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Tandem sigmatropic rearrangements and cyclizations of propargylic dialkoxy disulfides

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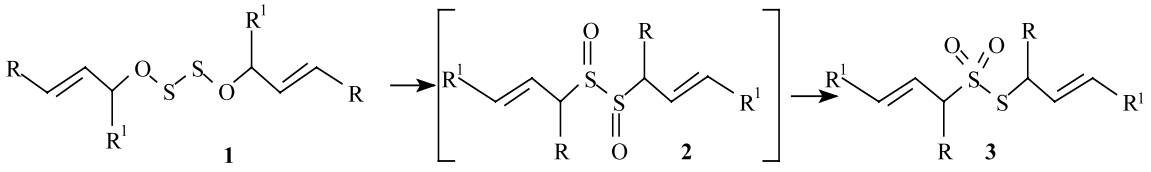
Abstract—The first successful preparation of propargylic dialkoxy disulfides in high yields is reported. These esters afforded novel 6,7-dithiabicyclo[3.1.1]heptane-2-one 6-oxide derivatives via an unprecedented sequence of three [2,3]- and one [3,3]-sigmatropic shifts followed by an intramolecular [2+2] cycloaddition. The latter are structurally related to the zwiebelanes, recently isolated from freshly cut onion.

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] Though, 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 successful synthesis and reactivity of allylic dialkoxy disulfides.[7] Thus, the allylic dialkoxy disulfides undergo a double [2,3]-sigmatropic rearrangement to the appropriate *vic*-disulfoxides. The latter are unstable[8] and undergo the usual well-known rearrangement to the corresponding thiosulfonates (Scheme 1).[7]

Following our successful preparation of allylic dialkoxy disulfides we have applied the same method for the preparation of propargylic analogues.[7b] We are glad now to report the first successful preparation of a series of such esters in high yields (91–98%). Furthermore, and contrary to previous reports, these compounds have been found to be stable in chloroform solution at –18°C for extended periods of time.[7] The rearrangement of these esters **5a**–**e**, which has been carried out at different temperatures in chloroform solution depends on substitution. For example, the reaction of the α-substituted esters is completed after 20 h at room temperature or after 2 h at reflux temperature. With γ-substituted esters, heating for about 10 h is required.

Unexpectedly, the products isolated by us were similar spectroscopically to some unusual sulfur compounds isolated and synthesized by Block,[9] namely the zwiebelanes. Thus, for products derived from propargylic dialkoxy disulfides, we propose the surprising dithiabicyclic structure **9a**–**e**[10] presented in Scheme 2. Based on analogy we suggest that propargylic dialkoxy disulfides undergo a double [2,3]-sigmatropic rearrangement to diallenic *vic*-disulfoxides. The latter, rather than transforming to the diallenic thiosulfonates (cf. diallylic disulfoxides **2**, Scheme 1), undergo a further sequence of one [2,3]- and one [3,3]-sigmatropic rearrangement,



Scheme 1.

Keywords: propargylic dialkoxy disulfides; synthesis; sigmatropic rearrangement; cycloaddition; thioaldehyde; sulfine.
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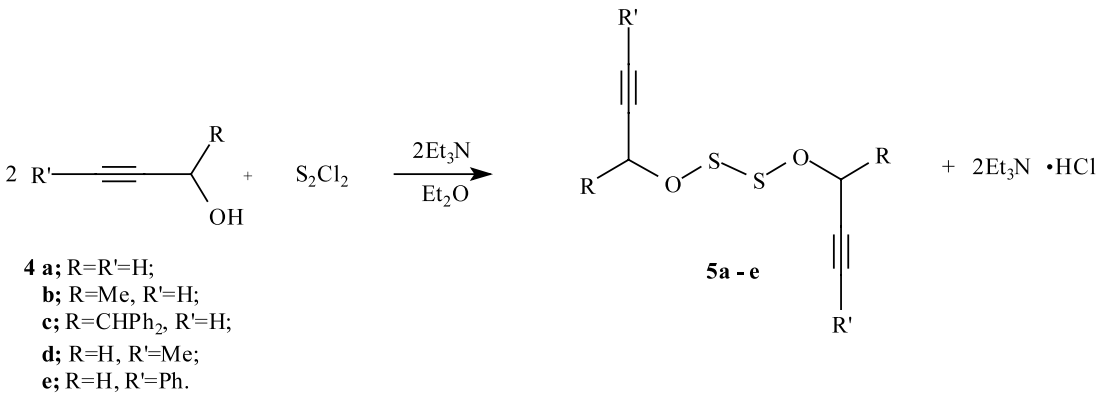
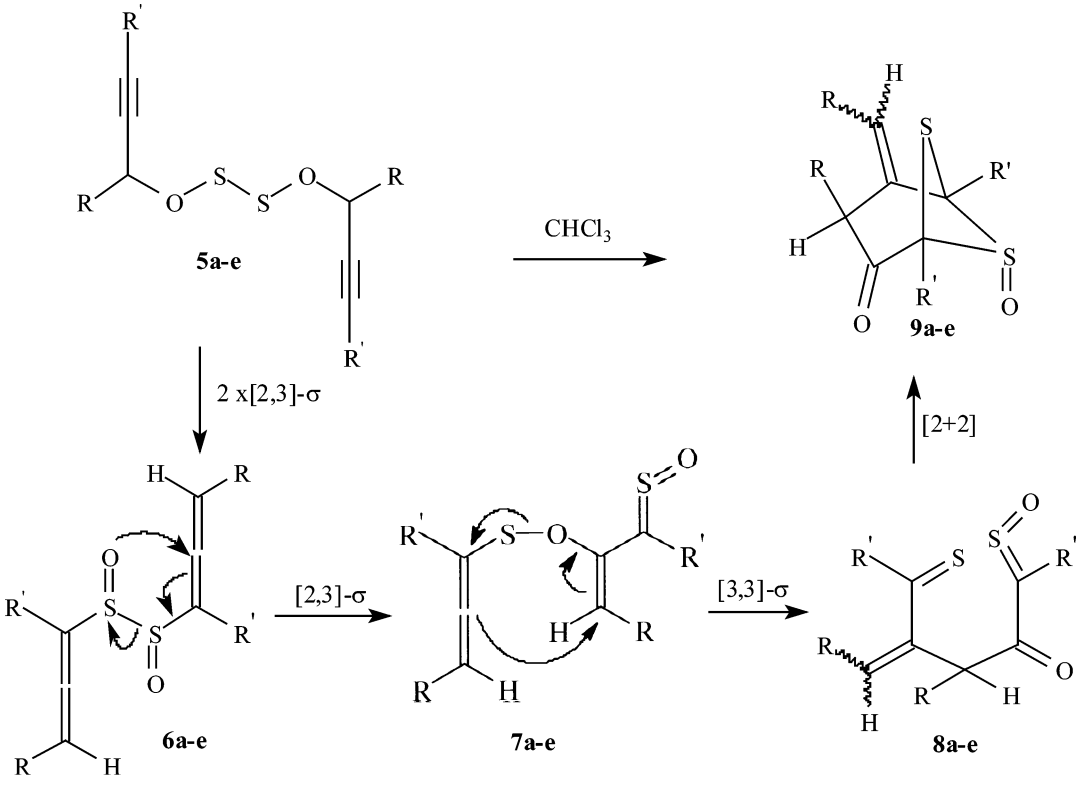
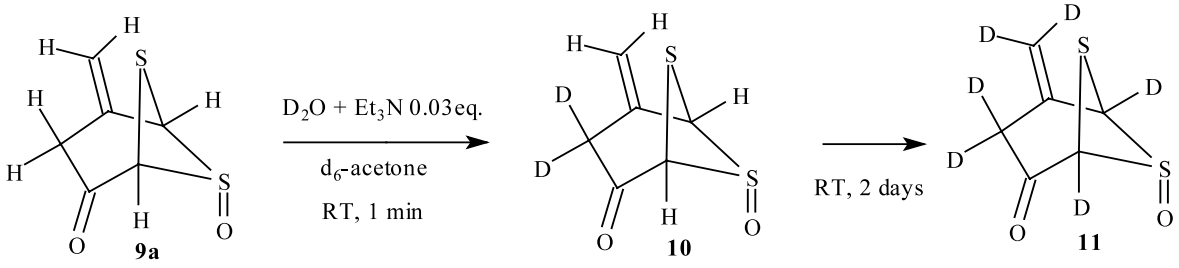


4 a; R=R'=H;
b; R=Me, R'=H;
c; R=$CHPh_2$, R'=H;
d; R=H, R'=Me;
e; R=H, R'=Ph.

followed by a head-to-tail intramolecular [2+2] cycloaddition of the generated sulfine and thioaldehyde moieties to form the dithiabicyclo products **9a**–**e**. There is a striking similarity between the last two steps in the formation of **9a**–**e**, as shown in Scheme 2 and the formation of zwiebelanes by rearrangement of the appropriate di-1-propenyl thiosulfinate.[9] One should add that the parent structure of **9a**–**e** has been recently reported,[11] but no derivatives such as **9a**–**e** appear in the literature, so far.



Scheme 2.



Scheme 3.

The structures of compounds **9a**–**e** are based on a full NMR analysis of the ^1H and ^{13}C NMR data, including several 2D techniques such as COSY, NOESY, HMQC and HMBC and is supported by IR and HRMS experiments. The most unusual feature of these spectra is the strong deshielding of the bridgehead carbons, e.g. δ 70.48 ppm (**C**H-C(O)) and δ 67.23 ppm (**C**H-S) for **9a**. When these positions are H – substituted, as in **9a** and **9d**,**e**, the bridgehead hydrogens show unusually high $^4J_{HH}$ values (e.g. 4.8 Hz for **9a**). In addition, the IR spectrum shows two strong signals corresponding to the sulfoxide and carbonyl group, respectively (1100 and 1718 cm^{-1}).[10] Supporting evidence for structures **9a**–**e** is provided by the observation that in the presence of triethylamine (0.03 equiv.) and D_2O in d_6-acetone solution the methylene protons α to the carbonyl group were immediately replaced by D (product **10**); after two days all other protons were replaced (see Scheme 3), as followed by ^1H NMR. The final perdeuterated product **11** was established by its HRMS with the corresponding pseudomolecular peak MH^+ at 181.024659 (calcd for $C_6{}^2H_6O_2S_2$ 181.026409). α-Substituted propargylic dialkoxy disulfides **5b**,**c** gave a mixture of (*Z*) and (*E*) bicyclic products **9b**,**c**. An analysis of the spectroscopic data leads us to believe that the S=O is in the *endo* stereochemistry and the substituent α to the carbonyl is in the pseudoequatorial position. All products were stable at low temperature (−18°C) for extended periods.

Based on our past experience with tandem sigmatropic rearrangements and cyclization reactions of propargylic systems,[3] and prompted by our discovery of an unexpected transformation of dipropargylic dialkoxy disulfides to novel dithiabicyclic derivatives related to zwiebelanes (involving an unprecedented sequence of sigmatropic rearrangements and cycloadditions), and the fascinating organosulfur chemistry of *allium* species,[9] we intend to determine the scope and limitations of this reaction, as well as the chemistry and synthetic utility of the new compounds. In view of the remarkable therapeutic properties of the zwiebelanes, we plan to systematically examine the biological activity of the various derivatives of our novel dithiabicyclic products.

Acknowledgements

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10. All new compounds showed spectral data in accord with assigned structures. Selected data: dipropargyloxy disulfide **5a** (yield 98%): ^1H NMR: ABX system; AB: δ 4.52 and 4.45 (J_{gem}=15.7, J=2.5 Hz, 2H each); X: 2.60 (t, J=2.5 Hz, 2H), ^{13}C NMR (300 MHz, $CDCl_3$): δ 78.43 (≡**C**–), 76.48 (≡**C**H), 61.23 (–**C**H_2–), IR (neat): 1000, 1347, 1350, 1439, 2124, 3301 cm^{-1}, MS (CI/CH_4): m/z 175 (MH^+, 41.83%), 131 (100%), 127 (45.52%), 111 (85.65%), HRMS (elemental composition): calcd ($C_6H_7O_2S_2$) 174.988748; found 174.988613, bis-γ-phenylpropargyloxy disulfide **5e** (yield 91%): ^1H NMR δ 7.45 (m, 4H), 7.31 (m, 6H), ABq: 4.75 and 4.68 (J_{gem}=15.6 Hz, 2H each), ^{13}C NMR (300 MHz, $CDCl_3$): δ 131.80, 128.74, 128.26, 122.06 (Ar), 87.99 (≡**C**–), 83.82 (≡**C**–), 62.16 (–**C**H_2–), IR (neat): 980, 1345, 1442, 1490, 2222, 2926 cm^{-1}, MS (CI/CH_4): m/z 327 (MH^+, 1.68%), 163 ($M^+/2$, 40.00%), 131 ($M^+/2$–'S', 44.26%), 115 ($C_9H_7^+$, 100%), HRMS (elemental composition): calcd ($C_{18}H_{15}O_2S_2$) 327.051348; found 327.052765, 4-methylene-6,7-dithiabicyclo[3.1.1]heptan-2-one 6-oxide **9a** (yield 69%): ^1H NMR (300 MHz, $CDCl_3$): δ 5.45 (ddd, J=2.1, 2.0, 0.4 Hz, 1H), 5.43 (dd, J=2.0, 1.5 Hz, 1H), 5.07 (dd, J=4.8, 0.4 Hz, 1H), 4.59 (d, J=4.8 Hz, 1H), ABX system: 3.86 (dt, J=20.7, 2.1 Hz, 1H) and 3.49 (dt, J=20.7, 1.5 Hz, 1H), ^{13}C NMR (300 MHz, $CDCl_3$): δ 197.29 (**C**=O), 133.46 (=**C**–), 120.36 (=**C**H_2), 70.48 (**C**H–C(O)), 67.23 (**C**H–S), 41.97 (–**C**H_2–), IR (neat): 1100, 1718 cm^{-1}, MS (CI/CH_4): m/z 175 (MH^+, 76.14%), 157 ($(M-H)^+$-'O', 14.33%), 141 ($(M-H)^+$–'S', 48.57%), 126 ($(M-H)^+$–'SO', 100%), HRMS (elemental composition): calcd ($C_6H_7O_2S_2$) 174.988748; found 174.990208, 4-ethylidene-3-methyl-6,7-dithiabicyclo[3.1.1]heptan-2-one 6-oxide **9b** (yield 57%) as a mixture of two isomers (*E* is a minor and *Z* is a major product in a ratio 1:4.7, respectively): ^1H NMR (300 MHz, $CDCl_3$): δ 6.09 (qd, J=7.0, 2.3 Hz, 1H (=CH–) for *Z* isomer) and 6.02 (qd, J=7.0, 1.8 Hz, 1H (=CH–) for *E* isomer), 5.54 (d, J=5.1 Hz, 1H (CH–C=) for *Z* isomer) and 5.47 (d, J=5.0 Hz, 1H (CH–C=) for *E* isomer), 4.584 (d, J=5.1 Hz, 1H (CH–C=O) for *Z* isomer) and 4.576 (d, J=5.0 Hz, 1H (CH–C=O) for *E* isomer), 4.08 (qquint, J=7.0, 2.3 Hz, 1H (CH–Me) for *Z* isomer) and 3.39 (qquint, J=7.0, 1.8 Hz, 1H (CH–Me) for *E* isomer), 1.80 (dd, J=7.0, 1.8 Hz, 3H

(**CH$_3$**–CH=) for *E* isomer) and 1.79 (dd, $J=7.0$, 2.3 Hz, 3H (**CH$_3$**–CH=) for *Z* isomer), 1.63 (d, $J=7.0$ Hz, 3H (**CH$_3$**–CH–C=O) for *E* isomer) and 1.40 (d, $J=7.0$ Hz, 3H (**CH$_3$**–CH–C=O) for *Z* isomer), ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.02 (**C**=O for *Z* isomer) and 199.51 (**C**=O for *E* isomer), 130.25 (=**C**– for *E* isomer) and 128.15 (=**C**– for *Z* isomer), 129.94 (=**C**H– for *E* isomer) and 129.13 (=**C**H– for *Z* isomer), 68.80 (**C**H–C=O for *Z* isomer) and 66.84 (**C**H–C=O for *E* isomer), 66.44 (**C**H–C= for *Z* isomer) and 64.44 (**C**H–C= for *E* isomer), 46.57 (–**C**H–CH_3 for *E* isomer) and 46.22 (–**C**H–CH_3 for *Z* isomer), 19.28 (–**C**H$_3$ for *E* isomer) and 13.72 (–**C**H$_3$ for *Z* isomer), 13.59 (–**C**H$_3$ for *E* isomer) and 10.30 (–**C**H$_3$ for *Z* isomer), IR (neat): 1110 (S=O), 1715 (C=O) cm^{-1}, MS (CI/CH_4): *m*/*z* 202 (M^+, 36.13%), 169 ($(M-H)^+$–'S', 17.24%), 154 (M^+–'SO', 100%), HRMS (elemental composition): calcd ($C_8H_{10}O_2S_2$) 202.012223; found 202.011517.

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