# Fused Isothiazole *S*-Oxide Systems from Cycloaddition Reactions of *N*-Benzylisothiazol-3-amine 1-Oxide

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The racemic *N*-benzylisothiazol-3-amine 1-oxide (**2**) was demonstrated to be an efficient partner in *Diels – Alder* reactions (*Schemes 2 – 4*) and a good dipolarophile in 1,3-dipolar cycloaddition reactions with nitrile oxides (*Scheme 5*). Polycyclic isothiazole *S*-oxides with different substitution patterns were obtained from **2** in good yield and in a fully regioselective way. Improved diastereoselection was observed performing the *Diels – Alder* or 1,3-dipolar cycloaddition reactions in H_2O.

Introduction. – Recently, we described the synthesis of chiral racemic isothiazol-amine *S*-oxides **A**, starting from the corresponding isothiazolamines **1**, and some preliminary studies on their reactivity toward S-nucleophiles which demonstrated the ability of the sulfoxide moiety to direct the addition affording the corresponding 5-(aryl- and alkylthio) derivatives in a fully diastereoselective way (*Scheme 1*) [1]. The availability of these new *S*-oxides **A** prompted us to continue our research on their reactivity. In particular, we concentrated our attention on the aptitude of this system to act as an effective reaction partner in cycloaddition reactions which would allow the preparation of fused isothiazole *S*-oxide derivatives of both chemical and pharmaco-logical interest. In fact, cycloaddition reactions appeared to be a very versatile tool to obtain new classes of isothiazoles or fused isothiazole systems or new or known heterocycles by the transformation of the primary cycloadducts similarly to the transformations described for the corresponding *S,S*-dioxides [2 – 6]. The exploitation of the sulfoxide system could be considered of large interest due to the significant stereodifferentiating ability of the sulfinyl function [7]. Moreover, taking into account the general interest in environmental contamination, efforts were devoted in this work to develop cycloaddition processes with reduced environmental impact.

Scheme 1
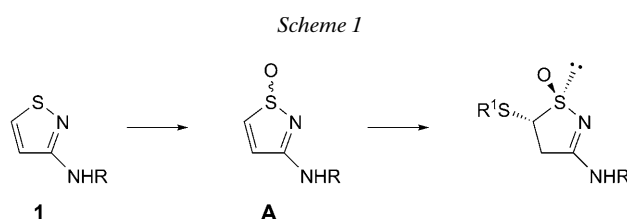
Results and Discussion. – *Diels – Alder Reactions.* The $[4\pi + 2\pi]$-cycloaddition reactions between the racemic dienophile *N*-benzylisothiazol-3-amine 1-oxide (**2**) and several dienes were performed at different temperatures mediated or not by *Lewis* acids, and in both cases, the influence of the application of microwaves and ultrasound was examined. For this study, 2,3-dimethylbuta-1,3-diene (**3**), cyclopenta-1,3-diene (**4**), and cyclohexa-1,3-diene (**5**) were chosen as dienes. Compound **2** did not undergo cycloaddition reaction with **3** in different solvents both at room temperature and under reflux (*Table 1, Entries 1* and *2*) but afforded the cycloaddition products **6** when the diene was used as the solvent at reflux temperature (80°; *Entry 3*) or in a sealed tube at 70° (*Entry 4; Scheme 2*). The application of ultrasound irradiation did not substantially improve the total yield (*Entry 5*), while application of microwave irradiation resulted in an improvement of the reaction both in terms of yield and of reaction time (*Entry 6*). Two cycloadducts, 'syn'- and 'anti'-**6**[1]), were always obtained in a different ratio depending on the reaction conditions (*Scheme 2, Table 1*). The two diastereoisomers were easily separated by column chromatography, and their structures were tentatively assigned on the basis of ^{1}H- and ^{13}C-NMR analyses. The minor, firstly eluted compound is characterized by two *s* at δ 1.66 and 1.73 (Me−C(5) and Me−C(6), resp.) and two *m* centered at δ 2.25 and 2.61 (CH$_2$(4) and CH$_2$(7)). Moreover, two *m* centered at δ 2.98 and 3.29 are attributed to H−C(3a) and H−C(7a), respectively. A sharp *d* appears at δ 4.61, easily associated with PhCH_2. The other, major diastereoisomer is characterized by two *s* at δ 1.62 and 1.68 (Me−C(5) and Me−C(6), resp.) and two *m* centered at δ 2.06 and 2.38 (CH$_2$(4) and CH$_2$(7)). The other two *m* centered at δ 3.26 and 3.73 are

Scheme 2
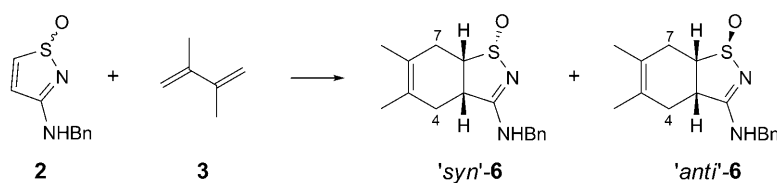
Table 1. Diels – Alder *Reaction between Dienophile* **2** *and 2,3-Dimethylbuta-1,3-diene* (**3**)

Entry	Reaction conditions[a])	Time [h]	Total yield [%] of **6**	'syn'/'anti' Ratio
1	25°, CH$_2$Cl$_2$ or toluene	96	–	–
2	reflux, CH$_2$Cl$_2$ or toluene	96	–	–
3	80°, neat	10	53	1 : 10
4	70°, neat, sealed tube	15	78	1 : 3.5
5	50°, neat, US	35	69	1 : 9
6	80°, neat, MW	5	82	1 : 4

[a]) US = Ultrasound, MW = microwaves.

[1]   The terms 'syn'/'anti' mean that the unshared electron pair of the S-atom is on the same/opposite side than the H-atoms at the fusion site, with respect to the mean plane of the isothiazol moiety. See also below, *Fig. 1*.

associated with H−C(7a) and H−C(3a), respectively, while the PhCH_2 H-atoms appear as a *dq* at *δ* 4.61. The main differences in the ^{1}H-NMR spectra of the two diastereoisomers concerned the multiplicity of the PhCH_2 H-atoms and the chemical shifts of H−C(7a) and H−C(3a). These differences could be ascribed to the deshielding effect exerted by the unshared electron pair of the *S*-atom on the adjacent H-atoms which – as a consequence – exhibit an evident downfield shift [8a,b]. This was confirmed by the ^{13}C-NMR spectra of the two isomers, which exhibit a remarkable difference of the chemical shifts of C(7a) (*δ* 66.6 for the major and *δ* 56.9 for minor isomer). On this basis, we assigned the structure of '*anti*'-**6** to the major isomer and the structure of '*syn*'-**6** to the minor cycloaddition product.

The cycloaddition of **2** and cyclopenta-1,3-diene (**4**) was also studied under different reaction conditions with the objective of achieving high yields and stereo-selectivity. The reaction gave good yields under all conditions tested (*Scheme 3*, *Table 2*) affording a mixture of two diastereoisomers **7**. Different to the results observed with diene **3**, ultrasounds and, in particular, microwaves dramatically accelerate the reaction rate in the case of **4**.
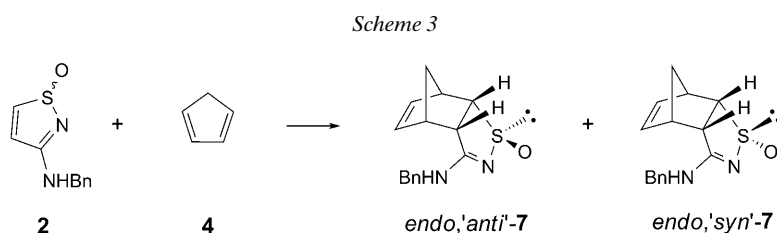
Scheme 3

Table 2. Diels – Alder *Reaction between Dienophile* **2** *and 1,3-Dienes* **4** (→ **7**) *and* **5** (→ **8**)

| Diene	Reaction conditions (neat)[a]	Time	Total yield [%] of **7** or **8**	endo,'syn'/endo,'anti' Ratio
4	reflux	5 h	99	1 : 3
4	50°, US	4 h	99	1 : 3
4	80°, sealed tube	4 h	99	1 : 3
4	80°, MW	10 min	99	1 : 3
4	25°, ZnI$_2$	1 h	98	1 : 3
4	50°, ZnI$_2$, US	20 min	85	1 : 3
4	25°, [Sc(OTf)$_3$]	1 h	99	1 : 3
4	50°, [Sc(OTf)$_3$], US	20 min	99	1 : 3
5	80°, sealed tube	2.5 h	99	1 : 1
5	50°, US	11 h	99	1 : 1

[a]) US = Ultrasound, MW = microwaves.

It is well known that *Diels – Alder* reactions can be catalyzed with *Lewis* acids [9]. For this reason, we selected two catalysts, *i.e.*, ZnI$_2$ and [Sc(OTf)$_3$], and the cycloaddition reactions were repeated at room temperature and under ultrasound irradiation at 50°. In both cases, high yields were obtained in a very short reaction time but without any differences in terms of the diastereoisomer ratio. The two

diastereoisomers **7** were easily separated by column chromatography, and the *endo* or *exo* configuration was determined by considering the chemical shifts in the ¹H-NMR spectra and confirmed by performing NOE experiments and by comparison with analogous adducts [3]. The preferred formation of the *endo* isomer is not unexpected according to the 'endo rule' of *Diels – Alder* reactions [10]. Analogously, the formation of the '*anti*'-isomer as the major compound is easily explained because it derives from the less-hindered approach with respect to the sulfoxide group (*Fig. 1*).

endo,'syn' approach   *endo,'anti'* approach
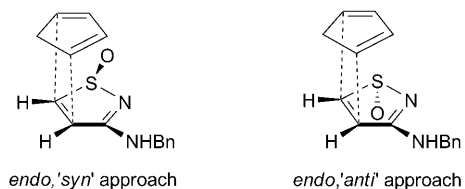
Fig. 1. *Cycloaddition of* **2** *and cyclopenta-1,3-diene* (**4**): endo,'syn' *and* endo,'anti' *approach*

The cycloaddition of **2** and cyclohexa-1,3-diene (**5**) was then studied, and also in this case, two diastereoisomers were obtained in nearly quantitative yield operating with the diene as the solvent both at 80° in a sealed tube and at 50° with ultrasound irradiation (*Scheme 4*, *Table 2*). The *endo*,'syn' and *endo*,'anti' configuration of the two adducts **8** was determined by comparison with the adducts *endo*,'syn'-**7** and *endo*,'anti'-**7** and confirmed by performing NMR experiments. In this case, the two adducts *endo*,'syn'-**8** and *endo*,'anti'-**8** were obtained in a 1:1 ratio.

Scheme 4

2   **5**   *endo,'anti'*-**8**   *endo,'syn'*-**8**
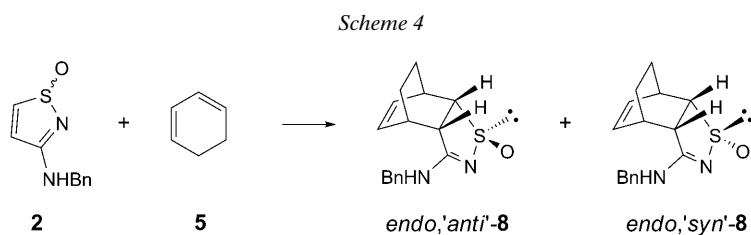
1,3-Dipolar Cycloaddition Reactions. The *N*-benzylisothiazol-3-amine 1-oxide (**2**) was then treated with nitrile oxides **9a** and **9b** in THF at room temperature. The reaction occurred highly regioselectively at the C(4)=C(5) bond of **2** producing the corresponding cycloadducts **10a/10′a** and **10b/10′b**, respectively, as the sole products in very good yields, confirming the good reactivity of **2** as a dipolarophile in 1,3-dipolar cycloaddition reactions (*Scheme 5*). Performing the reaction in a microwave oven, neither the ratio of the diastereoisomers nor the yields was substantially improved. The structure of the cycloadducts was assigned by virtue of analytical and spectroscopic data, and the regiochemistry was established by performing NOESY experiments. The main differences between the two diastereoisomers **10a,b** (($3aR^*,4R^*,6aR^*$)) and **10′a,b** (($3aR^*,4S^*,6aR^*$)), which were obtained in a 1:1 ratio, concerned the chemical shift of H−C(6a) and H−C(3a). Previous NMR studies of both an empirical and theoretical nature with a variety of different molecular systems containing a sulfoxide moiety have led several groups to propose that, qualitatively at least, the screening

environment around the sulfoxide bond approximates that of the acetylenic C≡C bond [11]. Taking into consideration these and other previously cited studies [8a,b], we reasoned that in the isomers **10′**, where H−C(3a) lies on the same side as the S−O bond, this H-atom should resonate upfield with respect to H−C(3a) of the isomers **10**. Accordingly, we tentatively assigned the structure of **10′a** ((3aR^*,4S^*,6aR^*)) to the cycloadduct whose H−C(3a) resonates at δ 4.90 and that of **10a** ((3aR^*,4R^*,6aR^*)) to the cycloadduct whose H−C(3a) signal is shifted downfield (δ 5.58). Interestingly, also a marked chemical-shift difference of C(6a) and C(3a) between the two diastereoisomers is evident in the ^{13}C-NMR spectra (*Table 3*).
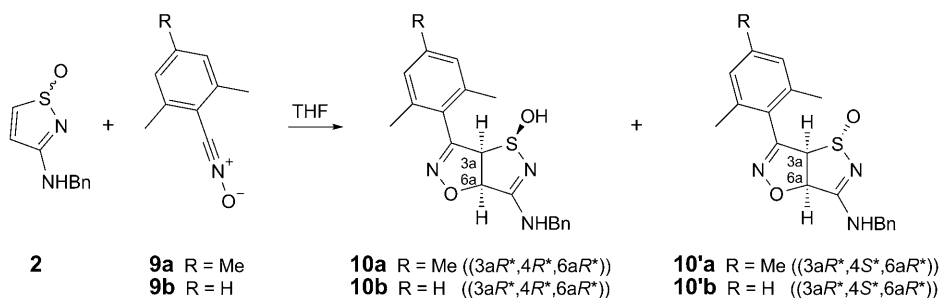
Scheme 5

| | **9a** R = Me | **10a** R = Me ((3aR^*,4R^*,6aR^*)) | **10′a** R = Me ((3aR^*,4S^*,6aR^*)) |
| **2** | **9b** R = H | **10b** R = H ((3aR^*,4R^*,6aR^*)) | **10′b** R = H ((3aR^*,4S^*,6aR^*)) |

Table 3. *Selected Experimental and Calculated ^{13}C-NMR Chemical Shifts for C(3a) and C(6a) of* **10b** *and* **10′b**. δ *in ppm.*

| | **10b** ((3aR^*,4R^*,6aR^*)) | | **10′b** ((3aR^*,4S^*,6aR^*)) | |
	δ (exper.)	δ (calc.)	δ (exper.)	δ (calc.)
C(3a)	4.239	76.004	84.5574	86.701
C(6a)	88.556	87.389	86.974	86.297

This ^{13}C-NMR chemical-shift difference of C(6a) and C(3a) between **10** and **10′** allowed us to take advantage of the quantum-chemical calculation of ^{13}C-NMR chemical shifts of structures **10b** ((3aR^*,4R^*,6aR^*)) and **10′b** ((3aR^*,4S^*,6aR^*)) (the **b** structures being considered for simplicity, as R = H) to assign the absolute configuration to diastereoisomers **10a,b** and **10′a,b** by comparison of the theoretical and experimental NMR spectra. Indeed, the very good correlation between the experimental δ(C) and those computed by *ab initio* and DFT methods (see below) allows the use of this strategy for both the investigation of dynamical equilibria in solution [12], including highly accurate conformational analysis [13], and configuration assignments in complex organic systems [14]. Starting geometries for compounds **10b** and **10′b** were obtained by an extensive conformational search at the molecular-mechanics level with the MMFF 94s forcefield as implemented in the MOE software package [15]. The most stable conformations were reoptimized with the Gaussian03 software package [16] at the B3LYP/6-31G** level [17] and confirmed as minima by a vibrational analysis (no imaginary frequencies were observed). It is well known that an NMR calculation requires quite extended basis sets to achieve accurate results and, for this reason,

absolute shieldings were computed on the previously optimized geometries by the GIAO method [18] at the B3LYP/TZVP level [19]. The TZVP is a triple split valence basis set which, in a previous work, provided an excellent accuracy in a reasonable computational time [12]. Absolute shieldings of C-atoms were then converted into chemical shifts by subtracting their value from the mean absolute shieldings of C-atoms computed for Me_4Si at the same level of theory. It is quite well known that including the solvent effect in ^{13}C-NMR calculations notably increases the computation time without producing an appreciable increase in accuracy and, for this reason, the solvent effects were considered by using the chemical shift computed for DMSO as a second internal reference.

Optimized geometries for isomers **10b** and **10′b** are represented in *Fig. 2*, while the comparison of their computed ^{13}C-NMR chemical shifts with the experimentally observed ones is depicted in *Fig. 3*. Critical calculated and experimental ^{13}C-NMR chemical shifts are reported in *Table 3* (see above). The data given in *Fig. 3* show an excellent concordance between computed and experimental δ(C) and, together with the detailed values reported in *Table 3* for C(3a) and C(6a), allow the unequivocal attribution of the relative configuration of **10b** and **10′b** ((4*R**,6a*R**,3a*R*) and (4*S**,6a*R**,3a*R*), resp.).
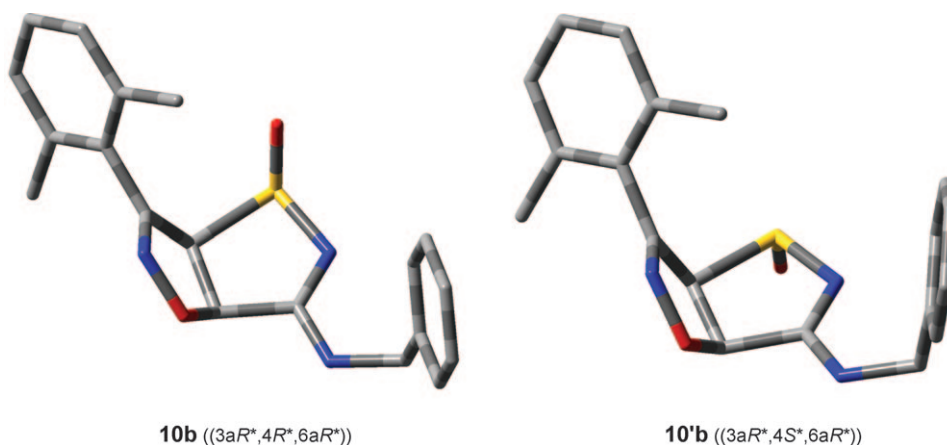

10b ((3a*R**,4*R**,6a*R*))   **10′b** ((3a*R**,4*S**,6a*R*))

Fig. 2. *Optimized geometries of diastereoisomers* **10b** ((*3a*R*,4*R*,6a*R**)) *and* **10′b** ((*3a*R*,4*S*,6a*R**))

Cycloaddition Reactions of **2** *in* H_2O. As mentioned in the *Introduction*, in the last years, we noticed a growing interest in environmental contamination, and considerable efforts are devoted to the development of benign methodologies. One of the most important objectives of 'Green Chemistry' is the elimination of toxic organic solvents in chemical processes, which can be achieved by different approaches, *e.g.*, by the use of 'solvent free' methodologies or of benign solvents such as the nontoxic H_2O. The increased focus on H_2O in synthetic organic chemistry during the past few decades has resulted in a large number of reactions that can now be performed successfully in an aqueous medium. Among them, also notoriously solvent-insensitive reactions such as the 1,3-dipolar cycloaddition and *Diels–Alder* reaction can benefit dramatically from an aqueous medium. With this in mind, we repeated the cycloaddition reactions of
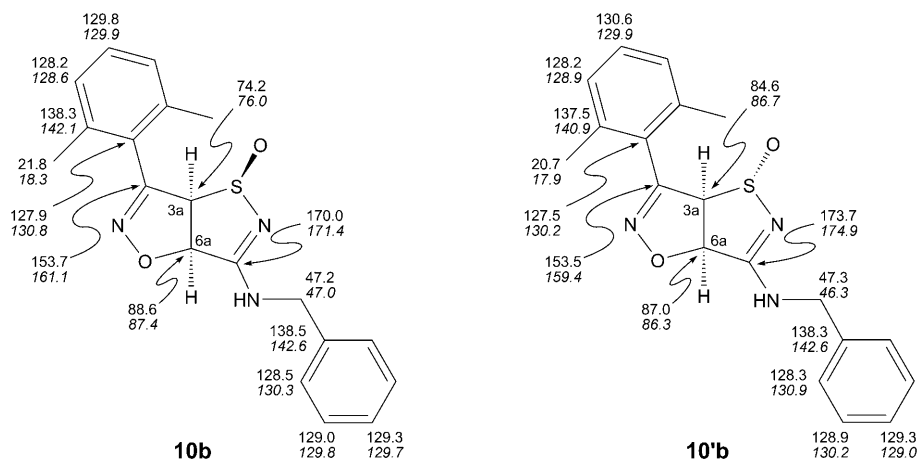
Fig. 3. *Experimental* (roman) *and calculated* (italic) ^{13}*C-NMR chemical shifts*

isothiazolamine *S*-oxide **2** in H$_2$O and obtained interesting results. First of all, despite the poor solubility of the reactants in H$_2$O, compound **2** successfully reacted both with dienes **3** and **4** and with nitrile oxides **9a,b** affording the corresponding cycloadducts in very good yields (*Table 4*). The main feature of the reactions in H$_2$O concerned the ratio of the formed diastereoisomers. In the case of butadiene **3**, a completely selective reaction occurred at 25° with [Sc(OTf)$_3$], affording the '*anti*'-**6** cycloadduct as the sole product (*Entry 1*). Also in the reaction between **2** and **4**, a larger amount of the *endo*,'*anti*'-**7** isomer was formed (see *Entry 5* for best conditions). The same holds for 1,3-dipolar cyloaddition reactions, the cycloadducts **10** and **10′** being formed in a 4:1 ratio in favor of the (3a*R**,4*S**,6a*R**)-isomers **10′a,b** in H$_2$O (*Entries 8* and *9*) instead of 1:1 (neat).

Table 4. *Cycloaddition Reactions in H$_2$O,* i.e.*, of Isoxazolamine* S*-Oxide* **2** *with Diene* **3** *(→ **6***) or* **4** *(→ **7***)* *or with Dipole* **9a** *(→ **10a/10′a***) or* **9b** *(→ **10b/10′b***)*

Entry	Diene or dipole	Reaction conditions (neat)[a]	Time	Total yield [%] of **6**, **7**, or **10/10′**	Ratio of diastereoisomers
1	**3**	25°, [Sc(OTf)$_3$]	48 h	80	0:1 ('*syn*'/'*anti*')
2	**3**	50°, [Sc(OTf)$_3$], US	30 h	84	1:6.5 ('*syn*'/'*anti*')
3	**4**	25°, [Sc(OTf)$_3$]	27 h	99	1:8 (*endo*,'*syn*'/*endo*,'*anti*')
4	**4**	50°, US	48 h	99	1:8 (*endo*,'*syn*'/*endo*,'*anti*')
5	**4**	50°, [Sc(OTf)$_3$], US	20 h	99	1:10 (*endo*,'*syn*'/*endo*,'*anti*')
6	**4**	80°, MW	10 min	99	1:4 (*endo*,'*syn*'/*endo*,'*anti*')
7	**4**	80°, [Sc(OTf)$_3$], MW	10 min	99	1:6.5 (*endo*,'*syn*'/*endo*,'*anti*')
8	**9a**	50°, US	48 h	60	1:4 (**10a/10′a**)
9	**9b**	50°, US	48 h	65	1:4 (**10b/10′b**)

[a]) US = Ultrasound, MW = microwaves.

Conclusions. – In summary, these studies demonstrate the good reactivity of isothiazolamine S-oxide **2** both as dienophile in *Diels – Alder* reactions and as dipolarophile in a 1,3-dipolar cycloaddition reaction and the possibility to synthesize polycyclic isothiazole S-oxides with a different substitution pattern in high yields. Moreover, we can conclude that H_2O is a good solvent to perform cycloaddition reactions with isothiazole S-oxides and that in this solvent, the sulfoxide group demonstrates an observable efficacy in the diastereoselection of the reaction. This effect is particularly evident in the reaction of **2** with the buta-1,3-diene **3** where a complete selectivity is achieved. This study opens the way to further studies on the synthesis and exploitation of chiral enantiomerically pure isothiazole S-oxides in the field of asymmetric cycloaddition reactions. Some preliminary experiments have already been performed, and results will be published in due course.

Experimental Part

General. All reagents and solvents were obtained from commercial sources. Cyclopenta-1,3-diene (**4**) was distilled before use. Microwave experiment: *MLS GmbH/Milestone Ltd.* instrument. Column chromatography (CC): silica gel *60* (70 – 230 mesh, ASTM). ^1H- and ^{13}C-NMR Spectra: *Bruker Avance-500* and *Varian Gemini-200* instruments; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. MS: *Finningan MD-800* spectrometer (70 eV); in *m/z* (rel. %).

*Cycloaddition Reactions of **2** and 2,3-Dimethylbuta-1,3-diene* (**3**): *General Procedure.* A mixture of isothiazolamine S-oxide **2** (0.050 g, 0.24 mmol) and **3** (2 ml) was treated under the conditions shown in *Table 1* (TLC and ^1H-NMR monitoring). After evaporation of **3**, the residue was subjected to CC (silica gel, CH_2Cl_2/MeOH 100:0 → 0:100): '*syn*'- and '*anti*'-**6**. For yields, see *Table 1*.

*(1*R*,3a*R*,7a*R*)-3a,4,7,7a-Tetrahydro-5,6-dimethyl-N-(phenylmethyl)-1,2-benzisothiazol-3-amine 1-Oxide* ('*syn*'-**6**): White powder. M.p. 172°. ^1H-NMR ($CDCl_3$): 1.66 (*s*, Me–C(5)); 1.73 (*s*, Me–C(6)); 2.16 – 2.34 (*m*, $H_{'syn'}$–C(4), $H_{'anti'}$–C(4), $H_{'anti'}$–C(7)); 2.56 – 2.65 (*m*, $H_{'syn'}$–C(7)); 2.92 – 3.04 (*m*, H–C(3a)); 3.23 – 3.35 (*m*, H–C(7a)); 4.61 (*d*, *J* = 5.1, PhCH_2); 5.82 (br. *s*, NH); 7.29 – 7.40 (*m*, 5 arom. H). ^{13}C-NMR ($CDCl_3$): 19.0 (*Me*–C(6)); 19.4 (*Me*–C(5)); 26.0 (C(7)); 34.8 (C(4)); 44.7 (C(3a)); 47.1 (PhCH_2); 56.9 (C(7a)); 124.2 (Me–*C*); 125.6 (Me–*C*); 127.7, 128.0, 128.7 (arom. CH); 137.3 (arom. C); 177.9 (C(3)). Anal. calc. for $C_{16}H_{20}N_2OS$ (288.41): C 66.63, H 6.99, N 9.71; found: C 66.72, H 7.02, N 9.57.

*(1*R*,3a*S*,7a*S*)-3a,4,7,7a-Tetrahydro-5,6-dimethyl-N-(phenylmethyl)-1,2-benzisothiazol-3-amine 1-Oxide* ('*anti*'-**6**): White powder. M.p. 134°. ^1H-NMR ($CDCl_3$): 1.62 (*s*, *Me*–C(5)); 1.68 (*s*, *Me*–C(6)); 2.01 – 2.10 (*m*, $H_{'syn'}$–C(4)); 2.32 – 2.44 (*m*, $H_{'anti'}$–C(4), $H_{'syn'}$–C(7), $H_{'anti'}$–C(7)); 3.21 – 3.31 (*m*, H–C(7a)); 3.68 – 3.77 (*m*, H–C(3a)); 4.61 (*dq*, *J* = 5.1, *J* = 14.7, 29.3, PhCH_2); 5.61 (br. *s*, NH); 7.28 – 7.37 (*m*, 5 arom. H). ^{13}C-NMR ($CDCl_3$): 19.4 (*Me*–C(6)); 19.7 (*Me*–C(5)); 28.8 (C(7)); 32.0 (C(4)); 44.2 (C(3a)); 47.7 (PhCH_2); 66.6 (C(7a)); 125.5 (Me–*C*); 126.4 (Me–*C*); 128.3, 128.4, 129.2 (arom. CH); 137.6 (arom. C); 176.4 (C(3)). Anal. calc. for $C_{16}H_{20}N_2OS$ (288.41): C 66.63, H 6.99, N 9.71; found: C 66.92, H 7.12, N 9.43.

*Cycloaddition Reactions of **2** and Cyclopenta-1,3-diene* (**4**): *General Procedure.* A mixture of **2** (0.050 g, 0.24 mmol) and **4** (2 ml) was treated under the conditions shown in *Table 2* (TLC and ^1H-NMR monitoring). After evaporation, the residue was subjected to CC (silica gel CH_2Cl_2/MeOH 100:0 → 0:100): *endo*,'*syn*'- and *endo*,'*anti*'-**7**. For yields, see *Table 2*.

*(1*R*,3a*R*,4*R*,7*S*,7a*R*)-3a,4,7,7a-Tetrahydro-N-(phenylmethyl)-4,7-methano-1,2-benzisothiazol-3-amine 1-Oxide* (*endo*,'*syn*'-**7**): White powder. M.p. 192°. ^1H-NMR($CDCl_3$): 1.51 (*d*, *J* = 8.4, 1 H–C(8)); 1.63 (*d*, *J* = 8.4, 1 H–C(8)); 3.24 (*s*, H–C(4), H–C(7)); 3.70 (*dd*, *J* = 4.4, 8.8, H–C(3a)); 4.15 (*dd*, *J* = 3.7, 8.8, H–C(7a)); 4.49 (*d*, *J* = 5.5, PhCH_2); 5.45 (br. *s*, NH); 5.97 – 6.01 (*m*, H–C(5)); 6.59 – 6.63 (*m*, H–C(6)); 7.29 – 7.38 (*m*, 5 arom. H). ^{13}C-NMR ($CDCl_3$): 45.6 (C(7)); 47.5 (PhCH_2); 47.3 (C(4)); 52.6

(C(8)); 57.6 (C(3a)); 65.8 (C(7a)); 128.0, 128.3, 129.0 (arom. CH); 130.7 (C(5)); 137.4 (C(6)); 137.7 (arom. C); 168.5 (C(3)). Anal. calc. for $C_{15}H_{16}N_2OS$ (272.16): C 66.15, H 5.92, N 10.29; found: C 66.45, H 5.64, N 9.94.

(1R*,3aS*,4S*,7R*,7aS*)-3a,4,7,7a-Tetrahydro-N-(phenylmethyl)-4,7-methano-1,2-benzisothiazol-3-amine 1-Oxide (*endo,'anti'*-**7**): White powder. M.p. 153°. ^{1}H-NMR (CDCl$_3$): 1.50 (*d*, *J* = 8.8, 1 H−C(8)); 1.68 (*d*, *J* = 8.8, 1 H−C(8)); 3.23 (*s*, H−C(7)); 3.35 (*s*, H−C(4)); 3.36 – 3.52 (*m*, H−C(3a)); 3.98 – 4.02 (*m*, H−C(7a)); 4.47 (*dq*, *J* = 5.1, 14.6, 28.2, PhCH_2); 5.89 – 5.94 (*m*, H−C(6)); 6.19 – 6.23 (*m*, H−C(5)); 6.60 – 6.62 (*m*, NH); 7.23 – 7.39 (*m*, 5 arom. H). ^{13}C-NMR (CDCl$_3$): 44.0 (C(4)); 46.0 (C(7)); 47.3 (PhCH_2); 52.9 (C(8)); 56.5 (C(7a)); 76.5 (C(3a)); 127.9, 128.2, 128.9 (arom. CH); 134.8 (C(6)); 135.6 (C(5)); 137.8 (arom. C); 175.2 (C(3)). Anal. calc. for $C_{15}H_{16}N_2OS$ (272.16): C 66.15, H 5.92, N 10.29; found: C 66.37, H 5.69, N 9.97.

Cycloaddition Reactions of **2** *and Cyclohexa-1,3-diene* (**5**): *General Procedure.* A mixture of **2** (0.050 g, 0.24 mmol) and **5** (2 ml) was treated under the conditions shown in *Table 2* (TLC and ^{1}H-NMR monitoring). After evaporation, the residue was subjected to CC (silica gel, CH$_2$Cl$_2$/MeOH 100 : 0 → 0 : 100): *endo,'syn'*- and *endo,'anti'*-**8**. For yields, see *Table 2*.

(1R*,3aR*,4R*,7S*,7aR*)-3a,4,7,7a-Tetrahydro-N-(phenylmethyl)-4,7-ethano-1,2-benzisothiazol-3-amine 1-Oxide (*endo,'syn'*-**8**): White powder. M.p. 207°. ^{1}H-NMR (CDCl$_3$): 1.36 – 1.37 (*m*, 1 H−C(8), 1 H−C(9)); 1.52 – 1.60 (*m*, 1 H−C(8), 1 H−C(9)); 2.96 (*s*, H−C(7)); 3.09 (*s*, H−C(4)); 3.24 (*s*, *J* = 8.6, H−C(3a)); 3.55 (*s*, *J* = 8.6, H−C(7a)); 4.56 (*d*, *J* = 4, PhCH_2); 5.74 (br. *s*, NH); 6.03 – 6.06 (*m*, H−C(5)); 6.44 – 6.46 (*m*, H−C(6)); 7.32 – 7.36 (*m*, 5 arom. H). ^{13}C-NMR (CDCl$_3$): 23.1 (C(8) or C(9)); 24.1 (C(8) or C(9)); 29.1 (C(7)); 33.9 (C(4)); 47.6 (PhCH_2); 54.5 (C(3a)); 63.3 (C(7a)); 127.9, 128.0, 128.2 (arom. CH); 129.0 (C(5)); 135.6 (C(6)); 137.8 (arom. C); 171.8 (C(3)). Anal. calc. for $C_{16}H_{18}N_2OS$ (286.29): C 67.10, H 6.33, N 9.78; found: C 67.25, H 6.15, N 9.52.

(1R*,3aS*,4S*,7R*,7aS*)-3a,4,7,7a-Tetrahydro-N-(phenylmethyl)-4,7-ethano-1,2-benzisothiazol-3-amine 1-Oxide (*endo,'anti'*-**8**): White powder. M.p. 172°. ^{1}H-NMR (CDCl$_3$): 1.32 – 1.37 (*m*, 1 H−C(8), 1 H−C(9)); 1.54 – 1.59 (*m*, 1 H−C(8), 1 H−C(9)); 2.96 (*s*, H−C(4)); 3.09 – 3.12 (*m*, H−C(7a)); 3.26 – 3.29 (*m*, H−C(7)); 3.55 – 3.58 (*m*, H−C(3a)); 4.57 (*dq*, *J* = 5.1, 14.7, 32.6, PhCH_2), 6.03 – 6.10 (*m*, H−C(5)); 6.20 – 6.28 (*m*, NH, H−C(6)); 7.26 – 7.32 (*m*, 5 arom. H). ^{13}C-NMR (CDCl$_3$): 23.5 (C(8) or C(9)); 23.6 (C(8) or C(9)); 30.5 (C(7)); 33.8 (C(4)); 47.6 (PhCH_2); 52.3 (C(3a)); 74.0 (C(7a)); 128.0, 128.1, 129.0 (arom. CH); 132.5 (C(5)); 133.1 (C(6)); 137.7 (arom. C); 175.1 (C(3)). Anal. calc. for $C_{16}H_{18}N_2OS$ (286.29): C 67.10, H 6.33, N 9.78; found: C 67.37, H 6.13, N 9.49.

Cycloaddition Reactions of **2** *and Nitrile Oxides* **9a,b**: *General Procedure.* Compound **2** (0.180 g, 0.87 mmol) was dissolved in THF by gently heating (40 – 50°). The soln. was then allowed to cool to r.t., and **9a** or **9b** (0.87 mmol) was added, and the mixture stirred for *ca.* 20 h (TLC (AcOEt/cyclohexane 3 : 2) monitoring). Sometimes, it was necessary to add an excess of **9a,b** (20%). After evaporation of the solvent, the two diastereoisomers were separated by CC (silica gel, AcOEt/cyclohexane 0 : 100 → 100 : 0) and crystallized from Et$_2$O: **10a/10′a** or **10b/10′b**.

(3aR*,4R*,6aR*)-3-(2,6-Dimethylphenyl)-3a,6a-dihydro-N-(phenylmethyl)isothiazolo[5,4-d]iso-xazol-6-amine 4-Oxide (**10b**): Yield 42%. White powder. M.p. 206°. ^{1}H-NMR (CD$_3$COCD$_3$): 2.46 (*s*, 2 Me); 4.70 (*d*, *J* = 5.9, CH$_2$); 5.62 (*d*, *J* = 9.9, H−C(3a)); 6.06 (*d*, *J* = 9.9, H−C(6a)); 7.07 – 7.47 (*m*, 7 arom. H); 8.22 – 8.26 (*m*, NH). ^{13}C-NMR ((D$_6$)DMSO): 21.8 (Me); 47.2 (CH$_2$); 74.2 (C(3a)); 88.5 (C(6a)); 127.9, 138.4 (arom. C (Bn and Me$_2$C$_6$H$_3$)); 128.2, 128.5, 129.0, 129.3, 129.8 (arom. CH); 138.3 (arom. C (Me$_2$C$_6$H$_3$)); 153.7 (C(3)); 170.0 (C(6)). Anal. calc. for $C_{19}H_{19}N_3O_2S$ (353.40): C 64.57, H 5.42, N 11.89; found: C 64.90, H 5.23, N 11.65.

(3aR*,4S*,6aR*)-3-(2,6-Dimethylphenyl)-3a,6a-dihydro-N-(phenylmethyl)isothiazolo[5,4-d]iso-xazol-6-amine 4-Oxide (**10′b**): Yield 38%. White powder. M.p. 211°. ^{1}H-NMR (CD$_3$COCD$_3$): 2.25 (*s*, 2 Me); 4.74 – 4.76 (*m*, CH$_2$); 4.94 (*d*, *J* = 8.8, H−C(3a)); 6.48 (*d*, *J* = 8.8, H−C(6a)); 7.17 – 7.45 (*m*, 7 arom. H); 8.39 – 8.41 (*m*, NH). ^{13}C-NMR ((D$_6$)DMSO): 20.6 (Me); 47.3 (CH$_2$); 84.5 (C(3a)); 87.0 (C(6a)); 128.2, 128.3, 128.9, 129.3, 130.6 (arom. CH); 127.5, 138.3 (arom. C (Bn and Me$_2$C$_6$H$_3$)); 137.5 (arom. C (Me$_2$C$_6$H$_3$)); 153.5 (C(3)); 173.7 (C(6)). Anal. calc. for $C_{19}H_{19}N_3O_2S$ (353.40): C 64.57, H 5.42, N 11.89; found: C 64.81, H 5.17, N 11.60.

(3aR*,4R*,6aR*)-3a,6a-Dihydro-3-(2,4,6-trimethylphenyl)-N-(phenylmethyl)isothiazolo[5,4-d]iso-xazol-6-amine 4-Oxide (**10a**): Yield 40%. White powder. M.p. 212 – 213°. ^{1}H-NMR (CD$_3$COCD$_3$): 2.25 (*s*,

Me); 2.40 (*s*, 2 Me); 4.65 (*d*, *J* = 5.9, CH$_2$); 5.58 (*d*, *J* = 9.9, H−C(3a)); 6.00 (*d*, *J* = 9.9, H−C(6a)); 6.89 (*s*, 2 arom. H); 7.31 – 7.45 (*m*, 5 arom. H); 8.18 – 8.22 (*m*, NH). ^{13}C-NMR ((D$_6$)DMSO): 21.3, 21.6 (Me); 47.1 (CH$_2$); 74.1 (C(3a)); 88.3 (C(6a)); 124.8 (arom. C); 128.0, 128.3, 129.1, 129.5 (arom. CH); 137.9, 138.3, 138.9 (arom. C); 153.6 (C(3)); 170. 0 (C(6)). Anal. calc. for C$_{20}$H$_{21}$N$_3$O$_2$S (367.46): C 65.37, H 5.76, N 11.44; found: C 65.52, H 5.56, N 11.21.

*(3a*R*,*4*S*,*6a*R*)*-3a,6a-Dihydro-3-(2,4,6-trimethylphenyl)-*N*-(phenylmethyl)isothiazolo[5,4-*d]isoxazol-6-amine 4-Oxide* (**10′a**): Yield 45%. White powder. M.p. 196 – 197°. ^{1}H-NMR (CD$_3$COCD$_3$): 2.18 (*s*, 2 Me); 2.29 (*s*, Me); 4.70 – 4.73 (*m*, CH$_2$); 4.90 (*d*, *J* = 8.4, H−C(3a)); 6.43 (*d*, *J* = 8.4, H−C(6a)); 6.98 (*s*, 2 arom. H); 7.35 – 7.39 (*m*, 5 arom. H); 8.34 – 8.36 (*m*, NH). ^{13}C-NMR ((D$_6$)DMSO): 20.4, 21.4 (Me); 47.1 (CH$_2$); 84.5 (C(3a)); 86.7 (C(6a)); 124.4 (arom. C); 128.0, 128.1, 129.1, 129.4 (arom. CH); 137.2, 138.2, 139.9 (arom. C); 153.3 (C(3)); 173.5 (C(6)). Anal. calc. for C$_{20}$H$_{21}$N$_3$O$_2$S (367.46): C 65.37, H 5.76, N 11.44; found: C 65.63, H 5.49, N 11.17.

Cycloaddition Reactions of **2** *in H$_2$O*. Cycloaddition reaction of **2** with dienes **3** and **4** and nitrile oxides **9a,b** were performed by mixing the reagents (an excess of cyclopentadiene was used) in H$_2$O and applying the conditions described in *Table 4* for the time indicated. Then, the mixture was extracted with AcOEt (4 ×), the org. layer dried (Na$_2$SO$_4$), and the solvent evaporated. The crude compounds were purified as described above.

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