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Interception of an Intermediate Thiocarbonyl Ylide by NH-Compounds

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By thermal decomposition of 1,1,3,3-tetramethyl-5-thia-7,8-diazaspiro[3.4]octan-2-one **(1)**, 2,2,4,4-tetramethyl-3-thioxocyclobutanone *S*-methylide **(2)** was generated as an intermediate. This reactive "thiocarbonyl ylide" was trapped by protic agents such as alcohols, NH- and SH-acidic compounds to give 1,3-adducts of the acetal type. In a mixture of methanol and ammonia, the spiroheterocycle **1** was deprotonated and competitive ring opening of the 2,5-dihydro-1,3,4-thiadiazole and the cyclobutane ring occurred to give the hydrazono derivative 7 and the 1,3,4-thiadiazole **8**, respectively. Surprisingly, **2** was intercepted by maleimide in a 1,3-dipolar cycloaddition.

Key words: thiocarbonyl ylides, 1,3-addition, 1,3-dipolar cycloaddition, ring opening, crystal structure

2,5-Dihydro-1,3,4-thiadiazole **1** is easily synthesized and well known as a convenient precursor of 2,2,4,4-tetramethyl-3-thioxocyclobutanone *S*-methylide **(2)** [1,2], which belongs to the class of reactive thiocarbonyl ylides [3,4]. The generation of the 1,3-dipole occurs by cyclo-elimination of N_2 in THF-solution at 45–50°C [5]. Recently, **2** was reported to react not only with dipolarophiles, but also with diverse HX compounds, thereby yielding 1,3-adducts. Thus, decomposition of **1** in the presence of alcohols leads to O,S-dialkyl acetals of type **3** [1,5] (Scheme 1). Other thiocarbonyl ylides were also intercepted with thiols, thiophenols, and phenols [6,7]. In an earlier study, we showed that NH-azoles efficiently trap **2** to give products of type **4** [8]. However, when the azole bears enolizable thiocarbonyl groups, the interception occurs via the more nucleophilic S-atom to give S,S-acetals **5** [9,10].

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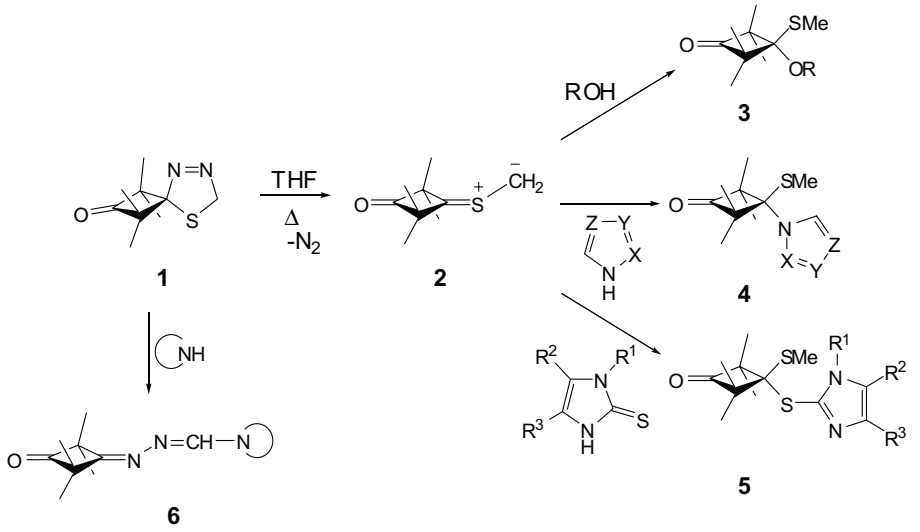
Scheme 1



On the other hand, conversions of **1**, which occur without elimination of N_2, are known. For example, treatment with secondary aliphatic amines leads to the opening of the heterocyclic ring and, after elimination of H_2S, to *N*-alkylidene hydrazones **6** [11] (Scheme 1).

In the present paper, we report new interceptions of **2** with NH compounds of the amide type. Furthermore, the competition of [2+3]-cycloaddititon of **2** with the 1,3-addition in the case of maleinimide has been investigated.

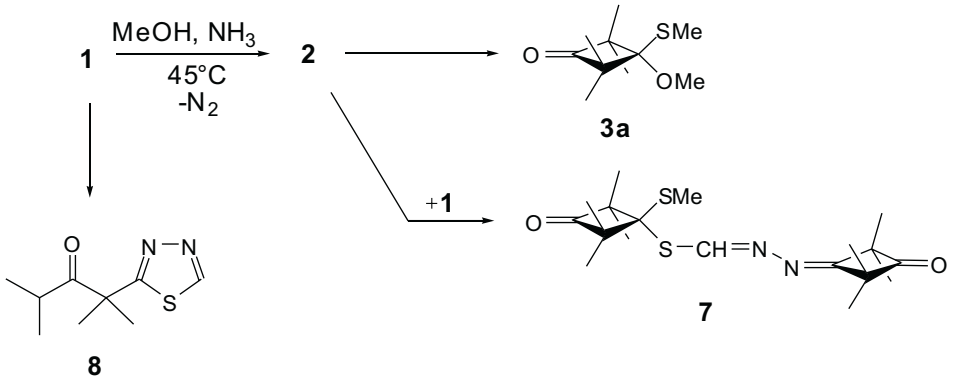
RESULTS AND DISCUSSION

As mentioned above, the typical procedure for reactions with **2** is the thermal decomposition of **1** in non-polar, aprotic solvents (*e.g*. THF, $CHCl_3$, benzene, *etc*.). In alcoholic solvents, O,S-dialkyl acetals **3** are formed, and this reaction can be catalyzed by proton acids [1,12]. In order to check the influence of a base, the thermolysis of **1** was carried out at 45°C in methanolic solution containing NH_3. In this case, the amount of extruded N_2 was only *ca*. 50% of the expected volume. Separation of the mixture led to three products, which were formed in comparable yields*. One of the products was identified as O,S-dimethyl acetal **3a** [5]. The structure of the second one, containing two cyclobutanone moieties and an imino group, was elucidated on

*The ratio is dependent on the concentration of NH_3 in the methanolic solution. Higher concentration enhances the amount of compound **8** (Scheme 2).

the basis of its spectroscopic data and confirmed unambiguously by X-ray crystallography as the hydrazone derivative **7** (Scheme 2, Figure 1).

Scheme 2



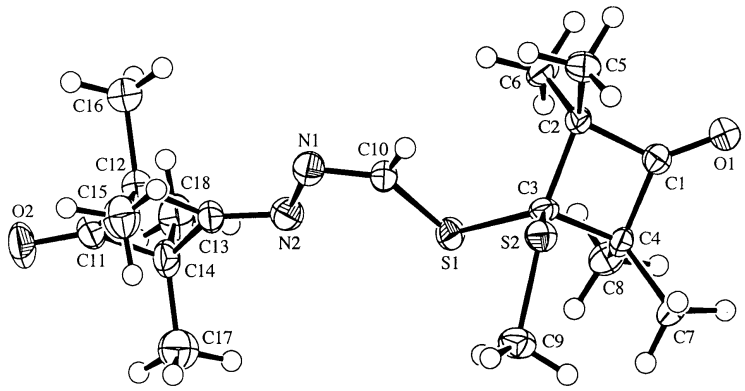


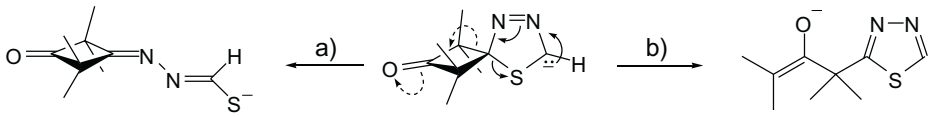
Figure 1. ORTEP-Plot [13] of the molecular structure of **7** (arbitrary numbering of the atoms; 50% probability ellipsoids).

It is worth mentioning that analogous derivatives are frequently formed in the thermolytic generation of adamantanethione *S*-methylide [14]. The formation of compound **7** has been reported previously [15]. It was found as a side product, when the decomposition of **1** was carried out without solvent in molten aromatic sulfines. A mechanistic proposal for its formation, including participation of thiocarbonyl ylide **2**, was formulated in [15]. The third product of the reaction showed a C=O absorption in the IR spectrum (KBr) at 1720 cm^{-1} which differed significantly from that of cyclobutanone derivatives at *ca*. 1790 cm^{-1}. The characteristic NMR-signals of an isopropyl group indicated that the formation of this compound occurred by ring opening of the strained cyclobutanone. Elemental analysis and mass spectrometry confirmed that the product is an isomer of the starting material **1**. The structure was elucidated as

the 1,3,4-thiadiazole derivative **8** on the basis of spectroscopic data. The formation of **8** can be rationalized as an aromatization of the spirocyclic 2,5-dihydro-1,3,4-thiadiazole **1** under basic conditions. A similar aromatization of a 2,5-dihydrothiophene *via* ring opening of a spirocyclic cyclobutanone was described in one of our recent papers [16]. In analogy to these processes, aromatization of spirocyclic 2,5-dihydro-1,3,4-thiadiazole derivatives can occur *via* ring-opening of other spiro-linked heterocyclic rings, *e.g.*, 4,5-dihydro-1,3-thiazoles are converted into thioamides [17,18].

For the formation of both **7** and **8**, deprotonation of **1** leading to anion **9** is the key step. Two different ring opening reactions of **9** are feasible: a) cleavage of the C(4),S bond leads to the thiolate **10**, which subsequently combines with protonated **2** to give **7**; b) under preservation of the heterocyclic ring, cleavage of the C(1),C(4) bond results in the formation of an enolate **11**, which gives **8** (Scheme 3). Basic and nucleophilic agents were reported to induce the ring-opening of 2,2,4,4-tetramethylcyclobutanone (*cf.* [19,20]).

Scheme 3



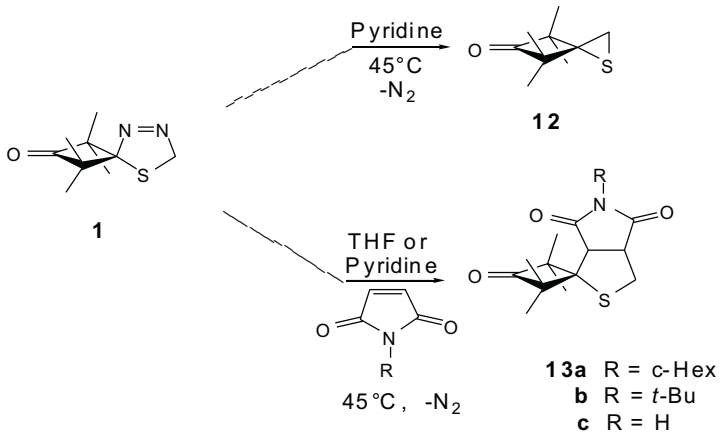
10 **9** **11**

Having in mind the results we obtained in methanol/NH_3, the decomposition of **1** was carried out in pyridine. The expected amount of N_2 was evolved and, after evaporation of the solvent, thiirane **12** (Scheme 4), which is formed by the 1,3-dipolar electrocyclization of **2**, was obtained as the only product in almost quantitative yield. This result shows that pyridine is an excellent solvent for the generation of thiocarbonyl ylide **2**. Both the quantitative evolution of N_2 and the very high yield of **12** evidence that there is no side reaction induced when pyridine is used as a base.

In order to test the properties of pyridine as a solvent for cycloaddition reactions with **2**, an experiment with *N*-cyclohexylmaleimide was carried out at 45°C in pyridine as well as in THF. In both cases, a single product was obtained, which was isolated in *ca.* 50% yield and identified as the cycloadduct **13a** (Scheme 4). A smooth cycloaddition to give **13b** was also observed with *N*-(*tert*-butyl)maleimide.

In spite of the fact that a multitude of dipolarophiles has been used in reactions with thiocarbonyl ylides (*cf.* [4]), to the best of our knowledge, there are no reports known on reactions with *N*-unsubstituted maleimides. The main reason is the expectation that this reagent will rather protonate 1,3-dipoles, leading to 1,3-adducts instead of cycloadducts. Nevertheless, heating equimolar amounts of **1** and maleimide in THF to 45°C gave a single product which, in the ^{1}H-NMR spectrum, along with other absorptions, showed 4 Me signals at 1.04, 1.30, 1.35, and 1.68 ppm and a broad sin-

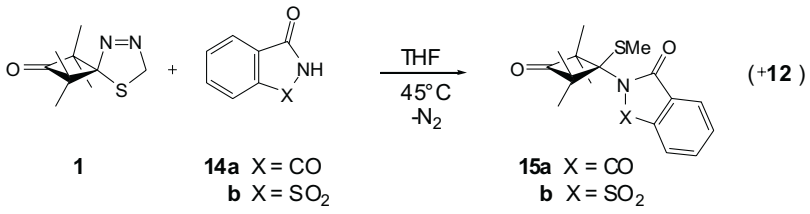
Scheme 4



glet at 11.32 ppm for NH. Thus, the structure corresponded to the [2+3]-cycloadduct **13c** (Scheme 4), and the alternative 1,3-adduct could be ruled out.

The unexpected result with maleimide prompted us to perform reactions with other compounds containing imido and amido groups. Under standard conditions, phthalimide (**14a**), which cannot act as a dipolarophile, reacted with **2** to give the 1,3-adduct **15a** along with thiirane **12** (Scheme 5), and the ratio of these components established in the crude mixture (^{1}H-NMR) was 87:13. In accordance with the structure of **15a**, the ^{1}H-NMR spectrum showed only two Me signals at 1.49 and 1.56 ppm, in addition to the singlet for MeS at 1.95 ppm.

Scheme 5

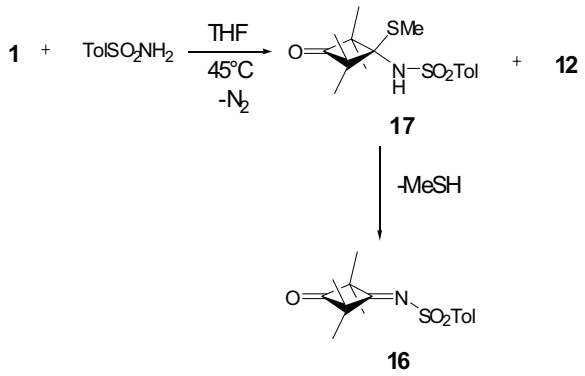


Under analogous condititons, saccharin (**14b**) intercepted **2** even more efficiently, and **15b** was the sole product detected in the crude mixture.

In the reaction of **1** with 4-toluenesulfonamide, evolution of methylmercaptane was observed, in addition to N_2. The crude mixture contained significant amounts of **12**. After chromatographic workup, **12** and a new crystalline product **16** were obtained in 50 and 30% yield, respectively (Scheme 6). A pure sample of **16** showed absorption bands for C=O and C=N at 1811 and 1667 cm^{-1}, respectively, in the IR spectrum (KBr), and in the ^{13}C-NMR spectrum the corresponding signals appear at 215.2 and

196.4 ppm. Recently, 2,2,4,4-tetramethyl-3-iminocyclobutanones have been of interest with respect to non-bonding orbital interactions [21]. N-Alkyl and N-aryl substituted derivatives have been prepared by classical methods from 2,2,4,4-tetramethylcyclobutane-1,3-dione (**18**) and the respective primary amines [22]*. Our methodology opens an access to hitherto unknown *N*-sulfonylated derivatives. The formation of imine **16** results from the elimination of MeSH from the initially formed interception product **17**.

Scheme 6



In contrast to 4-toluenesulfonamide, no stable 1,3-adduct could be detected in reactions of **1** with carboxamides. During the reaction, evolution of N_2 and methylmercaptane (MeSH) was observed, and after evaporation of the solvent, the ^{1}H-NMR spectra of the crude mixtures showed the presence of thiirane **12**, 2,2,4,4-tetramethylcyclobutane-1,3-dione (**18**), as well as the starting carboxamide. In the case of benzamide, the ratio **12**/**18** was *ca*. 2:1. The evolution of MeSH and the presence of **18** led to the conclusion that thiocarbonyl ylide **2** is partially intercepted by the carboxamide to give the N,S acetal **19**, which spontaneously decomposes to yield imine **20**. The latter hydrolyzes during workup to give **18** (Scheme 7).

A similar reaction course was observed when a mixture of **1** and uracil was heated in pyridine. The analysis (^{1}H-NMR) of the crude mixture showed two singlets at 1.92 and 1.98 ppm, which evidenced the presence of a 1:2-adduct**. The attempted isolation of this product failed and during workup MeSH was evolved and uracil was recovered.

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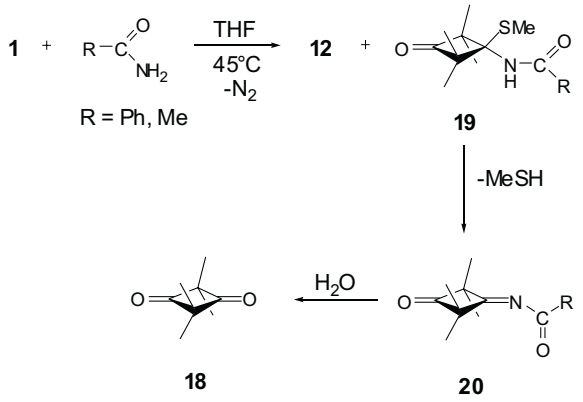
* Recently, a bis(*N*-arylimine) of **18** has been isolated from a Thai plant showing antifeedant activity [23], and some additional derivatives have been synthesized [24].

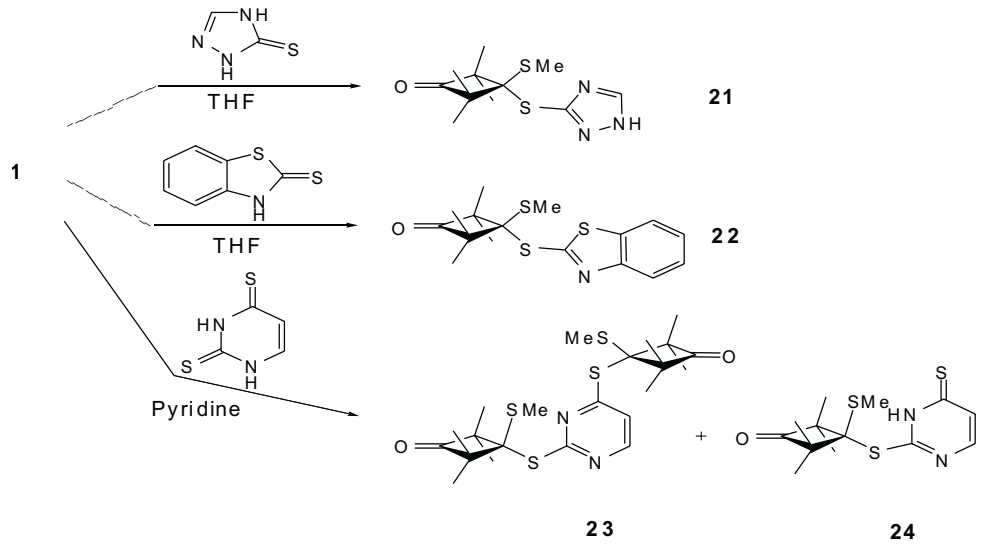
**The formation of a 1:2 adduct has been observed previously in the analogous reaction with thiouracil [9].

Scheme 7



According to our previous studies, enolizable azaheterocyclic thiones intercept **2** to yield stable 1,3-adducts *via* nucleophilic addition of the S-atom [9,10]. This result was confirmed in experiments with 1,2,4-triazole-3-thione (3-mercapto-1,2,4-triazole) and benzo-1,3-thiazole-2-thione (2-mercaptobenzo-1,3-thiazole). The adducts **21** and **22**, respectively, were obtained in good yields (Scheme 8).

Scheme 8



Based on the observations presented above, dithiouracil was used in the reaction with **1**. Similar to the experiment with 2-thiouracil [9], the 1:2-adduct **23** (Scheme 8) was the major product despite the fact that the starting materials were used in equimolar amounts. The corresponding 1:1 adduct **24** was obtained as a minor product.

In conclusion, the present study shows that NH-acidic compounds exhibit variable reactivity towards thiocarbonyl S-methylide **2**. The more acidic the NH group is, the more efficient is the interception of the dipole. The stability of the formed 1,3-adducts depends on the structure of the NH-acidic reagent. Whereas NH-amides afford unstable 1,3-adducts, which tend to hydrolyze, their thio-analogues lead to stable interception products. In the case of maleimide, in which competition between the [2+3]-cycloaddition and the 1,3-addition is possible, intermediate **2** preferentially forms the five-membered cycloadduct. This result is rather unexpected, and there are no analogous observations with other 1,3-dipoles known to date.

EXPERIMENTAL

1. General. See [25]. M.p.'s were determined in capillary on a Melt-Temp II apparatus and are not corrected. IR spectra were registered with a NEXUS FT-IR spectrophotometer (in KBr). ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ on a Bruker-AC-300 (300 and 75.5 MHz, resp.) or Tesla BS687 (80 and 20 MHz, resp.) instrument. Mass spectra were recorded with a MAT-90 spectrometer (EI (70 eV) or CI (NH_3)). Elemental analyses were performed by the Mikroanalytisches Laboratorium des Organisch-chemischen Instituts der Universität Zürich.

2. Starting materials. 2,5-Dihydro-1,3,4-thiadiazole **1** was prepared from 2,2,4,4-tetramethyl-3-thioxocyclobutanone [26] and diazomethane according to a published protocol [27]. *N*-(Cyclohexyl)maleimide and *N*-(*tert*-butyl)maleimide were synthesized from maleic anhydride and the corresponding amines following the method described in [28]. Dithiouracil was prepared by thionation of thiouracil with P_4S_{10} in pyridine (*cf*. [29]). All other reagents were commercial and were purified by crystallization prior to their use. Tetrahydrofuran (THF) was distilled over Na in the presence of benzophenone. Methanol (MeOH) was saturated with NH_3 gas while cooling in a water/ice bath and was used without accurate determination of the NH_3 concentration.

3. Thermal decomposition of 1. 3.1. In methanol containing ammonia. A magnetically stirred solution of **1** (396 mg, 2 mmol) in 2 ml of MeOH/NH_3 was heated in an oil bath (45°C). Evolution of N_2 was monitored with a gas burette connected to the reaction flask. After 2 h, the evolution of N_2 ceased and only 12 ml (25% of the theoretical amount) were produced. The solvent was evaporated carefully and the residue was analyzed by ^{1}H-NMR spectroscopy. Based on the comparison of the intensities of the signals at 9.24 (1 H of **8**), 8.25 (1 H of **7**), and 3.42 ppm (3 H of **3a**), the ratio of **8:7:3a** was established as *ca*. 5:4:1. In another experiment using a more concentrated NH_3 solution, only **8** and **7** (ratio 8:2) were detected in the crude mixture. Separation of **8** and **7** was achieved chromatographically on SiO_2 plates, using $CHCl_3$ as eluant. Yields reported refer to this experiment with higher NH_3 concentration.

*2,2,4,4-Tetramethyl-3-methylthio-3-{[*N*′-(2,2,4,4-tetramethyl-3-oxocyclobutylid-ene)hydrazono] methylthio}cyclobutan-1-one* **(7)**: Yield: 129 mg (35%). Colorless crystals. M.p. 127–129°C (MeOH; ref. [15]: 123–124°C).

2,4-Dimethyl-2-(1,3,4-thiadiazol-2-yl)pentan-3-one **(8)**. Yield: 208 mg (52%); after chromatography as the more polar fraction and bulb-to-bulb distillation (110°C/0.2 Torr). Colorless oil. IR (neat): 3088*m*, 2976*s*, 2935*s*, 2873*m*, 1716*vs* (C=O), 1470*s*, 1383*s*, 1367*s*, 1219*m*, 1095*s*, 1039*s*, 1026*s*, 999*s*, 903*s*. ^{1}H-NMR: 1.00 (*d*, *J* = 8.0, *Me*$_2$CH); 1.75 (*s*, 2 Me); 3.10 (*m*, Me$_2$C*H*); 9.24 (*s*, 1 arom. H). ^{13}C-NMR: 20.4 (*q*, 2 Me); 26.0 (*q*, 2 Me); 35.5 (*d*, Me$_2$*C*H); 52.4 (*s*, Me$_2$*C*); 173.6 (*d*, 1 arom. CH); 213.9 (*s*, C=O). CI-MS (NH_3+NaI): 221 (100, [*M*+Na]$^+$). Anal. Calc. for $C_9H_{14}N_2OS$ (198.29): C 54.52, H 7.12, N 14.13, S 16.17. Found: C 53.99, H 7.52, N 13.88, S 15.92.

3.2. In pyridine. A stirred solution of **1** (99 mg, 0.5 mmol) in abs. pyridine (1 ml) was heated in an oil bath (45°C), and the evolution of N_2 was monitored with a gas burette. After 3.5 h, the evolution of N_2 ceased and the expected volume of N_2 was collected. The pyridine was evaporated in vacuo using a Kugelrohr apparatus, and the oily residue was analyzed by ^{1}H-NMR spectroscopy. The known thiirane **12** was formed as sole product. After removal of $CDCl_3$, the residue was dissolved in 3 ml of MeOH and kept overnight in dry ice. The colorless crystals of **12** were filtered and characterized.

4,4,6,6-Tetramethyl-1-thiaspiro[2.3]hexan-5-one **(12)**. Yield: 55 mg (65%). Colorless crystals. M.p. 79–81°C (MeOH; ref. [30]: m.p. 80–82°C). ^{1}H-NMR: 1.12 (*s*, 2 Me); 1.23 (*s*, 2 Me); 2.59 (*s*, CH_2).

4. [2+3]-Cycloadditions of 2 with maleimides. 4.1. In tetrahydrofuran. A solution of **1** (198 mg, 1 mmol) and 1.1 mmol of the respective maleimide in 2 ml of freshly distilled abs. THF was stirred magnetically and heated in an oil bath (45°C) until the evolution of N_2 ceased (*ca*. 3 h). The solvent was evaporated and the crude products were examined by ^{1}H-NMR spectroscopy. In all reactions, cycloadducts **13** were obtained as the only products. Reported yields refer to isolated compounds.

7-Cyclohexyl-2′,2′,4′,4′-tetramethyl-3-thia-7-azaspiro[bicyclo[3.3.0]octane-2,1′-cyclobutane]-3′,6,8-trione **(13a)**. With *N*-cyclohexylmaleimide. Yield: 238 mg (68%). Colorless crystals. M.p. 168–170°C (MeOH). IR: 2934*m*, 1767*s* (C=O), 1706*vs* (C=O), 1393*s*, 1201*m*, 1124*w*, 1050*w*. ^{1}H-NMR: 1.21, 1.31, 1.41, 1.83 (4*s*, 4 Me); 1.20–2.30 (*m*, 10 H); 2.90–3.40 (*m*, 3 H); 3.60–4.20 (*m*, 2 H). ^{13}C-NMR: 20.2, 21.3, 23.1, 24.5 (4*q*, 4 Me); 25.1, 25.9, 26.0, 28.6, 29.0, 36.1 (6*t*, 6 CH_2); 46.6, 52.4, 52.9 (3*d*, 3 CH); 61.3, 65.8, 69.4 (3*s*, C(1′), C(2′), C(4′)); 176.1, 177.9, 218.7 (3*s*, 3 C=O). EI-MS: 349 (10, $M^{+\cdot}$), 279 (100), 126 (25), 111 (30). Anal. Calc. for $C_{19}H_{27}NO_3S$ (349.49): C 65.94, H 7.26, N 4.80, S 11.00. Found: C 65.80, H 7.48, N 4.51, S 10.78.

7-(tert-Butyl)-2′,2′,4′,4′-tetramethyl-3-thia-7-azaspiro[bicyclo[3.3.0]octane-2,1′-cyclobutane]-3′,6,8-trione **(13b)**. With *N*-(*tert*-butyl)maleimide. Yield: 204 mg (63%). Colorless crystals. M.p. 165–167°C (MeOH). IR: 1767*s* (C=O), 1703*vs* (C=O), 1344*m*, 1266*w*, 1180*w*, 1126*w*, 1037*w*. ^{1}H-NMR: 1.24, 1.39, 1.40, 1.78 (4*s*, 4 Me); 1.60 (*s*, Me_3C); 2.90–3.22 (*m*, 2 H); 3.58–3.85 (*m*, 2 H). ^{13}C-NMR: 20.2, 21.3, 23.1, 24.6 (4*q*, 4 Me); 28.4 (*q*, *Me*$_3$C); 36.2 (*t*, CH_2); 46.9, 53.0 (2*d*, 2 CH); 58.8 (*s*, Me_3C); 61.3, 65.8, 69.7 (3*s*, C(1′), C(2′), C(4′)); 176.9, 178.6, 219.0 (3*s*, 3 C=O). EI-MS: 323 (2, $M^{+\cdot}$), 302 (22), 270 (13), 253 (88), 247 (31), 200 (31), 197 (100), 126 (44), 111 (40). Anal. Calc. for $C_{17}H_{25}NO_3S$ (323.44): C 63.12, H 7.79, N 4.33, S 9.91. Found: C 63.13, H 8.07, N 4.14, S 9.75.

2′,2′,4′,4′-Tetramethyl-3-thia-7-azaspiro[bicyclo[3.3.0]octane-2,1′-cyclobutane]-3′,6,8-trione **(13c)**. With maleimide. Yield: 214 mg (80%). Colorless crystals. M.p. 283–285°C (MeOH). IR: 3229*s* (NH), 1797*s* (C=O), 1720*vs* (C=O), 1462*m*, 1343*s*, 1200*s*, 1107*s*, 1049*m*, 790*s* (br.), 633*m*. ^{1}H-NMR: 1.04, 1.30, 1.35, 1.68 (4*s*, 4 Me); 2.87–3.17 (*m*, 2 H); 3.44–3.53 (*m*, 1 H); 4.03 (*d*, *J* = 6.6, 1 H). ^{13}C-NMR: 19.6, 21.0, 22.3, 23.9 (4*q*, 4 Me); 34.9 (*t*, CH_2); 54.4, 59.9 (2*d*, 2 CH); 57.5, 65.2, 68.2 (3*s*, C(1′), C(2′), C(4′)); 177.9, 179.0, 218.6 (3*s*, 3 C=O). EI-MS: 267 (12, $M^{+\cdot}$), 252 (11), 224 (88), 197 (100), 182 (12), 126 (16), 111 (16). Anal. Calc. for $C_{13}H_{17}NO_3S$ (267.35): C 58.40, H 6.41, N 5.24, S 11.99. Found: C 58.40, H 6.47, N 5.27, S 11.90.

4.2. In pyridine. The reaction with maleimide was carried out according to the protocol described above, but THF was replaced by pyridine. After 2 h at 45°C, the evolution of N_2 was complete. After evaporation of the solvent *in vacuo*, the residue was examined by ^{1}H-NMR spectroscopy, and **13c** was the exclusive product. After crystallization from MeOH/CH_2Cl_2, 147 mg (42%) of colorless crystals of **13c** (^{1}H-NMR, IR, m.p.) were isolated.

5. Interception of 2 with phthalimide (14a) and saccharin (14b). A solution of 1 (198 mg, 1 mmol) and 1 mmol of **14a** and **14b**, respectively, in abs. THF (1 ml) was stirred magnetically and heated in an oil bath (45°C). The evolution of N_2 ceased after *ca.* 3 h and *ca*. 24 ml of N_2 (almost the theoretical amount) were collected. The crude mixtures were analyzed by ^{1}H-NMR spectroscopy. In the case of **14a**, the main product **15a** was found along with thiirane **12**, and the ratio of the two compounds, established by comparison of the intensities of the signals at 2.61 (2 H for **12**) and 1.96 ppm (3 H for **15a**), was *ca.* 87:13. Fractionated crystallization from MeOH containing small amounts of CH_2Cl_2 afforded pure **15a**. In the reaction with **14b**, no **12** was detected in the crude product.

N-(2,2,4,4-Tetramethyl-1-methylthio-3-oxocyclobutyl)phthalimide **(15a)**. With **14a**. Yield: 230 mg (72%). Colorless crystals. M.p. 120–122°C (MeOH/CH_2Cl_2). IR: 1768*s* (C=O), 1720*vs* (C=O), 1344*m*, 1200*m*, 1125*m*, 1049*m*, 789*m* (br.), 633w. ^{1}H-NMR: 1.49, 1.56 (2*s*, 4 Me); 1.95 (*s*, MeS); 7.72–7.85 (*m*, 4 arom. H): ^{13}C-NMR: 14.2 (*q*, MeS); 20.1, 24.0 (2*q*, 4 Me); 68.4 (*s*, 2 Me_2C); 71.9 (*s*, C(1′)); 123.4, 134.4 (2*d*, 4 arom. CH); 131.6 (*s*, 1 arom. C); 168.0, 218.4 (2*s*, 2 C=O). EI-MS: 318 (< 5, $[M\text{-}1]^+$), 302 (10), 270 (22), 247 (100), 242 (29), 200 (98), 160 (28), 132 (35), 104 (75). Anal. Calc. for $C_{17}H_{19}NO_3S$ (319.40): C 63.93, H 6.63, N 4.39, S 10.01. Found: C 64.47, H 6.91, N 4.61, S 9.81.

N-(2,2,4,4-Tetramethyl-1-methylthio-3-oxocyclobutyl)-2,3-dihydrobenzo[1,2]thiazol-3-one 1,1-dioxide **(15b)**. With **14b**. Yield: 111 mg (31%). Colorless crystals. M.p. 131–133°C (MeOH/CH_2Cl_2). IR: 3251*s* (NH), 1781*vs* (C=O), 1729*vs* (C=O), 1330*s*, 1270*vs*, 1171*vs*, 1088*vs*, 1017*s*, 904*m*, 859*m*,

764*m*, 736*m*. ^{1}H-NMR: 1.41, 1.43 (2*s*, 4 Me); 2.01 (*s*, MeS); 5.23 (br. *s*, NH); 7.90–8.35 (*m*, 4 arom. H). ^{13}C-NMR: 15.3 (*q*, MeS); 20.0, 25.0 (2 br. *q*, 4 Me); 70.0 (br. *s*, 2 Me_2C); 78.7 (*s*, C(1′)); 120.6, 125.3, 134.5, 135.3 (4*d*, 4 arom. CH); 126.5, 138.5 (2*s*, 2 arom. C); 160.3, 217.3 (2*s*, 2 C=O). EI-MS: 353 (5, $M^{+\cdot}$), 306 (12), 283 (79), 278 (32), 219 (100), 172 (82), 151 (30), 104 (95). Anal. Calc. for $C_{16}H_{19}NO_4S$ (353.46): C 54.37, H 5.42, N 3.96, S 18.14. Found: C 54.48, H 5.34, N 3.99, S 18.14.

6. Decomposition of 1 in the presence of 4-toluenesulfonamide. A solution of **1** (396 mg, 2 mmol) and 4-toluenesulfonamide (342 mg, 2 mmol) in abs. THF (4 ml) was stirred at 45°C. After *ca*. 3 h, the evolution of N_2 ceased and 46 ml (92% of the theoretical amount) of N_2 were collected. After evaporation of the solvent, the semi-solid residue was separated on preparative TLC-plates (SiO_2, CH_2Cl_2/MeOH 95.5/0.5). Thiirane **12** was isolated as the less polar fraction (95 mg, 28%) and identified by comparison with an original sample [30] (^{1}H-NMR, IR). Imine **16** was obtained as the more polar fraction.

2,2,4,4-Tetramethyl-3-(4′-toluenesulfonimino)cyclobutanone **(16)**. Yield: 64 mg (11%). Colorless needles. M.p. 139–141°C (hexane/CH_2Cl_2). IR: 1811*s* (C=O), 1667*vs* (C=N), 1318*s*, 1161*s*, 1091*m*, 1048*w*, 841*w*, 812*w*, 732*m*. ^{1}H-NMR: 1.33, 1.61 (2*s*, 4 Me); 2.45 (*s*, Me); 7.35, 7.87 (*AA′BB′*, *J* = 8.3, 4 arom. H). ^{13}C-NMR: 20.3, 20.4 (2*q*, 4 Me); 21.5 (*q*, Me); 67.6, 69.3 (2*s*, 2 Me_2C); 127.5, 129.6 (2*d*, 4 arom. CH); 136.4, 144.3 (2*s*, 2 arom. C); 195.8 (*s*, C=N); 214.7 (*s*, C=O). CI-MS: 295 (17), 294 (100, $[M+1]^+$), 266 (5). Anal. Calc. for $C_{15}H_{19}NO_3S$ (293.39): C 61.41, H 6.53, N 4.77, S 10.93. Found: C 61.21, H 6.48, N 4.57, S 10.81.

7. Decomposition of 1 in the presence of carboxamides. Solutions of **1** (198 mg, 1 mmol) and 1 mmol of acetamide and benzamide, respectively, in abs. THF (1 ml) were treated according to the protocol described above (stirring at 45°C) and the crude mixtures were analyzed by ^{1}H-NMR spectroscopy. During work-up and evaporation, an intense unpleasent smell revealed the formation of methanethiol. In both cases, the intensities of the singlets at 2.59 (2 H for **12**) and 1.30 ppm (12 H for 2,2,4,4-tetramethylcyclobutane-1,3-dione (**18**)) were compared and the ratio **12**/**18** was established as *ca*. 4:1 in the case of acetamide and *ca*. 2:1 in the case of benzamide.

8. Interception of 2 with 1,2,4-triazole-3-thione and benzo-1,3-thiazole-2-thione. A stirred solution of **1** (208 mg, 1.05 mmol) and 1 mmol of the respective thione in 2 ml of abs. pyridine was heated to 45°C. In both experiments, an equimolar amount of N_2 was evolved. After completion of the N_2 evolution, the pyridine was evaporated in a Kugelrohr apparatus and the oily residue was examined by ^{1}H-NMR spectroscopy. No thiirane **12** was detected in the crude products. The isolation of the dithioacetals **21** and **22** was achieved by fractionated crystallization. The reported yields refer to the isolated products.

2,2,4,4-Tetramethyl-3-methylthio-3-[(1,2,4-triazol-3-yl)thio]cyclobutanone **(21)**. Yield: 174 mg (64%). Colorless crystals. M.p. 142–144°C (Et_2O). IR: 3315*vs* (br., NH), 1766*vs* (C=O), 1491*m*, 1455*m*, 1278*m*, 1236*m*, 1032*w*, 981*m*, 970*m*, 759*m* (br.). ^{1}H-NMR: 1.46, 1.51 (2*s*, 4 Me); 2.27 (*s*, MeS); 8.12 (*s*, 1 arom. H). ^{13}C-NMR: 15.5 (*q*, MeS); 21.5, 23.5 (2*q*, 4 Me); 68.5 (*s*, 2 Me_2C); 72.1 (*s*, C(3)); 148.6 (*d*, 1 arom. CH); 154.1 (*s*, 1 arom. C); 217.9 (*s*, C=O). CI-MS (NH_3+NaI): 294 (100, $[M+Na]^+$). Anal. Calc. for $C_{11}H_{17}N_3OS_2$ (271.41): C 48.68, H 6.31, N 15.48, S 23.63. Found: C 48.18, H 6.45, N 15.39, S 23.74.

2,2,4,4-Tetramethyl-3-methylthio-3-[(benzo-1,3-thiazol-2-yl)thio]cyclobutanone **(22)**. Yield: 256 mg (76%). Pale yellow crystals. M.p. 92–94°C (hexane). IR: 2964*m*, 1788*vs* (C=O), 1448*s*, 1413*s*, 1029*m*, 1000*s*, 759*s*, 729*m*. ^{1}H-NMR: 1.52, 1.60 (2*s*, 4 Me); 2.22 (*s*, MeS); 7.30–8.02 (*m*, 4 arom. H). ^{13}C-NMR: 15.9 (*q*, MeS); 21.3, 23.7 (2*q*, 4 Me); 68.7 (*s*, 2 Me_2C); 72.5 (*s*, C(3)); 121.2, 122.8, 125.3, 126.5 (4*d*, 4 arom. CH); 136.5, 153.0, 163.2 (3*s*, 3 arom. C); 217.7 (*s*, C=O). EI-MS: 337 (4, $M^{+\cdot}$), 322 (42), 252 (96), 220 (37), 171 (58), 143 (97), 101 (30), 95 (100), 85 (40). Anal. Calc. for $C_{16}H_{19}NOS_3$ (337.50): C 56.97, H 5.64, N 4.15, S 28.49. Found: C 56.93, H 5.58, N 4.01, S 28.21.

9. Interception of 2 with dithiouracil. A stirred solution of 1 (196 mg, 1.0 mmol) and dithiouracil (144 mg, 1.0 mmol) in abs. pyridine (2 ml) was heated in an oil bath (45°C). After 4 h, the evolution of N_2 was complete (24 ml of N_2; 96% of the theoretical amount). The solvent was removed in vacuo using a Kugelrohr apparatus and the solid residue was examined by ^{1}H-NMR spectroscopy. Comparison of the intensities of the singlets at 2.34 (MeS for **24**) and 2.14 ppm (MeS for **23**) revealed a 2:8 ratio. The solid dithiouracil was removed by filtration and the crude mixture was separated chromatographically on SiO_2 plates using a mixture of CH_2Cl_2 and MeOH (99.5/0.5) as eluent. Yields refer to the isolated and purified products.

When similar reactions were carried out with dithiouracil and **1** in ratios of 1:2 and 3:1, the mono-adduct **24** was obtained in traces and in an equal amount to **23**, respectively.

2,4-Bis[(2,2,4,4-tetramethyl-1-methylthio-3-oxocyclobutyl)thio]pyrimidine **(23)**. Isolated a the less polar fraction. Yield: 116 mg (48%). Colorless crystals. M.p. 156–158°C (MeOH/CH_2Cl_2). IR: 2970*m*, 2930*m*, 1784*vs* (C=O), 1544*s*, 1520*s*, 1463*m*, 1406*m*, 1312*m*, 1213*w*, 1157*w*, 1028*w*, 812*m*. ^{1}H-NMR: 1.53 (*s*, 4 Me); 1.55 (*s*, 2 Me); 1.57 (*s*, 2 Me); 2.09, 2.13 (2*s*, 2 MeS); 7.17, 8.31 (2*d*, *J*= 5.1, 2 arom. H). ^{13}C-NMR: 15.7, 15.9 (2*q*, 2 MeS); 20.7, 20.9, 23.4, 23.8 (4*q*, 8 Me); 67.9, 68.1 (2*s*, 4 Me_2C); 69.9, 70.3 (2*s*, 2 C(1′)); 116.6, 154.4 (2*s*, 2 arom. CH); 168.2, 169.5 (2*s*, 2 arom. C); 217.7, 219.0 (2*s*, 2 C=O). CI-MS: 485 (100, $[M+1]^+$), 171 (35). EI-MS: 414 (7, $[M\text{-}(Me)_2C{=}C{=}O]^+$), 399 (17), 329 (30), 203 (25), 171 (15), 143 (100), 101 (27), 95 (39). Anal. Calc. for $C_{22}H_{32}N_2O_2S_4$ (484.77): C 54.51, H 6.65, N 5.78, S 26.46. Found: C 54.25, H 6.82, N 5.68, S 26.60.

2-[(2,2,4,4-Tetramethyl-1-methylthio-3-oxocyclobutyl)thio]pyrimidine-4(3H)-thione **(24)**. Isolated as the more polar fraction. Yield: 30 mg (10%). Colorless crystals. M.p. 232–234°C (decomp.). Decomposed during the attempted crystallization and during storage; **24** could not be obtained in analytically pure form. IR: 3100–2980*s* (br., NH), 1785*vs* (C=O), 1611*s*, 1582*s*, 1540*s*, 1211*m*, 1162*m*, 1133*s*, 1025*w*, 973*m*, 822*m* (br.). ^{1}H-NMR: 1.49, 1.54 (2*s*, 4 Me); 2.34 (*s*, MeS); 7.04, 7.70 (2*d*, *J* = 5.8, 2 arom. H).

10. X-ray crystal-structure determination of 7 (see Table 1 and Fig. 1)*. All measurements were made on a Nonius KappaCCD diffractometer [31] using graphite-monochromated MoK_α radiation (λ 0.71073 Å) and an Oxford Cryosystems Cryostream 700 cooler. It was found that the crystals were twinned. The program DIRAX [32] was used to determine the unit cell parameters for the two twin components and the twin law. The matrix used to convert between the two components was 1 0 0/0 –1 0/–0.33 0 –1. Data reduction was performed with EvalCCD [33], which allowed both twin domains to be integrated simultaneously and an appropriate treatment of those reflections suffering from full or partial overlap of reflections from the two twin domains. The intensities were corrected for Lorentz and polarization effects, but not for absorption. Equivalent reflections were not merged because of the twinning. Data collection and refinement parameters are given in Table 1, and a view of the molecule is shown in Fig. 1. The structure was solved by direct methods using SIR92 [34], which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. All of the H-atoms were placed in geometrically calculated positions and refined using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2U_{eq} of its parent C-atom (1.5U_{eq} for the Me groups). Refinement of the structure was carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. A correction for secondary extinction was applied. The refined value for the fraction of the major twin domain in the crystal was 0.5265(8). Neutral atom scattering factors for non-H-atoms were taken from [35a], and the scattering factors for H-atoms were taken from [36]. Anomalous dispersion effects were included in F_c [37]; the values for f' and f'' were those of [35b]. The values of the mass attenuation coefficients are those of [35c]. All calculations were performed using the SHELXL97 [38] program.

* CCDC-215349 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html (or from the *Cambridge Crystallographic Data Centre*, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

Table 1. Crystallographic data for compound **7**.

Crystallized from	EtOH
Empirical formula	$C_{18}H_{28}N_2O_2S_2$
Formula weight [g mol^{-1}]	368.55
Crystal color, habit	colorless, needle
Crystal dimensions [mm]	0.05×0.08× 0.15
Temperature [K]	160(1)
Crystal system	monoclinic
Space group	$P2_1/c$
Z	4
Reflections for cell determination	3663
2θ range for cell determination [°]	4–50
Unit cell parametrs a [Å]	6.6789(5)
b [Å]	14.1046(9)
c [Å]	21.272(4)
β [°]	92.97(1)
V [Å^3]	2001.2(4)
D_x [g cm^{-3}]	1.223
μ (Mo$K\alpha$) [mm^{-1}]	0.278
Scan type	ϕ and ω
$2\theta_{(max)}$ [°]	50
Total reflections measured	35620
Symmetry independent reflections	5124
Reflections with $I > 2\sigma(I)$	26156
Reflections used in refinement	35012
Parameters refined	228
Final $R(F)$ [$I > 2\sigma(I)$ reflections]	0.0822
$wR(F^2)$ (all data)	0.2467
Weights	$w = [\sigma^2(F_o^2) + (0.0968P)^2 + 5.1588P]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$
Goodness of fit	1.185
Secondary extinction coefficient	0.0046(8)
Final Δ_{max}/σ	0.001
$\Delta\rho$ (max; min) [e Å^{-3}]	0.50; –0.44

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REFERENCES

1. Giera H., Huisgen R., Langhals E. and Polborn K., *Helv. Chim. Acta*, **85**, 1523 (2002).
2. Huisgen R., Mlostoń G., Langhals E. and Oshima T., *Helv. Chim. Acta*, **85**, 2668 (2002).
3. Mlostoń G. and Heimgartner H., *Polish J. Chem.*, **74**, 1503 (2000).
4. Mlostoń G. and Heimgartner H., in "The Chemistry of Heterocyclic Compounds, Vol. 59: Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products", Padwa A. and Pearson W.H., Eds., J. Wiley & Sons, NY, 2002, p. 315.
5. Huisgen R., Mlostoń G. and Fulka C., *Heterocycles*, **23**, 2207 (1985).
6. Huisgen R. and Mlostoń G., *Tetrahedron Lett.*, **26**, 1049 (1985); Mlostoń G. and Huisgen R., *ibid*., **26**, 1053 (1985).
7. Kägi M., Mlostoń G., Linden A. and Heimgartner H., *Helv. Chim. Acta*, **77**, 1299 (1994).
8. Mlostoń G., Gendek T. and Heimgartner H., *Polish J. Chem*., **72**, 66 (1998).
9. Mlostoń G., Gendek T., Linden A. and Heimgartner H., *Polish J. Chem.*, **73**, 1219 (1999).
10. Mlostoń G., Gendek T., Linden A. and Heimgartner H., *Helv. Chim. Acta*, **82**, 290 (1999).
11. Mlostoń G., Romański J., Linden A. and Heimgartner H., *Helv. Chim. Acta*, **80**, 230 (1997).
12. Celeda M. and Mlostoń G., University of Łódź, unpublished results.
13. Johnson C.K., "ORTEP II", Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1976.
14. Mlostoń G. and Huisgen R., *Tetrahedron*, **57**, 145 (2001).
15. Mlostoń G., Linden A. and Heimgartner H., *Helv. Chim. Acta*, **79**, 31 (1996).
16. Gendek T., Mlostoń G., Linden A. and Heimgartner H., *Helv. Chim. Acta*, **85**, 451 (2002).
17. Petit M., Linden A., Mlostoń G. and Heimgartner H., *Helv. Chim. Acta*, **77**, 1076, (1994).
18. Kägi M., Mlostoń G., Linden A. and Heimgartner H., *Helv. Chim. Acta*, **77**, 1299 (1994).
19. Dehmlov E.V., Kinnius J., Buchholz M. and Hannemann D., *J. Prakt. Chem*., **342**, 409 (2000).
20. Mlostoń G., Romański J., Linden A. and Heimgartner H., *Helv. Chim. Acta*, **82**, 1302 (1999).
21. Naik A., Ferro M. and Worman J., *Org. Lett*., **4**, 1059 (2002).
22. Hasek R.H., Elam E.U. and Martin J.C., *J. Org. Chem*., **26**, 4340 (1961); Lee-Ruff E., *Can. J. Chem*., **50**, 952 (1972).
23. Miles D.H., Tunsuwan K., Chittawong V., Kokpol U., Choudhary M.I. and Clardy J., *Phytochem.*, **34**, 1277 (1993).
24. Mochizuki K., Takikawa H. and Mori K., *Biosci. Biotechnol. Biochem*., **64**, 647 (2000).
25. Mlostoń G., Romański J. and Heimgartner H., *Polish J. Chem*., **75**, 975 (2001).
26. Elam E.U. and Davis H.E., *J. Org. Chem.*, **32**, 1562 (1967).
27. Huisgen R., Penelle J., Mlostoń G., Padias A.B. and Hall H.K., *J. Am. Chem. Soc*., **114**, 266 (1992).
28. Wang Z.Y., *Synth. Commun*., **20**, 1607 (1990).
29. Elion G.B. and Hitchings G.H., *J. Am. Chem. Soc*., **69**, 2138 (1947).
30. Diebert C.E., *J. Org. Chem.*, **35**, 1501 (1970).
31. Hooft R., KappaCCD Collect Software, Nonius BV, Delft, The Netherlands, 1999.
32. Duisenberg A.J.M., *J. Appl. Crystallogr*., **25**, 92 (1992).
33. EvalCCD Data Reduction Software, Bruker-Nonius, Delft, The Netherlands, 2001.
34. Altomare A., Cascarano G., Giacovazzo C., Guagliardi A., Burla M.C., Polidori G. and Camalli M., SIR92, *J. Appl. Crystallogr.*, **27**, 435 (1994).
35. a) Maslen E.N., Fox A.G. and O'Keefe M.A., in "International Tables for Crystallography", Ed. Wilson A.J.C., Kluwer Academic Publishers, Dordrecht, 1992, Vol. C, Table 6.1.1.1, p. 477; b) Creagh D.C. and McAuley W.J., *ibid*. Table 4.2.6.8, p. 219; c) Creagh D.C. and Hubbell J.H., *ibid*. Table 4.2.4.3, p. 200.
36. Stewart R.F., Davidson E.R. and Simpson W.T., *J. Chem. Phys.*, **42**, 3175 (1965).
37. Ibers J.A. and Hamilton W.C., *Acta Crystallogr.*, **17**, 781 (1964).
38. Sheldrick G.M., SHELXL97, Program for the Refinement of Crystal Structures, University of Göttingen, Germany, 1997.