Pergamon

Tetrahedron Letters, Vol. 35, No. 31, pp. 5575-5578, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

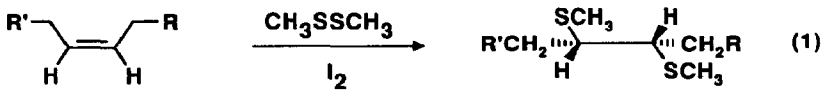
0040-4039(94)01145-1

Thietane, Tetrahydrothiophene and Tetrahydrothiopyran Formation in Reaction of Methylene-Interrupted Dienoates with Dimethyl Disulfide[1]

Néstor M. Carballeira*, Fathi Shalabi, and Clarisa Cruz
Department of Chemistry, University of Puerto Rico, P.O. Box 23346, San Juan, Puerto Rico 00931-3346.

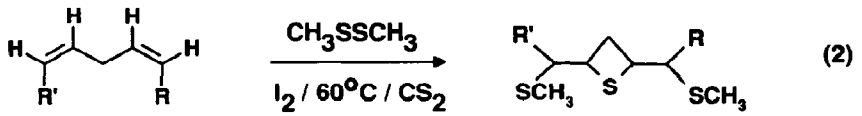
Abstract. *The reaction of dimethyl disulfide in I_2 with a series of methylene-interrupted methyl dienoates was examined. In all cases ring-closure occurs and thietane formation competes favorably with tetrahydrothiophene formation. When the I_2 concentration was increased, tetrahydrothiopyran formation was observed. These results are explained in terms of two distinct reaction pathways.*

Formation of dimethyl disulfide (DMDS) adducts has been one of the most useful reactions for exactly locating the double bonds in monounsaturated and diunsaturated fatty acid methyl esters by gas chromatography-mass spectrometry (gc-ms).[2] The olefins are normally reacted with dimethyl disulfide in I_2, methylsulfenyl iodide is generated in situ and adds to the double bonds via the well established episulfonium intermediate.[3] The generated thiiranium ion is then trapped by dimethyl disulfide to generate the corresponding dimethyl disulfide adduct (eq.1). Iodine acts as a catalyst in this reaction and the reaction is stereoselective.



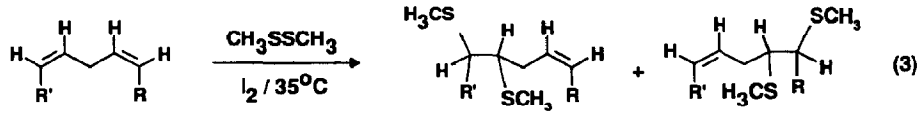
(1)

The reaction of methylene-interrupted dienes with dimethyl disulfide and I_2 has also recently been explored. M. Vincenti et. al.[4] reacted 0.4-1.0 nmol of diene with 50 µl of dimethyl disulfide (CH_3SSCH_3) and 300 mg of I_2 at 60°C for 40h in CS_2. Only thietane formation was observed (eq. 2). On the other hand, A. Shibahara



(2)

and collaborators[5] reacted 1 mmol of diene with 0.3 ml of dimethyl disulfide and 4 mg of I_2 at 35°C for only 30 min. Under these conditions only addition of dimethyl disulfide was observed resulting in a mixture of two monounsaturated dimethyl disulfide adducts (eq.3). The mass spectral data of these adducts permits the



(3)

unequivocal location of the double bonds in the original diunsaturated compounds, an important tool when unknowns must be characterized from natural sources in microgram to nanogram quantities.

Herein we report that reaction of methyl dienoates with DMDS in I_2 proceeds with ring closure to the corresponding thietane, tetrahydrothiophene and tetrahydrothiopyran derivatives given the appropriate reaction conditions. These results are not only important as a method to characterize unknown natural products in

microgram quantities, but also mechanistically since it demonstrates that sulfur can do internal cyclizations that other first row elements, such as oxygen, can not do.

Commercially available (SIGMA) ethyl (9Z,12Z)-9,12-octadecadienoate (7 mg, 0.02 mmol) was reacted with 1.4 mL (15.5 mmol) of dimethyl disulfide and 0.16 mmol of I_2 in 0.35 mL of diethyl ether at 53°C for 24h. Then, 5 mL of distilled hexane were added and the organic layer was washed with dilute sodium thiosulfate solution (2 X 5 mL), dried over sodium sulfate and the solvent evaporated to dryness. The product was dissolved in distilled hexane and submitted to gas chromatography-mass spectrometry (gc-ms) analysis. Four peaks were resolved (Fig.1) by capillary gc (5972A MS ChemStation equipped with a 30 m X 0.25 mm special performance capillary column, HP-5MS, crosslinked with 5% Ph Me silicone. The temperature program was as follows: 130° for 2 min, then increased at 3°/min to 270° and maintained for 40 min. The carrier gas was He at a pressure of 10 psi). The

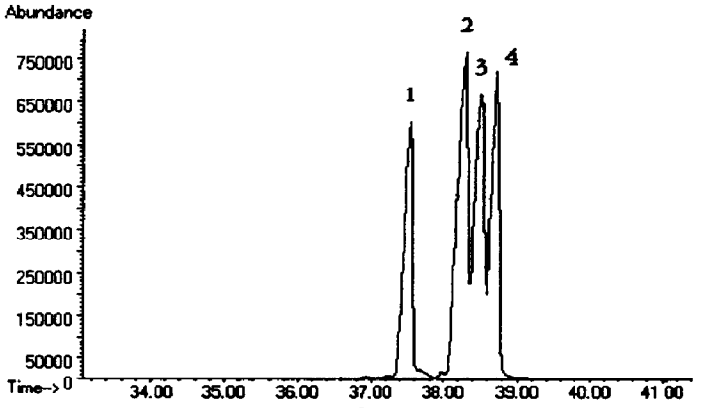
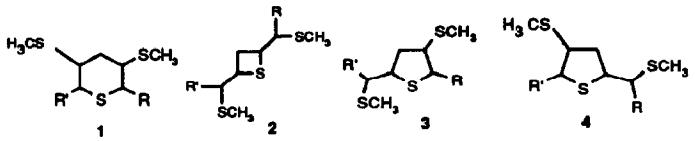


Figure 1. Gas Chromatogram of the Four Isomers from the Reaction of Ethyl (9Z,12Z)-9,12-Octacosadienoate with Dimethyl Disulfide and I_2.

first peak was characterized as 2-(7-ethoxycarbonylheptan-1-yl)-3,5-dimethylthio-6-(pentan-1-yl)tetrahydrothiopyran by its mass spectral fragmentation pattern. Tetrahydrothiopyran **1** exhibited a M^+ 434 and key fragmentations at *m/z* 387 (loss of CH_3S) and at *m/z* 339 (loss of CH_3S + CH_3SH). This double loss of methanethiol from the molecular ion dominated the mass spectrum.[4] The second peak corresponded to 2-(8-ethoxycarbonyl-1-methylthiooctan-1-yl)-4-(1-methylthiohexan-1-yl)thietane. Thietane **2** also displayed a M^+ 434 and key fragmentations between the carbon-carbon bonds containing the sulfur substituents, i.e., between C_9 and C_{10} and between C_{12} and C_{13}. Cleavage between C_9 and C_{10} afforded the fragments at *m/z* 231 [41%, $C_{12}H_{23}SO_2]^+$ and *m/z* 155 [100%, $C_9H_{15}S]^+$, the latter fragment resulting from loss of methanethiol from *m/z* 203 (21%). On the other hand, cleavage between C_{12} and C_{13} afforded the fragments at *m/z* 131 [35%, $C_7H_{15}S]^+$ and *m/z* 255 [34%, $C_{14}H_{23}SO_2]^+$, the latter also resulting from loss of methanethiol from the *m/z* 303 fragment which is not observed. Peak 3 was characterized as 2-(8-ethoxycarbonyl-1-methylthiooctan-1-yl)-4-methylthio-5-(pentan-1-yl)tetrahydrothiophene and peak 4 corresponded to 2-(7-ethoxycarbonylheptan-1-yl)-3-methylthio-5-(1-methylthiohexan-1-yl)tetrahydrothiophene. In the case of tetrahydrothiophene **3**, the ms fragmentation between C_9-C_{10} predominated in the spectrum affording the fragments at *m/z* 231 [30%, $C_{12}H_{23}SO_2]^+$ and at *m/z* 155 [100%, $C_9H_{15}S]^+$. In peak **4** the fundamental ms fragmentations occurred between C_{12}-C_{13}, but the base peak was observed at *m/z* 209 [100%, $C_{12}H_{17}SO]^+$, arising from loss of ethanol from *m/z* 255. The ratio of tetrahydrothiopyran/thietane/tetrahydrothiophene was 20:32:47. A similar isomer distribution was encountered with other dienoates of natural origin (Table 1). For example, the rare (7Z,10Z)-7,10-hexadecadienoic acid, identified in *Cladophorosis macromeres*,[6] gave a tetrahydrothiopyran/thietane/tetrahydrothiophene distribution of 16:36:48. A change in iodine concentration resulted in trace amounts of tetrahydrothiopyran(Table 1). For example, when ethyl (9Z,12Z)-9,12-octadecadienoate (55 mg, 0.18 mmol) was reacted with 1.5 mL (16.6 mmol) of DMDS and 0.057 mmol of I_2 in 0.12 mL of diethyl ether at 53°C for 24 h, only 1% of tetrahydrothiopyran **1** was formed. This fact was corroborated by reacting other acids of natural origin (Table 1). For example,

Table 1. Ratio of Tetrahydrothiopyran, Thietane and Tetrahydrothiophene Formation in the Reaction of Different Dienoates with Dimethyl Disulfide and I_2.[a]

Dienoate	Source	 1 2 3 4 Abundance (wt %)			
16:2 Δ 9,12	*Cymopolia barbata*[b]	1%	41%	31%	27%
18:2 Δ 9,12	*Sigma (standard)*[b]	1%	34%	34%	31%
20:2 Δ11,14	*Cyphoma gibbosuma*[b]	2%	37%	31%	30%
		1 ± 1%	37± 2 %	32 ± 1%	29 ± 2%
16:2 Δ 7,10	*C. macromeres*[c]	16%	36%	26%	22%
18:2 Δ 9,12	*Sigma (standard)*[c]	20%	32%	25%	22%
18:2 Δ 9,12	*C. macromeres*[c]	13%	38%	25%	24%
		16 ± 2%	35± 2 %	25 ± 1%	22 ± 1%
18:2 Δ 9,12	*Sigma (standard)*[d]	59%	10%	15%	16%

a. In the cyclic structures R' denotes the carbonyl end and R the methyl end of the chain.

b. Reaction conditions: 16.6 mmol of dimethyl disulfide and 0.057 mmol of I_2 at 53°C for 24h.

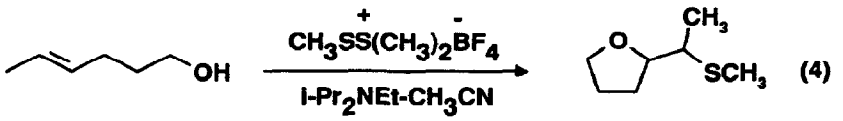
c. Reaction conditions: 15.5 mmol of dimethyl disulfide and 0.16 mmol of I_2 at 53°C for 24h.

d. Reaction conditions: 5.6 mmol of dimethyl disulfide and 0.16 mmol of I_2 in 1.25 mL of Et_2O at 53°C for 24h.

(9Z,12Z)-9,12-hexadecadienoic acid, from the algae *Cymopolia barbata*, and (11Z,14Z)-11,14-eicosadienoic acid, from the mollusk *Cyphoma gibbosum*, also afforded trace amounts (1-2%) of tetrahydrothiopyran when the above conditions were employed. One possible explanation for our results is to have two distinct reaction pathways, one leading to thietane formation and the other leading to a mixture of tetrahydrothiopyran and tetrahydrothiophene. The products of the second pathway seem to interconvert in an iodine-catalyzed reaction. In the second pathway tetrahydrothiopyran is the thermodynamic product and the tetrahydrothiophenes the kinetic products. It has been observed that when excess DMDS is used, the reaction rate increases[4]. If DMDS concentration is raised, then the

reaction is expected to go faster and tetrahydrothiopyran formation should decrease. In fact, when DMDS concentration was lowered, more tetrahydrothiopyran was formed (Table 1).

The DMDS/I_2 reaction is an excellent system to test four, five and six-membered ring formation with sulfur as an internal nucleophile. Formation of the six-membered ring seems to be highly solvent dependent in this reaction. It is of interest to mention that when 4-hexen-1-ol was reacted with dimethyl(methylthio)sulfonium fluoroborate (DMTSF), only tetrahydrofuran formation was observed[7], and not even traces of tetrahydropyran (eq.4). In the DMDS/I_2 reaction, sulfur can do both cyclizations depending on the reaction conditions.



(4)

A more interesting result was reported when 3-buten-1-ol was reacted with phenylsulfenyl chloride. No cyclization took place, but rather chlorine addition was observed (eq.5).[8] In the DMDS/I_2 reaction sulfur can adopt the necessary conformation to cyclize since thietane formation was readily formed in all the examples we

(5)

examined. It is evident that the C-S bond is longer (1.8 Å) than the C-O bond (1.4 Å), and therefore sulfur can attain conformations that are unavailable to first row atoms, such as oxygen. The 3d orbitals of sulfur can also play a role in this reaction. Work is in progress trying to elucidate the mechanistic aspects of this cyclization.

ACKNOWLEDGMENTS

We thank Mayra Pagán for technical assistance with the *Cladophorosis macromeres*. Financial support by the NSF-EPSCoR and NSF-MRCE programs is gratefully acknowledged.

REFERENCES AND NOTES

1. Presented at the 207th American Chemical Society National Meeting, San Diego, California, March 13-17, 1994.
2. Francis, G.; Veland, K. *J. Chromatogr.*, **1981**, *219*, 379-384.
3. Csizmadia, V.; Schmid, G.; Mezey, P.; Csizmadia, I. *J. Chem. Soc., Perkin Trans. 2*, **1977**, 1019-1024.
4. Vincenti, M.; Guglielmetti, G.; Cassani, G.; Tonini, C. *Anal. Chem.*, **1987**, *59*, 694-699.
5. Yamamoto, K.; Shibahara, A.; Nakayama, T.; Kajimoto, G. *Chem. Phys. Lipids*, **1991**, *60*, 39-50.
6. All organisms in this study were collected around La Parguera, Puerto Rico. For a representative isolation procedure see: Carballeira, N.; Negrón, V.; Reyes, E. *Tetrahedron*, **1992**, *48*, 1053-1058.
7. O' Malley, G.; Cava, M. *Tetrahedron Lett.*, **1985**, *26*, 6159-6162.
8. Tuladhar, S.; Fallis, A. *Tetrahedron Lett.*, **1987**, *28*, 523.

(*Received in USA* 6 *April* 1994; *revised* 8 *June* 1994; *accepted* 9 *June* 1994)