Episulfidation of *trans*-Cyclooctene with an 1,2,4-Oxadithiolane

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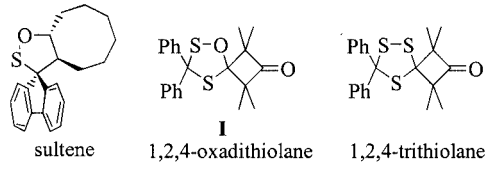
The dipolar cycloaddition of thiobenzophenone *S*-oxide (**1**) and 2,2,4,4-tetramethyl-3-thioxocyclobutanone (**2**) generates the labile 1,2,4-oxadithiolane **I**, which in the presence of *trans*-cyclooctene (**3**) affords *trans*-episulfide (**9**). In this direct sulfur transfer, the oxathiirane **II** and/or the dithiirane **IV**, both derived from the 1,2,4-oxadithiolane **I**, are proposed as elusive episulfidating agents.

Introduction

Recently we have reported that the 9*H*-fluorenyl-9-thione *S*-oxide engages readily in 1,3-dipolar cycloaddition with **3** to give a cyclic 1,2-oxathiolane (sulfenate, sultene) as persistent product.[1−3] The latter was shown to transfer efficiently a sulfur atom to strained cycloalkenes under acid catalysis, e.g., *trans*-cyclooctene, to afford the corresponding episulfide in high yield. In the light of these promising results obtained with the sultene as episulfidation agent, we anticipated that similarly, such direct sulfur-transfer methodology should be extendable to other sulfur heterocycles. In particular, we focused our attention on the related 1,2,4-oxadithiolane **I** as a promising candidate for the direct episulfidation of alkenes, since it also contains the reactive sulfenate functionality.



sultene **I** 1,2,4-oxadithiolane 1,2,4-trithiolane

The synthesis of a series of differently substituted 1,2,4-oxadithiolanes have been reported a few years ago in [2+3] cycloadditions of aliphatic thioketones with dialkyl or diaryl sulfines; some of them were shown to convert into 1,2,4-trithiolanes on thermal decomposition.[4] While the persistent 1,2,4-trithiolanes are ineffective for sulfur transfer,[5] we report herein that the in-situ-generated, similarly substituted 1,2,4-oxadithiolane **I** episulfidates the strained *trans*-cyclooctene (**3**) to afford its episulfide **9**. Several persistent 1,2,4-oxadithiolanes, that have been reported in literature,[4−6] were also tested, but they were inactive for sulfur transfer to the strained **3** under thermal conditions.

Results and Discussion

The thermally labile 1,2,4-oxadithiolane **I** was generated in situ,[6] by heating a solution of **1** and **2** in $CDCl_3$. In agreement with the literature data,[4−6] besides benzophenone (the main thermal decomposition product of the sulfine **1**[7]), thiobenzophenone, the 2,2,4,4-tetramethylcyclobutandione (**4**), as well as the 1,2,4-trithiolane **5**,[7] were observed by NMR spectroscopy. When, however, the same reaction was carried out in the presence of the reactive cycloalkene **3**, only traces of the cycloadduct **5** were obtained. In addition to the above-mentioned sulfine **1** and thioketone **2** products, the ^{13}C NMR spectrum of the crude reaction mixture revealed that the Diels−Alder adduct **6**,[8] its aromatized tautomer **7**[10], *cis*-cyclooctene (**8**), and *trans*-episulfide **9** had also been formed in variable amounts, which depended on the reaction conditions (Table 1).

Interestingly, norbornene was inert under comparable reaction conditions. After heating for 3.5 days in the presence of **3**, approximately equal amounts of both substrates had been consumed (entry 1). The monothione **2** was cleanly converted into dione **4**, whereas **1** gave expectedly thiobenzophenone as main product and minor amounts of benzophenone. The thiopyrans **6** and **7**, detected in the crude mixture are Diels−Alder products of the [4+2]-cycloaddition of thiobenzophenone with **3**. Although most of the **3** (76 mol %) was isomerized to **8** and appreciable quantities of the epi- sulfide **9** (about 24 mol %) were formed. As shown in an independent control experiment, elemental sul-

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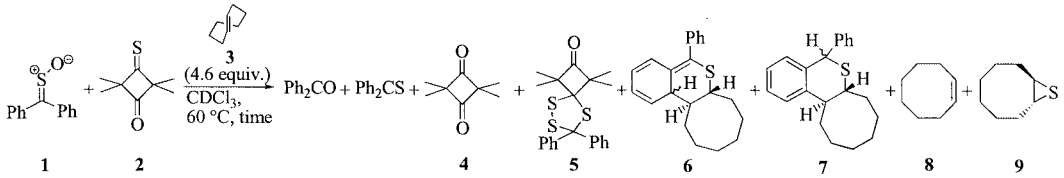
Table 1. Product distribution in the thermolysis of sulfine **1** and thione **2** in the presence of *trans*-cyclooctene (**3**)



Entry	Time (d)	2 (equiv.)	Conversion (%) 1	2	3	Material balance (%) 1	2	3	Ph_2CO	4	Ph_2CS	Products (mmol)[a] 5[b]	6	7	8	9
1	3.5	1.0	36	40	>84	92	>95	>95	0.072	0.390	0.130	–	0.081	traces	3.51	0.240
2	4.0	2.0	64	33	>69	95	94[b]	>96	0.051	0.535	0.199	traces	0.273	0.066	2.15	0.513
3	5.0	2.0	76	45	>95	>95	93[b]	>95	0.072	0.765	0.199	traces	0.365	0.070	3.54	0.647
4	13.0	2.0	84	59	>95	>95	89[b]	91	[c]	0.968	0.307	traces	0.321	0.171	3.01	0.684
5[d]	7.5	1.0	60	70	>95	>95	>95	83	0.080	0.710	0.144	–	0.280	0.102	6.26	0.470

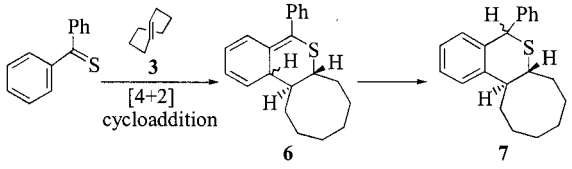
[a] Normalized to 1.0 mmol sulfine **1**, but 0.187 mmol were used; determined from the ^{1}H NMR spectra of the crude product mixture with the sum of all aryl protons as internal standard (error ±5% of the stated values). [b] The trithiolane **5** was detected but not quantified by ^{1}H NMR spectroscopy due to signal overlap. [c] Not quantified by ^{1}H NMR spectroscopy due to signal overlap. [d] 8.6 equiv. of *trans*-cyclooctene (**3**) were used instead of 4.6 equiv.

fur (detected in the reaction mixture) was not responsible for the episulfidation of **3** leading to **9**, but only for the isomerization of **3** to **8**.

When two equivalents of **2** were employed (entry 2), the consumption of the sulfine **1** was essentially doubled within about the same time period. More significantly, the yield of the episulfide **9** increased more than twice (compare entries 1 and 2), and substantially less *trans*-to-*cis* isomerization of **3** to **8** was observed. Even after longer reaction times (compare entries 2–4), the conversion of **1** was incomplete and the yield of thiirane **9** remained nearly constant. It is noteworthy that under the presented conditions (entries 3 and 4), the cycloalkene **3** was completely consumed, but most of it was isomerized to **8**. On prolonged heating considerably more thiobenzophenone was formed, which may be explained by the fact that the cycloalkene **3** was completely consumed and not available to trap more of the generated thiobenzophenone. Furthermore, additional heating converted the thiopyran **6** to its aromatized tautomer **7** (compare entries 3 and 4). Only traces of the trithiolane **5**[7] were observed in the ^{13}C NMR spectrum of the reaction mixture (entries 2–4).

On doubling the amount of cycloalkene **3** (compare entries 1 and 5), the conversion of the sulfine **1** and monothione **2** was approximately doubled. Expectedly, the yield of episulfide **9** was about twice; also more of Diels–Alder products **6** and **7** were observed in the mixture. The initially formed thiopyran **6** rearranges by stepwise[9] hydrogen migration to the aromatized thiopyran **7** (Scheme 1), a rearrangement that usually requires base catalysis.[10] In absence of a base catalyst, the thiopyran **6** was observed as the major product even after 13 days.

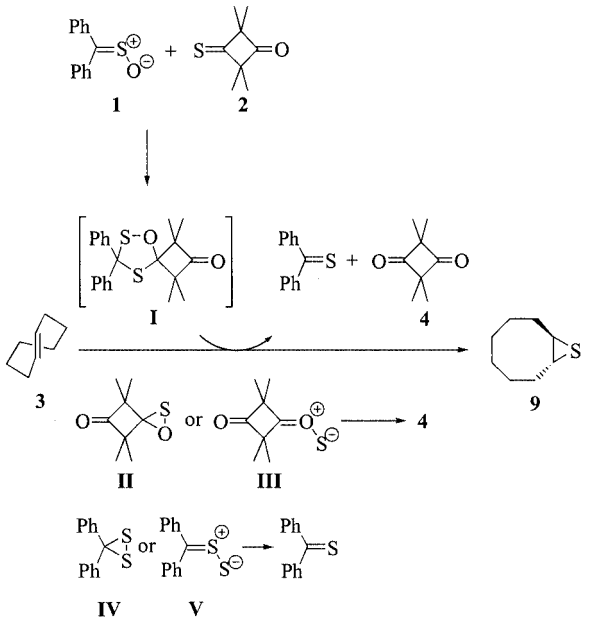
In order to explore the nature of the sulfur-transferring species, the following control experiments were conducted: Under the same reaction conditions the sulfine **1** (or monothione **2**), as well as the 1,2,4-trithiolane **5** (the side product derived from heating of **1** and **2**) alone did not afford thiirane **9** after heating with the cycloalkene **3**. Whereas merely 8% of sulfine **1** were converted into benzophenone, thione **2** and the authentic trithiolane **5** persisted completely under these conditions; only 20% of *trans*-cyclooctene **3** was isomerised to *cis*-cyclooctene **8** (see Exp. Sect.). The addition of *trans*-isomer **3** to the thermolysate and subsequent heating under identical conditions did not yield any episulfide **9**.



Scheme 1. Hetero-Diels–Alder reaction between thiobenzophenone and *trans*-cyclooctene (**3**)

As for the mechanism, it is relevant to mention that Huisgen[4–6] had studied the stoichiometric reaction between sulfine **1** and monothione **2** in the absence of an olefinic sulfur acceptor. Under these conditions, the intermediary 1,2,4-oxadithiolane **I** was proposed as an elusive precursor to the thiobenzophenone and dione **4** products (Scheme 2).

The oxathiirane **II** and the carbonyl *O*-sulfide **III** were postulated to desulfurize to **4**, whereas the dithiirane **IV** and the thiocarbonyl *S*-sulfide **V** were suggested to generate thiobenzophenone. Thus, the oxadithiolane **I** directly, or any of its sulfur-containing species **II**–**V**, may be postulated as active sulfur-transferring agents in the episulfidation process. The oxadithiolane **I** is probably sterically too hindered to engage in sulfur transfer and, therefore, presumably the short-lived and highly reactive intermediates **II**–**V** function as possible sulfurating entities. If the analogous oxygen donors may be taken as reactivity criterion, the oxathiirane **II**[10–11] and dithiirane **IV**,[12–13] which are akin to the dioxiranes,[14,15] should possess a higher sulfur-donating ability



Scheme 4. Episulfidation of *trans*-cyclooctene (**3**) in the thermolysis of in-situ-generated 1,2,4-oxadithiolane **I**

than the carbonyl *O*-sulfide **III** and the thione *S*-sulfide **V**; the latter are structurally similar to the for oxidation purposes inactive carbonyl oxides.[16,17−18] In the oxathiirane **II** the sulfur atom is positively polarized, whereas in the carbonyl *O*-sulfide **III** it is negatively charged. Thus, **II** should be more electrophilic than **III** and serve more likely as the sulfur-donating entity to a nucleophilic substrate such as *trans*-cyclooctene (**3**). In contrast to some isolable dithiiranes (appropriately substituted) analogous to **IV**, persistent derivatives of thiocarbonyl *S*-sulfides like **V** have not as yet been reported; presumably the open-ring form **V** is not sufficiently stablilized compared to the cyclic tautomer **IV** to allow direct detection.[19] Nonetheless, besides diphenyldithiirane (**IV**), also its open-ring isomer thiobenzophenone *S*-sulfide (**V**) has been invoked in the thermal fragmentation of tetraphenyl-1,2,4-trithiolane into thiobenzophenone and elemental sulfur.[20] On the basis of the afore-mentioned, we speculate that the intermediates **II** and **IV** act as sulfur-transfer agents in this episulfidation of the strained cycloalkene **3**.

Conclusion

We have shown that heating of a mixture of the sulfine **1** with monothione **2** in the presence of the strained *trans*-cyclooctene (**3**) results in the corresponding episulfide **9** by direct sulfur transfer. The oxadithiolane **I** is proposed as the initial intermediate, which readily converts under the reaction conditions to the transient oxathiirane **II** and dithiirane **IV**. Presumably, the latter two serve as the sulfur-transfering agents to the *trans*-cyclooctene (**3**), we favor the more electrophilic oxathiirane **II** as the more active episulfidating agent.

Experimental Section

General Remarks: All solvents were dried and distilled prior to use. For flash chromatography, Woelm silica gel (0.032−0.063 mm) was used. For TLC detection was performed on Polygram SIL/UV 254 plates from Machery−Nagel. The episulfide was visualized by means of elemental iodine, alkene spots by means of potassium permanganate. Chemical shifts are expressed in δ values relative to tetramethylsilane. For quantitative NMR analysis, a relaxation delay time for T_1 of 23 s was applied and dimethyl isophthalate was used as internal standard. The oxadithiolane **I** was prepared in situ.[4−6] *trans*-Cyclooctene (**3**) was synthesized from the corresponding *cis*-isomer **8** according to a literature procedure.[21]

General Procedure for the Reaction of Sulfine 1 with Monothione 2 and Cyclooctene (3). Analytical Scale: To a solution of 40.0 mg (0.187 mmol) of **1** and 29.2−58.4 mg (0.187−0.374 mmol) of **2** in 0.5 mL of $CDCl_3$ were added under an argon atmosphere 117 or 234 μL (0.860 or 1.72 mmol) of **3**. The NMR tube was sealed by means of a rubber stopper and Parafilm®, and heated in the dark in an oil bath at 60 °C for 13 days. At the beginning of the reaction a ^{1}H NMR spectrum was registered as reference point and at regular time intervals, aliquots of the crude reaction mixture were submitted to ^{13}C NMR and ^{1}H NMR analyses.

Preparative Scale: In a Schlenk tube were placed under an argon atmosphere 214 mg (1.00 mmol) of **1** and 312 mg (2.00 mmol) of **2** in 0.5 mL of $CHCl_3$, followed by 650 μL (5.00 mmol) of **3**. The tube was sealed and heated in an oil bath at 60 °C for 3 days in the dark. After evaporation of the solvent (40 °C/200 mbar), the known products **4**, **5**, **7**, **9** were isolated as pure compounds by silica-gel chromatography. Additionally, a mixture (67.6 mg) of **6** and **8** was isolated, of which the known cycloadduct **6**[22,23] was identified by its characteristic NMR signals. Benzophenone and thiobenzophenone were identified in the crude reaction mixture, the former by comparison with a commercial sample, the latter by comparison with a sample obtained from an independent synthesis.[24]

2,2,4,4-Tetramethylcyclobutan-1,3-dione (4):[25] Yield 62.3 mg (44%).

Spiro Compound 5:[7] Yield 153 mg (40%).

6a,7,8,9,10,11,12,12a-Octahydro-5-phenyl-5*H*-cycloocta[*c*][2]benzothiopyran (7):[31] Yield 117 mg (38%).

***trans*-9-Thiabicyclo[6.1.0]nonane (*trans*-9):**[26] Yield 82.6 mg (58%).

Determination of the Sulfur Balance in the Reaction of Sulfine 1 with Monothione 2 and Cyclooctene (3): After complete reaction, the tube was cooled to room temperature (ca. 20 °C) and 262 mg (1.00 mmol) of triphenylphosphane was added. After 2 h the solvent was evaporated (40 °C/200 mbar), and the products were purified by silica-gel chromatography. In a control experiment, no reaction between thiirane **9** and the triphenylphosphane was observed even after 3 days at ca. 20 °C.

***trans*-9-Thiabicyclo[6.1.0]nonane (*trans*-9):**[35] Yield 110 mg (77%).

Triphenylphosphane Sulfide:[36] Yield 26.0 mg (10%).

Treatment of the Thermolysate from the Reaction between Sulfine 1 and Monothione 2 with Cyclooctene (3): In a NMR tube was placed a solution of 40.0 mg (0.187 mmol) of **1** and 29.2 mg (0.187 mmol) of **2** in 0.5 mL of $CDCl_3$ under an argon atmosphere. The NMR tube was sealed by means of a rubber stopper and Parafilm®, and

heated in the dark at 60 °C for 4 days by means of an oil bath. Subsequently, to this thermolysate were added 117 μL (0.860 mmol) of **3**, immediately a ^{1}H NMR spectrum was taken as reference point and a sample of the crude reaction mixture was submitted to ^{1}H NMR analysis; no episulfide **9** was observed.

Reaction of Sulfine 1 with Cyclooctene (3): In a NMR tube were placed 40.7 mg (190 μmol) of **1** and 130 μL (940 μmol) of **3** in 0.5 mL of $CDCl_3$. The NMR tube was sealed by means of a rubber stopper and Parafilm®, and heated in the dark in an oil bath at 60 °C for 4 days. Immediately a ^{1}H NMR spectrum was taken as reference point and a sample of the crude reaction mixture was submitted to ^{1}H NMR analysis, which revealed that 179 μmol of its *cis*-isomer **8** and 15.0 μmol of benzophenone had been formed.

Reaction of Monothione 2 with Cyclooctene (3): In a NMR tube were placed 40.0 mg (256 μmol) of **2** and 154 μL (1.18 mmol) of **3** in 0.6 mL of $CDCl_3$. The NMR tube was sealed by means of a rubber stopper and Parafilm®, and heated in the dark at 60 °C for 3 days by means of an oil bath. Immediately a ^{1}H NMR spectrum was taken as reference point and a sample of the crude reaction mixture was submitted to ^{1}H NMR analysis, which revealed that the *trans*-isomer **3** had been completely (> 95%) converted into its *cis*-isomer **8**, but no episulfide **9** was detected.

Reaction of Trithiolane 5 with Cyclooctene (3): In a NMR tube were placed 37.0 mg (95.7 μmol) of **5** and 61.2 μL (440 μmol) of **3** in 0.6 mL of $CDCl_3$. The NMR tube was sealed by means of a rubber stopper and Parafilm®, and heated in the dark in an oil bath at 60 °C for 4 days. Immediately, a ^{1}H NMR spectrum was registered as reference point and a sample of the crude reaction mixture was submitted to ^{1}H NMR analysis, which revealed that **5** persisted under the reaction conditions, whereas the **3** was completely (> 95%) converted into **8**; no **9** was detected.

Acknowledgments

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