Unexpected Formation of Dimethylthioketene Cycloadducts in the Reaction of 1,3-Diphenylaziridine-2,2-dicarboxylate with Cyclobutanethione Derivatives

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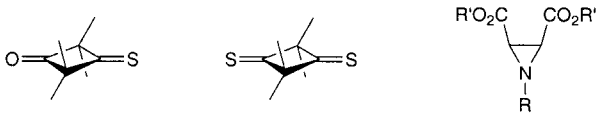
Dedicated to Professor *Albert Padwa* on the occasion of this 60th birthay

The reaction of 2,2,4,4-tetramethyl-3-thioxocyclobutanone (**1**) with *cis*-1-alkyl-2,3-diphenylaziridines **5** in boiling toluene yielded the expected *trans*-configured spirocyclic 1,3-thiazolidines **6** (*Scheme 1*). Analogously, dimethyl *trans*-1-(4-methoxyphenyl)aziridine-2,3-dicarboxylate (*trans*-**7**) reacted with **1** and the corresponding dithione **2**, respectively, to give spirocyclic 1,3-thiazolidine-2,4-dicarboxylates **8** (*Scheme 2*). However, mixtures of *cis*- and *trans*-derivatives were obtained in these cases. Unexpectedly, the reaction of **1** with dimethyl 1,3-diphenylaziridine-2,2-dicarboxylate (**11**) led to a mixture of the cycloadduct **13** and 5-(isopropylidene)-4-phenyl-1,3-thiazolidine-2,2-dicarboxylate (**14**), a formal cycloadduct of azomethine ylide **12** with dimethylthioketene (*Scheme 3*). The regioisomeric adduct **16** was obtained from the reaction between **2** and **11**. The structures of **6b**, *cis*-**8a**, *cis*-**8b**, **10**, and **16** have been established by X-ray crystallography.

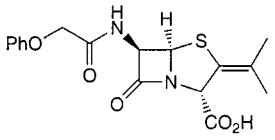
Introduction. – 1,3-Dipolar cycloadditions with thiocarbonyl compounds have been elaborated extensively in recent years [1][2]. Due to the convenient access and their remarkable stability, thiocarbonyl derivatives of 2,2,4,4-tetramethylcyclobutane-1,3-dione are among the most frequently explored representatives. In the case of the 'monothione' **1**, stable [3 + 2] cycloadducts were obtained from reactions with CH_2N_2 [3], nitrones [4], thiocarbonyl ylides [5][6], thiocarbonyl *S*-oxides (sulfines) [7][8], and thiocarbonyl *S*-sulfides (thiosulfines) [9]. When reactions were carried out with imidazole *N*-oxides, which are structural analogues of nitrones, a rearrangement of the primarily formed cycloadduct led to a S-transfer to the heterocyclic system to give imidazole-2-thiones [10]. Most of these cycloadditions occurred in a regioselective manner. Unlike **1**, the analogous 'dithione' **2** has not found many applications, although some reactions with nitrones [4] and diazo compounds [11], have also been described.

Azomethine ylides are 1,3-dipoles with great importance for the stereocontrolled synthesis of five-membered N-heterocycles and pyrroles [12][13]. In comparison with C,C dipolarophiles, reactions with heterodipolarophiles are less well-known, and, for C=S dipolarophiles, only few examples have been reported. However, some

[1]) Part of the planned Ph.D. thesis of *K. U.*, University of Łódź.



1 **2** **3**



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functionalized 1,3-thiazolidines, which are accessible by this reaction, are interesting as biologically active compounds. The recently published new approaches to the penam skeleton, based on the cycloaddition of azomethine ylides with C=S dipolarophiles, deserve special attention [14].

In our previous work, some reactions of azomethine ylides, generated by different methods, with 1,3-thiazole-5(4*H*)-thiones [15][16] and aromatic thioketones [17–19] have been studied. Thermal reactions of aziridine-2,3-dicarboxylates **3** with thiocarbonyl compounds offer a convenient stereocontrolled approach to 1,3-thiazolidine-2,4-dicarboxylates. Nevertheless, this approach has been explored only to a limited extent, and thioketones **1** and **2** have not been used so far in reactions with **3**. An additional question emerges in thermal reactions with **1** and **2**, as the thermal dissociation of **2** leads to dimethylthioketene [20], which is expected to react easily with 1,3-dipolar species [21]. However, no reaction of a thioketene with an azomethine ylide has been reported so far, and penicillin **4**, which has a 5-isopropylidene-1,3-thiazolidine moiety, and, therefore, is a formal cycloadduct of an azomethine ylide and dimethylthioketene, was synthesized by other methods [22].

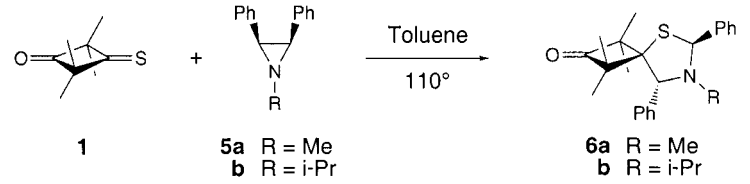
The goal of the present work was to study the behavior of **1** and **2** in thermal reactions with aziridine carboxylates.

Results and Discussion. – The only known reaction of an azomethine ylide with **1** was carried out by heating *cis*-1-methyl-2,3-diphenylaziridine (**5a**) in toluene [17]. Based on the well-documented conrotatory course of the thermal ring opening of aziridines [23], the structure of the only product isolated was tentatively formulated as the *trans*-6,8-diphenyl derivative **6a** (*Scheme 1*). In an extension of this preliminary experiment, the analogous reaction with *cis*-1-isopropyl-2,3-diphenylaziridine **5b**[2]) was performed, leading to **6b** as the sole cycloadduct. Compared with **5a**, the reaction with **5b** was remarkably slow and accompanied by significant decomposition of the starting materials. The isolated product **6b** showed similar spectroscopic properties as **6a**. In the ^{1}H-NMR spectrum, the 4 Me groups of the cyclobutanone moiety show resonances at 1.60, 1.40, 1.17, and 0.67 ppm for **6a**, and at 1.66, 1.39, 1.07, and 0.63 ppm for **6b**. On the

[2]) The *cis*-configuration of **5b** has been established by X-ray crystallography [24].

other hand, a remarkable difference appears with respect to the chemical shifts of H–C(6) and H–C(8): whereas in **6a** both absorb at 4.73 ppm [17], two *singlets* at 5.37 and 5.09 ppm appear in the case of **6b**. This difference could indicate that the two products have different configurations. Finally, an X-ray crystal-structure determination of **6b** was performed and confirmed the proposed *trans*-substitution in the 1,3-thiazolidine (*Fig. 1*).

Scheme 1



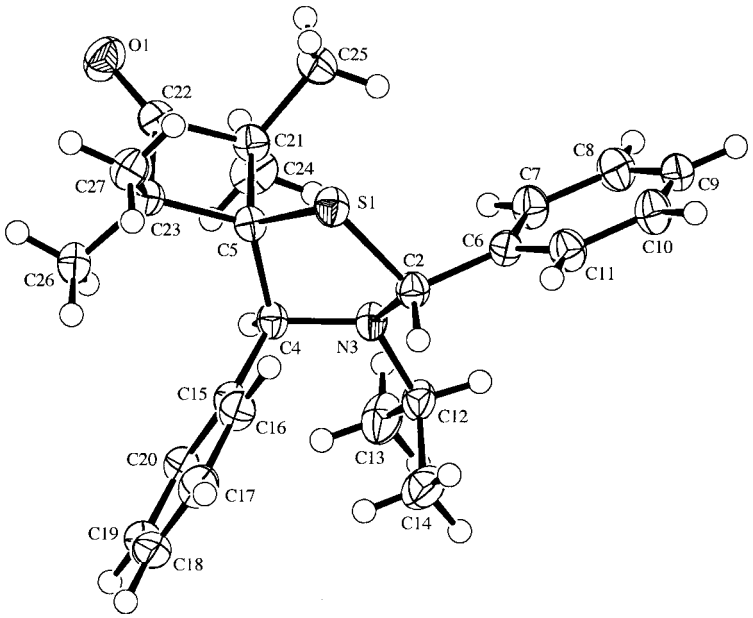
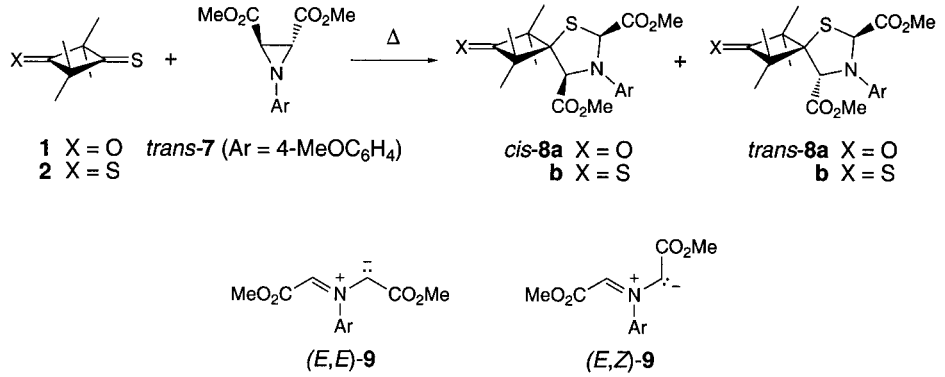


Fig. 1. *ORTEP Plot* [25] *of the molecular structure of* **6b** (50% probability ellipsoids, arbitrary numbering of atoms)

The reaction of **1** with dimethyl *trans*-1-(4-methoxyphenyl)aziridine-2,3-dicarboxylate (*trans*-**7**) in toluene at 110°, as well as in xylene at 130°, afforded mixtures of two stereoisomeric cycloadducts of type **8a** in a ratio of 4:1 and 1:1, respectively (*Scheme 2*). The reactions with *trans*-**7**, in contrast to those with **5b**, occurred smoothly and gave the products in good yields.

A characteristic difference between *cis*-**8a** and *trans*-**8a** appears in the ^{1}H-NMR spectrum. The major product formed in toluene showed two *singlets* at 5.35 and

Scheme 2



5.07 ppm ($\Delta\delta = 0.28$), whereas, for the minor product, the signals appear at 5.27 and 5.13 ppm ($\Delta\delta = 0.14$). Crystallization from MeOH gave the major component in pure form. The X-ray crystal-structure determination of this compound confirmed the expected *cis*-configuration (*cis*-**8a**, *Fig. 2*, *a*).

The minor component *trans*-**8a** was separated from the mother liquor by means of chromatography. Except for the $\Delta\delta$ mentioned above, there were only slight differences in the spectrosopic properties of *cis*-**8a** and *trans*-**8a**.

The formation of *cis*-**8a** is in line with the expected reaction course, *i.e.*, a conrotatory electrocyclic ring opening of *trans*-**7**, leading to the azomethine ylide (*E*,*E*)-**9**, followed by a suprafacial [3 + 2] cycloaddition with the C=S group of **1**. It is well known, however, that, at elevated temperatures, (*E*,*E*)-**9** is in equilibrium with (*E*,*Z*)-**9**, and both ylides react with dipolarophiles at comparable rates [23][26]. For this reason, the formation of both stereoisomeric cycloadducts in temperature-dependent ratios is easy to explain. Attempts to isomerize *cis*-**8a** in boiling toluene showed that, under these conditions, no secondary isomerization takes place.

When the analogous reaction was carried out with **1** and *cis*-**7** in boiling xylene for 3 h, *trans*-**8a** was obtained as the sole product.

Similarly, a mixture of dithione **2** and *trans*-**7** was heated in toluene and in xylene, and, in analogy to the experiments with **1**, mixtures of *cis*-**8b** and *trans*-**8b** (*Scheme 2*) were detected in approximately same ratios in the crude mixture. The major product *cis*-**8b** crystallized from MeOH solution as orange needles. The characteristic absorption at 279.6 ppm (C=S) in the ^{13}C-NMR spectrum confirmed the presence of a cyclobutanethione fragment. The *cis*-configuration has been established by X-ray crystallography (*Fig. 2*, *b*). The crystal structure of the thioxo compound *cis*-**8b** is very similar to that of the O-analogue *cis*-**8a**.

In analogy to the reaction with **1**, heating **2** with *cis*-**7** led to the formation of *trans*-**8b**, and none of the isomeric *cis*-1,3-thiazolidine was detected in the mixture.

Earlier attempts to react **1** with dimethyl 1,3-diphenylaziridine-2,2-dicarboxlate (**11**), generated *in situ* from dimethyl 4,5-dihydro-1,5-diphenyl-1*H*-1,2,3-triazole-4,4-dicarboxylate (**10**; *Scheme 3*) in toluene, were in vain [17]. The structure of **10**, which

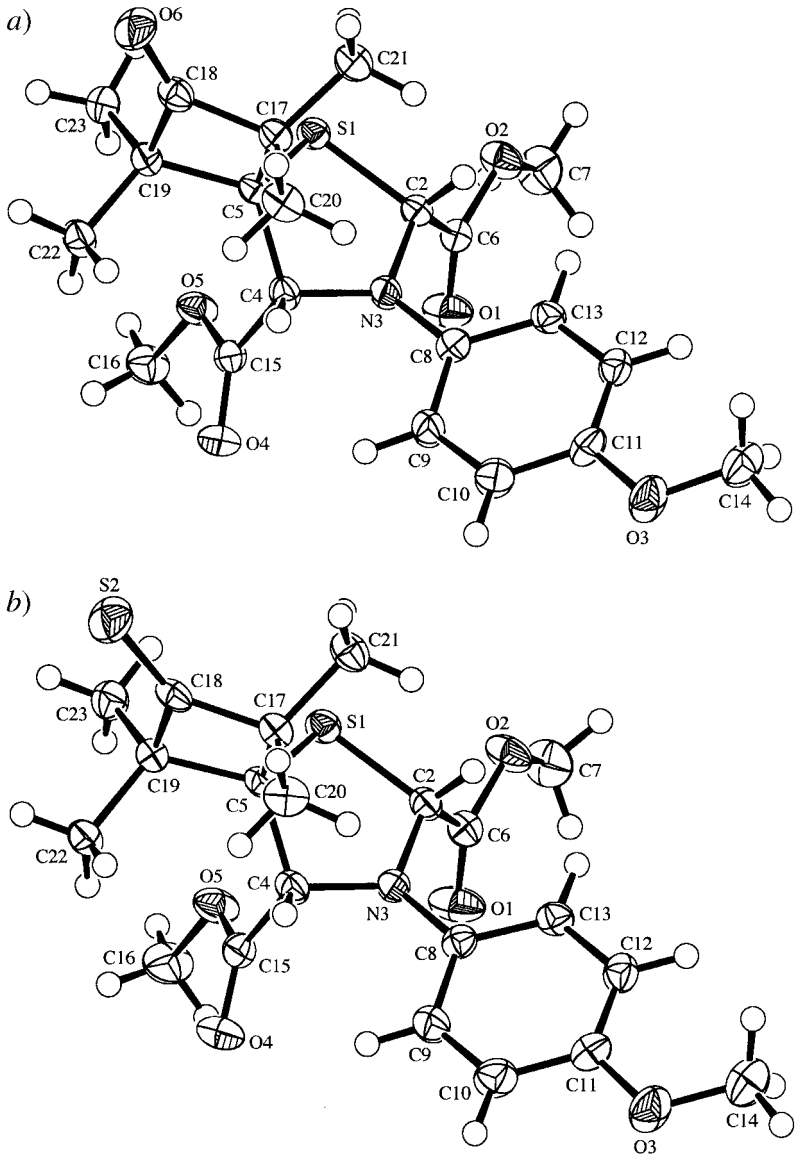
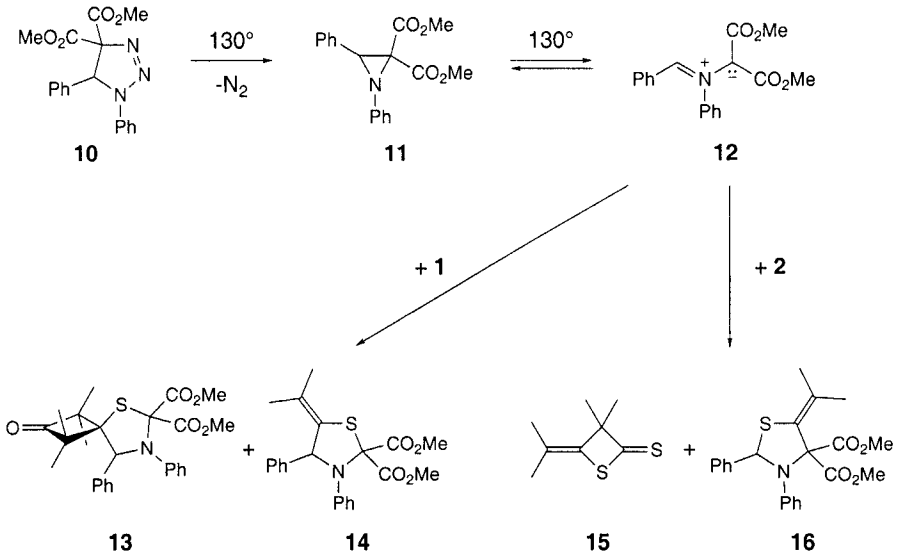


Fig. 2. *ORTEP Plot* [25] *of the molecular structure of* a) cis-**8a** *and* b) cis-**8b** (50% probability ellipsoids, arbitrary numbering of atoms)

was prepared by treatment of dimethyl benzylidenemalonate with PhN_3 [27], has now been established by X-ray crystallography (*Fig. 3*). When the reaction with **1** was carried out in boiling xylene for 60 h, leading to the formation of the intermediate azomethine ylide **12**, no **1** remained according to TLC analysis. Chromatographic separation of the mixture yielded two products in a ratio that was dependent upon the

Scheme 3



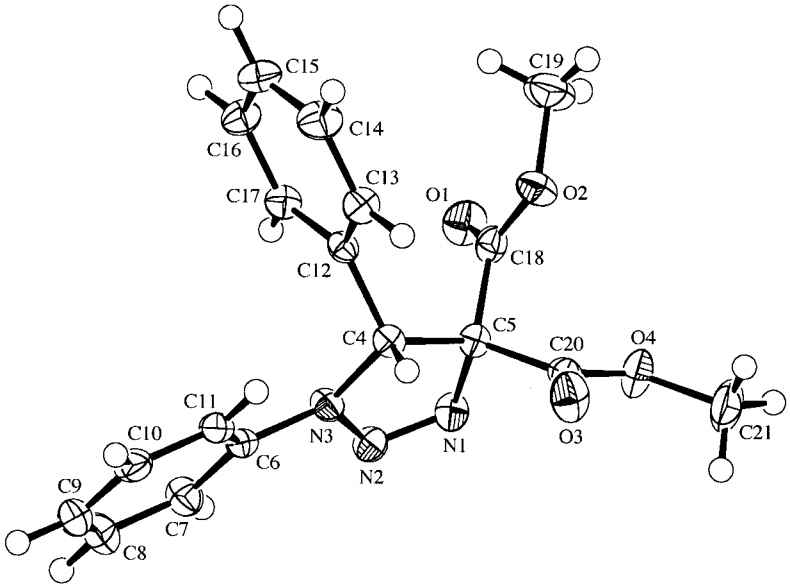


Fig. 3. *ORTEP Plot* [25] *of the molecular structure of* **10** (50% probability ellipsoids, arbitrary numbering of atoms)

concentration of the reactants.[3]) The more polar crystalline product **13** (6%) was the expected [3 + 2] cycloadduct (*cf.* [28]).

From the less polar fraction, a compound was isolated for which the ^{1}H-NMR spectrum showed only two signals for MeC groups at 1.92 and 1.80 ppm, as well as two signals for MeO at 3.88 and 3.70 (intensity 1:1:1:1). In the ^{13}C-NMR spectrum, four signals for quaternary C-atoms appeared at 144.4, 142.1, 127.7, and 126.6 ppm. Whereas the two signals at lower field can be attributed to C_q (arom.), the other two originate from a novel structural fragment. Both, the ^{13}C-NMR and IR spectra confirmed the presence of two ester C=O groups, but there were no signals for a cyclobutanone C=O group[4]). Finally, the ESI-MS revealed $[M + Na]^+$ at *m/z* 420, corresponding to the molecular formula $C_{22}H_{23}NO_4S$. Compared with the cycloadduct **13**, the molecular mass differed by 70 mass units, indicating the loss of dimethylketene. On the basis of these spectroscopic data and the correct elemental analysis, structure **14** (7%; *Scheme 3*), which is a formal cycloadduct of **12** and dimethylthioketene, was proposed. This conclusion was confirmed by an X-ray crystal-structure determination [28].

The unexpected formation of **14** could be explained by three pathways. The first interpretation involves a primary [2 + 2] cycloreversion of **1** to equimolar amounts of dimethylketene and dimethylthioketene. Subsequently, the latter could intercept **12** to give the product **14**. As there are no data available indicating a thermal dissociation of **1**, we consider this mechanism rather unlikely. As a second possibility, a thermal extrusion of dimethylketene from the primarily formed cycloadduct **13** is conceivable. To test this hypothesis, a sample of **13** was heated in xylene at 130° for 60 h. After evaporation of the solvent, the ^{1}H-NMR analysis showed that no **14** was formed, and only **13**, along with small amounts of decompositon products, was present. A third mechanistic explanation *via* a multistep process could also be considered. Thioketones are electron-rich dipolarophiles, and the 1,3-dipole **12** with two electron-withdrawing groups is considered an electron-poor intermediate. Thus, the fundamental requirements for a stepwise mechanism of cycloaddition are fulfilled, *i.e.*, steric hindrance at one terminus of the dipolar species and a large gap between the frontier orbitals of the reaction partners [29–31]. However, it is rather difficult to formulate a convincing zwitterionic intermediate, which, after elimination of dimethylketene, would subsequently convert to **14**. Finally, the observed influence of the concentration of the reagents on the ratio **13**/**14** may suggest that elimination of dimethylketene from **13** could be supported by some components of the reaction mixture[5]).

According to [20], thermal decomposition of dithione **2** yields dimethylthioketene, a highly reactive heterocumulene. To test its cycloaddition with **12** to give **14**, a mixture of **10** and **2** in xylene was heated until **12** completely disappeared (TLC). In this case, the conversion was much faster than with **1** (5 h). The ^{1}H-NMR analysis of the mixture showed that the expected **14** has not been formed. After chromatographic workup, the less polar orange substance was identified as the known dithiolactone **15** (*Scheme 3*; *cf.*

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[3]) In an experiment with 2.2 mmol of **1** and 2.0 mmol of **10** in 1.5 ml of xylene, the ratio **13**/**14** was *ca.* 1:2, whereas, in 4.5 ml of xylene, it was 2:1.

[4]) Typically, cycloclobutanone derivatives show the C=O absorption at *ca.* 1780 cm^{-1} (IR) and at 220–218 ppm (^{13}C-NMR).

[5]) At the moment, an unambigous reaction pathway leading to **13** and **14** cannot be formulated. Further studies are needed for additional arguments.

[32]). The compound from the more polar main fraction showed similar patterns of signals in the ^{1}H- and ^{13}C-NMR spectra as **14**. However, in the IR spectrum, the fingerprint region of **14** and the new compound were significantly different. The MS and elemental analysis confirmed that the two compounds have isomeric structures. This conclusion was unambiguously confirmed by an X-ray crystal-structure determination, which established structure **16** (*Fig. 4*) for the product from the reaction between **11** and **2**.

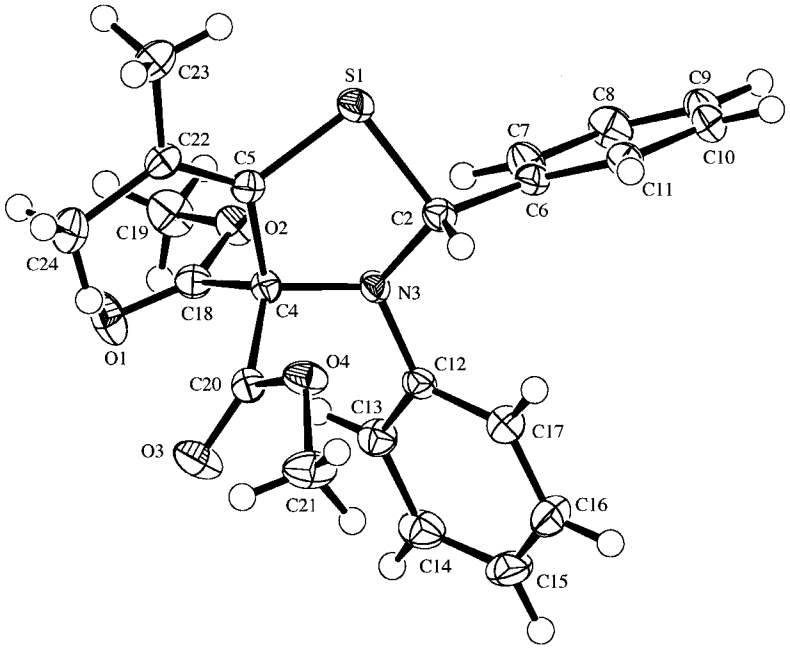

Fig. 4. *ORTEP Plot* [25] *of the molecular structure of* **16** (50% probability ellipsoids, arbitrary numbering of atoms)

The formation of the regioisomer **16** in the reaction of **2** with **12** suggests that, in this case, a different reaction mechanism must be formulated. It is plausible that a 1,3-dipolar cycloaddition of **12** with *in situ* generated dimethylthioketene leads to **16**. An additional evidence for the appearence of dimethylthioketene is the formation of the isomer **15**. This isomerization has been reported earlier (*cf.* [20]).

In conclusion, we have shown that thermal additions of symmetrically substituted aziridine **7** with both 'monothione' **1** and 'dithione' **2** occur smoothly to give mixtures of diastereoisomers of the expected 1,3-thiazolidine-dicarboxylates. The ratio of the stereoisomers reflects an isomerization of the initially formed azomethine ylide (*E*,*E*)-**9**. The reaction of the asymmetrically substituted aziridine dicarboxylate **11** with **1** is proposed to occur stepwise *via* a zwitterionic intermediate, which eliminates dimethylketene to give **14** or undergoes a 1,5-cyclization affording **13**. In boiling xylene, 'dithione' **2** dissociates, and the highly reactive dimethylthioketene either dimerizes to

give **15** or is intercepted by azomethine ylide **12** to yield **16**. These results show that **2** can be exploited as a source of dimethylthioketene. To the best of our knowledge, the formation of **16** is the first example of a 1,3-dipolar cycloaddition with dimethylthioketene, and, on the other hand, it is the first reaction of an azomethine ylide with a thioketene.

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Experimental Part

1. *General*. See [19].

2. *Starting Materials. 2,2,4,4-Tetramethyl-3-thioxocyclobutanone* (**1**) and *2,2,4,4-tetramethylcyclobutane-1,3-dithione* (**2**) were prepared by thionation of 2,2,4,4-tetramethylcyclobutane-1,3-dione with P_4S_{10} in pyridine as described in [33]. cis-1-*Isopropyl-2,3-diphenylaziridine* (**5b**) was synthesized by *Gabriel*'s method according to [34], cis- and trans-*1-(4-methoxyphenyl)aziridine-2,3-dicarboxylates* (*cis*- and *trans*-**7**) were obtained by a modified procedure based on the reaction of 4-methoxyphenyl azide with dimethyl fumarate and subsequent thermal decomposition of the primarily formed 4,5-dihydro-1*H*-1,2,3-triazole derivative as reported by *Szeimies* and *Huisgen* [35]. *Dimethyl 4,5-dihydro-1,5-diphenyl-1*H-*1,2,3-triazole-4,4-dicarboxylate* (**10**) was obtained from dimethyl benzylidenemalonate and phenyl azide according to *Texier* and *Carrié* [27].

3. *Reaction of* **1** *with* **5b**. A soln. of **5b** (521 mg, 2.2 mmol) and **1** (312 mg, 2.0 mmol) in 5 ml of freshly purified toluene was heated under reflux for 30 h. After evaporation of the solvent, the crude mixture was analyzed by ^{1}H-NMR spectroscopy, and complete conversion of **1** was evidenced by the absence of the characteristic *s* of **1** at 1.35 ppm. Separation of the mixture was achieved by CC (SiO_2; petroleum ether with increasing amounts of CH_2Cl_2). The main fraction isolated with petroleum ether/CH_2Cl_2 7:3 was identified as **6b**. Anal. pure **6b** was obtained by recrystallization from MeOH.

trans-*7-Isopropyl-1,1,3,3-tetramethyl-6,8-diphenyl-5-thia-7-azaspiro[3.4]octan-2-one* (**6b**). Yield: 240 mg (30%). Colorless crystals. M.p. 114–116° (MeOH). IR (KBr): 2966*s*, 1776v*s* (C=O), 1460*m*, 1365*m*, 1171*m*, 1034*m*, 723*m*, 702*m*. ^{1}H-NMR: 0.41, 1.05 (2*d*, J = 6.7, *Me*$_2$CH); 0.63, 1.07, 1.39, 1.66 (4*s*, 4 Me); 2.47 (*sept.*, J = 6.7, Me$_2$C*H*); 5.09, 5.37 (2*s*, H–C(6), H–C(8)); 7.24–7.46 (*m*, 8 arom. H); 8.50–8.53 (*m*, 2 arom. H). ^{13}C-NMR: 18.3, 20.7, 21.5, 23.6, 23.7, 25.5 (6 Me); 48.2 (Me$_2$*C*H); 61.0, 66.6 (C(1), C(3)); 67.1, 70.2 (C(6), C(8)); 68.3 (C(4)); 127.6, 127.8, 127.9, 128.2, 128.4, 128.8, 131.7 (10 arom. CH); 140.4, 141.3 (2 arom. C); 222.4 (C=O). ESI-MS (NaI): 416 (100, $[M+Na]^+$). Anal. calc. for $C_{25}H_{31}NOS$ (393.60): C 76.29, H 7.94, N 3.56, S 8.15; found: C 75.88, H 7.53, N 3.41, S 7.53.

4. *Reaction of* **1** *with* trans-**7**. A soln. of *trans*-**7** (265 mg, 1 mmol) and **1** (156 mg, 1 mmol) in 3 ml of toluene was heated under reflux, until the red color of **1** completely disappeared (14 h). A similar experiment carried out in boiling xylene was complete after 5.5 h. After evaporation of the toluene, the crude mixture was analyzed by ^{1}H-NMR and a 4:1 ratio for *cis*-**8**/*trans*-**8** was established based on the intensities of the *s* attributed to H–C(6)/H–C(8) in each product (the ratio in xylene was 1:1). A first crop of *cis*-**8** (180 mg) was obtained after crystallization from MeOH. The mother liquor, after evaporation of the solvent, was separated by means of CC (SiO_2; petroleum ether with increasing amounts of CH_2Cl_2). The reported yields refer to total amounts of isolated products.

Dimethyl cis-*7-(4-Methoxyphenyl)-1,1,3,3-tetramethyl-2-oxo-5-thia-7-azaspiro[3.4]octane-6,8-dicarboxylate* (*cis*-**8a**). Yield: 210 mg (50%). Colorless crystals. M.p. 135–137° (MeOH). IR (KBr): 1778v*s* (C=O, ketone), 1753v*s* (C=O, ester), 1730v*s* (C=O, ester), 1516v*s*, 1437*m*, 1275*s*, 1248*s*, 1205*s*, 1178*s*, 1038*m*, 1016*m*. ^{1}H-NMR: 1.19, 1.28, 1.32, 1.38 (4*s*, 4 Me); 3.73, 3.76, 3.77 (3*s*, 3 MeO); 5.07, 5.35 (2*s*, H–C(6), H–C(8)); 6.84, 6.75 (*AA′BB′*, J = 9.2, 4 arom. H). ^{13}C-NMR: 21.6, 21.9, 22.1, 22.3 (4 Me); 52.0, 52.8, 55.5 (3 MeO); 60.1, 66.3 (C(1), C(3)); 61.7, 65.1 (C(6), C(8)); 68.7 (C(4)); 113.7, 115.0 (4 arom. CH); 137.5, 152.8 (2 arom. C); 169.8, 169.9 (2 C=O, ester); 218.6 (C=O, ketone). ESI-MS (NaI): 444 (100, $[M+Na]^+$). Anal. calc. for $C_{21}H_{27}NO_6S$ (421.51): C 59.84, H 6.46, N 3.32, S 7.61; found: C 59.71, H 6.27, N 3.25, S 7.49.

Dimethyl trans-*7-(4-Methoxyphenyl)-1,1,3,3-tetramethyl-2-oxo-5-thia-7-azaspiro-[3.4]octane-6,8-dicarboxylate* (*trans*-**8a**). Yield: 45 mg (11%). Colorless crystals. M.p. 120–122° (MeOH). IR (KBr): 1782*s* (C=O, ketone), 1745*s* (br.) (C=O, ester), 1514v*s*, 1435*m*, 1246v*s*, 1200v*s*, 1171v*s*, 1038*s*, 820*m*. ^{1}H-NMR: 1.26, 1.27, 1.36,

1.52 (4*s*, 4 Me); 3.57, 3.74, 3.75 (3*s*, 3 MeO); 5.13, 5.27 (H–C(6), H–C(8)); 6.80, 6.74 (*AA′BB′*, *J* = 8.2, 4 arom. H). ^{13}C-NMR: 19.3, 21.4, 23.2, 24.2 (4 Me); 51.6, 52.5, 55.3 (3 MeO); 60.3, 67.2 (C(1), C(3)); 61.9, 69.4 (C(6), C(8)); 65.4 (C(4)); 114.7, 118.2 (4 arom. CH); 137.2, 154.3 (2 arom. C); 169.8, 170.7 (2 C=O, ester); 219.3 (C=O, ketone). CI-MS (NH_3): 422 (100, $[M+1]^+$). Anal. calc. for $C_{21}H_{27}NO_6S$ (421.51): C 59.84, H 6.46, N 3.32, S 7.61; found: C 59.78, H 6.38, N 3.15, S 7.48.

5. *Reaction of* **2** *with* trans-**7**. A soln. of **2** (172 mg, 1 mmol) and *trans*-**7** (265 mg, 1 mmol) in 3 ml of abs. toluene was heated under reflux for 15 h. Analysis of the mixture was accomplished as described in *Sect. 4*. The ratio *cis*-**8b**/*trans*-**8b** (^{1}H-NMR) was *ca.* 4:1. The crude mixture was dissolved in 2 ml of MeOH and stored overnight in the refrigerator; then, 150 mg of colorless crystals of *cis*-**8b** were filtered. The mother liquor was evaporated, and the residue was separated (CC, SiO_2; petroleum ether with increasing amounts of CH_2Cl_2) to give *trans*-**8b** (40 mg) as the less polar fraction. The more polar *cis*-**8b** (60 mg) was isolated as a thick oil, which crystallized at r.t.

Dimethyl cis-*7-(4-Methoxyphenyl)-1,1,3,3-tetramethyl-2-thioxo-5-thia-7-azaspiro[3.4]octane-6,8-dicarboxylate* (*cis*-**8b**). Yield: 210 mg (48%). Orange crystals. M.p. 143–146° (MeOH). IR (KBr): 2953*m*, 1755v*s* (C=O), 1726v*s* (C=O), 1514v*s*, 1464*m*, 1437*m*, 1277v*s*, 1218v*s*, 1203v*s*, 1174v*s*, 1041*s* (C=S), 818*m*. ^{1}H-NMR: 1.24, 1.36, 1.40, 1.45 (4*s*, 4 Me); 3.73, 3.76, 3.77 (3*s*, 3 MeO); 5.18, 5.36 (2*s*, H–C(6), H–C(8)); 6.77, 6.84 (*AA′BB′*, *J* = 9.2, 4 arom. H). ^{13}C-NMR: 25.6, 26.1, 26.2, 26.3 (4 Me); 52.0, 52.8, 55.3 (3 MeO); 61.8, 65.4 (C(6), C(8)); 63.1, 68.4 (C(1), C(3)); 70.6 (C(4)); 113.7, 115.0 (4 arom. CH); 137.6, 152.7 (2 arom. C); 169.7, 169.9 (2 C=O); 279.6 (C=S). ESI-MS (NaI): 460 (100, $[M+Na]^+$). Anal. calc. for $C_{21}H_{27}NO_5S_2$ (437.57): C 57.64, H 6.22, N 3.20, S 14.65; found: C 57.52, H 6.03, N 3.06, S 14.57.

Dimethyl trans-*7-(4-Methoxyphenyl)-1,1,3,3-tetramethyl-2-thioxo-5-thia-7-azaspiro[3.4]octane-6,8-dicarboxylate* (*trans*-**8b**). Yield: 50 mg (11%). Orange crystals. M.p. 128–130° (MeOH). IR (KBr): 2968*m*, 1738v*s* (C=O), 1514v*s*, 1362*m*, 1269v*s*, 1248v*s*, 1200v*s*, 1174v*s*, 1036v*s* (C=S), 985*m*, 833*m*. ^{1}H-NMR: 1.33, 1.34, 1.45, 1.59 (4*s*, 4 Me); 3.57, 3.74, 3.75 (3*s*, 3 MeO); 5.21, 5.29 (2*s*, H–C(6), H–C(8)); 6.75, 6.80 (*AA′BB′*, *J* = 9.2, 4 arom. H). ^{13}C-NMR: 23.1, 25.3, 27.4, 28.6 (4 Me); 51.6, 52.5, 55.4 (3 MeO); 62.0, 69.7 (C(6), C(8)); 63.2, 69.6 (C(1), C(3)); 69.4 (C(4)); 114.7, 118.2 (4 arom. CH); 137.3, 154.3 (2 arom. C); 170.0, 170.7 (2 C=O); 280.3 (C=S). CI-MS (NH_3): 438 (100, $[M+1]^+$). Anal. calc. for $C_{21}H_{27}NO_5S_2$ (437.57): C 57.64, H 6.22, N 3.20, S 14.65; found: C 57.48, H 6.12, N 3.11, S 14.51.

6. *Reactions of* cis-**7** *with* **1** *and* **2**. Solns. of *cis*-**7** (88 mg, 0.3 mmol) and 0.3 mmol of **1** or **2** in 1 ml of abs. xylene were heated under reflux for 3 h. In both experiments, TLC tests showed complete conversion of *cis*-**7**. After evaporation of the solvent, the residual thick oils were examined by ^{1}H-NMR spectroscopy, and *trans*-**8a** or *trans*-**8b**, respectively, were identified as exclusive products. After crystallization, pure *trans*-**8a** (71 mg, 56%) and *trans*-**8b** (81 mg, 62%), identical (m.p., ^{1}H-NMR, IR) with the products of *Sect. 4* and *5*, were obtained.

7. *Reaction of* **10** *with* **1**. A soln. of **10** (678 mg, 2.0 mmol) and **1** (345 mg, 2.2 mmol) in 1.5 ml (or 4.5 ml) of xylene was heated under reflux for 60 h. The initially red color of the mixture changed to brown. After evaporation of the solvent, the partially decomposed residues were analyzed by ^{1}H-NMR spectroscopy, and the ratio **13**/**14** was established based on the intensities of *s* at 0.67 ppm (3 H) for **13** and *s* at 1.92 ppm (3 H) for **14**. CC (SiO_2; petroleum ether/CH_2Cl_2 4:6) gave a fraction containing **14**, and the more polar **13** was eluted with CH_2Cl_2. Anal. pure samples were obtained by recrystallization.

Dimethyl 1,1,3,3-Tetramethyl-7,8-diphenyl-5-thia-7-azaspiro[3.4]octan-6,6-dicarboxylate (**13**). Yield: 60 mg (6%, from the less concentrated mixture). Colorless crystals. M.p. 196–198° (hexane/CH_2Cl_2). IR (KBr): 2958*m*, 1778v*s* (C=O), 1741v*s* (C=O), 1597*s*, 1504v*s*, 1454*s*, 1335*s*, 1254v*s*, 1213*s*, 1171*s*, 1049*m*, 1034*s*, 748*m*, 704*m*. ^{1}H-NMR: 0.67, 1.28, 1.42, 1.53 (4*s*, 4 Me); 3.48, 3.74 (2*s*, 2 MeO); 6.00 (*s*, H–C(8)); 6.77–7.26 (*m*, 10 arom. H). ^{13}C-NMR: 20.4, 23.6, 23.7, 24.1 (4 Me); 52.9, 53.4 (2 MeO); 61.4, 67.3 (C(1), C(3)); 68.5 (C(4)); 69.8 (C(8)); 75.8 (C(5)); 116.8, 119.5, 128.1, 128.2, 128.6 (10 arom. CH); 138.9, 142.1 (2 arom. C); 168.6, 169.0 (2 C=O); 220.5 (C=O, cyclobutanone). ESI-MS (NaI): 420 (100, $[M+Na]^+$). Anal. calc. for $C_{26}H_{29}NO_5S$ (467.59): C 66.79, H 6.25, N 2.99, S 6.86; found: C 66.82, H 6.38, N 3.06, S 7.01.

Dimethyl 5-Isopropylidene-3,4-diphenyl-1,3-thiazolidine-2,2-dicarboxylate (**14**). Yield: 55 mg (7% from the more concentrated mixture). Colorless crystals. M.p. 116–118° (hexane/CH_2Cl_2). IR (KBr): 1755*s* (C=O), 1740*s* (C=O), 1597*m*, 1504*s*, 1433*m*, 1240*s* (br.), 1055*m*, 1041*m*, 748*m*, 712*m*. ^{1}H-NMR: 1.80, 1.92 (2*s*, 2 Me); 3.70, 3.88 (2*s*, 2 MeO); 5.81 (*s*, H–C(4)); 6.61-7.60 (*m*, 10 arom. H). ^{13}C-NMR: 22.0, 23.7 (2 Me); 53.2 (br., 2 MeO); 71.4 (C(4)); 76.9 (C(2)); 116.0, 119.5, 126.8, 127.3, 128.4, 128.6 (10 arom. CH); 126.6, 127.6 (C=C); 124.1, 144.4 (2 arom. C); 167.2, 169.5 (2 C=O). ESI-MS: 420 (100, $[M+Na]^+$), 302 (20). Anal. calc. for $C_{22}H_{23}NO_4S$ (397.49): C 66.48, H 5.83, N 3.52, S 8.07; found: C 66.27, H 5.60, N 3.47, S 7.91.

8. *Reaction of* **10** *with* **2**. A soln. of **10** (678 mg, 2 mmol) and **2** (344 mg, 2 mmol) in 2 ml of abs. xylene was heated under reflux for 5 h. After this time, the TLC analysis showed complete conversion of **2**. Xylene was

Table. *Crystallographic Data of* **6b**, cis-**8a**, cis-**8b**, **10**, *and* **16**

	6b	*cis*-**8a**	*cis*-**8b**	**10**	**16**
Crystallized from	MeOH	MeOH	MeOH/CH_2Cl_2	MeOH/CH_2Cl_2	MeOH/CH_2Cl_2
Empirical formula	$C_{25}H_{31}NOS$	$C_{21}H_{27}NO_6S$	$C_{21}H_{27}NO_5S_2$	$C_{18}H_{17}N_3O_4$	$C_{22}H_{23}NO_4S$
Formula weight [g mol^{-1}]	393.59	421.50	437.57	339.35	397.49
Crystal color, habit	colorless, plate	colorless, prism	orange, needle	colorless, prism	colorless, prism
Crystal dimensions [mm]	$0.05 \times 0.15 \times 0.22$	$0.07 \times 0.12 \times 0.22$	$0.02 \times 0.05 \times 0.25$	$0.10 \times 0.22 \times 0.28$	$0.15 \times 0.17 \times 0.20$
T [K]	160(1)	160(1)	160(1)	160(1)	160(1)
Crystal system	monoclinic	orthorhombic	orthorhombic	monoclinic	triclinic
Space group	$P2_1/c$	$P2_12_12_1$	$P2_12_12_1$	$P2_1/n$	$P\bar{1}$
Z	4	4	4	4	2
Reflections for cell determination	5212	3531	52251	5042	5662
2θ Range for cell determination [°]	4 – 55	4 – 60	4 – 50	4 – 60	4 – 60
Unit-cell parameters					
a [Å]	11.1313(2)	8.0291(1)	8.0658(1)	8.2591(1)	7.8680(1)
b [Å]	12.7310(2)	12.9780(2)	12.9688(2)	15.2263(2)	11.4916(2)
c [Å]	15.3727(2)	20.3603(3)	21.0148(3)	13.8455(2)	12.0825(2)
α [°]	90	90	90	90	106.0120(7)
β [°]	93.1073(7)	90	90	106.5616(6)	103.8056(7)
γ [°]	90	90	90	90	98.3705(7)
V [Å^3]	2175.30(6)	2121.58(5)	2198.23(5)	1668.91(4)	993.24(3)
D_x [g cm^{-3}]	1.202	1.319	1.322	1.350	1.329
μ (MoK_α) (mm^{-1})	0.164	0.189	0.274	0.0973	0.191
Scan type	ϕ and ω	ϕ and ω	ω	ϕ and ω	ϕ and ω
$2\theta_{(max)}$ [°]	55	60	50	60	60
Transmission factors (min; max)	–	–	0.940; 0.994	–	–
Total reflections measured	81085	53589	28596	45127	27274
Symmetry independent reflections	4980	6212	3875	4863	5787
Reflections used [$I > 2\sigma(I)$]	3470	4471	3368	3568	4416
Parameters refined	254	264	264	227	254
Final R	0.0435	0.0437	0.0368	0.0463	0.0437
wR	0.0440	0.0416	0.0339	0.0447	0.0459
Weights: p in $w = [\sigma^2(F_o) + (pF_o)^2]^{-1}$	0.012	0.015	0.005	0.005	0.005
Goodness-of-fit	1.865	1.420	1.807	2.888	2.454
Secondary extinction coefficient	$1.3(2) \times 10^{-6}$	$1.1(1) \times 10^{-6}$	$1.1(1) \times 10^{-6}$	$2.6(4) \times 10^{-6}$	$1.5(6) \times 10^{-6}$
Final Δ_{max}/σ	0.0004	0.0004	0.0005	0.0006	0.0003
$\Delta\rho$ (max; min) [e Å^{-3}]	0.23; −0.26	0.26; −0.28	0.23; −0.22	0.26; −0.22	0.29; −0.25

evaporated, and the residue was separated by means of CC (SiO_2; petroleum ether with increasing amount of CH_2Cl_2). As the less polar fraction, an orange oil was obtained, which was identified as **15**. After increasing the polarity of the eluent, **16** was isolated.

4-Isopropylidene-3,3-dimethylthietane-2-thione (**15**). Yield: 150 mg (43%). Orange oil ([32]: b.p. 112-116°/20 Torr). ^{1}H-NMR: 1.40 (*s*, 2 Me); 1.67 (*s*, Me); 1.80 (*s*, Me). ^{13}C-NMR: 19.9 (Me); 21.7 (Me); 25.0 (2 Me); 73.9 (C(3)); 122.3, 130.7 (C=C); 243.0 (C=S).

Dimethyl 5-Isopropylidene-2,3-diphenyl-1,3-thiazolidine-4,4-dicarboxylate (**16**). Yield: 210 mg (26%). Colorless crystals. M.p. 188–190° (MeOH/CH_2Cl_2). IR (KBr): 1763v*s* (C=O), 1597*w*, 1498*m*, 1456*m*, 1254v*s*, 1221*s*, 1053v*s*, 768*m*, 742*m*, 694*m*. ^{1}H-NMR: 1.83 (*s*, 2 Me); 3.50, 3.88 (2*s*, 2 MeO); 6.43 (*s*, H–C(2)); 6.75–7.68 (*m*, 10 arom. H). ^{13}C-NMR: 21.5, 25.5 (2 Me); 52.5, 53.1 (2 MeO); 69.5 (C(2)); 80.2 (C(4)); 121.9, 122.7, 127.9, 128.5, 128.7, 128.8, 129.4, 129.6 (10 arom. CH); 127.3, 128.1 (C=C); 139.6, 143.8 (2 arom. C); 168.6, 169.9 (2 C=O). CI-MS (NH_3): 398 (100, $[M+1]^+$). Anal. calc. for $C_{22}H_{23}NO_4S$ (397.49): C 66.48, H 5.83, N 3.52, S 8.07; found: C 66.47, H 5.67, N 3.41, S 7.82.

9. *Attempted Thermal Elimination of Dimethylketene from* **13**. A soln. of **13** (20 mg, 0.04 mmol) in 1 ml of abs. xylene was heated under reflux for 60 h. The solvent was evaporated, and the residue was analyzed by ^{1}H-NMR spectroscopy, which confirmed that only partially decomposed starting material was present.

10. *X-Ray Crystal-Structure Determination of* **6b**, cis-**8a**, cis-**8b**, **10**, *and* **16** (see the *Table* and *Figs. 1–4*)[6]. All measurements were made on a *Nonius KappaCCD* diffractometer [36] with graphite-monochromated MoK_α radiation (λ 0.71073 Å) and an *Oxford Cryosystem Cryostream 700* cooler. Data reduction was performed with *HKL Denzo* and *Scalepack* [37]. The intensities were corrected for *Lorentz* and polarization effects, and, in the case of *cis*-**8b**, an absorption correction based on the multiscan method [38] was applied. Equivalent reflections were merged; except for *cis*-**8a** and *cis*-**8b**, where *Friedel* pairs were not merged. Data collection and refinement parameters are given in the *Table*, and views of the molecules are shown in *Figs. 1–4*. Each structure was solved by direct methods by means of SIR92 [39], which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. All of the H-atoms were fixed in geometrically calculated positions (d(C–H) = 0.95 Å), and each was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{eq}$ of its parent atom. Refinement of each structure was carried out on F by means of full-matrix least-squares procedures, which minimized the function $\Sigma w(|F_o|-|F_c|)^2$. Corrections for secondary extinction were applied. For **6b**, *cis*-**8a**, *cis*-**8b**, **10**, and **16**, three, two, two, two, and three reflections, resp., whose intensities were considered to be extreme outliners, were omitted from the final refinement. The compounds *cis*-**8a** and *cis*-**8b** crystallize in a polar space group, and refinement of the absolute structure parameter [40] yielded values of 0.18(6) and 0.08(5), resp. These values are not particularly precise [41], but are suggestive of a partial inversion twin for *cis*-**8a** and probably an enantiomerically pure *cis*-**8b**, although enantiomeric purity or some degree of inversion twinning cannot be excluded for either compound. As enantiomerically pure reaction products were not expected, some degree of spontaneous resolution may have taken place. Neutral-atom-scattering factors for non-H-atoms were taken from [42a], and the scattering factors for H-atoms were taken from [43]. Anomalous dispersion effects were included in F_c [44]; the values for f' and f'' were those of [42b]. The values of the mass attenuation coefficients are those of [42c]. All calculations were performed by means of the teXsan crystallographic software package [45].

REFERENCES

[1] P. Metzner, *Top. Curr. Chem.* **1999**, *204*, 127.
[2] M. T. Molina, M. Yanez, O. Mo, R. Notario, J.-L. Abboud, in 'The chemistry of double-bonded functional groups', Suppl. A3, Ed. S. Patai, John Wiley & Sons, New York, 1997, p. 1355.
[3] R. Huisgen, J. Penelle, G. Mlostoń, A. Buyle Padias, H. K. Hall Jr., *J. Am. Chem. Soc.* **1992**, *114*, 266.
[4] D. S. C. Black, K. G. Watson, *Austr. J. Chem.* **1973**, *26*, 2491.
[5] G. Mlostoń, R. Huisgen, K. Polborn, *Tetrahedron* **1999**, *55*, 11475.
[6] R. Huisgen, X. Li, G. Mlostoń, C. Fulka, *Eur. J. Org. Chem.* **2000**, 1695.

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[6] Crystallographic data (excluding structure factors) for the structures of **6b**, *cis*-**8a**, *cis*-**8b**, **10**, and **16** have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publications No. CCDC-185696 to CCDC-185700. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: +44-((0)1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

[7] R. Huisgen, G. Mlostoń, K. Polborn, *J. Org. Chem.* **1996**, *61*, 6570.
[8] R. Huisgen, G. Mlostoń, K. Polborn, R. Sustmann, W. Sicking, *Liebigs Ann. Recl.* **1997**, 179; R. Huisgen, G. Mlostoń, K. Polborn, F. Palacios-Gambra, *Liebigs Ann. Recl.* **1997**, 187.
[9] G. Mlostoń, H. Heimgartner, *Helv. Chim. Acta* **1995**, *78*, 1293.
[10] G. Mlostoń, T. Gendek, H. Heimgartner, *Helv. Chim. Acta* **1998**, *81*, 1585.
[11] M. Kägi, A. Linden, G. Mlostoń, H. Heimgartner, *Helv. Chim. Acta* **1996**, *79*, 855; **1998**, *81*, 285.
[12] L. Harwood, in 'The Chemistry of Heterocyclic Compounds, Vol. 59: Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products', Eds. A. Padwa, W. H. Pearson, John Wiley & Sons, New York, 2002, p. 315; J. W. Lown, in '1,3-Dipolar Cycloaddition Chemistry', Vol. 1, Ed. A. Padwa, John Wiley & Sons, New York, 1984, p. 653.
[13] E. Vedejs, in 'Advances in Cycloaddition', Vol. 3, Ed. D. P. Curran, JAI Press, London, 1993, p. 33.
[14] T. Gallagher, *J. Heterocycl. Chem*. **1999**, *36*, 1365.
[15] G. Mlostoń, A. Linden, H. Heimgartner, *Pol. J. Chem*. **1997**, *71*, 32; G. Mlostoń, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **1998**, *81*, 558.
[16] A. Gebert, A. Linden, G. Mlostoń, H. Heimgartner, *Heterocycles* **2002**, *56*, 393; A. Gebert, H. Heimgartner, *Helv. Chim. Acta* **2002**, *85*, 2073.
[17] G. Mlostoń, Z. Skrzypek, *Bull. Soc. Chim. Belg*. **1990**, *99*, 167.
[18] A. Gebert, A. Linden, H. Heimgartner, *Heterocycles* **2001**, *54*, 691.
[19] K. Urbaniak, G. Mlostoń, H. Heimgartner, *Helv. Chim. Acta* **2002**, *85*, 2056.
[20] G. Seybold, *Tetrahedron Lett*. **1974**, 555, and refs. cited therein.
[21] E. Schaumann, *Tetrahedron* **1988**, *44*, 1827.
[22] N. F. Osborne, *J. Chem. Soc., Perkin Trans. 1* **1982**, 1429.
[23] R. Huisgen, in '1,3-Dipolar Cycloaddition Chemistry', Vol. 1, Ed. A. Padwa, John Wiley & Sons, New York, 1984, p. 1; R. M. Kellogg, *Tetrahedron* **1976**, *32*, 2165.
[24] T. Olszak, T. Skarzynski, G. Mlostoń, *Acta Crystallogr., Sect. C* **1988**, *44*, 205.
[25] C. K. Johnson, 'ORTEP II', Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, TN, 1976.
[26] G. Gonzalez, M. V. Martin, M. C. Paredes, *Heterocycles* **2000**, *52*, 237.
[27] F. Texier, R. Carrié, *Bull. Soc. Chim. Fr.* **1971**, 4119; D. Greé, R. Carrié, *Can. J. Chem*. **1984**, *62*, 939.
[28] M. Domagala, K. Urbaniak, G. Mlostoń, *Acta Crystallogr., Sect. C*, submitted.
[29] R. Huisgen, G. Mlostoń, E. Langhals, *Helv. Chim. Acta* **2001**, *84*, 1805.
[30] R. Huisgen, G. Mlostoń, H. Giera, E. Langhals, *Tetrahedron* **2002**, *58*, 507.
[31] R. Huisgen, E. Langhals, G. Mlostoń, T. Oshima, J. Rapp, *J. Heterocycl. Chem*. **1987**, *9*, S-1.
[32] K. Muthuramu, B. Sundari, V. Ramamurthy, *Tetrahedron* **1983**, *39*, 2719.
[33] G. Mlostoń, J. Romański, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **1993**, *76*, 2147.
[34] R. Bartnik, G. Mlostoń, S. Lesniak, *Pol. J. Chem.* **1979**, *5*, 537.
[35] G. Szeimies, R. Huisgen, *Chem. Ber.* **1966**, *99*, 491.
[36] R. Hooft, KappaCCD Collect Software, Nonius BV, Delft, The Netherlands, 1999.
[37] Z. Otwinowski, W. Minor, in 'Methods in Enzymology, Vol. 276, Macromolecular Crystallography', Part A, Eds. C. W. Carte Jr., R. M. Sweet, Academic Press, New York, 1997, p. 307.
[38] R. H. Blessing, *Acta Crystallogr., Sect. A* **1995**, *51*, 33.
[39] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, SIR92, *J. Appl. Crystallogr*. **1994**, *27*, 435.
[40] a) H. D. Flack, *Acta Crystallogr., Sect. A* **1983**, *39*, 876; b) G. Bernardinelli, H. D. Flack, *Acta Crystallogr., Sect. A* **1985**, *41*, 500.
[41] H. D. Flack, G. Bernardinelli, *J. Appl. Crystallogr.* **2000**, *33*, 1143.
[42] a) E. N. Maslen, A. G. Fox, M. A. O'Keefe, in 'International Tables for Crystallography', Ed. A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992, Vol. C, Table 6.1.1.1, p. 477; b) D. C. Creagh, W. J. McAuley, in 'International Tables for Crystallography', Ed. A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992, Vol. C, Table 4.2.6.8, p. 219; c) D. C. Creagh, J. H. Hubbell, in 'International Tables for Crystallography', Ed. A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992, Vol. C, Table 4.2.4.3, p. 200.
[43] R. F. Stewart, E. R. Davidson, W. T. Simpson, *J. Chem. Phys.* **1965**, *42*, 3175.
[44] J. A. Ibers, W. C. Hamilton, *Acta Crystallogr.* **1964**, *17*, 781.
[45] 'teXsan: Single Crystal Structure Analysis Software', Version 1.10, Molecular Structure Corporation, The Woodlands, TX, 1999.

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