5-Morpholino-1,2,3,4-thiatriazole as a Sulfur-Transfer Reagent in the Reactions with Thioketones

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The thermal decomposition of 5-morpholino-1,2,3,4-thiatriazole (**7**), which leads to the extrusion of an active form of sulfur, in the presence of different thioketones is described. The interception of the S-atom by the C=S bond leads to *in situ* formation of an elusive thiocarbonyl *S*-sulfide of type **5**. This intermediate is a prone 1,3-dipole, which undergoes effectively [2 + 3] cycloadditions with thioketones to yield 1,2,4-trithiolane derivatives in a regioselective manner. Unexpectedly, 3,3-dichloro-2,2,4,4-tetramethyl-3-thioxocyclobutanone (**1c**) does not lead to the expected symmetrical 1,2,4-trithiolane. This result can be explained by the reduced stability of the corresponding thiosulfine **5c**. Three-component reactions, which were carried out in the presence of equimolar amounts of two different thioketones, result in the formation of 'mixed' 1,2,4-trithiolanes of type **8**.

1. Introduction. – Sulfur-transfer reactions have been reported frequently in recent years [1][2]. The C=S bonds of thioketones are prone interceptors of sulfur, and thiocarbonyl *S*-sulfides ('thiosulfines') are believed to be formed as the reactive intermediates. They can be trapped efficiently with dipolarophiles, and, in the case of the thiocarbonyl group, the [2 + 3] cycloaddition leads to 1,2,4-trithiolanes [3–7]. In these sulfur-transfer reactions, strained three-membered sulfur heterocycles such as thiiranes [3], or *in situ* formed thiaziridines [4][5] or oxathiiranes [6][7] are the sulfur donors. The appearance of thiaziridines as intermediates was proposed for the reactions of thiocarbonyl compounds with organic azides, which are initiated by the [2 + 3] cycloaddition to give 2,5-dihydro-1,2,3,4-thiatriazoles, followed by extrusion of N_2. A typical example with adamantanethione (**1a**) and PhN_3 is presented in *Scheme 1* [5].

On the other hand, some S-containing five-membered heterocycles, which are stable at room temperature, are reported to undergo thermal or photochemical decomposition under sulfur-extrusion, *e.g.*, 1,3,4-oxathiazol-2-ones decomposed in boiling xylene in the presence of **1a** to give **6a** in moderate yield [8]. In this case, a thiazirine is believed to act as the S-donor. Similarly, the photochemical decomposition of the same type of precursor at 10 K was reported to yield phenyl thiazirine, which, upon warming, isomerized to 'benzonitrile sulfide'. Finally, the latter decomposed to give benzonitrile and sulfur [9]. Analogous intermediates were detected in the

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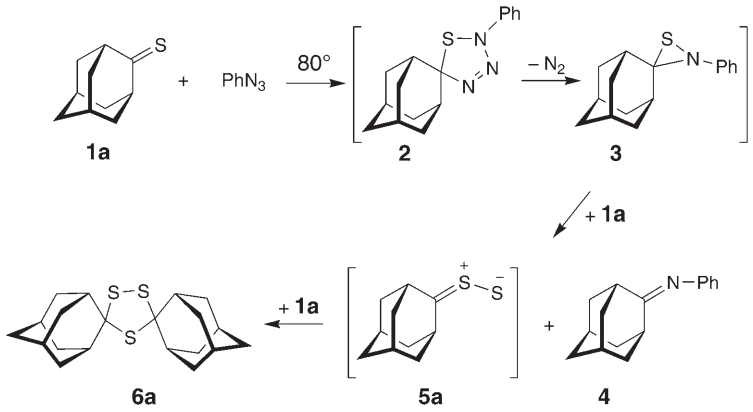
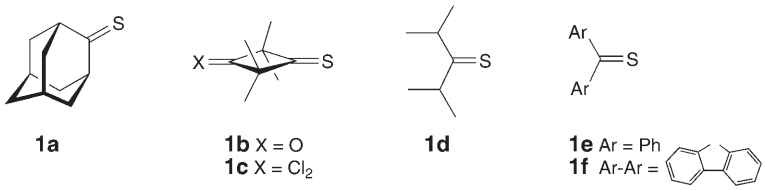
Scheme 1



photochemical reactions of 5-phenyl-1,2,3,4-thiatriazole and 5-phenyl-1,2,3,4-thiatriazole-2-thione [9].

The thermal decomposition of easily available 5-amino-1,2,3,4-thiatriazoles was studied by *Neidlein* and *Tauber* [10]. The formation of phenyl cyanamide was proposed to occur *via* a thiazirine intermediate. Therefore, the final product is formed *via* a stepwise elimination of N_2 and S. On the other hand, *Wentrup et al.* claimed that the thermal decomposition of 5-(phenyloxy)-1,2,3,4-thiatriazole occurs by elimination of the labile N_2S [11]. This interpretation was adopted by *Adam* and *Bargon* to explain the S-transfer from the same precursor to strained cycloalkenes leading to the corresponding thiiranes ('episulfidation') [12].

The successful 'episulfidation' of strained alkenes with 5-(aryloxy)-1,2,3,4-thiatriazoles prompted us to examine possible applications of analogous reactions with 5-morpholino-1,2,3,4-thiatriazole (**7**), which is more convenient in its handling, as a S-donor in reactions with thioketones. The study was aimed at the examination of a new method for the generation of thiocarbonyl *S*-sulfides as reactive intermediates. As potential S-acceptors, the aliphatic thioketones **1a**–**1d** as well as the aromatic thioketones **1e** and **1f** were used.



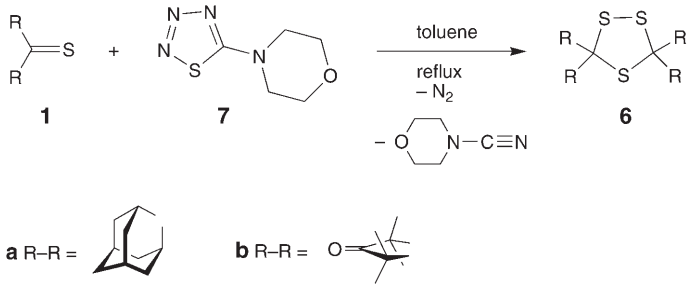
Furthermore, the proposed equilibrium between 'thiosulfine' and dithiirane, which has been discussed in recent papers [1][13–15], was of interest.

2. Results and Discussion. – The crystalline precursor **7** was prepared from morpholine, thiophosgene ($Cl_2C{=}S$), and NaN_3 without isolation of the intermediate

thiocarbamoyl chloride, in analogy to other 1,2,3,4-thiatriazole derivatives (for other preparations, see [16][17]). When heated to *ca.* 115° (m.p.), **7** decomposed with N_2 evolution and formation of elemental sulfur. Therefore, the reactions with thioketones were performed in boiling toluene. Under these conditions, the decomposition was complete after *ca.* 2 h.

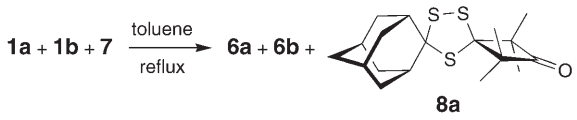
The reaction of **7** with adamantanethione (**1a**) gave the known symmetrical 1,2,4-trithiolane **6a** in moderate yield. Similarly, 2,2,4,4-tetramethyl-3-thioxocyclobutanone (**1b**) was smoothly converted into the known trithiolane **6b** (*Scheme 2*)[2]). In contrast, the attempted transformations of 3,3-dichloro-2,2,4,4-tetramethylcyclobutanethione (**1c**) as well as of diisopropyl thioketone (**1d**) were in vain.

Scheme 2



Heating **7** in the presence of a mixture of equimolar amounts of **1a** and **1b** led to three different 1,2,4-trithiolanes, *i.e.*, the symmetrical **6a** and **6b** along with the unsymmetrical **8a** (45% yield) in a *ca.* 1:1:2 ratio (*Scheme 3*). An analogous experiment, in which **1b** was replaced by **1c**, led to the symmetrical trithiolane **6a** exclusively, and the unconverted thioketone **1c** remained in the mixture (^{1}H-NMR). It is worth mentioning that the same result was obtained, when a mixture of **1a** and **1c**, dissolved in excess PhN_3, was heated to 80°. In this system, the intermediate thiaziridine of type **3** is believed to be the S-donor (*cf.* [5] and *Scheme 1*)[3]).

Scheme 3



An aromatic thioketone, *i.e.*, thiobenzophenone (**1e**), was used in the three-component reaction with **7** and **1b**. In this case, the mixed trithiolane **8b** was the sole product (*Scheme 4*). This result corresponds with an earlier observation, when **8b** was formed in the three-component reaction of PhN_3 with a mixture of thioketones **1b** and

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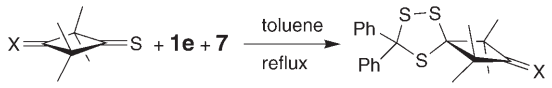
[2]) The trithiolane **6b** was also obtained (60%), when a solution of **1b** in xylene was heated in the presence of S_8 under reflux according to the protocol described in [18].

[3]) Heating a mixture of **1a** and *N*-methylbenzylidenamine in PhN_3 at 80° led to **6a**, *N*-methylthiobenzamide, and *N*-methyladamantan-2-ylidenamine. Thus, **1a** as well as the benzaldimine act as S-acceptors, and a thiaziridine was proposed as the S-donor [19].

1e [4]. Similarly, heating a solution of **7** and an equimolar mixture of **1c** and **1e** in toluene resulted in the formation of the corresponding mixed trithiolane **8c**. In both cases, the crystalline trithiolanes were isolated in 50–60% yield.

Scheme 4



1b X = O
1c X = Cl_2

8b X = O
8c X = Cl_2

The reactivity of 9*H*-fluorene-9-thione (**1f**) exceeds that of thiobenzophenone (**1e**) toward 1,3-dipoles, but it is thermally less stable and undergoes easily dimerization by a [2 + 4] cycloaddition [20]. Probably for this reason, no interception product, neither symmetrical nor mixed trithiolanes, were formed in the experiment with **1c**, **1f**, and **7**.

The formation of the 1,2,4-trithiolane is the result of a [2 + 3] cycloaddition of the respective thioketone and the *in situ* formed thiocarbonyl *S*-sulfide ('thiosulfine') [3]. In the reactions reported in the present paper, the thermolabile 5-morpholino-1,2,3,4-thiatriazole (**7**) acts as the S-donor. In the light of the literature data, two pathways for the S-transfer reaction can be discussed. Whereas photochemical decompositions of 1,2,3,4-thiatriazoles occur *via* N_2 elimination, leading to a thiazirine/nitrile sulfide system [9][10], thermolysis results in the fragmentation to give N_2S and the nitrile [11]. It is likely that the type of substituent at C(5) of the 1,2,3,4-thiatriazole influences the mode of decomposition and, thereby, the type of the active S-donor. The reaction conditions applied in the present study favor rather the pathway *via* N_2S elimination.

In accordance with previous observations, thioketones, in general, are good interceptors for the S-atom delivered during decomposition of **7**. Once again, adamantanethione (**1a**) acted as a superior acceptor leading to the thiocarbonyl *S*-sulfide **5**, which, in turn, easily underwent a [2 + 3] cycloaddition with the C=S group to give the corresponding 1,2,4-trithiolane.

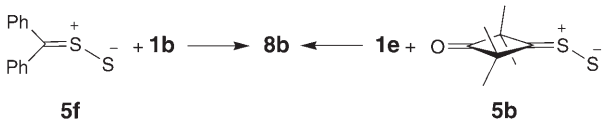
The second-efficient S-acceptor of the selected thioketones was 2,2,4,4-tetramethyl-3-thioxocyclobutanone (**1b**). On the other hand, its 3,3-dichloro derivative **1c** and diisopropyl thioketone (**1d**) were not able to form a sufficiently stable thiocarbonyl *S*-sulfide, which could undergo the [2 + 3] cycloaddition with the C=S bond.

The astonishing difference in the behavior of **1b** and **1c** suggests that the stability and/or reactivity of the corresponding *S*-sulfides are influenced by the substitution pattern. The enhanced stability of the intermediate derived from **1b** can result from a stabilizing transannular interaction with the C=O group (*cf.* [21]).

In none of the studied systems was the presence of a dithiirane evidenced. Obviously, the intermediate thiocarbonyl *S*-sulfides either undergo a [2 + 3] cycloaddition or decompose to give the parent thioketone.

The results of the three-component reactions with thiobenzophenone (**1e**), and **1b** or **1c** deserve a short comment. The formation of **8b** results either from the interception of thiobenzophenone *S*-sulfide (**5f**) with **1b** or of 2,2,4,4-tetramethyl-3-thioxocyclobutanone *S*-sulfide (**5b**) with **1e**. The absence of the symmetrical 1,2,4-trithiolane **6b** and 2,2,4,4-tetraphenyl-1,2,4-trithiolane can be explained by the observation that tetraaryl-

Scheme 5



5f **5b**

substituted trithiolanes are thermally unstable and, under the reaction conditions, easily undergo the [2 + 3] cycloreversion [3]. On the other hand, if the *S*-sulfide **5b** should be formed, it would react preferably with the 'superdipolarophile' **1e** to give **8b**.

As it was shown that **1c** does not form the expected symmetrical 1,2,4-trithiolane of type **6**[4]), the formation of **8c** in 52% yield is most likely the result of the [2 + 3] cycloaddition of **5f** with **1**.

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Experimental Part

1. *General*. M.p.: *Meltemp 2* apparatus; uncorrected. IR Spectra: in KBr pellets with a *Nexus* spectrophotometer. ^{1}H- and ^{13}C-NMR spectra: *Tesla BS 687* (80 and 20 MHz, resp.) or a *Bruker 300* (300 and 75 MHz, resp.) spectrometer with TMS (δ(TMS) = 0 ppm) as an internal standard. CI-MS: *Finnigan-Mat-90* or *Finnigan-SSQ-700* spectrometer. Elemental analyses were performed in the Analytical Laboratory of the University of Zurich.

2. *Starting Materials. 3,3-Dichloro-2,2,4,4-tetramethylcyclobutanethione* (**1c**) [22], *adamantanethione* (**1a**) [24], and *2,2,4,4-tetramethyl-3-thioxocyclobutanone* (**1b**) [25] were prepared from the corresponding ketones by thionation with P_4S_{10} in pyridine soln. *2,4-Dimethylpentane-3-thione* (**1d**) [26] and *9H-fluorene-9-thione* (**1f**) [27] were prepared by treatment of the corresponding ketones with a mixture of HCl and H_2S in MeOH, in the presence of cat. amounts of $HC(OMe)_3$. Thioketone **1d** was purified by column chromatography (CC) on SiO_2. *Thiobenzophenone* (**1e**) was obtained by thionation of benzophenone with *Lawesson*'s reagent in boiling toluene [20]. *5-Morpholino-1,2,3,4-thiatriazole* (**7**) was obtained from morpholine-4-thiocarbonyl chloride (synthesized from $Cl_2C{=}S$ and morpholine according to [28]) and NaN_3. The crude morpholine-4-thiocarbonyl chloride was stirred with 2 equiv. of NaN_3 in acetone at r.t. for 19 h to afford colorless crystals; overall yield 58%. M.p. 109–112° (hexane/CH_2Cl_2) ([16][17]: 114–115°).

3. *Synthesis of Trithiolane* **6b** *from* **1b** *and Elemental Sulfur*. To a soln. of **1b** (156 mg, 1 mmol) in xylene (1 ml) was added S_8 (128 mg, 0.5 mmol). After heating to reflux, the yellow solid dissolved completely, and heating was continued for 75 h. The soln. was evaporated to dryness *in vacuo* with a *Kugelrohr* apparatus, and the crude product was dissolved in Et_2O to separate residual S_8. The Et_2O was evaporated, and the product was purified by crystallization from hexane to yield 103 mg (60%) of *1,1,3,3,7,7,9,9-octamethyl-5,10,11-trithiadispiro[3.1.3.2]undecane-2,8-dione* (**6b**). Colorless crystals. M.p. 88–92° ([29]: 100–102°).

The attempted analogous synthesis of the corresponding symmetrical 1,2,4-trithiolane from **1c** and S_8 in toluene at 120° was in vain. After heating for 50 h, no trace of the expected trithiolane was detected in the mixture (^{1}H-NMR).

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[4]) However, heating **1c** in excess PhN_3 at 80° gave this trithiolane in 36% yield [22]. Remarkably, no interception of the proposed thiocarbonyl *S*-imide with **1c** was observed (for comparison, see [23]).

4. *Two-Component Reactions of* **7** *with Thioketones.* A soln. of **7** (218 mg, 1 mmol) and 2 mmol of the corresponding thioketone **1** in 1 ml of toluene was stirred for 2 h at 120° (oil bath). After evaporation of the solvent, trithiolanes **6** were isolated either by crystallisation (for **6a**) or after prep. TLC with plates precoated with SiO_2 (for **6b**).

Dispiro[adamantane-2,3′-[1,2,4]trithiolane-5′,2″-adamantane] (**6a**). Yield: 140 mg (38%). Colorless crystals. M.p. 195–200° (hexane/CH_2Cl_2) ([30]: 203–205°).

1,1,3,3,7,7,9,9-Octamethyl-5,10,11-trithiadispiro[3.1.3.2]undecane-2,8-dione (**6b**). Yield: 132 mg (38%). Colorless crystals. M.p. 97–101° (MeOH/CH_2Cl_2) ([29]: 100–102°).

5. *Three-Component Reactions of* **7** *with Thioketones.* A soln. of **7** (218 mg, 1 mmol) and two thioketones (1 mmol each) in 1 ml of toluene was stirred for 2 h at 120° (oil bath). Then, the solvent was evaporated, and the mixture was separated by prep. TLC. Pure products **6** and **8** were obtained by subsequent crystallisation.

Reaction of **7**, **1a**, *and* **1b**. *Compound* **6a**. Yield: 75 mg (41%). Colorless crystals. M.p. 195–200° (hexane/CH_2Cl_2) ([29]: 203–205°).

Compound **6b**. Yield: 30 mg (17%). Colorless crystals. M.p. 98–101° (MeOH/CH_2Cl_2) ([30]: 100–102°).

2″,2″,4″,4″-Tetramethyldispiro[adamantane-2,3′-[1,2,4]trithiolane-5′,3″-cyclobutane]-1″-one (**8a**). Yield: 70 mg (40%). Colorless crystals. M.p. 113–115° (hexane/CH_2Cl_2). IR (KBr): 2924*m*, 1787*s* (C=O), 1452*m*. ^{1}H-NMR ($CDCl_3$): 1.42 (*s*, 2 Me); 1.45 (*s*, 2 Me); 1.77–1.97, 2.14–2.35 (2*m*, 14 H). ^{13}C-NMR ($CDCl_3$): 21.3 (4 Me); 25.9, 26.3, 26.6, 39.6 (4 CH); 36.6, 37.6, 37.7 (5 CH_2); 66.4 (2 C_q); 86.3 (C_q); 89.2 (C_q); 219.2 (C=O). CI-MS: 356 (22), 355 (100, $[M+1]^+$), 167 (45). Anal. calc. for $C_{18}H_{26}OS_3$ (354.60): C 60.97, H 7.39, S 27.13; found: C 59.26, H 6.89, S 26.98.

Reaction of **7**, **1b**, *and* **1e**. *1,1,3,3-Tetramethyl-7,7-diphenyl-5,6,8-trithiaspiro[3.4]octan-2-one* (**8b**). Yield: 240 mg (62%). Colorless crystals. M.p. 99–100° (EtOH/CH_2Cl_2) ([30]: 101–102°).

Reaction of **7**, **1c**, *and* **1e**. *2,2-Dichloro-1,1,3,3-tetramethyl-7,7-diphenyl-5,6,8-trithiaspiro[3.4]octane* (**8c**). Yield: 230 mg (52%). Colorless crystals. M.p. 115–118° (MeOH/CH_2Cl_2). IR (KBr): 2981*m*, 1466*m*, 1443*s*, 808*m*, 749*m*, 725*s*, 697*s*. ^{1}H-NMR ($CDCl_3$): 1.49 (*s*, 2 Me); 1.63 (*s*, 2 Me); 7.24–7.66 (*m*, 10 arom. H). ^{13}C-NMR ($CDCl_3$): 25.2 (2 Me); 29.5 (2 Me); 59.9 (2 C_q); 88.2 (C_q); 91.8 (C_q); 99.9 (C_qCl_2); 128.2 (6 arom. CH); 129.4 (4 arom. CH); 141.9 (2 arom. C_q). CI-MS: 441 (5, M^+), 231 (23), 200 (15), 199 (100). Anal. calc. for $C_{21}H_{22}Cl_2S_3$ (441.51): C 57.13, H 5.02, S 21.79; found: C 57.11, H 4.93, S 21.71.

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