Thermal [2 + 3]-Cycloadditions of *trans*-1-Methyl-2,3-diphenylaziridine with C=S and C=C Dipolarophiles: An Unexpected Course with Dimethyl Dicyanofumarate

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The thermal reaction of *trans*-1-methyl-2,3-diphenylaziridine (*trans*-**1a**) with aromatic and cycloaliphatic thioketones **2** in boiling toluene yielded the corresponding *cis*-2,4-diphenyl-1,3-thiazolidines *cis*-**4** *via* conrotatory ring opening of *trans*-**1a** and a concerted [2 + 3]-cycloaddition of the intermediate (*E*,*E*)-configured azomethine ylide **3a** (*Scheme 1*). The analogous reaction of *cis*-**1a** with dimethyl acetylenedicarboxylate (**5**) gave dimethyl *trans*-2,5-dihydro-1-methyl-2,5-diphenylpyrrole-3,4-dicarboxylate (*trans*-**6**) in accord with orbital-symmetry-controlled reactions (*Scheme 2*). On the other hand, the reactions of *cis*-**1a** and *trans*-**1a** with dimethyl dicyanofumarate (**7a**), as well as that of *cis*-**1a** and dimethyl dicyanomaleate (**7b**), led to mixtures of the same two stereoisomeric dimethyl 3,4-dicyano-1-methyl-2,5-diphenylpyrrolidine-3,4-dicarboxylates **8a** and **8b** (*Scheme 3*). This result has to be explained *via* a stepwise reaction mechanism, in which the intermediate zwitterions **11a** and **11b** equilibrate (*Scheme 6*). In contrast, *cis*-1,2,3-triphenylaziridine (*cis*-**1b**) and **7a** gave only one stereoisomeric pyrrolidine-3,4-dicarboxylate **10**, with the configuration expected on the basis of orbital-symmetry control, *i.e.*, *via* concerted reaction steps (*Scheme 10*). The configuration of **8a** and **10**, as well as that of a derivative of **8b**, were established by X-ray crystallography.

1. Introduction. – Azomethine ylides, generated by different methods, were extensively explored in 1,3-dipolar cycloadditions aimed at the preparation of five-membered heterocycles. In many instances, the cycloadducts are important final products or building blocks for the synthesis of biologically active substances as well as in materials science [1–5]. Furthermore, the cycloadditions of azomethine ylides belong to the most frequently studied reactions used to test new catalysts for the stereocontrolled synthesis [6–8].

The oldest method for the generation of azomethine ylides consists in the thermal ring opening of properly substituted aziridines. The fundamental experiments by *Huisgen* evidenced the orbital control of this process [9]. Irrespective of the development of new methods, the thermal, conrotatory ring opening of aziridines is

still frequently applied for stereoselective syntheses of highly functionalized heterocyclic systems.

In our earlier reports, reactions of *N*-substituted aziridines with acetylenes [10], alkenes [10][11], carbonyl [11][12], and thiocarbonyl groups [10][13–15] were described. All of the reported reactions yielded [2 + 3]-cycloadducts with the expected configuration, *i.e.*, *cis*-2,3-disubstituted aziridines led to *trans*-disubstituted products, and *trans*-2,3-disubstituted aziridines gave *cis*-disubstituted cycloadducts. Unexpectedly, the attempted [2 + 3]-cycloaddition of *cis*-1-methyl-2,3-diphenylaziridine (*cis*-**1a**; *cf. Scheme 1*) with the electron-deficient dimethyl dicyanofumarate (DCFM) [16] afforded two stereoisomeric products. The same mixture of products was formed in the reaction of *trans*-1-methyl-2,3-diphenylaziridine (*trans*-**1a**) with DCFM. This surprising result prompted us to reinvestigate some [2 + 3]-cycloadditions of thioketones with the thermally generated azomethine ylide from *trans*-**1a**. Furthermore, the reactions of *cis*-**1a** and *trans*-**1a** with DCFM will be described in order to elucidate the unexpected course of the reaction.

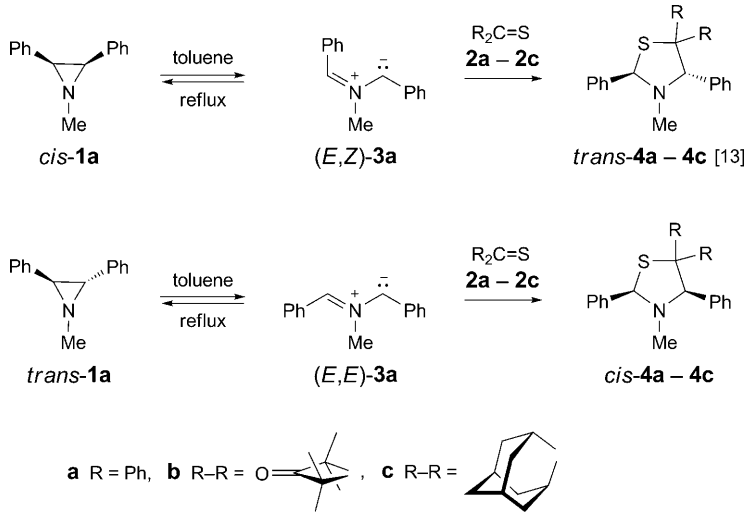
2. Results and Discussion. – As shown in a competitive study with thiobenzophenone *S*-methanide, thioketones, and especially aromatic thioketones, exceed typical C≡C and C=C dipolarophiles in their reactivity [17]. The [2 + 3]-cycloadditions of azomethine ylides with C=S dipolarophiles are less well-known. In extension of the earlier studies, performed with 1-substituted *cis*-2,3-diphenylaziridines [10][13–15], thermal [2 + 3]-cycloadditions of *trans*-**1a** with thiobenzophenone (**2a**), 2,2,4,4-tetramethyl-3-thioxocyclobutane (**2b**), and adamantanethione (**2c**) were carried out in boiling toluene. In the case of **2a**, the blue color of the mixture disappeared already after 45 min, and according to the ^{1}H-NMR spectrum of the mixture, only one product was formed. The characteristic *singlet*s of H–C(2) and H–C(4) of a 1,3-thiazolidine of type **4**, appeared at 5.00 and 4.80 ppm, respectively[1]). These absorptions differed significantly from those reported for *trans*-**4a**, the product obtained from the reaction of *cis*-**1a** and **2a** (5.40 and 5.13 ppm) [13] (see also [15]). This comparison and the stereoselective course of both reactions led to the conclusion that the obtained 1,3-thiazolidine derivative was *cis*-**4a** (*Scheme 1*). Thus, the intermediate azomethine ylide **3a** possesses the (*E*,*E*)-configuration predicted by the symmetry rules, and the cycloaddition step occurs as a concerted process. The *cis*-configuration was established by X-ray crystallography in the case of the *N*-benzyl derivative [18].

In analogy to the experiment with **2a**, reactions of *trans*-**1a** with the cycloaliphatic thioketones **2b** and **2c** were carried out. However, in these cases, the reactions were completed only after *ca*. 6 h, confirming the lower reactivity of **2b** and **2c** compared to that of **2a**. In each case, only a single cycloadduct was formed, and the structures of *cis*-**4b** and *cis*-**4c**, respectively, were attributed to these products.

The stereoselective reaction of *trans*-**1a** with dimethyl acetylenedicarboxylate (**5**) leading to dimethyl *cis*-2,5-dihydro-1-methyl-2,5-diphenylpyrrole-3,4-dicarboxylate (*cis*-**6**) was already reported [19]. In our earlier publication, the reaction of *cis*-1-isopropyl-2,3-diphenylaziridine with **5** in refluxing toluene was described to give a mixture of the corresponding *trans*-2,5-dihydropyrrole-3,4-dicarboxylate and the

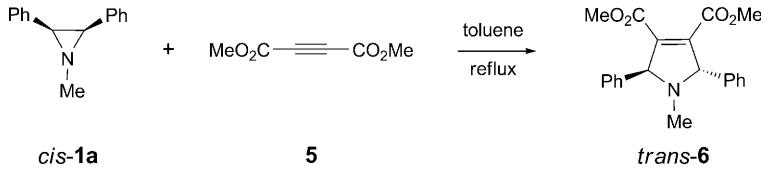
[1]) All chiral products described in this article are racemic.

Scheme 1



aromatized pyrrole derivative in a 85 : 15 ratio [10]. In the present study, a 1 : 1 mixture of *cis*-**1a** and **5** in toluene was heated to reflux for 10 h, and the progress of the reaction was monitored by ^{1}H-NMR spectroscopy, which indicated that only one product was formed. After chromatographic workup and recrystallization, dimethyl *trans*-2,5-dihydro-1-methyl-2,5-diphenylpyrrole-3,4-dicarboxylate (*trans*-**6**) was obtained in 77% yield (*Scheme 2*).

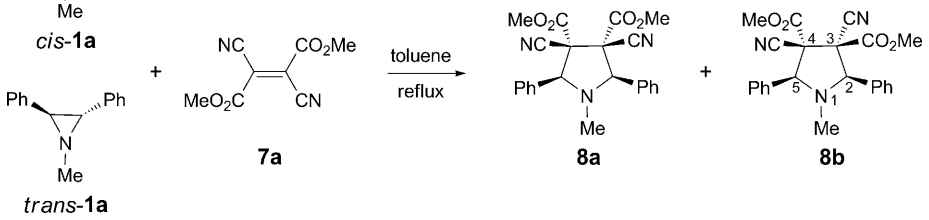
Scheme 2



It is well-documented that dimethyl dicyanofumarate (DCFM; **7**) is an excellent dienophile and dipolarophile for reactions with electron-rich dienes or 1,3-dipoles. Especially important are reactions with 1,1-dimethoxybuta-1,3-diene [20] and sterically crowded thiocarbonyl ylides [21], which were established to occur stepwise *via* intermediate zwitterions. To the best of our knowledge, apart from thiocarbonyl ylides, the only other 1,3-dipoles used in reactions with **7** were diazo compounds [22], and the addition with di(*tert*-butyl)diazomethane was also shown to occur stepwise [23]. For our study aimed at reactions of **7** with thermally generated azomethine ylides, *cis*-**1a** and *trans*-**1a** as well as *cis*-1,2,3-triphenylaziridine (*cis*-**1b**) were selected. The conditions of the reactions were analogous to those described above for the reactions with thioketones **2** and acetylene dicarboxylate **5**. Whereas the reaction with *cis*-**1a** was completed after 13 h, the isomeric *trans*-**1a** was consumed already after 4 h. Unexpectedly, it turned out that the reaction mixtures obtained with *cis*-**1a** and

trans-**1a** contained the same two stereoisomeric cycloadducts in a ratio of *ca.* 2:1 and 1:1, respectively (*Scheme 3*). Moreover, an additional experiment with *cis*-**1a** and dimethyl dicyanomaleate (**7b**) afforded also the same products in comparable amounts. Both products were separated chromatographically, and from the less polar fraction the pyrrolidine-dicarboxylate **8b** was obtained as an oily material. The more polar fraction, however, gave the isomer **8a** as colorless crystals, which were subjected to the X-ray crystal-structure determination (*Fig. 1*).

Scheme 3



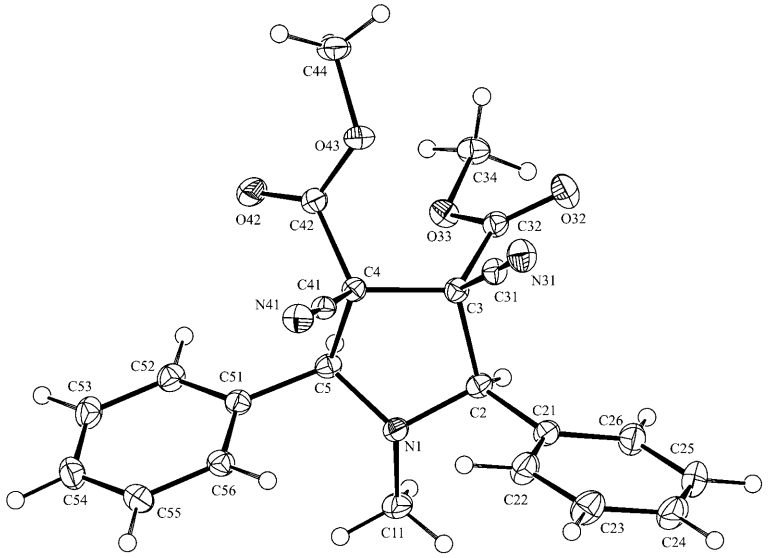
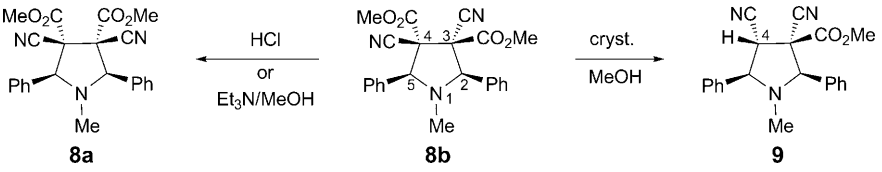


Fig. 1. *ORTEP Plot* [24] *of the molecular structure of* **8a** (arbitrary numbering of the atoms, 50% probability ellipsoids).

The crystal structure of **8a** shows that the Ph rings at C(2) and C(5) are *cis*-oriented, as well as the CN groups and the ester moieties at C(3) and C(4). Thus, the orientation of the substituents does not correspond to the structure predicted on the basis of the expected conrotatory ring opening of the aziridine, followed by the concerted [2s + 3s]-cycloaddition.

The symmetric structure of **8a** is reflected in the ^{1}H- and ^{13}C-NMR spectra. For instance, the absorptions of H–C(2) and H–C(5) appear as a *singlet* at 4.99 ppm, and the two MeO groups absorb as a *singlet* at 3.84 ppm. The ^{1}H-NMR spectrum of the oily product **8b** revealed two *singlet*s for H–C(2) and H–C(5) at 4.48 and 4.59 ppm, and two MeO *singlet*s at 3.40 and 3.96 ppm. This pattern must be attributed to a non-symmetrical structure presented tentatively as **8b**. The attempted crystallization of **8b** from MeOH afforded a crystalline product, of which the ^{1}H-NMR spectrum differed fundamentally from that of **8b**, as only one MeO group was present! Other relevant signals were an *AB* system at 3.85 and 4.03 ppm ($J_{AB} = 11.0$ Hz) for two H-atoms and a *singlet* at 4.25 ppm for one H-atom. Finally, the structure was established by X-ray crystallography (*Fig. 2*), which disclosed that compound **9** was formed (*Scheme 4*). It is likely that, during the crystallization, the hydrolysis (with traces of H_2O?) of one ester group took place, followed by a spontaneous decarboxylation. With respect to the determined structure **9**, the decarboxylation with subsequent inversion of the configuration occurred at C(4). On the other hand, we propose that the configurations at C(2), C(3), and C(5) are retained during the decarboxylation. Therefore, the *cis*-orientation of the Ph groups in **9** reflects their orientation in the precursor **8b**.

Scheme 4



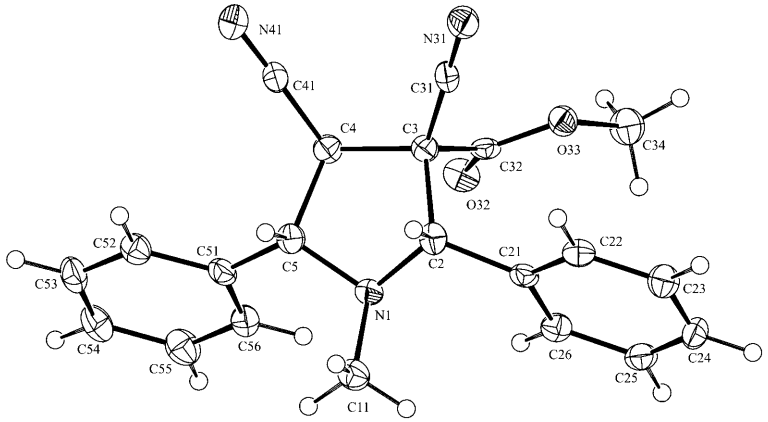


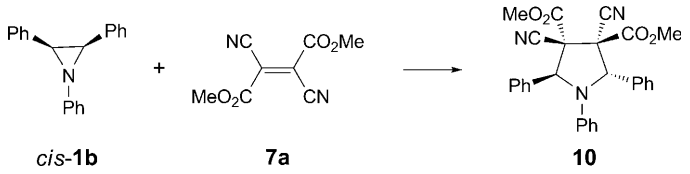
Fig. 2. *ORTEP Plot* [24] *of the molecular structure of* **9** (arbitrary numbering of the atoms, 50% probability ellipsoids).

In a series of independent experiments, the isomerization **8b** → **8a** was studied. A very fast and complete conversion was observed, when a solution of **8b** in MeOH, after addition of a drop of aq. HCl, was warmed to reflux for 15 min (*Scheme 4*). The same effect was achieved using Et_3N in MeOH, but also in pure MeOH after boiling for 3 h.

All these results point out that **8a** is the thermodynamically favored product. This isomerization deserves a comment. All experimental evidences support a mechanism *via* a zwitterion formed by cleavage of the C(4)–C(5) bond. The subsequent rotation about the C(3)–C(4) bond, followed by ring closure, leads to the thermodynamically favored diastereoisomer.

In an additional experiment, the reaction of *cis*-**1b** [25] with **7a** afforded stereoselectively a crystalline product, the structure of which was unambiguously established as **10** by X-ray crystallography (*Scheme 5* and *Fig. 3*). In this case, the orientation of all substituents in accordance with the prediction based on a conrotatory ring opening of *cis*-**1b** and a concerted [2s + 3s]-cycloaddition of the intermediate (*E*,*Z*)-configured azomethine ylide.

Scheme 5



cis-**1b** **7a** **10**

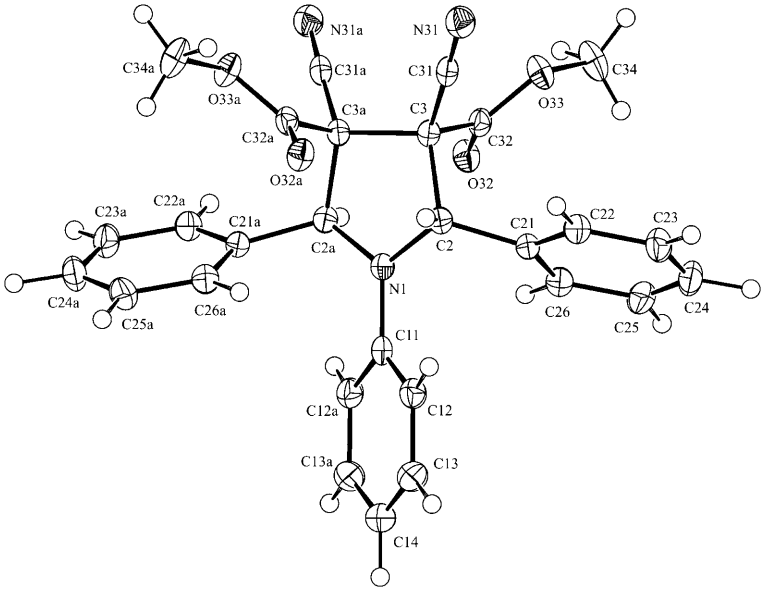
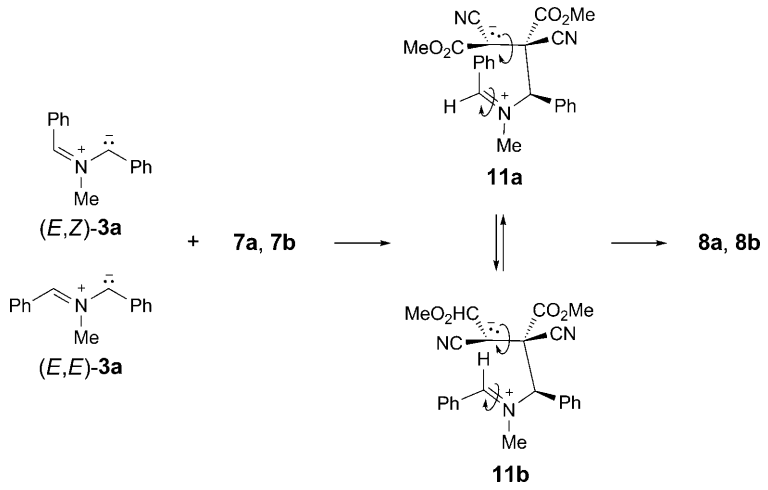


Fig. 3. *ORTEP Plot* [24] *of the molecular structure of* **10** (arbitrary numbering of the atoms, 50% probability ellipsoids).

The formation of the same products **8a** and **8b** in the reactions of *cis*-**1a** with **7a** and **7b** as well as of *trans*-**1a** with **7a** is a strong evidence for a stepwise cycloaddition of **7** with other 1,3-dipols, *i.e.*, the isomeric *N*-methylazomethine ylides **3a**. A plausible intermediate in these reactions with the strongly electron-deficient dipolarophiles **7** is

the zwitterion **11** (*Scheme 6*). The rotation about the indicated C,N and C,C bonds results in the loss of the stereochemical integrity of the reactants. Apparently, the same zwitterion **11** is formed in the key-step of the isomerization **8b** → **8a**. It seems likely that, in the presence of H^+, the ring opening is facilitated as well as in polar solvents.

Scheme 6



Remarkably, the replacement of the N–Me group in *cis*-**1a** and, therefore, in (*E*,*Z*)-**3a**, by a N–Ph group results in the expected stereoselective formation of the cycloadduct **10**. The change of the reaction mechanism may be caused by steric and/or electronic factors.

3. Conclusions. – The presented [2 + 3]-cycloadditions of *trans*-**1a** with thioketones **2a** – **2c** supplement the earlier published results with the isomeric *cis*-**1a**. In all these examples, the reactions occur stereoselectively, and the configuration of the products is an accordance with the prediction for concerted processes.

The reaction of **1a** with the strongly electron-deficient DCFM (**7a**) with a low-lying LUMO [17] [20] occurs stepwise *via* the intermediate zwitterion **11**. To the best of our knowledge, this is the first case reported in which a $HOMO_{dipole}/LUMO_{dipolarophile}$-controlled reaction of an azomethine ylide occurs in a non-stereospecific manner. The formation of an intermediate zwitterion **11** and its isomerization depend on the substituent attached to the N-atom. It is worth mentioning that some examples of non-stereospecific [2 + 3]-cycloadditions of azomethine ylides were reported by *Sauer* and co-workers [26]. In these cases, however, the reactions are $LUMO_{dipole}/HOMO_{dipolarophile}$-controlled processes. Moreover, photochemically induced [2 + 3]-cycloadditions of *cis*-1-butyl-2,3-diphenylaziridine with electron-deficient alkenes and alkines occur in a non-stereospecific manner. These reactions, however, proceed *via* an initially formed azomethine radical cation (PET mechanism) and not an azomethine ylide [27].

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Experimental Part

1. *General.* TLC: *Merck 5554* aluminum-backed SiO_2 plates; spots were visualized by UV light. Column chromatography (CC): silica gel (SiO_2; *Merck 60*, 0.063–0.200 μm). M.p.: *Mel-Temp. II* apparatus (*Aldrich*) in capillaries; uncorrected. IR Spectra: *Nexus* FT-IR spectrometer; in KBr or as films, $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Bruker AC-300* (^1H: 300.1 MHz, ^{13}C: 75.5 MHz) or *Varian Gemini 200* (^1H: 200 MHz, ^{13}C: 50 MHz) or *Tesla BS-687* (^1H: 80 MHz) spectrometer with $CDCl_3$ as solvent; δ in ppm rel. to Me_4Si as internal standard, J in Hz. The majority of the ^{13}C signals were assigned with the aid of DEPT spectra. MS: *LKB-2091*, *Finnigan MAT-95*, or *Finnigan TSQ-700* instruments; in *m*/*z* (rel. %). HR-MS: *Finnigan MAT-95*; in *m*/*z* (rel. %). Elemental analyses were performed in the Analytical Laboratory of the University of Zürich.

2. *Starting Materials. Thiobenzophenone* (**2a**) [28], *2,2,4,4-tetramethyl-3-thioxocyclobutanone* (**2b**) [29], and *adamantanethione* (**2c**) [30] were obtained according to published procedures. trans-*1-Methyl-2,3-diphenylaziridine* (*trans*-**1a**) was prepared from *erythro*-2-(methylamino)-1,2-diphenylethanol by treatment with $Ph_3P/CCl_4/Et_3N$, according to a known procedure [19], as well as *cis*-**1a** [31] and cis-*1,2,3-triphenylaziridine* (*cis*-**1b**) [32]. *Dimethyl dicyanofumarate* (DCFM; **7a**) was synthesized from methyl cyanoacetate and $SOCl_2$ [16].

3. *Reactions of* trans-**1a** *with Thiones* **2a**–**2c**. 3.1. *Reaction of* trans-**1a** *with* **2a**. A soln. of **2a** (198 mg, 1 mmol) and *trans*-**1a** (209 mg, 1 mmol) in toluene (5 ml) was heated under reflux for 45 min. After evaporation of the solvent, the crude mixture was purified by CC (SiO_2; CH_2Cl_2/petroleum ether (PE) 2:3). Anal. pure product was obtained by recrystallization from PE in the refrigerator.

cis-*3-Methyl-2,4,5,5-tetraphenyl-1,3-thiazolidine* (*cis*-**4a**). Yield 270 mg (66%). Pale yellow crystals. M.p. 132–134° (PE). IR: 3027*m*, 3035*m*, 2790*m*, 1598*m*, 1491*s*, 1443*s*, 749*s*, 736*s*, 695v*s*. ^1H-NMR: 7.70–6.90 (*m*, 20 arom. H); 4.99, 4.82 (2*s*, H–C(2), H–C(4)); 2.02 (*s*, MeN). ^{13}C-NMR: 146.8, 143.2, 139.5, 138.5 (4*s*, 4 arom. C); 131.8, 130.2, 128.8, 128.2, 128.1, 127.9, 127.7, 127.4, 127.3, 126.6, 126.4, 126.2 (12*d*, 20 arom. CH); 79.5, 73.3 (2*d*, C(2), C(4)); 69.2 (*s*, C(5)); 39.2 (*q*, MeN). EI-MS: 407 (<0.5, M^+), 406 (<1), 405 (<1), 356 (1), 332 (1), 328 (3), 288 (6), 287 (8), 256 (8), 210 (16), 209 (100), 208 (88), 198 (16), 194 (24), 179 (10), 178 (13), 166 (10), 165 (36), 121 (22), 118 (15), 77 (11). ESI-MS (MeOH): 431 (25), 430 (90, $[M+Na]^+$), 408 (33, $[M+1]^+$), 309 (15), 301 (12), 287 (23), 286 (100), 232 (43). HR-ESI-MS (MeOH): 430.16023 ($[M+Na]^+$, $C_{28}H_{25}NNaS^+$; calc. 430.15999).

3.2. *Reaction of trans-***1a** *with* **2b**. A soln. of **2b** (156 mg, 1 mmol) and *trans*-**1a** (209 mg, 1 mmol) in toluene (5 ml) was heated under reflux for 6 h. After evaporation of the solvent, the crude mixture was dissolved in hexane and crystallized in the refrigerator. The crystalline product was filtered and dried in vacuum.

cis-*1,1,3,3,7-Pentamethyl-6,8-diphenyl-5-thia-7-azaspiro[4.5]octan-2-one* (*cis*-**4b**). Yield 230 mg (63%). Pale yellow crystals. M.p. 156–158° (hexane). IR (KBr): 3065*w*, 3022*w*, 2972*m*, 2962*m*, 1768v*s* (C=O), 1464*s*, 1456*s*, 1188*m*, 1022*m*, 742*s*, 703*s*. ^1H-NMR: 7.85–7.75 (*m*, 2 arom. H); 7.55–7.47 (*m*, 2 arom. H); 7.40–7.25 (*m*, 6 arom. H); 4.68, 4.20 (2*s*, H–C(6), H–C(8)); 2.31 (*s*, MeN); 1.61, 1.59, 0.99, 0.57 (4*s*, 4 Me). ^{13}C-NMR: 220.0 (*s*, C=O); 144.2, 138.5 (2*s*, 2 arom. C); 129.0, 128.4, 128.3, 128.1, 127.7, 127.5 (6*d*, 10 arom. CH); 74.1, 73.9 (2*d*, C(6), C(8)); 68.7, 67.2, 61.8 (3*s*, C(4), 2 Me_2C); 37.7 (*q*, MeN); 25.1, 24.1, 22.2, 19.6 (4*q*, 4 Me). EI-MS: 365 (2, M^+), 350 (2), 295 (8), 294 (9), 278 (7), 248 (7), 247 (18), 246 (100), 176 (25), 161 (56), 144 (36), 143 (12), 129 (20), 128 (16), 120 (22), 118 (20), 91 (13). ESI-MS (MeOH): 388 (100, $[M+1]^+$), 366 (10, $[M+1]^+$), 318 (33). HR-ESI-MS (MeOH): 388.17039 ($[M+Na]^+$, $C_{23}H_{27}NNaOS^+$; calc. 388.17056).

3.3. *Reaction* of trans-**1a** *with* **2c**. A soln. of **2c** (166 mg, 1 mmol) and *trans*-**1a** (209 mg, 1 mmol) in toluene (5 ml) was heated under reflux for 6 h. After evaporation of the solvent, the crude mixture was purified by CC (SiO_2; CH_2Cl_2/hexane 2:3). Anal. pure product was obtained by recrystallization from hexane in the refrigerator.

cis-*3-Methyl-2,4-diphenylspiro[1,3-thiazolidine-5,2'-tricyclo[3.3.1.1^{3,7}]decane]* (*cis*-**4c**). Yield 225 mg (60%). Pale yellow crystals. M.p. 138–140° (hexane). IR (KBr): 3062*m*, 3027*m*, 2904*s*, 2848*s*, 1455*m*, 1445*m*, 1213*m*, 744*s*, 701*s*. ^{1}H-NMR: 7.75–7.65 (*d*-like, 2 arom. H); 7.60–7.50 (*d*-like, 2 arom. H); 7.40–7.20 (*m*, 6 arom. H); 4.87, 3.82 (2*s*, H–C(2), H–C(4)); 2.90–2.75, 2.30–2.20 (2*m*, 2 H of adamantane); 2.14 (*s*, MeN); 2.10–1.00 (*m*, 12 H of adamantane). ^{13}C-NMR: 142.7, 139.1 (2*s*, 2 arom. C); 130.1, 128.2, 127.9, 127.8, 127.5, 127.0 (6*d*, 10 arom. CH); 80.5, 71.6 (2*d*, C(2), C(4)); 67.6 (*s*, C(5)); 38.5 (*q*, MeN); 39.4, 35.0, 26.7, 26.6 (4*d*, 4 CH of adamantane); 38.5, 37.2, 35.6, 33.6, 33.1 (5*t*, 5 CH_2 of adamantane). EI-MS: 374 (3, $[M-1]^+$), 298 (3), 224 (4), 210 (16), 209 (100), 208 (70), 194 (15), 118 (12), 91 (13). ESI-MS (MeOH): 398 (12, $[M+Na]^+$), 377 (28), 376 (100, $[M+1]^+$), 309 (8), 120 (24). HR-ESI-MS (MeOH): 376.20860 ($[M+1]^+$, $C_{25}H_{30}NS^+$; calc. 376.20935).

4. *Reaction of cis*-**1a** *with Dimethyl Acetylenedicarboxylate* (**5**). A soln. of **5** (142 mg, 1 mmol) and *cis*-**1a** (209 mg, 1 mmol) in toluene (5 ml) was heated under reflux for 10 h. After evaporation of the solvent, the crude mixture was purified by CC (SiO_2; CH_2Cl_2/PE 4:1). Anal. pure product was obtained by recrystallization from PE with a small amount of Et_2O.

Dimethyl trans-*2,5-dihydro-1-methyl-2,5-diphenylpyrrole-3,4-dicarboxylate* (*trans*-**6**). Yield 270 mg (77%). Pale yellow crystals. M.p. 90–93° (PE/Et_2O). IR (KBr): 3027*w*, 2955*w*, 2785*m*, 1740v*s* and 1721v*s* (C=O), 1457*m*, 1442*m*, 1326*s*, 1295*m*, 1199*s*, 1172*s*, 1006*s*, 702*s*. ^{1}H-NMR: 7.25–7.45 (*m*, 10 arom. H); 5.22 (*s*, H–C(2), H–C(5)); 3.60 (*s*, 2 MeO); 1.98 (*s*, MeN). ^{13}C-NMR: 163.7 (*s*, C=O); 140.3, 137.8 (2*s*, 2 arom. C, C(3), C(4)); 130.4, 128.4, 128.2 (3*d*, 10 arom. CH); 74.6 (*q*, 2 MeO); 52.0 (*d*, C(2), C(5)); 34.0 (*q*, MeN). EI-MS: 351 (17, M^+), 320 (17), 319 (13), 318 (17), 292 (43), 275 (17), 274 (100), 261 (13), 260 (34), 243 (15), 242 (90), 230 (16), 215 (19), 198 (21), 184 (33), 171 (10), 118 (15), 115 (11). ESI-MS (MeOH): 375 (20), 374 (100, $[M+Na]^+$), 353 (10), 352 (44, $[M+1]^+$). HR-ESI-MS (MeOH): 374.13594 ($[M+Na]^+$, $C_{21}H_{21}NNaO_4^+$; calc. 374.13628); 352.15387 ($[M+1]^+$, $C_{21}H_{22}NO_4^+$; calc. 352.15433).

5. *Reaction of cis*-**1a** *with DCFM* (**7a**). A soln. of **7a** (194 mg, 1 mmol) and *cis*-**1a** (209 mg, 1 mmol) in toluene (5 ml) was heated under reflux for 13 h. After evaporation of the solvent, the crude mixture was separated by prep. TLC (SiO_2; CH_2Cl_2/hexane 3:2). Anal. pure **8a** was obtained by recrystallization from hexane with a small amount of CH_2Cl_2. The attempted isolation of the isomeric product **8b** by chromatography was in vain.

Dimethyl 2,3-trans,*3,4*-cis,*4,5*-trans-*3,4-Dicyano-1-methyl-2,5-diphenylpyrrolidine-3,4-dicarboxylate* (**8a**). Yield 220 mg (55%). Colorless crystals. M.p. 124–126° (hexane/CH_2Cl_2). IR (KBr): 3065*w*, 3035*w*, 2959*m*, 2250*w* (C≡N); 1770v*s* and 1754v*s* (C=O); 1494*m*, 1456*m*, 1436*m*, 1266v*s*, 1243*s*, 1172*s*, 1024*m*, 736*m*, 699*s*. ^{1}H-NMR: 7.66–7.64 (*m*, 4 arom. H); 7.50–7.40 (*m*, 6 arom. H); 4.39 (*s*, H–C(2), H–C(5)); 3.84 (*s*, 2 MeO); 2.14 (*s*, MeN). ^{13}C-NMR: 165.0 (*s*, 2 C=O); 134.5 (*s*, 2 arom. C); 129.7, 129.1, 128.8 (3*d*, 10 arom. CH); 114.0 (*s*, 2 CN); 73.9 (C(2), C(5)); 60.9 (*s*, C(3), C(4)); 54.7 (*q*, 2 MeO); 37.9 (*q*, MeN). CI-MS (NH_3): 406 (5), 405 (26), 404 [100, $[M+1]^+$), 209 (6). Anal. calc. for $C_{23}H_{21}N_3O_4$ (403.44): C 68.48, H 5.25, N 10.42; found: C 68.44, H 5.25, N 10.42.

6. *Reaction of trans*-**1a** *with DCFM* (**7a**). A soln. of **7a** (194 mg, 1 mmol) and *trans*-**1a** (209 mg, 1 mmol) in toluene (5 ml) was heated under reflux for 4 h. After evaporation of the solvent, the crude mixture was separated by prep. TLC (SiO_2; hexane/AcOEt 4.5:0.5). The more-polar fraction contained **8a** (120 mg, 30%). The less-polar fraction was the isomeric product **8b**, which was isolated as a pale yellow oil (115 mg, 29%). By chance, crystallization of this material from MeOH led to the unexpected formation of crystalline **9**. In spite of attempted repetitions of this crystallization, compound **9** could neither be obtained again from MeOH nor from other solvents (CH_2Cl_2, hexane, Et_2O). Crystals of **9** were additionally purified by recrystallization from PE/Et_2O or from PE/CH_2Cl_2 (crystals for X-ray measurement).

Dimethyl 2,3-cis,*3,4*-trans,*4,5*-trans-*3,4-Dicyano-1-methyl-2,5-diphenylpyrrolidine-3,4-dicarboxylate* (**8b**). Yield 115 mg (29%). Pale yellow oil. IR (film): 3033*m*, 2957*s*, 2850*m*, 2253 (C≡N), 1747*s* (br., C=O), 1455*s*, 1436*s*, 1244*s*, 1181*s*, 1025*s*, 731*s*, 701*s*. ^{1}H-NMR: 7.30–7.80 (*m*, 10 arom. H); 4.48, 4.59 (2*s*, H–C(2), H–C(5)); 3.40, 3.96 (2*s*, 2 MeO); 2.20 (*s*, MeN). ^{13}C-NMR: 162.2, 166.1 (2*s*, 2 C=O); 133.2, 134.8 (2*s*, 2 arom. C); 128.4, 128.7, 128.8, 129.1, 129.5, 129.7 (6*d*, 10 arom. CH); 113.7, 115.5 (2*s*, 2 CN); 74.6, 76.5 (2*d*, C(2), C(5)); 59.1, 59.7 (2*s*, C(3), C(4)); 53.6, 55.1 (2*q*, 2 MeO); 38.2 (*q*, MeN). EI-MS: 403 (3, M^+), 344 (4), 317 (4), 216 (28), 210 (14), 209 (89), 208 (100), 194 (23), 184 (10), 118 (18), 91 (21), 77

Table. *Crystallographic Data for Compounds* **8a**, **9**, *and* **10**

	8a	**9**	**10**
Crystallized from	hexane/Et_2O	EtOH/CH_2Cl_2	Et_2O/petroleum ether
Empirical formula	$C_{23}H_{21}N_3O_4$	$C_{21}H_{19}N_3O_2$	$C_{28}H_{23}N_3O_4$
Formula weight	403.43	345.40	465.49
Crystal color, habit	colorless block	translucent colorless prism	colorless flat parallelepiped
Crystal dimensions [mm]	$0.40 \times 0.30 \times 0.30$	$0.14 \times 0.10 \times 0.06$	$0.28 \times 0.06 \times 0.02$
Temp. [K]	173(2)	123(1)	123(1)
Crystal system	monoclinic	monoclinic	orthorhombic
Space group	$P2_1/c$	$P2_1/c$	$P2_12_12_1$
Z	4	4	2
Reflections for cell determination	8000	8000	8000
2θ Range for cell determination [°]	4.64 – 53.2	4.1 – 51.7	4.48 – 51.7
Unit cell parameters			
a [Å]	15.781(5)	20.427(4)	6.471(1)
b [Å]	10.768(5)	8.043(2)	16.423(1)
c [Å]	12.891(5)	22.772(6)	10.939(1)
β [°]	105.266(5)	150.860(10)	90.00
V [Å^3]	2113.3(1)	1821.8(7)	1162.5(2)
D_x [g cm^{-3}]	1.268	1.259	1.330
Linear absorption coefficient [mm^{-1}]	0.088	0.083	0.090
Scan type	rotation	rotation	rotation
$2\theta_{(max)}$ [°]	53.2	51.7	51.7
Total reflections measured	25895	13210	10286
Symmetry-independent reflections	4099	3489	2236
Reflections with $I > 2\sigma(I)$	3323	1749	1748
Reflections used in refinement	4099	3489	2236
Parameters refined; restraints	274; 0	238; 0	161; 0
Final $R(F)$ ($I > 2\sigma(I)$ reflections)	0.0301	0.0617	0.0349
$wR(F^2)$ (all data)	0.0729	0.1423	0.0736
Weighting parameters [a; b][a])	0.0350; 0.2323	0.0617; 0.0000	0.0318; 0.0000
Goodness-of-fit	1.079	0.882	0.881
Final Δ_{max}/σ	0.000	0.000	0.001
$\Delta\rho$ (max; min) [e Å^{-3}]	0.226; −0.163	0.278; −0.222	0.225; −0.151

[a]) $w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$, where $P = (F_o^2 + 2F_c^2)/3$

(14). ESI-MS (MeOH): 427 (26), 426 (100, $[M+Na]^+$). HR-ESI-MS (MeOH): 426.14190 ($[M+Na]^+$, $C_{23}H_{21}N_3NaO_4^+$; calc. 426.14243).

*Methyl 2,3-*cis*,3,4-*trans*,4,5-*trans*-3,4-Dicyano-1-methyl-2,5-diphenylpyrrolidine-3-carboxylate* (**9**). Colorless crystals. M.p. 60–62° (PE/Et_2O). IR (KBr): 3065*w*, 2956*m*, 2251*w* (C≡N), 1759*s* (C=O), 1497*m*, 1455*s*, 1232*s*, 1180*s*, 1022*m*, 751*m*, 701*m*. ^{1}H-NMR: 7.61–7.57 (*m*, 2 arom. H); 7.50–7.38 (*m*, 8 arom. H); 4.24 (*s*, H–C(2)); 4.01, 3.82 (*AB*, $^3J = 10.1$, H–C(4), H–C(5)); 3.22 (*s*, MeO); 2.07 (*s*, MeN). ^{13}C-NMR: 164.7 (*s*, C=O); 136.1, 134.3 (2*s*, 2 arom. C); 129.6, 129.5, 129.3, 128.8, 128.3, 127.7 (6*d*, 10 arom. CH); 116.4, 115.6 (2*s*, 2 CN); 79.3, 72.9 (2*d*, C(2), C(5)); 54.9 (*s*, C(3)); 53.9 (*q*, MeO); 44.0 (*d*, C(4)); 37.7 (*q*, MeN). ESI-MS (MeOH): 368 (47, $[M+Na]^+$), 346 (100, $[M+1]^+$). HR-ESI-MS (MeOH): 368.13734 ($[M+Na]^+$, $C_{21}H_{19}N_3NaO_2^+$; calc. 368.13695); 346.15557 ($[M+1]^+$, $C_{21}H_{20}N_3O_2^+$; calc. 346.15500).

7. *Reaction of* cis-**1b** *with DCFM* (**7a**). A soln. of **7a** (194 mg, 1 mmol) and *cis*-**1b** (271 mg, 1 mmol) in toluene (5 ml) was heated under reflux for 4.5 h. After evaporation of the solvent, the crude mixture was

separated by prep. TLC (CH_2Cl_2/hexane 3.5:1.5). An anal. pure sample of **10** was obtained by recrystallization from PE with a small amount of CH_2Cl_2.

*Dimethyl 2,3-*trans*,3,4-*trans*,4,5-*trans*-3,4-Dicyano-1,2,5-triphenylpyrrolidine-3,4-dicarboxylate* (**10**). Yield 290 mg (62%). Colorless crystals. M.p. 247–251° (hexane/CH_2Cl_2). IR (KBr): 3064*w*, 3036*w*, 1748v*s* (C=O), 1597*m*, 1500*s*, 1455*m*, 1330*m*, 1248*s*, 1223*s*, 703*s*. ^{1}H-NMR: 7.38–6.20 (*m*, 15 arom. H); 6.45 (*s*, H–C(2), H–C(5)); 3.35 (*s*, 2 MeO). ^{13}C-NMR: 163.4 (*s*, 2 C=O); 133.6, 141.9 (2*s*, 3 arom. C); 119.1, 119.3, 128.0, 128.4, 128.5, 129.1 (6*d*, 15 arom. CH); 114.6 (*s*, 2 CN); 71.4 (2*d*, C(2), C(5)); 59.3 (*s*, C(3), C(4)); 54.1 (*q*, 2 MeO). EI-MS: 465 (17, M^+), 272 (21), 271 (100), 270 (95), 219 (14), 218 (13), 181 (17), 180 (31), 167 (35), 165 (10), 104 (13), 77 (27). ESI-MS (MeOH): 489 (33), 488 (100, $[M+Na]^+$), 466 (5, $[M+1]^+$). HR-ESI-MS (MeOH): 488.15737 ($[M+Na]^+$, $C_{28}H_{23}N_3NaO_4^+$; calc. 488.15808); 466.17574 ($[M+1]^+$, $C_{28}H_{24}N_3O_4^+$; calc. 466.17613).

8. *X-Ray Crystal-Structure Determination of* **8a**, **9**, *and* **10** (*Table* and *Figs. 1–3*)[2]). All measurements were made on a *Stoe IPDS* diffractometer [33] with graphite monochromated MoK_α radiation (λ 0.71073 Å) and an *Oxford Cryosystems Cryostream 700* cooler. The data collection and refinement parameters are given in the *Table*, views of the molecules are shown in *Figs. 1–3*. For all compounds, the data reduction was performed with *Stoe IPDS* [33]. The intensities were corrected for *Lorentz* and polarization effects. No absorption correction was applied. Each structure was solved by direct methods [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 with a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2 U_{eq} of its parent C-atom (1.5 U_{eq} for Me groups). Refinement of each structure was carried out on F^2 by full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. Refinement of the absolute structure parameter [35] of **10** yielded a value of $-1.0(13)$, which suggests that the absolute structure parameter is meaningless because the compound is a weak anomalous scatterer, which emphases the large s.u. of the *Flack* parameter. Neutral atom scattering factors for non-H-atoms were taken from [36a], and the scattering factors for H-atoms were taken from [37]. Anomalous dispersion effects were included in F_c [38]; the values for f' and f'' were those of [36b]. The values of the mass attenuation coefficients are those of [36c]. All calculations were performed using SHELXL97 [39].

REFERENCES

[1] L. M. Harwood, R. J. Vickers, in 'The Chemistry of Heterocyclic Compounds, Vol. 59: Synthetic Application of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products', Eds. A. Padwa, W. H. Pearson, J. Wiley & Sons, New York, 2002, p. 169.

[2] C. Nájera, J. M. Sansano, *Curr. Org. Chem.* **2003**, *7*, 1105.

[3] A. F. Khlebnikov, M. S. Novikov, A. A. Bespokoev, R. R. Kostikov, J. Kopf, Z. A. Starikova, M. Yu. Antipin, *Russ. J. Org. Chem.* **2005**, *41*, 922.

[4] L. M. Stanley, M. P. Sibi, *Chem. Rev.* **2008**, *108*, 2887.

[5] X. Wang, D. Jiang, S. Dai, *Chem. Mater.* **2008**, *20*, 4800.

[6] C. Nájera, M. de Garcia Retamosa, J. M. Sansano, A. de Cózar, F. P. Cossio, *Tetrahedron: Asymmetry* **2008**, *10*, 2913; C. Nájera, M. de Garcia Retamosa, J. M. Sansano, *Angew. Chem., Int. Ed.* **2008**, *47*, 6055.

[7] M. Alvarez-Corral, M. Muñoz-Dorado, I. Rodriguez-Garcia, *Chem. Rev.* **2008**, *108*, 3174.

[8] S.-I. Fukuzawa, H. Oki, *Org. Lett.* **2008**, *10*, 3174.

[9] R. Huisgen, W. Scheer, H. Huber, *J. Am. Chem. Soc.* **1967**, *89*, 1753; R. Huisgen, *Angew. Chem., Int. Ed.* **1963**, *2*, 633.

[10] K. Urbaniak, R. Szymański, J. Romański, G. Mlostoń, M. Domagała, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **2004**, *87*, 496.

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[2]) CCDC-729141–729143 contain the supplementary crystallographic data for this article. These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre via* www.ccdc.cam.ac.uk/data_request/cif.

[11] R. Bartnik, G. Mlostoń, *Tetrahedron* **1984**, *40*, 2569.
[12] T. Skarżyński, A. M. Brzozowski, Z. Derewenda, G. Mlostoń, *Acta Crystallogr., Sect. C* **1983**, *39*, 1051.
[13] G. Mlostoń, Z. Skrzypek, *Bull. Soc. Chim. Belg.* **1990**, *99*, 167.
[14] G. Mlostoń, K. Urbaniak, H. Heimgartner, *Helv. Chim. Acta* **2002**, *85*, 2056.
[15] G. Mlostoń, K. Urbaniak, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **2002**, *85*, 2644.
[16] C. J. Ireland, J. S. Pizey, *J. Chem. Soc., Chem. Commun.* **1972**, 4.
[17] L. Fišera, R. Huisgen, I. Kalwinsch, E. Langhals, X. Li, G. Mlostoń, K. Polborn, J. Rapp, W. Sicking, R. Sustmann, *Pure Appl. Chem.* **1996**, *68*, 789.
[18] M. Domagała, S. J. Grabowski, K. Urbaniak, G. Mlostoń, *J. Mol. Struct.* **2004**, *690*, 69.
[19] W. K. Anderson, A. S. Milowsky, *J. Med. Chem.* **1986**, *29*, 2241.
[20] R. Sustmann, S. Tappanchai, H. Bandmann, *J. Am. Chem. Soc.* **1996**, *118*, 12555; see also C. S. Kniep, R. Boese, R. Sustmann, *Tetrahedron* **2000**, *56*, 4157; M. Rese, M. Dern, K. Luecking, R. Sustmann, *Liebigs Ann. Chem.* **1995**, 1139; R. Sustmann, M. Rogge, U. Nuechter, H. Bandmann, *Chem. Ber.* **1992**, *125*, 1657.
[21] R. Huisgen, G. Mlostoń, E. Langhals, *J. Am. Chem. Soc.* **1986**, *108*, 6401; R. Huisgen, G. Mlostoń, E. Langhals, *Helv. Chim. Acta* **2001**, *84*, 1805; R. Huisgen, G. Mlostoń, H. Giera, E. Langhals, *Tetrahedron* **2002**, *58*, 507; M. Woźnicka, M. Rutkowska, G. Mlostoń, A. Majchrzak, H. Heimgartner, *Pol. J. Chem.* **2006**, *80*, 1683.
[22] R. Huisgen, H. Giera, K. Polborn, *Tetrahedron* **2005**, *61*, 6143.
[23] R. Huisgen, P. Pöchlauer, G. Mlostoń, K. Polborn, *Helv. Chim. Acta* **2007**, *90*, 983.
[24] A. L. Spek, 'PLATON', Program for the Analysis of Molecular Geometry, University of Utrecht, The Netherlands, 2003.
[25] J. H. Hall, R. Huisgen, *J. Chem. Soc., Chem. Commun.* **1971**, 1187; J. H. Hall, R. Huisgen, C. H. Ross, W. Scheer, *J. Chem. Soc., Chem. Commun*. **1971**, 1188; A. C. Oehlschlager, A. S. Yim, M. H. Akhtar, *Can. J. Chem.* **1978**, *56*, 273.
[26] T. Böhm, A. Weber, J. Sauer, *Tetrahedron* **1999**, *55*, 9535; K. Elender, H. Nöth, P. Riebel, A. Weber, J. Sauer, *Tetrahedron* **2000**, *56*, 5443.
[27] V. Caër, A. Laurent, E. Laurent, R. Tardivel, Z. Cebulska, R. Bartnik, *Nouv. J. Chim.* **1987**, *11*, 351.
[28] B. S. Pedersen, S. Scheibye, N. H. Nilsson, S.-O. Lawesson, *Bull. Soc. Chim. Belg.* **1978**, *87*, 223.
[29] J. W. Greidanus, *Can. J. Chem*. **1970**, *48*, 3530.
[30] E. W. Elam, H. E. Davis, *J. Org. Chem*. **1967**, *32*, 1563.
[31] R. Bartnik, G. Mlostoń, S. Leśniak, *Pol. J. Chem*. **1979**, *53*, 537.
[32] T. W. J. Taylor, J. S. Owen, D. Whittaker, *J. Chem. Soc*. **1938**, 206.
[33] STOE IPDS-Software, Version 2.89, STOE & CIE GmbH, Darmstadt, Germany, 1998.
[34] G. M. Sheldrick, *Acta Crysallogr., Sect. A* **1990**, *46*, 467.
[35] H. D. Flack, G. Bernardinelli, *Acta Crystallogr., Sect. A* **1999**, *55*, 908; H. D. Flack, G. Bernardinelli, *J. Appl. Crystallogr.* **2000**, *33*, 1143.
[36] 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.
[37] R. F. Stewart, E. R. Davidson, W. T. Simpson, *J. Chem. Phys.* **1965**, *42*, 3175.
[38] J. A. Ibers, W. C. Hamilton, *Acta Crystallogr.* **1964**, *17*, 781.
[39] G. M. Sheldrick, 'SHELXL97', Program for the Refinement of Crystal Structures, University of Göttingen, Germany, 1997.

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