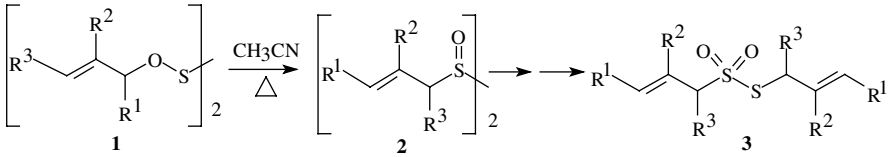
Abstract—The first successful preparation of propargylic and allylic chloroalkoxy disulfides in high yields is reported. Facile 1,4-electrophilic addition of these to 2,3-dimethyl-1,3-butadiene, followed by [2,3]-sigmatropic rearrangements affords mixed allyl allenic and bis-allylic thiosulfinates, respectively. Due to their similarity to allicin, the latter are of potential biological interest.

Our past experience with [2,3]-sigmatropic rearrangements of allylic and propargylic thio-esters such as sulfenates,[1] sulfinates[2] and sulfoxylates[3] led us to the discovery and study of the double [2,3]-sigmatropic rearrangement of allylic and propargylic dialkoxy disulfides. Until recently dialkoxy disulfides have been little studied.[4–6] Although Thompson reported[4] failure in his attempts to prepare allylic and propargylic dialkoxy disulfides, we have tried to prepare such esters. Recently, we reported on the successful synthesis and the reactivity of allylic[7a] and propargylic[7b,c] dialkoxy disulfides. Thus, the allylic dialkoxy disulfides **1** undergo a double [2,3]-sigmatropic rearrangement to the appropriate *vic*-disulfoxides **2**. The latter are unstable[8] and undergo the usual well-known rearrangement to the corresponding thiosulfonates **3** (Scheme 1).[7a]

By a parallel series of reactions, dipropargyloxy disulfides would have been expected to yield bis-allenyl thiosulfonates. In fact, the first isolated products were found to have a new and unusual type of structure.[7b] They were 6,7-dithiabicyclo[3.1.1]heptane-2-one-6-oxides (**5**, Scheme 2) incorporating the 1,3-dithiacyclobutane-1-oxide moiety recently identified by Block et al.[9] in the zwiebelanes isolated from freshly cut onion. Moreover, study of such propargylic esters also led us to the discovery of the novel and unprecedented structures **6**/**7**, **8** and **9** whose formation is the result of a remarkable sequence of sigmatropic rearrangements and cycloadditions (Scheme 2).[7c]

Prompted by our experience with symmetrical ROSSOR esters and their unexpected transformation to novel structures, and by the fascinating organosulfur chemistry of *allium* species,[9] we were interested in preparing and exploring the synthetic utility of unsymmetrical propargylic and allylic dialkoxy disulfides.

As a first step to this end we set out to prepare propargylic monoalkoxy chlorodisulfides ROSSCl. As far as we are aware, no such compound has been reported before. Herein, we report the successful preparation of a series of propargyloxy chlorodisulfides **11** by appropriate modification of our procedure for the preparation of dialkoxy disulfides, that is, by the addition of an ether solution of the appropriate alcohol to a mixture of



Scheme 1.

Keywords: Alkynes; Alkenes; Allenes; Chloroalkoxy disulfides; Thiosulfinates; [2,3]-Sigmatropic rearrangements.
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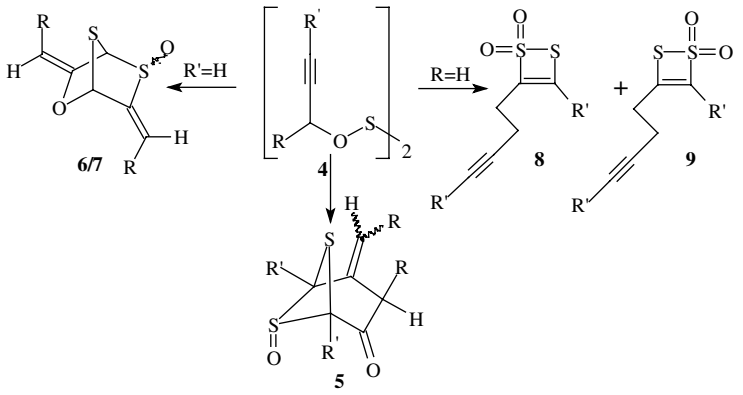
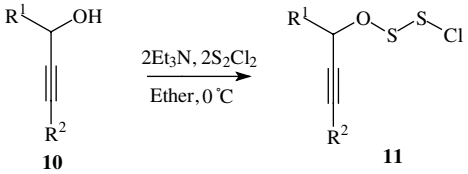


Scheme 2.



a; R^1=Methyl, R^2=H, 93%, **e;** R^1=*iso*-Butyl, R^2=H, 74%,
b; R^1=Ethyl, R^2=H, 95%, **f;** R^1=Neopentyl, R^2=H, 52%,
c; R^1=Pentyl, R^2=H, 94%, **g;** R^1=R^2=H, 77%,
d; R^1=*iso*-Propyl, R^2=H, 84%, **h;** R^1=H, R^2=Me, 97%,
i; R^1=Me, R^2=Ph, 75%.

Scheme 3.

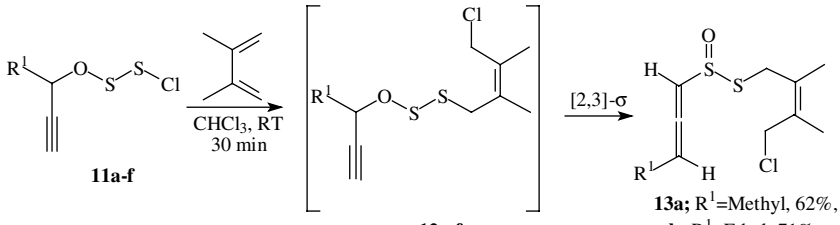
2 equiv of both Et_3N and S_2Cl_2 in ether, under high dilution conditions (Scheme 3).[10] The new compounds (**11**) were found to be very unstable.

Disappointingly, further attempts to use these monoesters for the preparation of unsymmetrical dialkoxy disulfides (ROSSOR′) have been unsuccessful, due to the formation of complex reaction mixtures. With compounds **11** in hand, we explored their synthetic utility. The reactions of **11a**–**f** with 2,3-dimethyl-1,3-butadiene by 1,4 addition followed by a [2,3]-sigmatropic rearrangement, yielded the thiosulfinates **13a**–**f** (Scheme 4, Table 1).[11] These compounds have been found to be stable in chloroform solution at −18 °C. The structures of compounds **13a**–**f** are based on a full NMR analysis of

Table 1. Summary of the significant NMR and IR data for mixed allyl allenyl thiosulfinates **13a**–**f**

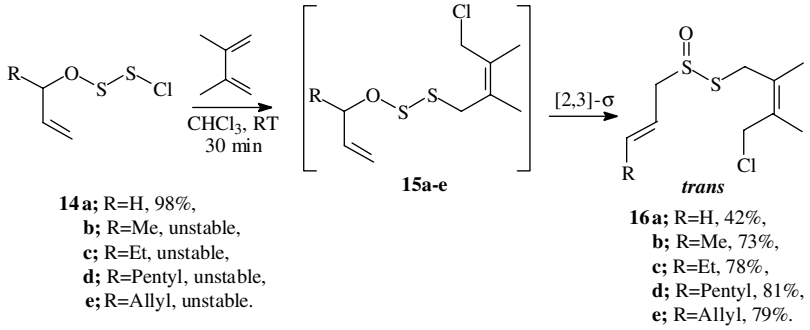
No.	^{1}H NMR, ppm $2\times(-CH_2-)$, AB_q	^{13}C NMR, ppm =C=	IR, cm^{-1} S=O, =C=
13a	4.21 and 4.12 (d, J = 11.0 Hz, 1H each); 3.94 and 3.76 (d, J = 12.6 Hz, 1H each)	202.61	1086[a]; 1947[b]
13b	4.22 and 4.12 (d, J = 11.0 Hz, 1H each); 3.95 and 3.76 (d, J = 12.9 Hz, 1H each)	201.97	1089[a]; 1947[b]
13c	4.22 and 4.11 (d, J = 11.5 Hz, 1H each); 3.94 and 3.75 (d, J = 12.9 Hz, 1H each)	202.18; 202.12	1079[a]; 1947[b]
13d	4.22 and 4.12 (d, J = 11.1 Hz, 1H each); 3.95 and 3.76 (d, J = 12.6 Hz, 1H each)	201.00; 200.93	1092[a]; 1947[b]
13e	4.15 and 4.05 (d, J = 11.0 Hz, 1H each); 3.88, 3.87 and 3.69 (×2) (d, J = 12.9 Hz, 1H each)	201.96	1076[a]; 1947[b]
13f	4.22, 4.21 and 4.11 (×2) (d, J = 11.1 Hz, 1H each); 3.95, 3.93 and 3.75 (×2) (d, J = 12.9 Hz, 1H each)	202.92; 202.86	1090[a]; 1947[b]

[a] For S=O.
[b] For =C=.



13a; R^1=Methyl, 62%,
b; R^1=Ethyl, 71%,
c; R^1=Pentyl, 61%,
d; R^1=*iso*-Propyl, 54%,
e; R^1=*iso*-Butyl, 66%,
f; R^1=Neopentyl, 71%.

Scheme 4.



Scheme 5.

Table 2. Summary of the significant NMR and IR data for mixed bis-allyl thiosulfinates **16a–e**

No.	^{1}H NMR, ppm		IR, cm^{-1} for S=O
	2 × (–CH_2–), AB_q	–CH_2–, AB system	
16a	4.20 and 4.11 (d, J = 11.0 Hz, 1H each); 3.94 and 3.78 (d, J = 13.0 Hz, 1H each)	3.87 and 3.78 (dd, J = 13.0, 7.5 Hz, 1H each)	1086
16b	4.20 and 4.12 (d, J = 11.4 Hz, 1H each); 3.93 and 3.76 (d, J = 13.0 Hz, 1H each)	3.79 and 3.73 (ddquintet, J = 13.0, 7.5, 1.0 Hz, 1H each)	1074
16c	4.21 and 4.12 (d, J = 11.0 Hz, 1H each); 3.93 and 3.76 (d, J = 13.0 Hz, 1H each)	3.81 and 3.74 (ddq, J = 13.0, 7.3, 1.1 Hz, 1H each)	1073
16d	4.20 and 4.11 (d, J = 11.0 Hz, 1H each); 3.93 and 3.76 (d, J = 13.0 Hz, 1H each)	3.81 and 3.73 (br ddd, J = 13.0, 7.5, 1.0 Hz, 1H each)	1073
16e	4.21 and 4.11 (d, J = 11.0 Hz, 1H each); 3.93 and 3.77 (d, J = 13.0 Hz, 1H each)	3.83 and 3.77 (ddq, J = 13.0, 7.2, 1.0 Hz, 1H each)	1081

the ^{1}H and ^{13}C NMR data, including several 2D techniques such as COSY, HMQC and HMBC and are supported by IR and HRMS experiments. All new compounds exhibited the characteristic NMR splitting pattern of two groups of diastereotopic methylene protons due to the chirality of the sulfinyl group. In addition, the IR spectra show a strong signal at 1080–1090 cm^{-1} corresponding to the thiosulfinate moiety.[12] For each thiosulfinate two diastereoisomers were observed due to the two chiral elements existing in such molecules (thiosulfinate and allene). The first step of the above reaction sequence parallels the 1,4-electrophilic addition of arenesulfenyl chlorides to dienes.[13] It is also interesting to note, that the preparation of mixed allylic allenic thiosulfinates, such as **13a–f**, is not easily achieved by other methods. The γ-substituted and unsubstituted propargylic monoalkoxy chlorodisulfides **11g–i** do not react at all in the same fashion and undergo decomposition, probably due to their inability to undergo the rearrangement step. A similar dependence on substitution pattern was observed for the rearrangement of allylic thiosulfoxylates to allylic thiosulfinates.[14]

In addition to their chemical interest,[12,15] thiosulfinates play a considerable biological role in allicin chemistry. For example, allicin, which is isolated from common garlic *Allicin sativum* and is responsible for its remarkable medicinal properties, is diallyl thiosulfinate.[9] The compound shows antibacterial activity, tumour inhibiting properties, anti-viral activity and fungicidal properties. Consequently, we intend to examine systematically the biological activity of the new mixed allylic allenic thiosulfinates.

In continuation, we succeeded in preparing a series of allylic chloroalkoxy disulfides. Their reaction with 2,3-dimethyl-1,3-butadiene occurred in a similar manner (Scheme 5) and afforded variously substituted diallylic thiosulfinates **16a–e**. Extensive spectroscopic determinations as detailed above for products **13a–f** led to the identification of the new products (Table 2).[11] As found for the corresponding propargylic derivatives, the γ-methyl substituted allylic ester (yield 88%) was unreactive towards the above diene. This result is consistent with Baldwin's report on rearrangement of allylic thiosulfoxylates to allylic thiosulfinates.[14] With a simple method, for the preparation of diallylic thiosulfinates (e.g., **16a–e**) in hand, study of the effect of substitution on the biological activity of allicin is now possible.

General procedure for the reaction of propargylic and allylic chloroalkoxy disulfides with 2,3-dimethyl-1,3-butadiene

To a cooled solution of S_2Cl_2 (20 mmol) in 100 mL of dry ether at −10 °C, under a nitrogen atmosphere, was added dropwise with stirring a solution of triethylamine (20 mmol) in 50 mL of dry ether. After further stirring for 20 min at the same temperature, a solution of the appropriate alcohol (10 mmol) in 50 mL of dry ether was added slowly and dropwise. After further stirring for 30 min at this temperature, the reaction mixture was filtered under vacuum with external cooling using an ice water bath to remove triethylammonium chloride. Next, the filtrate was washed with 50 mL of ice-water. After drying over anhydrous $MgSO_4$ and removal of

the solvent, the product was obtained as a viscous liquid. Due to the low stability of these products, they were immediately dissolved in cold chloroform and further reacted as follows. To a solution of chloroalkoxy disulfide (10 mmol) in dry chloroform (20 mL) was added 2,3-dimethyl-1,3-butadiene (20 mmol) and the reaction mixture was stirred at room temperature under a nitrogen atmosphere for 30 min. After the solvent and the remaining diene were removed under reduced pressure, the products were separated by column chromatography using silica gel with chloroform as eluent. All products were obtained as viscous oils.

Acknowledgements

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11. All new compounds showed spectral data in accord with the assigned structures. Selected data: *S*-[(2*Z*)-4-chloro-2,3-dimethylbut-2-enyl] buta-1,2-diene-1-sulfinothioate (**13a**, yield 62%), as a mixture of two diastereoisomers: ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.213 and 6.205 (dq, J = 6.0, 3.0 Hz, 1H each), 5.90 and 5.88 (qd, J = 7.5, 6.0 Hz, 1H each), AB_q: 4.21 (d, J = 11.0 Hz, 1H for both isomers) and 4.12 (d, J = 11.0 Hz, 1H for both isomers), AB_q: 3.94 (d, J = 12.6 Hz, 1H for both isomers) and 3.76 (d, J = 12.6 Hz, 1H for both isomers), 1.82–1.89 (br m, 9H for both isomers), ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.61 (=*C*= for both isomers), 131.03 (=*C*–CH_3 for both isomers), 129.60 (=*C*–CH_3 for both isomers), 100.65 and 100.56 (=*C*H– each), 97.18 and 97.08 (=*C*H– each), 45.52 (–*C*H_2–Cl for both isomers), 35.46 and 35.34 (–*C*H_2–S each), 18.41 (*C*H_3–C= for both isomers), 17.51 (*C*H_3–C= for both isomers), 13.67 and 13.50 (*C*H_3–CH= each), IR (neat): 1086 (S=O), 1327, 1374, 1455, 1654, 1947 (=C=), 2977 cm^{-1}, MS (CI/CH_4): *m*/*z* 251 (MH^+, 5%), 215 (MH^+–'HCl', 7%), 113 (100%), HRMS (elemental composition): calcd ($C_{10}H_{16}OS_2Cl$) 251.033112; found 251.032173, *S*-[(2*Z*)-4-chloro-2,3-dimethylbut-2-enyl] (2*E*)-oct-2-ene-1-sulfinothioate (**16d**, yield 81%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.85 (br dt, J = 15.5, 7.0 Hz, 1H), 5.55 (dtt, J = 15.5, 7.5, 1.0 Hz, 1H), AB_q: 4.20 and 4.11 (d, J = 11.0 Hz, 1H each), AB_q: 3.93 and 3.76 (d, J = 13.0 Hz, 1H each), AB system: 3.81 and 3.73 (br ddd, J = 13.0, 7.5, 1.0 Hz, 1H each), 2.11 (br q, J = 7.2 Hz, 2H), 1.84 (s, 6H), 1.41 (br quint, J = 7.2 Hz, 2H), 1.29 (m, 4H), 0.89 (br t, J = 7.0 Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.44 (=*C*H–), 131.12 (=*C*–CH_3), 130.23 (=*C*–CH_3), 117.13 (=*C*H–), 59.47 (–*C*H_2–S=O), 45.79 (–*C*H_2–Cl), 35.36 (–*C*H_2–S), 32.71 (–*C*H_2–), 31.36 (–*C*H_2–), 28.59 (–*C*H_2–), 22.53 (–*C*H_2–), 18.57 (*C*H_3–C=), 17.75 (*C*H_3–C=), 14.11 (–*C*H_3), IR (neat): 1082 (S=O), 1379, 1462, 1656, 2359, 2926 cm^{-1}, MS (CI/CH_4): *m*/*z* 309 (MH^+, 9%), 149 ($C_6H_{10}SCl$, 15%), 69 (100%), HRMS (elemental composition): calcd ($C_{14}H_{26}OS_2Cl$) 309.111362; found 309.109395.
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