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Reactions of a sterically hindered tetrasubstituted thiocarbonyl ylide with acceptor-substituted ethylenes; regioselectivity and stereochemistry☆

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Dedicated to Professor Günther Maier on the occasion of his 70th birthday

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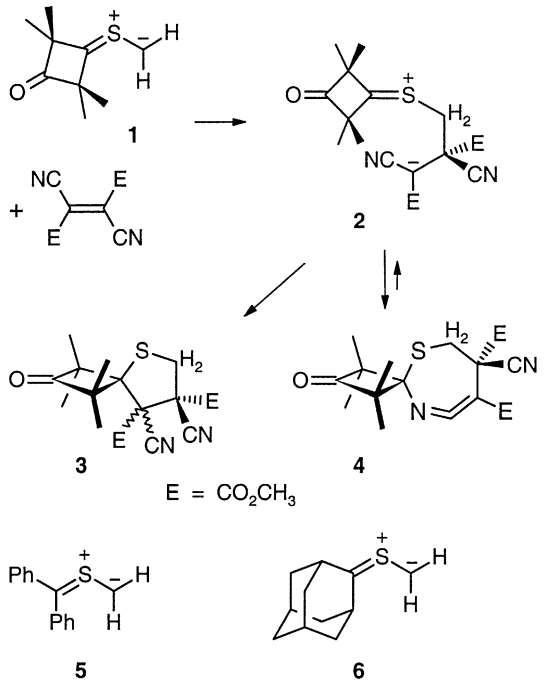
Abstract—The 1,3-cycloadditions of the tetra-substituted thiocarbonyl ylide **8**, set free by N_2 extrusion from thiadiazoline **7**, with methyl acrylate and acrylonitrile furnish 3′-and 4′-substituted thiolanes, probably by a concerted pathway. In the reactions of **8** with dimethyl 2,3-dicyanofumarate (**27**) and dimethyl 2,3-dicyanomaleate (**28**), zwitterionic intermediates, which are capable of conformational rotation, sit at the branching point of two irreversible reactions: cyclization to thiolanes **23/24** and fragmentation to cyclopropanes **31/32** plus thione **12**. Both reactions are accompanied by some loss of stereochemical purity. Two mechanisms for the cyclopropane formation are discussed: intramolecular nucleophilic substitution in *anti*-zwitterions **29/30** or unassisted heterolysis leading to a *tert*-carbenium zwitterion as further intermediate.

1. Introduction

A cooperation of electronic and steric effects is required to deflect 1,3-dipolar cycloadditions from the normal concerted pathway to a two-step process via a zwitterionic intermediate, as we recently described.[1,2] The reactions of the electron-rich thiocarbonyl ylide **1** with the electron-deficient double bond of dimethyl 2,3-dicyanofumarate and dimethyl 2,3-dicyanomaleate proceed nonstereospecifically. The ratios of retention/inversion in the isolated thiolanes **3** indicate that ring closure and conformational rotation are competing processes acting on the intermediates.[1]

Furthermore, the *gauche* zwitterion **2** is in equilibrium with the seven-membered cyclic ketene imine **4** (Scheme 1) which can be intercepted by water to form a lactam.[1] It contributes to the charm of this study that **1**, **2**, and **4** are nonisolable intermediates.[3] Only the *trans*- and *cis*-cycloadducts **3** and the mentioned lactam can be isolated. The corresponding 1,3-cycloadditions of thiocarbonyl ylides **5** and **6** took place with retention, and no ketene imine was interceptible.[4,5]

In 2,2,4,4-tetramethyl-3-thioxocyclobutanone *S*-isopropylide (**8**), two more methyl groups increase steric demands.



Scheme 1.

☆ 1,3-Dipolar cycloadditions, Part 124. For Part 123 see Ref. 1.

Keywords: thiocarbonyl ylides; 1,3-dipolar cycloadditions; zwitterionic intermediates; cyclopropanes; steric and strain effects.

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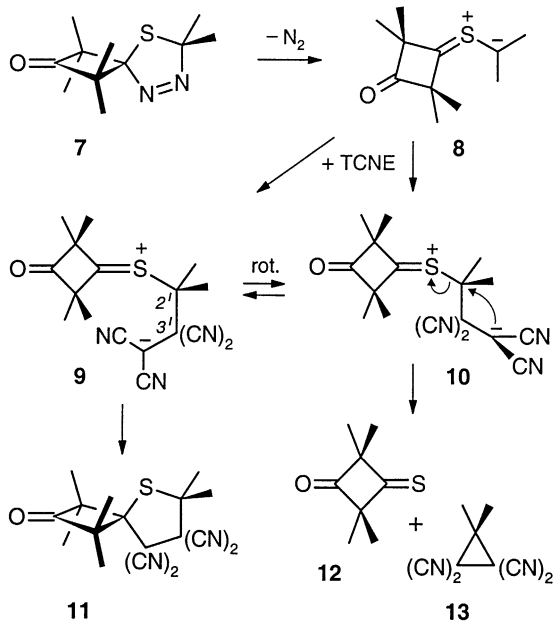
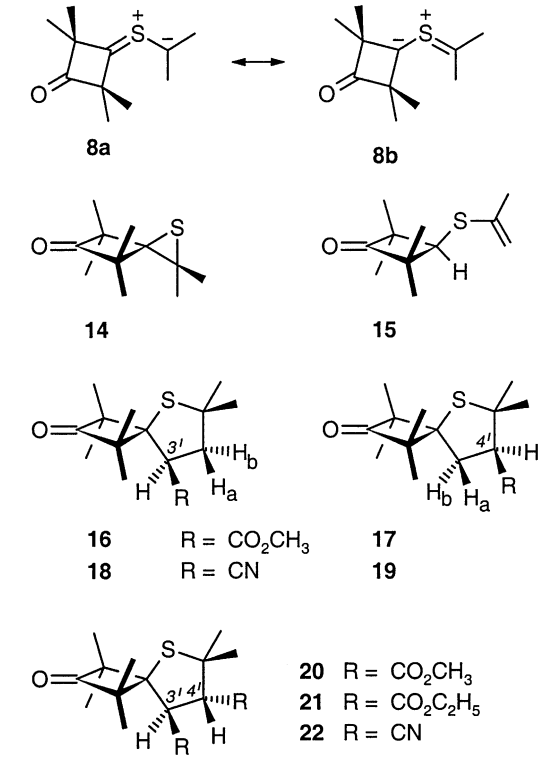


Scheme 2.

Recently we described the reaction of **8** with tetracyanoethylene, which furnished the cyclopropane derivative **13** plus thione **12** along with cycloadduct **11**. The *gauche*-and *anti*-conformations of the zwitterion, **9** and **10**, were invoked as precursors (Scheme 2).[2] Here we report on the reactivity, regioselectivity, and stereochemistry in the 1,3-cycloadditions of the tetrasubstituted thiocarbonyl ylide **8** with further acceptor-substituted ethylenes.



Scheme 3.

2. Mono- and bis-acceptor ethylenes: reactivity and regiochemistry

The thiadiazoline **7** is available from thione **12** and 2-diazopropane. The formation of **8** by N_2 elimination proceeds in toluene with a half-life of 18 min at 70°C. In the absence of dipolarophiles, **8** either undergoes electrocyclization to give thiirane **14** or furnishes the thioenol ether **15** by sigmatropic 1,4-H shift (Scheme 3).[2]

The 1,3-dipole **8** is sterically hindered at both termini, and almost certainly, the approach of the dipolarophile is more strongly impeded by the tetramethylcyclobutanone system than by the *gem*-dimethyl group. The reaction of thiadiazoline **7** with an excess of methyl acrylate (used as solvent) at 60°C provided 21% of **16** and 48% of **17** (ratio of 3′-CO_2Me/4′-CO_2Me=30:70) besides 13% of **15** (^{1}H NMR analysis with weight standard). Partial separation of the cycloadducts was achieved by chromatography. The products of the analogous reaction of **7** with acrylonitrile (as solvent) contained 13% of **18** and 17% of **19** (3′-CN/4′-CN=43:57), accompanied by substantial amounts of thiirane **14** (6%) and of *S*-2-propenyl sulfide **15** (23%).

The tentative regiochemical assignments of **16**–**19** rest on the ^{1}H NMR parameters (400 MHz) of the three ring protons which form AMX spectra in **16** and **18** (3′-*R*) and ABC patterns in **17** and **19** (4′-*R*). This empirical feature appears also in the (more complex) ^{1}H NMR spectra of the corresponding cycloadducts of **1** in which 5′-H_2 enters into the coupling.[6] Consistently, the inequality $J_{cis-vic}>J_{trans-vic}$ was found for the 3′-H,4′-H coupling, in accordance with parameters for pyrazolidine derivatives which we recently described.[7] A conspicuous chemical shift difference between **1**-adducts and those of **8** arises in the *tert*-4′-H of **17** (δ 2.43) and **19** (2.76), compared with 2.92 and 2.99, respectively, in the adducts of **1**; we ascribe the lower δ values to the shielding by 5′-Me_2. On the other hand, the *tert*-3′-H in **16**, **18** and the analogous **1**-adducts appear at higher frequencies (δ 3.48–3.57), which is probably a consequence of the more remote methyl groups in the cyclobutane moiety.

Reactivity and regiochemistry of concerted cycloadditions can be described as functions of FMO energies and atomic orbital coefficients.[8,9] Electronic and steric effects in the directive forces can be discussed in the language of resonance structures **8a** and **8b** (Scheme 3).

The cycloadditions of thiobenzophenone *S*-methylide (**5**) and adamantanethione *S*-methylide (**6**) with methyl acrylate and acrylonitrile exclusively furnished the 3′-substituted thiolanes (corresponding to **16**, **18**).[4,5] The methylene terminus of **5** and **6** commands a higher nucleophilicity than the substituted one, and its interaction with the β-position of the acceptor-ethylene steers the carboxylic ester or nitrile group into the sterically unfavorable *vic*-position of the voluminous groups in position 2′. The increased steric demand of the tetramethyl-3-oxocyclobutylidene group in **1** enforces a partial switching to the 4′-substituted regioisomer (corresponding to **17**, **19**). The reaction of **1** with methyl acrylate afforded 96% of thiolanes which showed

Table 1. Ratios and yields of 3′-and 4′-substituted thiolanes generated with methyl acrylate and acrylonitrile

1,3-Dipole	CO_2CH_3/3′/4′	% Yield	CN:3′/4′	% Yield
5	100:0	79[a]	100:0	76[a]
6	100:0	89	100:0	82
1	65:35	96	80:20	82
8	30:70	69	43:57	30

[a] Isolated yields.

3′-CO_2CH_3/4′-CO_2CH_3=65:35.[6] Table 1 indicates a similar phenomenon for **1**+acrylonitrile.

The change from the *S*-methylide **1** to the *S*-isopropylide **8** is connected with a drop in reactivity, i.e. the yields of cycloadducts decreased in favor of **14** and **15** (Table 1). This decrease would have been more dramatic if **8** had been reacted with the usual 1.1 equiv. of dipolarophile, diluted by solvent, instead of using a large excess of methyl acrylate and acrylonitrile as solvent. The increase of van der Waals pressure probably strengthens the helical twisting of **8**, compared with **1**, thus facilitating the electrocyclic ring closure (→**14**) as well as the sigmatropic shift (→**15**); the concerted cycloaddition becomes more difficult. Perhaps concomitant with the decrease of nucleophilicity of **8** is a reduction of resonance contributor **8a** in weight. As a consequence, the share of 4′-CO_2CH_3 (**17**) and 4′-CN (**19**) in the products rises.

The reaction of **7** with 1.1 equiv. of dimethyl fumarate in THF (initially 1.2 M) at 65°C provided 36% of thiolane **20**, 51% of thiirane **14**, and 7% of **15**. The use of 4.6 equiv. of diethyl fumarate as solvent (initially about 5 M) afforded adduct **21** in 79% yield. The reaction of **7** with fumaronitrile gave the *trans*-dicarbonitrile **22** (70% yield).

For the cycloadditions of **1** with dimethyl fumarate and dimethyl maleate, a stereoretention of >99.97 and 99.95%, respectively, was observed.[1] We have no reason to doubt the concertedness of the reaction of **8** with dimethyl fumarate or fumaronitrile either.

The MS of thiolanes **20**–**22** show base peaks for $[M-\text{dimethylketene}]^+$, as was observed for many cycloadducts of **1**[1,2] and **8**. The elimination of ketenes is a general fragmentation pathway for the radical cations of cyclobutanone and its derivatives.[10,11]

3. Two-step cycloadditions with *cis, trans*-isomeric tetra-acceptor-ethylenes

In 1976, a kinetic criterion to distinguish between concerted cycloadditions and two-step processes via zwitterionic intermediates was proposed by the Munich laboratory.[12] Stepwise introduction of cyano groups into acrylonitrile up to TCNE steeply increases the rate constants of Diels–Alder reactions with cyclopentadiene. Values of log k_2 are a function of the FMOs of reactants, in accordance with early transition structures (TS) of the concerted process. In contrast, the rates of (2+2) cycloadditions from isobutenyl methyl ether with 1,1-dicyano-, tricyano-, and tetracyanoethylene decrease slightly. The late TS resembles the zwitterion, which is stabilized by two terminal CN groups in all three cases. Acrylonitrile and fumaronitrile are unreactive because the zwitterion is insufficiently stabilized by one terminal cyano group.

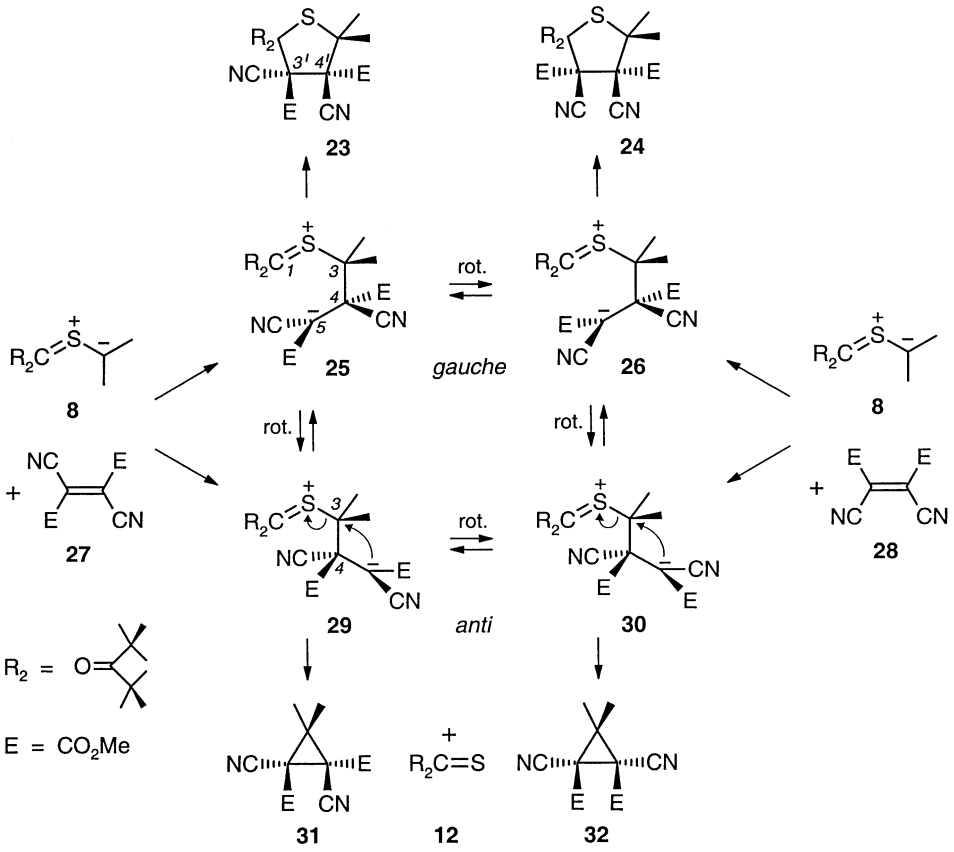
Sterically hindered thiocarbonyl ylides like **1** and **8** have the capacity of undergoing both concerted and two-step cycloadditions. When **7** was reacted with dimethyl 2,3-dicyanofumarate (**27**) or dimethyl 2,3-dicyanomaleate (**28**) (1.1 equiv. at 60°C), thiolanes **23** and **24** as well as dimethyl *trans*- and *cis*-1,2-dicyano-3,3-dimethylcyclopropane-1,2-dicarboxylates (**31**, **32**) plus thione **12** were obtained (Scheme 4). The total yields were high, and the products of formal isopropylidene transfer, i.e. the cyclopropanes **31** and **32**, predominated. The principle of retention of dipolarophile configuration was violated in both types of products. C_2 symmetry reduces the ^{1}H NMR spectrum of **31** to two signals, whereas the σ-plane of **32** gives rise to two Me and one MeO singlet.

Reactions of thiocarbonyl ylide **8** with the highly electrophilic reagents **27** and **28** are imaginable at both termini of **8**, and both zwitterions formed could furnish thiolanes **23** and **24**. However, the fragmentation products, **12** plus **31**, **32**, can only originate from zwitterions, which stem from the attack on the CMe_2 terminus of **8**. In contrast to the concerted, four-center cycloadditions of **8** with the acrylic ester type, zwitterion formation is a two-center process and is expected to take place at the less screened terminus, i.e. the CMe_2 group of **8**.

The structural inversion observed in the formation of thiolanes **23**, **24** and cyclopropanes **31**, **32** has mechanistic significance only, if it occurs during the cycloaddition and not before or after the interaction with **8**. As shown in a preceding paper, 1,3,4-thiadiazolines, i.e. the precursors of thiocarbonyl ylides, catalyze the *cis*, *trans* isomerization of **27** and **28** (equilibrium 88:12, $CDCl_3$, 20°C). For several thiadiazolines—**7** amongst them—this catalysis was counteracted by a small concentration of a strong acid.[1]

In the tests for the steric course, **7** and 1.9 equiv. of **27** or **28** were reacted in 7.6 mM H_2SO_4 in $CDCl_3$ (80°C, 25 min). The ^{1}H NMR analysis (360 MHz) of the multi-component system with weight standard was, whenever feasible, based on the integrals of several signals for each compound (Table 2, Section 5). Small yields of thiirane **14** (1–4%) indicate a high affinity of thiocarbonyl ylide **8** to the tetra-acceptor-substituted ethylenes **27** and **28**, the excess of which was not significantly isomerized after the reaction. Furthermore, thiolane **24** survived unchanged when heated to 150°C in $CDCl_3$, thus ruling out subsequent stereoisomerization or conversion to cyclopropanes **31** and **32**. The *trans*, *cis* ratios observed are kinetically controlled.

	Reaction with dimethyl 2,3-dicyano-	
	fumarate	maleate
% Cycloadducts **23**+**24**	38	24
Ratio **23**/**24** (*trans*/*cis*)	71:29	14:86
% Cyclopropanes **31**+**32**	60	71
Ratio **31**/**32** (*trans*/*cis*)	93:7	7:93
% Thioketone **12**	Not determined	66



Scheme 4.

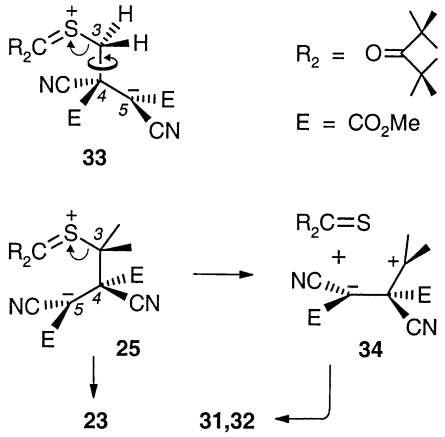
Cyano and methoxycarbonyl groups stabilize the anionic center of the zwitterionic intermediate which is supposed to be the branching point of the two product-forming routes. Scheme 4 is based on the assumption that the cyclopropanes **31** and **32** are generated by an intramolecular displacement which requires the *anti*-conformations (with respect to the 3,4 bond) of the zwitterions, **29** and **30**.

According to the above compilation of data, retention exceeds inversion, for the cyclopropanes even more than for the cycloadducts. Conformational rotations in the zwitterionic intermediates are responsible for the loss of stereochemical purity. These rotations are distinctly slower than the irreversible closure of the thiolane ring or the intramolecular substitution, i.e. the conformations of the zwitterion are far from reaching rotational equilibrium. The ring closure of **25** and **26** requires a helical conformation, which allows the interaction of the π-orbitals at C-1 and C-5.

Why do the reactions of thione *S*-methylide **1** with the *trans*, *cis*-isomers **27** and **28** produce only the cycloadducts[1] and no cyclopropanes+thione **12** via **33**? The following scenario is conceivable: the *gauche*-zwitterions **25** and **26** are favored by Coulombic potential since the distance between the centers of charge is less than half of that in the *anti*-conformers **29** and **30**. As a consequence of opposing steric hindrance, not all collisions lead to the favorable *gauche* forms. The 3,4 rotation *anti*→*gauche* is probably faster for the 3-H_2 zwitterion **33**, formed from **1** and **27**, than for the 3-Me_2 zwitterion **29**. For 1,4-biradicals, the ratio k_{rot}/k_{cycl} has been shown to decrease dramatically on going from primary to secondary and tertiary termini.[13,14] A similar trend for k_{rot}/k_{subst} could explain the phenomenon.

However, the decrease in readiness of C-3 to enter S_N2 type substitution in the sequence primary>secondary>tertiary is even more dramatic. The intramolecular character may promote some participation of the carbanionic center of **29** and **30** in the displacement. The heterolysis of the S–C3 bond without assistance from the carbanion would offer an alternative pathway with less structural constraints, since *anti*-conformations are no longer required (Scheme 5). Only the *tert*-carbenium zwitterion **34** has a chance of being generated (from various conformations), not the *prim*-carbocation from **2** (*gauche*) or **33** (*anti*). Therefore, **2** cyclizes to the thiolane, whereas in the case of **25** the S–C3 heterolysis competes with thiolane formation, and the trimethylene-type zwitterion **34** cyclizes to **31/32**, with or without rotation (Scheme 5). Carbenium-carbanion type trimethylenes have been postulated before.[15]

The hexasubstituted cyclopropanes **31** and **32** were identified with samples, which were prepared by reacting **27** or **28** with 2-diazopropane. The red color of the diazoalkane disappeared at 0°C before N_2 evolution was observed, and 1-pyrazoline **36** is the presumed intermediate. Whether the N_2 extrusion from 1-pyrazolines is a one-step or two-step process, is a much discussed problem[16] that will not be touched upon here. It has even been surmised that it escapes conventional mechanistic analysis.[17] In

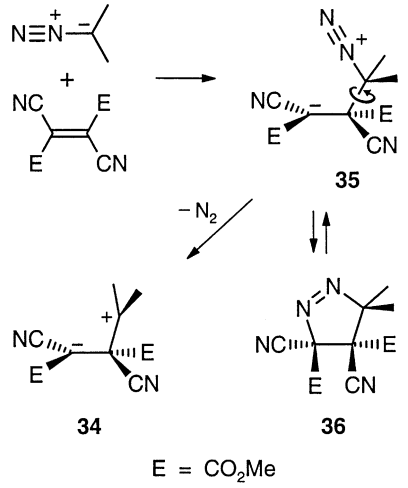


Scheme 5.

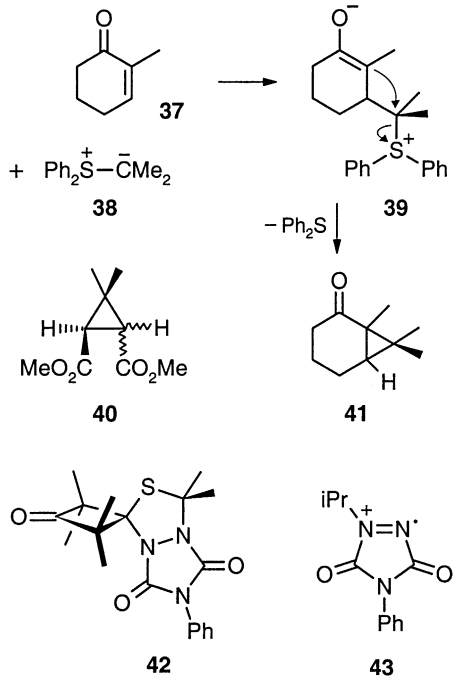
the two-step pathway, **36** returns to **35**, and the same mechanistic dichotomy has to be considered for the N_2 elimination from **35**, as discussed above for the cyclopropane formation, i.e. heterolysis of $C–N_2^+$ with or without participation by the carbanionic center (Scheme 6).

Sulfonium methylides are known as methylene transfer reagents, which convert α,β-unsaturated carbonyl compounds to cyclopropane derivatives; the oxodimethylsulfonium methylide is widely used.[18] A two-step mechanism with a zwitterionic intermediate, capable of conformational rotation, appears to be generally accepted.[19,20] Corey and Jautelat described an isopropylidene transfer to **37** by treatment with diphenylsulfonium isopropylide (**38**) which furnished **41** (86%); the reaction of **38** with dimethyl maleate provided *cis*- and *trans*-**40** in a 7:1 ratio (Scheme 7).[21] On assuming a two-step pathway, the cyclization of the zwitterion **39** would be a direct counterpart of the process **29→31**, i.e. a nucleophilic displacement involving persubstituted C-atoms. We are not aware of mechanistic studies with these sulfonium ylides.

The sulfonium isopropylide **38**, which has been employed repeatedly,[22,23] is lacking the stabilizing allyl anion-type resonance of thiocarbonyl ylide **8** and surpasses the latter in nucleophilicity. In fact, **38** is a lithiumorganic compound.



Scheme 6.



Scheme 7.

On the side, we briefly mention the reactivity of **8** versus 4-phenyl-1,2,4-triazoline-3,5-dione which is an aggressive electrophile. The 1:1 adduct **42** was formed in 61% yield, but the occurrence of 21% of thione **12** points to a second reaction path which is not yet clarified. In the MS of **39**, the elimination of dimethylketene (17%, $[M-C_4H_6O]^+$, *m/z* 303) steps back behind the 1,3-cycloreversion (81% of $\mathbf{8}^+$ or $\mathbf{14}^+$, *m/z* 198). The intensities of the isotope peaks confirm $C_{11}H_{12}N_3O_2^+$ for the base peak (*m/z* 218), possibly the radical cation **43**.

4. Conclusions

The change from the disubstituted thiocarbonyl ylide **1** to the tetrasubstituted **8** is accompanied by a decrease of reactivity in the concerted cycloadditions with methyl acrylate, acrylonitrile, and dimethyl fumarate. The interplay of steric and electronic forces—not fully transparent in detail—leads to regioisomeric cycloadducts of mono-acceptor-ethylenes.

In the two-step reactions of **8**, the *cis*, *trans* isomeric dipolarophiles **27** and **28** attack at the least hindered terminus (CMe_2) to form the zwitterion. In the reactions of **8** with **27** and **28**, the loss of stereochemical integrity in the formation of thiolanes **23** and **24** is smaller than observed for the cycloadditions of **1**, i.e. the 4,5-rotations in the zwitterions are more hindered. The fragmentation leading to cyclopropane derivatives **31** and **32** and thione **12** is the major reaction of the zwitterion. An intramolecular nucleophilic displacement requires the 3,4-*anti*-conformation of the zwitterion. An unassisted cleavage to give a carbenium zwitterion is discussed—and left open—as a second alternative.

5. Experimental

5.1. General

Instruments.[1] ^{1}H NMR 80 MHz, ^{13}C NMR 22 MHz, acid-free $CDCl_3$, if not stated otherwise. MS: intensities of isotope peaks are given in the form, e.g., ^{13}C % calc/% found. CC is column chromatography on silica gel, and PLC is preparative layer chromatography (20×20 glass plates, 2 mm of Merck silica gel 60 PF_{254}).

5.1.1. Methyl 2,2,4,4,5′,5′-hexamethyl-1-oxospiro[cyclobutane-3,2′-thiolane]-3′-carboxylate (16) and 4′-carboxylate 17. Thiadiazoline **7**[2] (679 mg, 3.00 mmol) in freshly distilled methyl acrylate (6 mL) was stirred for 4 h in the 60°C-bath; the expected N_2 volume (75 mL) was set free. The excess of dipolarophile was removed at the rotary evaporator, and the residue subjected to ^{1}H NMR analysis (400 MHz) with *sym*-$C_2H_2Cl_4$ as weight standard: 21% of **16** (s δ 1.47, Me), 48% of **17** (s 1.60, Me), 13% of 2-propenyl sulfide **15** (s 2.02, Me). Partial separation by PLC (3×with pentane/diethyl ether 8:2) gave a main fraction (210 mg) as a colorless oil. Thiolane **17** (80 mg, 9%, ^{1}H NMR pure) crystallized from pentane at −78°C, mp 73–75°C. The residue of the mother liquor furnished crystals (95 mg, 11%) of **16/17**, ca. 50:50), from methanol at −20°C, mp 59–63°C. **16** was not obtained pure.

*Data of **17***. IR (KBr); ν 1036 cm^{-1} s; 1133m, 1164vs, 1217m, 1287s (C–O); 1364s, 1382m, 1432m, 1467s; 1738vs (C═O, ester), 1779vs (C═O, cyclobutanone). ^{1}H NMR (400 MHz): δ 1.19, 1.21, 1.24 (3s, 3Me), 1.31 (s, 2Me), 1.60 (s, Me); the ABC spectrum of the ring protons was solved by the computer program DavinX:[24] 2.43 (4′-H), 2.57 (3′-H_b), 2.72 (3′-H_a) with $J_{3'a,3'b}$=−13.6 Hz, $J_{3'b,4'}$ = 13.6 Hz, $J_{3'a,4'}$=4.6 Hz); 3.72 (s, 2MeO). Anal. calcd for $C_{15}H_{24}O_3S$ (284.41): C 63.34, H 8.51, S 11.28; found: C 63.38, H 8.32, S 11.33.

*Data of **16***. (**16/17**∼50:50). ^{1}H NMR (400 MHz), by subtraction): δ 1.23, 1.27, 1.31, 1.34, 1.36, 1.47 (6s, 6Me), 1.95 (dd, $J_{4'a,4'b}$=13.5 Hz, $J_{3',4'b}$=6.7 Hz, 4′-H_b), 2.36 (dd, $J_{4'a,4'b}$=13.5 Hz, $J_{3',4'a}$=1.8 Hz, 4′-H_a), 3.48 (dd, $J_{3',4'b}$=6.7 Hz, $J_{3',4'a}$=1.8 Hz, 3′-H). Anal. calcd for $C_{15}H_{24}O_3S$ (284.41): C 63.34, H 8.51, S 11.28; found: C 63.49, H 8.39, S 11.25.

5.1.2. 2,2,4,4,5′,5′-Hexamethyl-2-oxospiro[cyclobutane-3,2′-thiolane]-3′-carbonitrile (18) and 4′-carbonitrile 19. The analogous reaction of **7** with freshly distilled acrylonitrile (6 mL) furnished (^{1}H NMR analysis) 13% of **18** (dd, δ 3.57, 3′-H), 17% of **19** (dd, 2.76, 4′-H), 23% of **15** (s 2.02, Me), and 6% of **14** (s 1.16, 2Me). PLC (4×with pentane/diethyl ether 7:3) provided a zone with R_f 0.3 (15%) which afforded crystalline **19**, mp 73–75°C, from pentane at −78°C. The second PLC zone (R_f 0.3) gave **18** (11%), mp 141–142°C, from pentane/CH_2Cl_2.

*Data of **18***. IR (KBr): ν 1126 cm^{-1}, 1368m, 1457m; 1778s (C═O), 2236w (C≡N). ^{1}H NMR (400 MHz): δ 1.27, 1.34, 1.35, 1.51, 1.60, 1.73 (6s, 6Me), 1.90 (dd, $J_{4'a,4'b}$=13.4 Hz, $J_{3',4'b}$=5.5 Hz, 4′-H_b), 2.36 (dd, $J_{4'a,4'b}$=13.4 Hz, $J_{3',4'a}$ = 2.3 Hz, 4′-H_a), 3.57 (dd, $J_{3',4'b}$=5.5 Hz, $J_{3',4'a}$=2.3 Hz, 3′-H). Anal. calcd for $C_{14}H_{21}NOS$ (251.38): C 66.89, H 8.42, N 5.57, S 12.76; found: C 66.69, H 8.17, N 5.39, S 12.75.

*Data of **19***. IR (KBr): ν 1032 cm^{-1} m, 1138m, 1381m, 1447+1463m, br.; 1775s (C═O), 2236 (C≡N). ^{1}H NMR (400 MHz): δ 1.20, 1.23, 1.25, 1.28, 1.56, 1.57 (6s, 6Me); ABC of ring protons solved by DavinX:[24] 2.49 (3′-H_b), 2.63 (3′-H_a), 2.76 (4′-H) with $J_{3'a,3'b}$=−13.5 Hz, $J_{3'b,4'}$=12.5 Hz, $J_{3'a,4'}$=4.9 Hz. Anal. calcd for $C_{14}H_{21}NOS$ (251.38): C 66.89, H 8.42, N 5.57, S 12.76; found: C 66.57, H 8.05, N 5.72, S 12.54.

5.1.3. Dimethyl 2,2,4,4,5′,5′-hexamethyl-1-oxospiro [cyclobutane-3,2′-thiolane]-3′,4′-*trans*-dicarboxylate (20). In the first experiment, **7** was reacted with dimethyl fumarate (low solubility) in dilute solution in toluene at 60°C; the ^{1}H NMR analysis showed **14**+**15**, but **20** was not recognized. A higher concentration of dipolarophile was achieved in abs. THF. Dimethyl fumarate (317 mg, 2.2 mmol) was dissolved in THF (1.5 mL) at 65°C (bath) with magnetic stirring. After adding **7** (452 mg, 2.0 mmol), the N_2 elimination was monitored by gas burette (3 h). ^{1}H NMR analysis in $CDCl_3$ with *sym*-$C_2H_2Cl_2$ indicated **20** (36%), **14** (51%), and **15** (7%). Excess of dimethyl fumarate (156 mg) crystallized from methanol at 5°C. CC (CH_2Cl_2) of the mother liquor gave **14**+**15** (198 mg); **20** (228 mg, 33%) was eluted with CH_2Cl_2/MeOH (97:3), mp 69–71°C (MeOH). IR (KBr): ν 1163 cm^{-1} s, 1213s, 1321s (C–O); 1734s, 1737s (C═O, ester), 1778s (C═O, ketone). ^{1}H NMR (400 MHz): δ 1.04, 1.30, 1.38, 1.40, 1.49, 1.56 (6s, 6Me), 3.42, 3.97 (AX, *J*=12.5 Hz, 3′-H, 4′-H), 3.65, 3.74 (2s, 2MeO). ^{13}C NMR (100 MHz, DEPT): δ 19.3, 20.9, 27.8, 28.2, 28.8, 30.4 (6Me), 47.9 (C-5′), 51.9, 52.1 (2MeO), 54.0, 62.2 (C-3′, C-4′), 63.8, 64.2, 64.7 (C-2, C-4, C-2′), 170.9, 171.7 (2C═O, ester), 218.7 (C═O, ketone). MS (35°C); *m/z* (%): 342 (0.2, M^+), 311 (5.3, $[M-MeO]^+$, ^{13}C 0.92/0.90, $^{13}C_2+^{34}S$ 0.31/0.31), 272 (100, $[M-C_4H_6O]^+$, ^{13}C 14.5/14.4, $^{13}C+^{34}S$ 5.4/5.7), 240 (26, $[272-MeOH]^+$, $C_{12}H_{16}O_3S^+$, ^{13}C 3.8/3.9, $^{13}C_2+^{34}S$ 1.4/1.4), 213 (15, $[272-CO_2Me]^+$), 212 (55, $[272-HCO_2Me]^+$, 197 (40, $[212-Me]^+$, ^{13}C 4.4/4.8), 171 (12), 165 (17, $[197-MeOH]^+$, $C_9H_9OS^+$), 153 (37, $[212-CO_2Me]^+$, $C_9H_{13}S^+$ fits (isopropylio-dimethylthiophene), 139 (11), 59 (9, $MeOC{\equiv}O^+$), 41 (11); additional criterion for assignment: $\Delta m/z$ 28, 14, or 0 in comparison with MS of diethyl ester **21**. Anal. calcd for $C_{17}H_{26}O_5S$ (342.44): C 59.62, H 7.65; found: C 59.42, H 7.86.

5.1.4. Diethyl ester 21. Thiadiazoline **7** (2.00 mmol) was dissolved in freshly distilled diethyl fumarate (1.50 mL, 1.58 g, 9.2 mmol) by stirring. After the reaction (3 h, 65°C), the excess of diethyl fumarate was removed by Kugelrohr distillation at 1 mm, and the ^{1}H NMR analysis (*sym*-$C_2H_2Cl_4$) indicated **21** (79%), **14** (19%), and **15** (3%). CC, as reported for **20**, gave **21** as a viscous oil (454 mg, 61%), which crystallized from ethanol at −78°C, mp 71–73°C. IR (KBr): ν 1028 cm^{-1} m, 1178s, 1257s, br., 1313m (C–O), 1730vs (C═O, ester), 1780s (C═O, ketone). ^{1}H NMR (400 MHz): δ 1.07, 1.31, 1.38, 1.40, 1.51, 1.57 (6s, 6Me), 1.24, 1.29 (2t, 2*Me*CH_2), 3.39, 3.95 (AX, *J*=12.7 Hz, 3′-H, 4′-H), 4.00–4.27 (m, 2AA′X_3, 2Me*CH*$_2$O). ^{13}C NMR (100 MHz, DEPT): δ 13.5, 14.3 (2*Me*CH_2), 19.4, 20.9, 27.9, 28.4, 28.8, 30.6 (6Me), 47.7 (C-5′), 54.2, 62.1 (C-3′, C-4′),

60.8, 61.7 (2Me*C*H_2O), 63.7, 64.2, 64.6 (C-2, C-4, C-2′), 170.5, 171.2 (2 C═O, ester), 218.8 (C═O, ketone). MS (35°C); *m/z* (%): 370 (0.4, M^+), 325 (13, $[M-EtO]^+$, ^{13}C 2.4/2.5), 300 (100, $[M-C_4H_6O]^+$, ^{13}C 17/16, $^{13}C_2+^{34}S$ 5.8/5.9), 254 (41, $[300-EtOH]^+$), ^{13}C 6.0/7.0, 227 (21, $[300-CO_2Et]$, 226 (83, $[300-HCO_2Et]^+$), 211 (50, [226−Me], $C_{11}H_{15}O_2S^+$, ^{13}C 6.1/6.5, $^{13}C+^{34}S$ 2.6/2.8), 165 (24, $[211-EtOH]^+$), 153 (60), 139 (29), 41 (14). Anal. calcd for $C_{19}H_{30}O_5S$ (370.50): C 61.59, H 8.16, S 8.66; found: C 61.72, H 8.09, S.

5.1.5. 2,2,4,4,5′,5′-Hexamethyl-1-oxospiro[cyclobutane-3,2′-thiolane]-3′,4′-*trans*-dicarbonitrile (20). Thiadiazoline **7** (2.00 mmol) and fumaronitrile (2.2 mmol) in toluene (4 mL) were reacted for 6 h in the 60°C-bath. The ^1H NMR analysis (80 MHz) was based on the AB of 3′-H and 4′-H and indicated 70% of **20**. Two crystallizations from pentane/CH_2Cl_2 furnished **20** (173 mg, 31%) as glistening platelets, mp 139–140°C. IR (KBr): ν 1024 cm^{-1} m, 1126m, 1251m, 1373m, 1387m, 1456m, br.; 1782 (C═O), 2246w (C≡N). ^1H NMR (80 MHz): δ 1.35 (s, 2Me), 1.50, 1.60, 1.63, 1.67 (4s, 4Me), 3.30, 3.77 (2d, J=8.8 Hz, 4′-H, 3′-H). MS (60°); *m/z* (%): 276 (0.3, M^+), 261 (1, $[M-Me]^+$), 233 (1.5), 206 (100, $[M-C_4H_6O]^+$), 191 (14, $[206-Me]^+$), 179 (16, $[206-HCN]^+$), 164 (7), 126 (10), 81 (7), 70 (17, $C_4H_6O^+$), 42 (17), 41 (29, $allyl^+$). Anal. calcd for $C_{15}H_{20}N_2OS$ (276.39): C 65.18, H 7.29, N 10.14, S 11.60; found: C 65.17, H 7.32, N 10.05, S 11.70.

5.2. Dimethyl 3′,4′-dicyano-2,2,4,4,5′,5′-hexamethyl-1-oxospiro[cyclobutane-3,2′-thiolane]-3′,4′-*trans*-dicarboxylate (23) and *cis*-isomer 24

5.2.1. Reaction of 8 with dimethyl 2,3-dicyanofumarate (27). Thiadiazoline **7** (1.00 mmol) and **27** (1.20 mmol) in $CDCl_3$ (2 mL) were heated at 80°C for 1 h in a sealed tube. The ^1H NMR analysis showed that the cyclopropane **31** (59%) and thione **12** (50%) were the major products, accompanied by the *trans*-thiolane **23** (about 20%) and thiirane **15** (9%). The resolution of the 80 MHz spectrum was insufficient for the detection of the *cis*-isomers **32** and **24** (see Section 5.2.6). The mixture of **31** and **23** could not be separated by fractional crystallization. PLC on neutral alumina (pentane/CH_2Cl_2 4:1) afforded **23** (15%) as colorless crystals, mp 213–214°C (ethanol), from a zone with R_f 0.3. The NMR spectrum of **31** was identical with that of an independently synthesized sample (see Section 5.2.7).

5.2.2. Data of *trans*-thiolane 23. IR (KBr): ν 929 cm^{-1} m, 1014m; 1076m, 1174m, 1250+1267s, br. (C–O); 1437m, 1465m; 1748s, br. (C═O, ester), 1791s (C═O, ketone), 2253vw (C≡N). ^1H NMR (360 MHz): δ 1.37, 1.52, 1.66, 1.75, 1.85, 1.91 (6s, 6Me), 3.95, 3.96 (2s, 2MeO). MS (100°C); *m/z* (%): 392 (<0.1, M^+), 333 (0.7, $[M-CO_2Me]^+$), 322 (100, $[M-C_4H_6O]^+$), 286 (6), 222 (13), 219 (13), 183 (15), 178 (10), 70 (22, $C_4H_6O^+$), 59 (27, $MeOC{\equiv}O^+$), 41 (29, $allyl^+$). Anal. calcd for $C_{19}H_{24}N_2O_5S$ (392.46): C 58.14, H 6.16, N 7.14, S 8.17; found: C 58.07, H 6.17, N 7.08, S 8.19.

5.2.3. Stability of 23. Thiolane **23** (50 mg) in $CDCl_3$ (0.5 mL) was sealed in a NMR tube. The ^1H NMR spectrum showed no change after heating at 150°C for 220 h.

5.2.4. Reaction of 8 with dimethyl 2,3-dicyanomaleate (28). The ^1H NMR analysis (80 MHz) indicated the *cis*-cyclopropane **32** (59%), *cis*-thiolane **24** (25%), and *trans*-thiolane **23** (~7%). PLC on alumina (pentane/CH_2Cl_2 3:1) allowed the isolation of **24**; recrystallization from methanol and from CH_2Cl_2/hexane furnished **24**, mp 153–155°C. A broad zone near the starting line suggested that **32** did not survive the PLC.

5.2.5. Data of *cis*-thiolane 24. IR (KBr): ν 931 cm^{-1} m, 1058m; 1172m, 1223+1251s, br. (C–O); 1438+1467m, br.; 1759s (C═O, ester), 1788 (C═O, ketone), 2233w (C≡N). ^1H NMR (360 MHz): δ 1.10, 1.53, 1.61, 1.66, 1.94, 2.02 (6s, 6Me), 3.94, 3.96 (2s, 2MeO). Anal. calcd for $C_{19}H_{24}N_2O_5S$ (392.46): C 58.14, H 6.16, N 7.14, S 8.17; found: C 58.09, H 6.10, N 7.10, S 8.24.

5.2.6. Steric course of cycloaddition and cyclopropane formation. The experiments A and B of Table 2 were carried out in 7.6 mM H_2SO_4 in $CDCl_3$ at 80°C, and experiment C in $CDCl_3$ without acid. The ^1H NMR spectra (360 MHz) of the product mixtures covered 22 Me singlets in the expanded section of δ 1.0–2.1, and their machine integrals were compared with that of dibenzyl (δ 2.92), which served as weight standard. Another expanded section recorded the 8 MeO singlets at δ 3.85–4.05. The general problem of comparing large and small ^1H NMR integrals was accentuated here by numerous partial overlaps; also the ^{13}C satellites of large signals are an irritation. Of course, the ^1H NMR spectra of the pure products were known.

Any concentration measurement was based on several signals, and too high integrals due to overlap were eliminated. Integrals of isolated signals usually agree within ±5% (relative). Nevertheless, high precision cannot be claimed.

The procedure is described for the reaction of **7** with **28** in acidic medium (B of Table 1). Freshly recrystallized **7**

Table 2. Reactions of thiadiazoline **7** with dimethyl 2,3-dicyanofumarate (**27**) and dimethyl 2,3-dicyanomaleate (**28**) in 7.6 mM H_2SO_4 in $CDCl_3$ at 80°C (experiment C without H_2SO_4); percent yield by ^1H NMR analysis (360 MHz)

	A (**27**)	B (**28**)	C (**28**)	Signals of analysis (δ)
trans-Thiolane **23**	27	3	4	1.85, 1.92, 3.95
cis-Thiolane **24**	11	21	23	1.10, 1.61, 1.66, 1.94, 2.02
trans-Cyclopropane **31**	56	5	4	1.64, 3.93
cis-Cyclopropane **32**	4	66	59	1.56, 1.73, 3.86
Thiirane **14**	1	3	4	1.16, 1.71
Thione **12**	[a]	66	[a]	1.36

[a] Not integrated.

(24.05 mg, 106.3 μmol) and **28** (39.90 mg, 205.3 μmol, free of **27**) in 300 μL of 7.6 mM H_2SO_4 in $CDCl_3$ were heated in a sealed tube in a 80°C bath for 25 min. After cooling of the red solution to −78°C, the tube was carefully opened (N_2 pressure), and dibenzyl (9.40 mg, 51.6 μmol) in 600 μL of $CDCl_3$ was added. Most of the signals of the 360 MHz ^{1}H NMR spectrum, but not all of those listed in Table 1, could be used in the analysis of experiment B; e.g. the integrals of s at δ 1.66, 1.94, and 2.02 corresponded to 21.2, 22.6, and 20.6 μmol of *cis*-thiolane **24**. The ester signals of **24** at δ 3.94 and 3.96 were disturbed by overlap. Unconsumed thiadiazoline **7** (3%) was recognized by the 6H-signals at δ 1.24 and 1.27, and the yields in Table 1 are based on consumed **7** (103.1 μmol). Among the MeO signals, the big one at δ 3.97 integrated for 109 μmol of excess **28** (calcd 105 μmol). The occurrence of only 0.9 μmol of 2,3-dicyanofumarate (**27**) showed the efficiency of the protection by acid. The amounts of the cyclopropane derivatives **31** (5%) and **32** (66%) allowed to expect 1 equiv. (71%) of thione **12**. The integral of the 12H-singlet at δ 1.36 indicated 68 μmol (66%) of **12**.

5.2.7. Dimethyl 1,2-dicyano-3,3-dimethylcyclopropane-1,2-*trans*-dicarboxylate (31).[25] The solution of **27** (217 mg, 1.12 mmol) in abs. THF (20 mL) at 0°C was treated with 1 equiv. of 2-diazopropane[26] in ether. The red color disappeared in 1.5 h, and N_2 evolution took place on warming to room temperature. After 1 h the solvent was removed, and **31** (184 mg, 70%), mp 184°C, crystallized from methanol (2 mL). ^{1}H NMR (360 MHz): δ 1.64 (s, 2Me), 3.93 (s, 2MeO). Anal. calcd for $C_{11}H_{12}N_2O_4$ (236.22): C 55.93, H 5.12, N 11.86; found: C 55.91, H 5.22, N 11.68.

5.2.8. Dimethyl 1,2-dicyano-3,3-dimethylcyclopropane-1,2-*cis*-dicarboxylate (32). Analogously prepared from **28**. After PLC (ether/pentane 2:3), colorless needles (40%), mp 90–92°C, were obtained from ether/pentane. IR (KBr): ν 1107 cm^{-1} m, 1160m, 1241m, 1263s, 1287s (C–O), 1440m; 1752s, 1759s (C=O), 2250w. ^{1}H NMR (360 MHz): δ 1.56, 1.73 (2s, 2Me), 3.86 (s, MeO). MS (40°C); *m/z* (%): 236 (0.1, M^+), 221 (1, $[M-Me]^+$), 205 (15, $[M-MeO]^+$), 177 (100, $[M-CO_2Me]^+$), 145 (13, $[177-MeOH]^+$), 133 (7), 117 (5, $[177-HCO_2Me]^+$), 92 (9), 73 (9), 59 (9, CO_2Me^+), 42 (13). Anal. calcd for $C_{11}H_{12}N_2O_4$ (236.22): C 55.93, H 5.12, N 11.86; found: C 55.95, H 5.12, N 11.98.

5.2.9. 2,2,4,4,5′,5′-Hexamethyl-1-oxospiro[cyclobutane-3,2′-(1,3,4)-thiadiazolidine]-3′,4′-dicarboxylic *N*-phenylimide (42). 4-Phenyl-1,2,4-triazoline-2,5-dione (2.2 mmol) and **7** (2.00 mmol) in toluene (5 mL) were heated for 6 h at 60°C. The ^{1}H NMR analysis showed **42** (61%, s δ 1.92) and 21% of thione **12** (s δ 1.36, 12H). An unknown product displayed 4s (Me) at 1.20, 1.22, 1.70, 2.30. PLC (CH_2Cl_2/EtOH 9:1) provided **42** as a colorless oil (450 mg), which crystallized from pentane (285 mg, 38%), mp 136–139°C. IR (KBr): ν 762 cm^{-1} m, 1132m, 1294m, 1408s; 1499m, 1600w (Ph ring vibr.); 1718s, 1769m (C=O, diacylimide), 1788s (C=O, ketone). ^{1}H NMR (80 MHz): δ 1.42, 1.45, 1.92 (3s, 3×2Me), 7.15–7.45 (m, Ph). MS (70°C); *m/z* (%): 373 (0.2, M^+], 303 (17, $[M^+-C_4H_6O]^+$, ^{13}C 2.9/2.7; $^{13}C_2+^{34}S$ 0.99/0.82), 290 (11, $C_{15}H_{18}N_2O_3S^+$, probably $[M-$isopropenyl isocyanate$]^+$, ^{13}C 1.81/1.76, $^{13}C_2+^{34}S$ 0.62/0.58), 218 (100, $C_{11}H_{12}N_3O_2^+$, probably **43**, ^{13}C 12/13), 198 (81, $C_{11}H_{18}OS^+$. **14**$^+$, ^{13}C 9.9/8.3, $^{13}C_2+^{34}S$ 4.1/3.9), 170 (10), 156 (13, $C_8H_{12}OS^+$, **12**$^+$, ^{13}C 1.2/1.1, $^{13}C_2+^{34}S$ 0.64/0.69), 119 (61, $PhNCO^+$), 96 (16, $C_7H_{12}^+$), 91 (16, $C_7H_7^+$), 85 (12), 71 (22), 70 (9, $Me_2C=C=O^+$), 41 (17, allyl$^+$). Anal. calcd for $C_{19}H_{23}N_3O_3S$ (373.46): C 61.10, H 6.21, N 11.25, S 8.59; found: C 61.35, H 6.14, N 11.11, S 8.68.

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References

1. Huisgen, R.; Mloston, G.; Giera, H.; Langhals, E. *Tetrahedron* **2002**, *58*, 507.
2. Huisgen, R.; Mloston, G.; Langhals, E. *Helv. Chim. Acta* **2001**, *84*, 1805.
3. Matrix isolation technique at 10 K suggested the presence of **1**, but the photo process leading from the thiadiazoline to **1** is more complex: Mloston, G.; Romanski, J.; Schmidt, C.; Reisenauer, H. P.; Maier, G. *Chem. Ber.* **1994**, *127*, 2527.
4. Huisgen, R.; Li, X.; Giera, H.; Langhals, E. *Helv. Chim. Acta* **2001**, *84*, 981.
5. Mloston, G.; Huisgen, R.; Huber, H.; Stephenson, D. S. *J. Heterocycl. Chem.* **1999**, *36*, 959.
6. Huisgen, R.; Penelle, J.; Mloston, G.; Buyle Padias, A.; Hall Jr., H. K. *J. Am. Chem. Soc.* **1992**, *114*, 266.
7. Huisgen, R.; Temme, R. *Eur. J. Org. Chem.* **1998**, 387.
8. Review:Sustmann, R. *Pure Appl. Chem.* **1974**, *40*, 569.
9. Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301. Houk, K. N. *Top. Curr. Chem.* **1979**, *79*, 2.
10. Turro, N. J.; Neckers, D. C.; Leermakers, P. A.; Seldner, P.; D'Angelo, P. *J. Am. Chem.Soc.* **1965**, *87*, 4097. Weiss, S. D.; Gagosian, R. B.; Turro, N. *J. Org. Mass Spectrosc.* **1970**, *3*, 145.
11. Audier, H.; Conia, J.-M.; Fétizon, M.; Goré, J. *Bull. Soc. Chim. Fr.* **1967**, 787.
12. Huisgen, R.; Schug, R. *J. Am. Chem. Soc.* **1976**, *98*, 7819.
13. Bartlett, P. D.; Porter, N. A. *J. Am. Chem. Soc.* **1968**, *90*, 5317.
14. Dervan, P. B.; Uyehara, T.; Santilli, D. S. *J. Am. Chem. Soc.* **1979**, *101*, 2069. Dervan, P. B.; Santilli, D. S. *J. Am. Chem. Soc.* **1980**, *102*, 3863.
15. Cram, D. J.; Ratajczak, A. *J. Am. Chem. Soc.* **1968**, *90*, 2198.
16. Reviews: Mackenzie, K. In *The Chemistry of Hydrazo, Azo, and Azoxy Groups*; Patai, S., Ed.; Wiley: New York, 1975; pp. 354–374; Part 1. (b) Bergman, R. G. Diradicals: A Case

Study of Trimethylenes Part 1. In *Free Radicals*; Kochi, J. K., Ed.; Wiley-Interscience: New York, 1973; pp. 191–237.
17. Clarke, T. C.; Wendling, L. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1977**, *99*, 2740.
18. Corey, E. J.; Chaikovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.
19. Johnson, A. W.; LaCount, R. B. *J. Am. Chem. Soc.* **1961**, *83*, 417.
20. Agami, C.; Prevost, C. *Bull. Soc. Chim. Fr.* **1967**, 2299. Johnson, C. R.; Haake, M.; Schroeck, C. W. *J. Am. Chem. Soc.* **1970**, *92*, 6594.
21. Corey, E. J.; Jautelat, M. *J. Am. Chem. Soc.* **1967**, *89*, 3912.
22. Zimmerman, H. E.; Baum, A. A. *J. Am. Chem. Soc.* **1971**, *93*, 3646. Zimmerman, H. E.; Factor, R. E. *J. Am. Chem. Soc.* **1980**, *102*, 3538.
23. Tang, C. S. F.; Rapoport, H. *J. Org. Chem.* **1973**, *38*, 2806.
24. Stephenson, D. S. In *Encyclopedia of Nuclear Magnetic Resonance*; Grant, T. M., Harris, R. K., Eds.; Wiley: New York, 1996; pp. 816–821.
25. Experiment by Rapp J., University of Munich, 1988.
26. Andrews, S. D.; Day, A. C.; Raymond, P.; Whiting, H. C. *Org. Synth.* **1970**, *50*, 27.