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STEREOSELECTIVE 1,3-DIPOLAR CYCLOADDITION OF AN AZOMETHINE YLIDE WITH A CHIRAL 1,3-THIAZOLE-5(4*H*)-THIONE

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(Dedicated to Professor James P. Kutney on the occasion of his 70th birthday)

Abstract – The reaction of *cis*-1-methyl-2,3-diphenylaziridine (**2**) with racemic 4-benzyl-4-methyl-2-phenyl-1,3-thiazole-5(4*H*)-thione (*rac*-**1b**) in toluene at 100-105°C gave a single spirocyclic [2+3] cycloadduct (*rac*-**5**). Its structure and relative configuration was established by X-Ray crystallography. Starting with enantiomerically pure (*R*)-**1b** and (*S*)-**1b**, the enantiomers (4*R*,5*R*,7*S*,9*R*)-**5** and (4*S*,5*S*,7*R*,9*S*)-**5**, respectively, were formed in a regio- and stereoselective 1,3-dipolar cycloaddition of the *in situ* generated (*E*,*Z*)-configured *N*-methyl-1,3-diphenylazomethine ylide (**4**).

INTRODUCTION

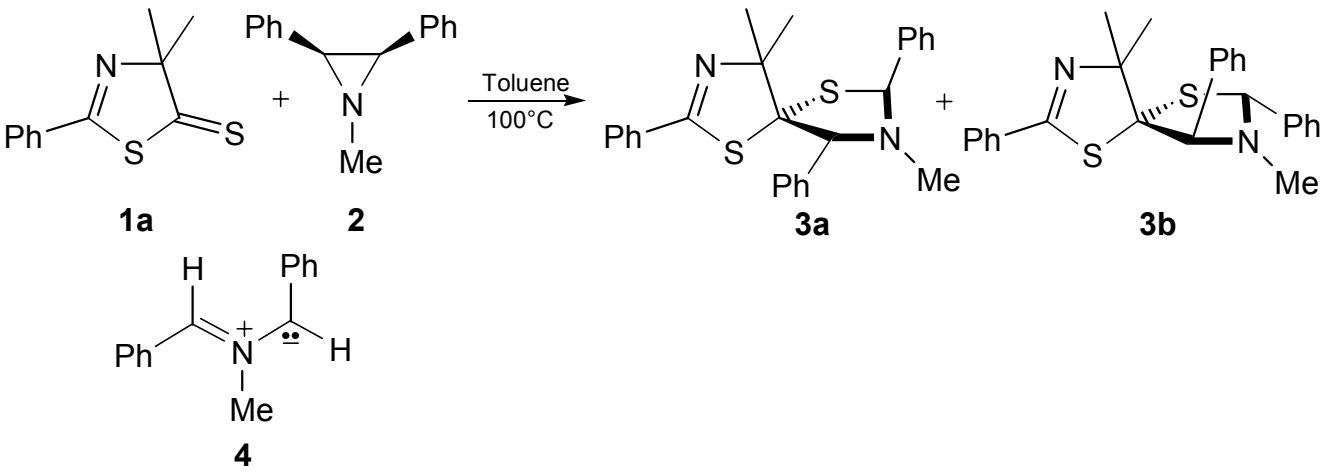
A well-known and frequently used method for the preparation of five-membered nitrogen heterocycles is the [2+3] cycloaddition of nitrogen-centered 1,3-dipoles. Among them, azomethine ylides take up a special place as they were used in the classical experiments of *Huisgen* and coworkers to elaborate the mechanism and sterical course of 1,3-dipolar cycloadditions (*cf.* ref.[2-3]). Since then, the synthetic potential of this reaction in heterocyclic

chemistry has been demonstrated in a large number of papers.[4-15] A convenient method for the generation of non-stabilized azomethine ylides is the stereoselective thermal ring opening of appropriate aziridines.[4,5,16-19] According to the rules of the conservation of orbital symmetry (Woodward-Hoffmann rules[20]), the thermal electrocyclic ring opening occurs in a conrotatory manner, *i.e. cis*-2,3-disubstituted aziridines lead to (*E*,*Z*)-configured azomethine ylides whereas the *trans*-isomers give (*E*,*E*)-configured 1,3-dipoles. Together with the stereoselective 1,3-dipolar cycloaddition of these reactive intermediates and the broad variability of the usable dipolarophiles, azomethine ylide chemistry is recognized as a very attractive tool for the stereoselective synthesis of heterocyclic compounds.[21]

In contrast to 1,3-dipolar cycloadditions of azomethine ylides with olefins or acetylenes leading to pyrrolidine and dihydropyrrol derivatives, analogous reactions with thiocarbonyl compounds as dipolarophiles are rarely described. Although first examples with carbon disulfide and phenyl isothiocyanate have been reported by *Huisgen et al*. already in 1963,[24] only a few reactions with non-cumulated C=S compounds have been published in the last 15 years.[25-29] The attractiveness of this 1,3-thiazolidine synthesis is shown by the elegant studies of *Gallagher* and coworkers towards the preparation of penam and penem skeletons.[30]

As our research interest has been focused on the reactivity of the C=S group of thiocarbonyl and related compounds, we also carried out reactions with azomethine ylides.[22,23,31,32] Besides thioketones, 1,3-thiazol-5(4*H*)-thiones of type (**1**) were used as dipolarophiles.[33] Recently, we reported on 1,3-dipolar cycloadditions of azomethine ylides, which were thermally generated from aziridines.[22,31] For example, the reaction of *cis*-*N*-methyl-2,3-diphenylaziridine (**2**) with 4,4-dimethyl-2-phenyl-1,3-thiazole-5-(4*H*)-thione (**1a**) at 100°C led to a 5:1 mixture of the cycloadducts (**3a**) and (**3b**)[31] (*Scheme 1*). In both cases, the two phenyl groups of the new

Scheme 1



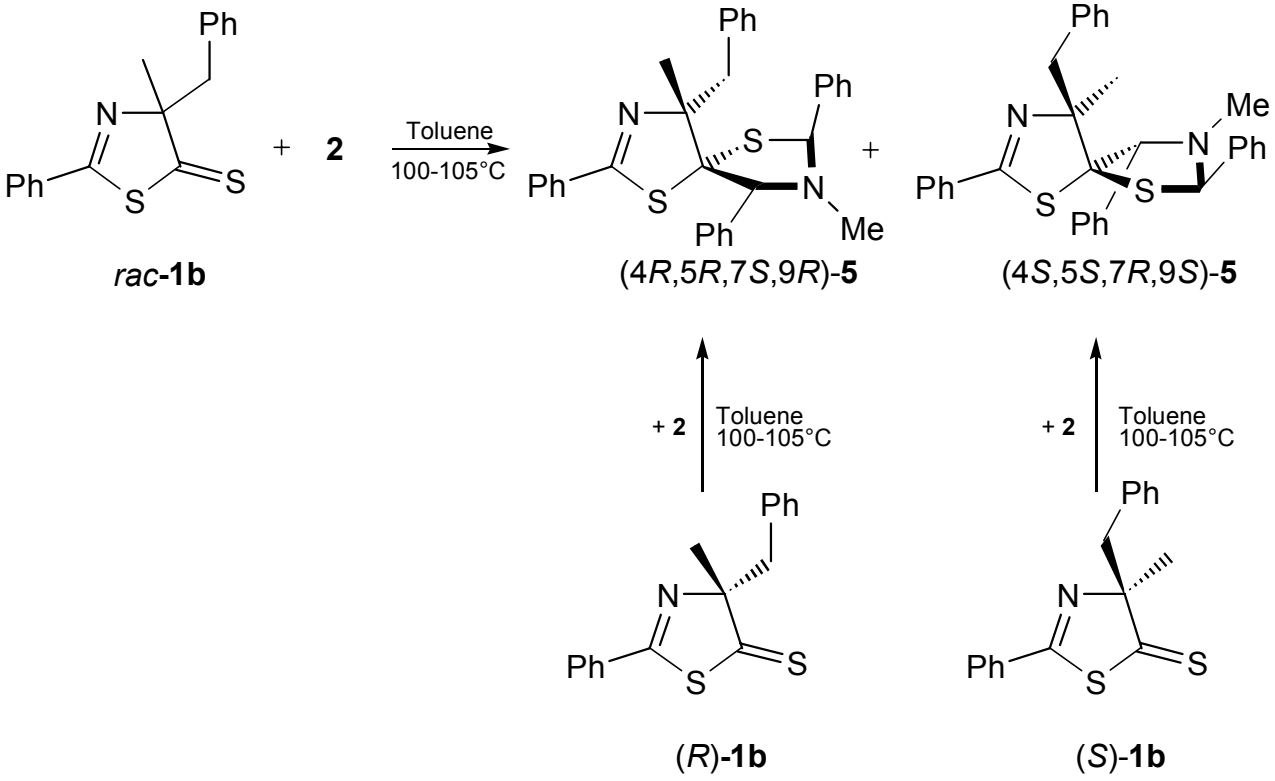
1,3-thiazolidine ring have the *trans*-relationship, *i.e*. the (*E*,*Z*)-configured azomethine ylide (**4**) is the actual intermediate. The major product (**3a**) is the sterically less hindered one.

In the present paper, we describe the results of the reaction of **2** with the unsymmetrically substituted 4-benzyl-4-methyl-2-phenyl-1,3-thiazole-5(4*H*)-thione (**1b**).[32,34] The aim of the study was to get more insight into the stereochemical course of this cycloaddition.

RESULTS AND DISCUSSION

A solution of racemic 1,3-thiazole-5(4*H*)-thione (*rac*-**1b**)[35] and 1.1 equivalent of aziridine (**2**) in toluene was heated to 100-105°C for 24 h. After this time, the characteristic orange color of **1b** has disappeared and the mixture remained pale yellow. After usual workup, preparative TLC (SiO_2, hexane/ethyl acetate 20:1) gave a single cycloadduct in 49% yield as a colorless solid.[36] All spectral data were in accordance with the structure of the expected product (*rac*-**5**), present as a racemic mixture (*Scheme 2*).

Scheme 2



Crystallisation of *rac*-**5** from 2-propanol/methanol yielded colorless crystals suitable for an X-Ray crystal structure determination. The molecular structure is shown in *Figure 1*. The two phenyl groups of the saturated five-membered ring have the *trans*-relationship; the benzyl group

and the phenyl group at the C-atom neighboring the spiro-C atom are located on opposite sides of the thiazolidine ring, *i.e.*, the sterically less hindered isomer has been formed. Since the space group is centrosymmetric, the crystals are racemic. There are two independent molecules in the asymmetric unit which are of the same stereoisomer and have virtually identical conformations. The most significant difference between the conformations of the two molecules is a small twist in the orientation of the phenyl substituent adjacent to the S-atom of the saturated ring by about 15°. In both molecules the saturated five-membered ring has a half-chair conformation twisted on C(3)-N(4),[38] while the other five-membered ring has an envelope conformation with the spiro-C atom, C(2), as the envelope flap.

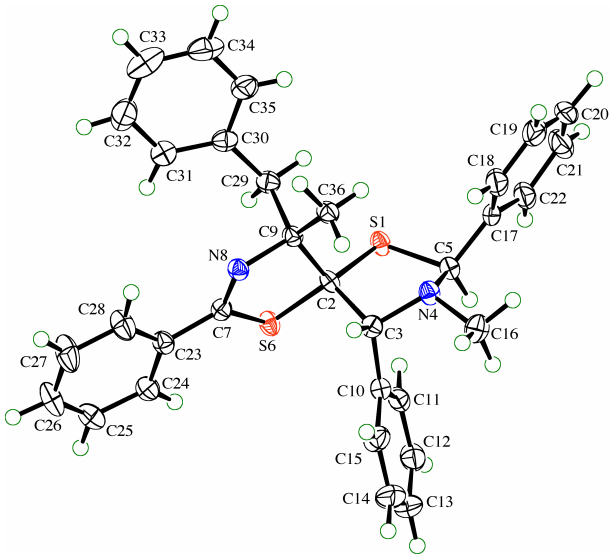
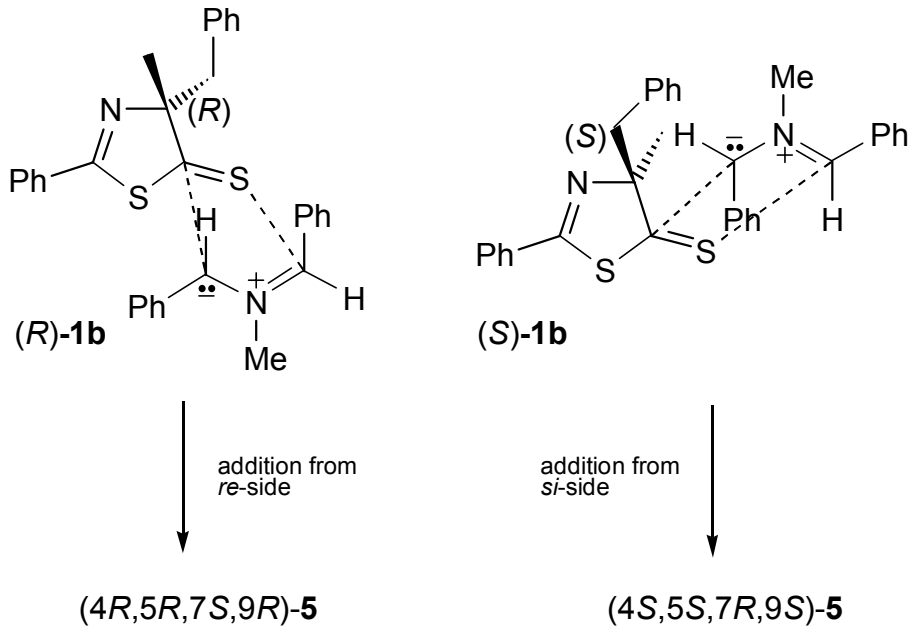


Figure 1. ORTEP plot[37] of the molecular structure of one of the two symmetry-independent molecules of *rac*-**5** (displacement ellipsoids with 50% probability, arbitrary numbering of the atoms)

Analogous reactions were carried out with **2** and the enantiomerically pure 1,3-thiazole-5(4*H*)-thiones ((*R*)-**1b**) and ((*S*)-**1b**),[39] respectively. In these cases, two equivalents of aziridine (**2**) were used, and the mixtures were heated to 100-105°C for 4 days. Even then, the starting material (**1b**) has not been completely consumed. The remaining starting material was separated by means of column chromatography (SiO_2, hexane/ethyl acetate 10:1), and the more polar fraction was purified by preparative TLC. In each experiment, a single optically active product was obtained in 34% and 31% yields, respectively. Based on IR, NMR, and MS spectral data, which in both cases were identical with those of *rac*-**5** (*vide supra*), the cycloadducts are the enantiomers (4*R*,5*R*,7*S*,9*R*)-**5** and (4*S*,5*S*,7*R*,9*S*)-**5**, respectively (*Scheme 2*).

The stereoselective formation of the [2+3] cycloadducts can be rationalized by a concerted 1,3-dipolar cycloaddition of the (*E*,*Z*)-configured azomethine ylide (**4**) from the sterically less hindered side of the 1,3-thiazole-5(4*H*)-thione*, i.e. anti* to the benzyl group at C(4). The result is a *re*-side attack in the case of (*R*)-**1b**, whereas the addition occurs from the *si*-side in the case of (*S*)-**1b** (*Scheme 3*). Furthermore, in both transition states the azomethine ylide (**4**) is oriented in such a manner that sterical interaction of the phenyl group with the substituents at C(4) of the 1,3-thiazol-5(4H)-thione (**1b**) is avoided, *i.e*. the phenyl group neighboring the spiro-C atom is *trans* oriented with respect to the disubstituted C-atom of the other ring.

Scheme 3



In conclusion, the described results show that the thermally generated (*E*,*Z*)-azomethine ylide (**4**) undergoes a highly stereoselective 1,3-dipolar cycloaddition with the C=S group of the chiral 4,4-disubstituted 1,3-thiazole-5(4*H*)-thione (**1b**).

EXPERIMENTAL

General remarks. If not otherwise stated, IR spectra were recorded on a *Perkin-Elmer-781* instrument (KBr, cm^{-1}), ^{1}H-NMR and ^{13}C-NMR spectra on a *Bruker-AC-300* or *ARX-300* instrument ($CDCl_3$, 300 and 75.5 MHz, respectively, δ in ppm, *J* in Hz), and MS spectra on a *Finnigan-MAT-90* (70 eV, CI with NH_3) or *Finnigan-SSQ-700* spectrometer (ESI). Column chromatography (CC) and prep. TLC on silica gel (SiO_2). Toluene was dried over sodium.

Reaction of cis-N-*methyl-2,3-diphenylaziridine* (**2**) *with 4-benzyl-4-methyl-2-phenyl-1,3-thiazole-5(4*H*)-thione* (**1b**). A solution of 149 mg (0.50 mmol) of *rac*-**1b**[35] and 107 mg (0.55 mmol) of aziridine (**2**) in 1-1.5 mL of toluene was heated to 100-105°C for 1-4 days. Then, toluene was distilled off and the crude product was purified by CC using hexane/AcOEt followed by preparative TLC (hexane/AcOEt 20:1).

4-Benzyl-4,8-dimethyl-2,7,9-triphenyl-1,6-dithia-3,8-diazaspiro[4.4]non-2-ene (*rac*-**5**). Yield: 49% (124 mg). Colorless solid. ^{1}H-NMR: 1.58 (*s*, Me-C(4)), 1.86 (*s*, Me-N), 3.20, 3.76 (*AB*, *J* = 13.0, $PhCH_2$), 4.89, 5.16 (2*s*, H-C(7), H-C(9)), 7.15-7.34 (*m*, 12 arom. H), 7.37-7.53 (*m*, 8 arom. H). ^{13}C-NMR: 19.7 (*q*, *Me*-C(4)), 35.9 (*q*, Me-N), 44.3 (*t*, $PhCH_2$), 72.0, 76.4 (2*d*, C(7), C(9)), 83.6, 87.1 (2*s*, C(4), C(5)), 126.5, 127.5, 128.0, 128.1, 128.2, 128.3, 128.5, 128.6, 129.5, 131.0, 131.4 (11*d*, 20 arom. CH), 133.4, 137.2, 138.4, 139.1 (4*s*, 4 arom. C), 164.0 (*s*, C=N). IR: 3062*s*, 3028*s*, 2945*s*, 2847*s*, 2798*s*, 1954*w*, 1809*w*, 1702*m*, 1597*s*, 1575*s*, 1493*s*, 1452*s*, 1377*m*, 1313*s*, 1282*m*, 1242*s*, 1217*s*, 1176*m*, 1142*s* 1114*s*, 1083*m*, 1074*m*, 1028*m*, 1009*m*, 987*w*, 958*s*, 932*s*, 878*m*, 834*m*, 794*m*, 759*s*, 701*s*, 667*m.* ESI-MS: 530 (8), 529 (30, $[M+Na]^+$), 513 (40), 507 (18, $[M+1]^+$), 506 (25, $M^{+\bullet}$), 505 (65), 490 (35), 489 (100). Suitable crystals for an X-Ray crystal structure determination were grown from *i*-PrOH/MeOH.

*(4*R*,5*R*,7*S*,9*R*)-4-Benzyl-4,8-dimethyl-2,7,9-triphenyl-1,6-dithia-3,8-diazaspiro[4.4]non-2-ene* (*(4*R*,5*R*,7*S*,9*R*)*-**5**). Yield: 34% (86 mg). Pale yellow oil. $[\alpha]_D^{22}$ = +5.2° (c = 2.95, $CHCl_3$).

*(4*S*,5*S*,7*R*,9*S*)-4-Benzyl-4,8-dimethyl-2,7,9-triphenyl-1,6-dithia-3,8-diazaspiro[4.4]non-2-ene* (*(4*S*,5*S*,7*R*,9*S*)*-**5**). Yield: 31% (78 mg). Pale yellow oil. $[\alpha]_D^{22}$ = -2.4° (c = 2.20, $CHCl_3$).

Crystal Structure Determination of rac-**5** (see *Table 1* and *Figure 1*).[40] The intensities were collected on a *Rigaku AFC5R* diffractometer in the $\omega/2\theta$-scan mode using graphite-monochromated MoK_α radiation (λ = 0.71069 Å) and a 12 kW rotating anode generator. The intensities were corrected for *Lorentz* and polarization effects, but not for absorption. Data collection and refinement parameters are listed in *Table 1*, a view of the molecule is shown in *Figure 1*. The structure was solved by direct methods using SIR92,[41] which revealed the positions of all non-H atoms. There are two independent molecules in the asymmetric unit. The atomic coordinates of the two molecules were tested carefully for a relationship from a higher symmetry space group using the program PLATON,[42] but none could be found. The non-H

atoms were refined anisotropically. All of the H-atoms were located in a difference electron density map and their positions were allowed to refine together with individual isotropic displacement parameters. The structure was refined on *F* using full-matrix least-squares procedures, which minimized the function $\Sigma w(|F_o| - |F_c|)^2$. Neutral atom scattering factors for non-H atoms were taken from ref.[43a], and the scattering factors for H-atoms were taken from ref.[44] Anomalous dispersion effects were included in F_{calc};[45] the values for *ƒ*' and *ƒ*'' were those of ref.[43b] The values of the mass attenuation coefficients are those of ref.[43c] All calculations were performed using the TEXSAN crystallographic software package.[46]

ACKNOWLEDGMENTS

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Table 1. Crystallographic Data for Compound (*rac*-**5**)

Crystallised from		*i*-PrOH/MeOH
Empirical formula		$C_{32}H_{30}N_2S_2$
Formula weight [g mol^{-1}]		506.72
Crystal color, habit		colorless, prism
Crystal dimensions [mm]		0.20 x 0.25 x 0.45
Temperature [K]		173 (1)
Crystal system		triclinic
Space group		$P\bar{1}$
Z		4 (2 formula units per asymmetric unit)
Reflections for cell determination		25
2θ range for cell determination [°]		34-39
Unit cell parameters	*a* [Å]	14.558 (3)
	b [Å]	15.338 (3)
	c [Å]	12.130 (3)
	α [°]	92.52 (2)
	β [°]	100.02 (2)
	γ [°]	90.62 (2)
	V [Å^3]	2664 (1)
D_x [g cm^{-3}]		1.263
μ(MoK_α) [mm^{-1}]		0.224
$2\theta_{(max)}$ [°]		55
Total reflections measured		12705
Symmetry independent reflect.		12221
Reflections used [$I>2\sigma(I)$]		7660
Parameters refined		889
Final *R*, *wR*		0.0502, 0.0411
Weights: *p* in $w = [\sigma^2(F_o) + (pF_o)^2]^{-1}$		0.005
Goodness of fit		1.547
Final Δ_{max}/σ		0.0009
$\Delta\rho$ (max; min) [e Å^{-3}]		0.42; -0.32
$\sigma(d_{(C-C)})$ [Å]		0.004-0.006

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40. Crystallographic data (excluding structure factors) for structure (*rac*-**5**) reported in this paper has been deposited with the *Cambridge Crystallographic Data Center* as supplementary publications No. CCDC-171090. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
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