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Regioselectivity of Cycloadditions of Nitrile Oxides and Nitrones to 4-Methylene-tetrahydrothiopyrane

J. Fröhlich[1], L. Fišera[2,*], F. Sauter[1,*], Y. Feng[1], and P. Ertl[3]

[1] Institute of Organic Chemistry, Technical University Vienna, A-1060 Vienna, Austria
[2] Department of Organic Chemistry, Slovak Technical University, SK-81237 Bratislava, Slovakia
[3] Institute of Chemistry, Comenius University, SK-84215 Bratislava, Slovakia

Summary. The cycloaddition of nitrile oxides and nitrones to 4-methylene-tetrahydrothiopyrane proceeds regioselectively under the formation of spiro-substituted isoxazole derivatives **4** and **9**. Semiempirical calculations (AM1) were used to analyze the electronic structure of reactants, energies of products, and activation barriers leading to these products in order to rationalize this exclusive regioselectivity. It was shown that the main factor responsible for the high stereoselectivity of this reaction is not frontier orbital control, but mainly electrostatic and steric interactions. The spiro compounds **4** were cleaved by hydrogenolysis to γ-amino-alcohols **11**, which were recyclized to spiro-oxazines **12** and **13**. **4** and **9** as well as **12** and **13** are derivatives of novel heterocylic systems.

Keywords. 1,3-Dipolar cycloaddition; Nitrile oxides; Nitrones; 4-Methylene-tetrahydrothiopyrane; Spirothiacyclohexane; AM1 calculations.

Regioselektive Cycloadditionen von Nitriloxiden und Nitronen an 4-Methylen-tetrahydrothiopyran

Zusammenfassung. Die Cycloaddition von Nitrilen und Nitriloxiden an 4-Methylen-tetrahydrothiopyran zeigt einen regioselektiven Verlauf unter Bildung der spiro-substituierten Isoxazolderivate **4** und **9**. Die elektronischen Strukturen von Reaktanden, Energien von möglichen Reaktionsprodukten und die Aktivierungsbarrieren der durchgeführten Reaktionen wurden mittels semiempirischer Verfahren (AM1) untersucht, um die beobachteten eindeutigen Regioselektivitäten zu interpretieren. Es zeigte sich, daß dafür nicht ausschließlich Frontorbitalkontrolle, sondern vor allem elektrostatische und sterische Wechselwirkungen verantwortlich sind.

Die Spiroverbindungen **4** wurden in weiterer Folge durch Reduktion zu den entsprechenden γ-Aminoalkoholen **11** gespalten, welche wiederum zu Spiro-oxazinen des Typs **12** und **13** recyclisiert wurden. Die Verbindungen **4** und **9** sind ebenso wie **12** und **13** Derivate von neuen heterocyclischen Grundsystemen.

Introduction

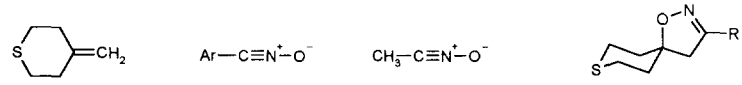
The recent observation of strong herbicidal activity of spirocyclic lactams, coupled with the absence of toxicity to microorganisms [1] and also of the natural occurrence of some spiroisoxazolines (Araplysillins as inhibitors of ATPase [2]) stimulated our interest in the synthesis of related spirocyclic derivatives.

In continuation of our efforts [3–6] to utilize heterocyclic compounds as dipolarophiles in 1,3-dipolar cycloaddition reactions leading to novel spiro-heterocyclic systems, we have recently demonstrated that nitrile oxides and nitrones react regio- and stereoselectively with 1-methyl-4-methylene-piperidine to afford spiro-substituted isoxazole derivatives bearing a piperidine moiety [7]. We now report on cycloaddition reactions of 4-methylene-tetrahydrothiopyrane with nitrile oxides and nitrones as well as on subsequent transformations of the spiro-substituted isoxazoles thus obtained to spiro-substituted 1,3-oxazines possessing a thiacyclohexane moiety, together with quantum mechanical calculations using the AM1 method.

Results and Discussion

Reaction of **1** *with nitrile oxides* **3** *and* **4**

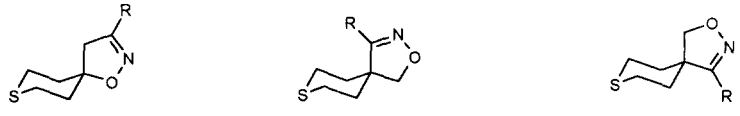
4-Methylene-tetrahydrothiopyrane (**1**) was prepared by reacting 4-thiacyclohexanone with phosphorus ylide [8]. *Ar*-substituted benzenenitrile oxides **2** (where *Ar* is phenyl-, 4-Cl-phenyl-, and 3-NO_2-phenyl) were generated from the corresponding benzaldoximes, N-chlorosuccinimide, and triethylamine [9] in chloroform in the presence of dipolarophile **1**. The formation of the cycloadducts **4a–c** (R = *Ar*) was accompanied by 3,4-diarylfuroxan – the nitrile oxide dimer [10] – as a by-product (Scheme 1). Cycloaddition of **1** with acetonitril oxide (**3**) proceeded analogously to give cycloadduct **4d** (R = CH_3).



1 2 3 4a-c

Scheme 1

Due to the incomplete conversion of starting materials, the cycloadducts **4a–d** were formed in lower yields as compared to those observed in the cycloaddition of nitrile oxides to methylenecycloalkanes possessing a 5-membered ring [3–5]. This can be explained by the well known fact that angular strain in a dipolarophile can effect its reactivity [11]. Stereoisomer **5** and regioisomers **6** and **7** have not been detected in the crude reaction mixture by NMR spectroscopy (Scheme 2).



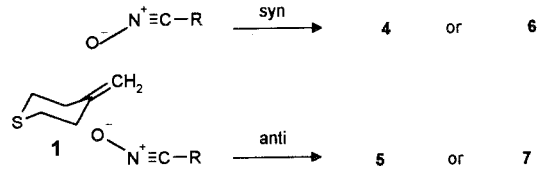
5 6 7

Scheme 2

The regiochemistry in isoxazolines **4a–d** was unequivocally assigned from diagnostic ^1H and ^{13}C NMR data of the isoxazoline ring moiety as well as by the comparison with the cycloadducts derived by cycloaddition to 1-methyl-4-methylene-piperidine [7]. Their C-5 resonances appear at lower field (δ = 83.21–

85.89 ppm) and are about 50 ppm different from those of the other possible regioisomers **6** and **7** [3]. On the other hand, C-4 resonances ($\delta = 45.69$–49.96 ppm) attest to the shielding effect of a spiro-fused thiacyclohexane ring. Moreover, the ^1H NMR spectrum shows the isoxazoline ring H_2-4 protons in the region $\delta = 2.67$–3.14 ppm, which is consistent with an isoxazoline unsubstituted at position 4. If the spiro atom were at position 4 of the isoxazoline ring (representing the possible regioisomers **6** and **7**), the protons at the 5-position would appear at lower field [12].

We have shown that NMR spectra indicate the regiochemistry of the cycloadducts **4a–d** which are formed by the attack of the carbon of the nitrile oxide at the CH_2 terminus of the exocyclic double bond. We also observed similar regioselectivity in the cycloaddition of nitrile oxides to 1-methyl-4-methylene-piperdine [7] as well as to the other methyleneheterocycles [3–5, 13]. From the reaction of **1** and nitrile oxides, four adducts are conceivable: two regioisomers **4** and **6** resulting from *syn* approach of the 1,3-dipole, and two corresponding isomers **5** and **7** from *anti* attack (Scheme 3).



Scheme 3

In order to rationalize the high regioselectivity of the reaction, quantum-chemical calculations were performed. The semiempirical AM1 method [14] was used to analyze the electronic structure of reactants, energies of the four possible products **4a–7a**, and activation barriers of these reactions (a summary of all results concerning energy calculations is presented in Table 2; for comparison, the ΔH_f-values of compounds analogous to **1** and **4a–7a** [7], but with N–Me instead of S, are given in parentheses).

The HOMO of dipolarophile **1**, lying at -8.43 eV, is a lone pair orbital on sulfur, whereas HOMO-1 is a π orbital on the C=C bond with an energy of -10.17 eV. LUMO + 1, lying 0.21 eV higher than LUMO (1.10 eV), is a π^* orbital on the C=C bond (Fig. 1). The frontier orbital energies of dipole **2a** are -9.38 and -0.50 eV, respectively.

According to the energy differences $E_{\pi^* \text{dipolarophile}} - E_{\text{HOMO dipole}} = 10.48$ eV and $E_{\pi \text{ dipolarophile}} - E_{\text{LUMO dipole}} = 9.67$ eV, the reaction is controlled by the LUMO of the

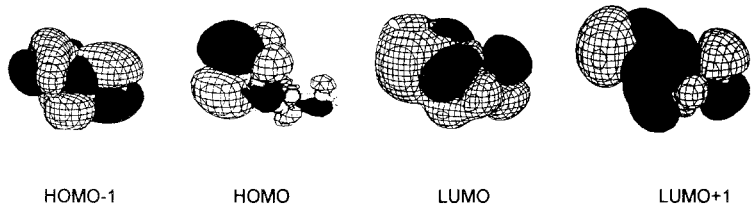


Fig. 1. Frontier orbitals of **1**

dipole. The MO coefficients of this orbital are 0.23 and 0.21 for C and O, whereas the coefficients of the π orbital of the dipolarophile are 0.58 and 0.65 for ring and terminal methylene carbons. Thus, according to FMO theory [15, 16], the predicted structure **4a** is in agreement with the observed and confirmed one, *i.e.* a 5-substituted isoxazoline derivative is formed. The overall values, however, as well as the difference between the carbon- and oxygen-MO coefficients of the dipole, are small and therefore not significant to explain such a high degree of regioselectivity.

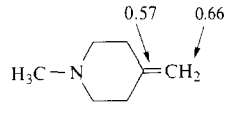
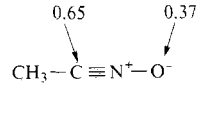
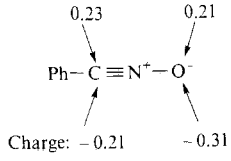
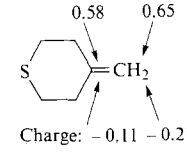
Electrostatic factors may also play a role: the charges at C and O of the dipole are −0.21 and −0.31, respectively, and −0.11 and −0.21 at the ring- and methylenecarbons of the dipolarophile. This, again, favors the formation of the observed regioisomers **4a**.

A summary of all semi-empirically obtained orbital calculations is presented in Table 1, additionally supplemented by data from recently published work on piperidine analogues [7] for comparison.

Analysis of ΔH_f-values (AM1) and MM + minimized energies of compounds **4a**–**7a** (Table 2) did not account for a preference of one specific isomer from a thermodynamic point of view except from the fact that both the nitrogen and sulfur analogues of **6a** exhibited significant higher energies as compared to the other isomers. This observation can be mainly attributed to steric reasons caused by *van der Waals* congestion between the C-aryl moiety and the thiopyrane (or piperidine) ring.

Finally, the analysis of transition states (*TS*) leading to all four possible products **4a**–**7a** was performed. All *TS*s found are concerted ones. No attempts were made to localize biradical *TS*s, which, according to *ab initio* MC SCF analysis of simple model compounds, exhibit values about 18 kcal/mol higher [17]. In agreement with results of FMO analysis, the activation barriers leading to "forbidden" products **6a** and **7a** are higher, whereas the lowest is the barrier leading to product **5a** (16.6 kcal/mol) (Table 2). This may be compared with the reported *ab initio* MC SCF result for the reaction of HCNO with ethylene, exhibiting a barrier of 15.3 kcal/mol [17]. Transition bond lengths in *TS* **4a** are 2.07 Å for the C–C bond and 2.28 Å for the C–O bond. The imaginary frequency of *TS* **4a** is 548 cm^{-1}. The corresponding

Table 1. Summary of orbital energies, orbital coefficients and atom charges (interacting orbitals – due to lowest differences between HOMO/LUMO – are printed in bold)

Coefficient / Orbital	HOMO-1	LUMO	LUMO	HOMO-1
				
LUMO + 1	–	–	–	1.10
LUMO	1.26	**0.94**	**−0.51**	0.89
HOMO	−9.00	−10.12	−9.38	−8.43
HOMO − 1	**−9.76**	–	–	**−10.17**

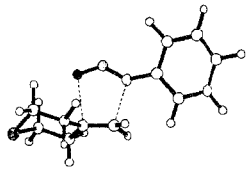


Fig. 2. *TS* **4a**

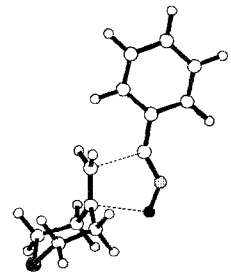


Fig. 3. *TS* **5a**

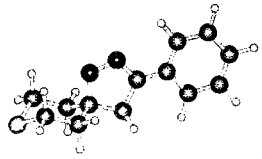


Fig. 4. **4a**

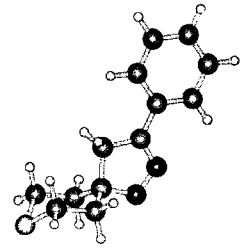


Fig. 5. **5a**

Table 2. Energies of reactants, products, transition states, and activation barriers (data in kcal/mol); $E_{min,MM+}$: MM+ force-field minimized energies; corresponding values of N–Me-analogous compounds are given in parentheses

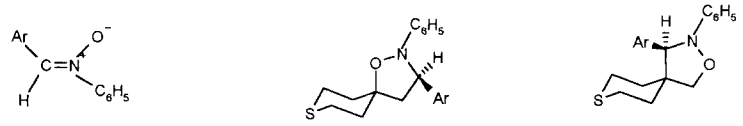
Molecule	ΔH_f [14]	Activation barrier [14]	$E_{min,MM+}$ [20]
1	0.4(8.5)	–	4.1(8.1)
4a	30.6(38.1)	–	8.3(12.5)
5a	30.5(38.3)	–	9.0(13.2)
6a	35.1(42.3)	–	22.5(26.2)
7a	34.1(38.1)	–	13.9(18.0)
TS **4a**	84.6	17.2	–
TS **5a**	84.0	16.6	–
TS **6a**	91.2	23.8	–
TS **7a**	89.3	22.0	–

values for *TS* **5a** are 2.08 Å, 2.22 Å, and 560 cm^{-1}. The structure of both *TS*s as well as that of the preferred products **4a** and **5a** (minimized by MM+, geometry optimized by AM1 through HyperChem [20], visualization by ChemPlus [21]) are shown in Figs. 2–5.

Since the energy difference between *TS* **4a** and *TS* **5a** is very small (only 0.6 kcal/mol), it is not possible to predict which one of products **4a** or **5a** will be formed preferentially on the basis of these values. Moreover, these two molecules may isomerize more or less freely, as they only differ in the conformation of the cyclohexane ring. The AM1 calculated barrier for interconversion of **4a** to **5a** is merely 7.5 kcal/mol.

Reaction of **1** *with nitrones* **8**

1,3-Dipolar cycloaditions of C-(X-phenyl)-N-phenyl nitrones **8** (where X is H, 4-Cl, and 2,4-di-Cl) and **1** in toluene at 110 °C afforded exclusively the spiro-isoxazolidines **9a–c** (Scheme 4).



8 **9a-c** **10**

Ar = X-Phenyl; X = H, 4-Cl, 2,4-di-Cl;

Scheme 4

The differentiation between the two possible adducts **9** and **10** was made from the presence of an ABX system in the ^{1}H NMR spectrum of **9**. This excludes the possibility of the regioisomer **10** having been formed. In the contrary, the ^{1}H NMR spectrum of the regioisomers **10a–c** would be expected to show a singlet for H-3 and an AB system for the two hydrogens at position 5 of the isoxazole ring. The structure of **9a–c** was further confirmed by the chemical shift of the adjacent spiro-carbon (C-5, $\delta = 80.47$–81.37 ppm), indicating a strong shielding influence of the spiro-heterocyclic ring on the 5-position of the isoxazolidine, together with the expected value for C-4 ($\delta = 49.52$–52.29 ppm). The same regioselectivity was also observed in several other cycloadditions of nitrones with heterocyclic compounds possessing an exocyclic double bond [4, 7].

Ring enlargement of **4** *to* **12** *and* **13**

Isoxazoline derivatives are known to be versatile synthetic equivalents of γ-amino-alcohols [18]. Based on our previous work [19] in which we have developed a new route to spiroheterocyclic derivatives through cycloaddition of 1,3-dipolar reagents to heterocycles with an exocyclic double bond, followed by reduction and subsequent recyclization with ring expansion, we have focused our attention to prepare 1-oxa-9-thia-3-azaspiro[5.5]undecane, a novel spiro-heterocyclic parent system (Fig. 6).

This was accomplished by reductive cleavage of isoxazoline **4a**, successfully effected by treatment with $LiAlH_4$ in tetrahydrofuran (Scheme 5). The structure of the γ-amino-alcohol **11** thus obtained was confirmed by comparing its spectral data with results obtained from analogous compounds previously published [19].

Reaction of **11** with 4-nitrobenzaldehyde proceeded smoothly with formation of spiro-1,3-oxazine **12**, which is a derivative of the new spiro-heterocyclic parent system mentioned above. It turned out that only one out of two possible diastereo-isomers was obtained. The cyclization of **11** with carbonyldiimidazole (*CDI*) to spiro-1,3-oxazine-2-one **13** proceeded in good yield.

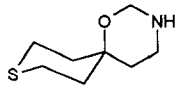
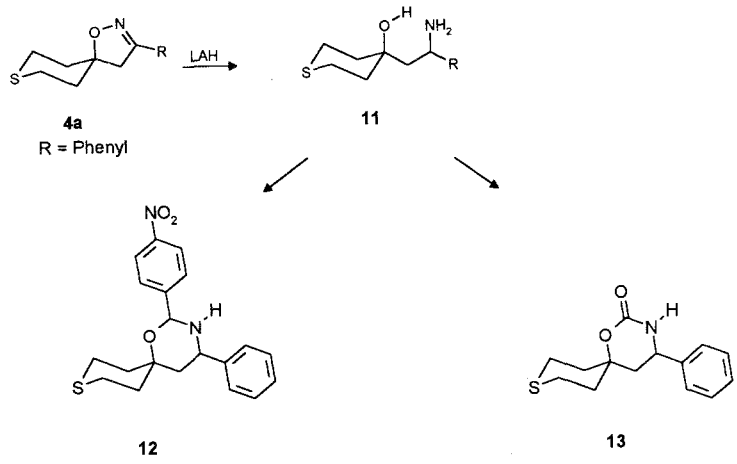


Fig. 6. 1-Oxa-9-thia-3-azaspiro[5.5]undecane



Scheme 5

Experimental

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Brucker AC 200 spectrometer (*TMS* as internal standard, $CDCl_3$, δ-values in ppm, J in Hz). 4,4-Methylene-thiacyclohexane (**1**) was prepared by treatment of 4-thiacyclohexanone with phosphorus ylide [8].

Quantum-chemical calculations were performed using the semiempirical AM1 method [14]. Geometries of the reactants and four possible products **4–7** were fully optimized using the PRECISE option increasing the precision of results one hundred times. Transition states were roughly optimized by the reaction coordinate method and then refined by minimization of gradient norm. All transition states were characterized as true transition states by the analysis of the force constant matrix.

Visualization (cylinder models, HOMOs and LUMOs) of structures depicted in Figs. 1, 4, and 5 and calculations required for this purpose (pre-minimization with MM+, AM1, conformation analyses) were performed with HyperChem 3.0 for Windows [20] and ChemPlus for HyperChem [21]. Compounds **4a–d** and **9a–c** gave satisfactory elemental analyses (max. deviation 0.13–0.24%).

3-(X-Phenyl)- and 3-Methyl-1-oxa-8-thia-2-azaspiro[4.5]dec-2-enes (**4**)

N-Chlorosuccinimide (26.3 mmol) was suspended in dry chloroform. Then the corresponding benzaldoxime (32.8 mmol) and 2 drops of pyridine were added and the mixture heated to 40–50 °C for 20 min. After cooling at 0 °C, a solution of **1** (25.3 mmol) in dry chloroform (12 ml) was added dropwise during 20 min followed by dry triethylamine (26.8 mmol) in dry chloroform (20 ml). The reaction mixture was stirred for 0.5 h at 0 °C and for 0.5 h at room temperature, subsequently refluxed for 15 h and then allowed to cool. The mixture was distilled and the obtained solid residue was chromatographed on a silica gel column (eluant: hexane-ethyl acetate 7:3).

3-Phenyl-1-oxa-8-thia-2-azaspiro[4.5]dec-2-ene (**4a**; $C_{13}H_{15}NOS$)

Yield 67%; m.p. 119–121 °C; $R_f = 0.44$; ^1H NMR: 1.98 (m, 2H), 2.20 (m, 2H), 2.55 (m, 2H), 2.98–3.18 (m, 4H), 3.10 (s, 2H, H_2-4), 7.40 (m, 3H, aromat. H), 7.68 (m, 2H, aromat. H); ^{13}C NMR: 25.36 (t, C-6, C-10), 37.19 (t, C-7, C-9), 46.27 (t, C-4), 84.58 (s, C-5), 126.31, 128.58, 129.68, 129.90 (aromat. C), 155.99 (s, C-3).

3-(4-Chlorophenyl)-1-oxa-8-thia-2-azaspiro[4,5]dec-2-ene (**4b**; $C_{13}H_{14}ClNOS$)

Yield 38%; m.p. 157–158 °C; $R_f = 0.34$; ^1H NMR: 1.98 (m, 2H), 2.20 (m, 2H), 2.52 (m, 2H), 2.98–3.15 (m, 4H), 3.14 (s, 2H, H_2-4), 7.38 (d, 2H, aromat. H), 7.60 (d, 2H, aromat. H); ^{13}C NMR: 25.31 (t, C-6, C-10), 37.17 (t, C-7, C-9), 46.10 (t, C-4), 84.99 (s, C-5), 127.53, 128.21, 128.81, 135.73 (aromat. C), 155.04 (s, C-3).

3-(3-Nitrophenyl)-1-oxa-8-thia-2-azaspiro[4.5]dec-2-ene (**4c**; $C_{13}H_{14}N_2O_3S$)

Yield 23%; m.p. 115–117 °C; $R_f = 0.28$; ^1H NMR: 2.00 (m, 2H), 2.20 (m, 2H), 2.58 (m, 2H), 3.00–3.16 (m, 4H), 3.10 (s, 2H, H_2-4), 7.60–8.25 (m, aromat. H); ^{13}C NMR: 25.22 (t, C-6, C-10), 37.12 (t, C-7, C-9), 45.69 (t, C-4), 85.89 (s, C-5), 121.03, 124.22, 129.64, 131.49, 131.79, 148.14 (aromat. C), 155.33 (s, C-3).

3-Methyl-1-oxa-8-thia-2-azaspiro[4.5]dec-2-ene (**4d**; $C_8H_{13}NOS$)

Yield 28%; m.p. 94–97 °C; $R_f = 0.23$; ^1H NMR: 1.85 (m, 2H), 1.98 (s, 3H, CH_3), 2.10 (m, 2H), 2.50 (m, 2H), 2.67 (s, 2H, H_2-4), 2.98 (m, 2H); ^{13}C NMR: 13.36 (q, CH_3), 25.32 (t, C-6, C-10), 37.03 (t, C-7, C-9), 49.96 (t, C-4), 83.21 (s, C-5), 154.85 (s, C-3).

2-Phenyl-3-(X-phenyl)-1-oxa-8-thia-2-azaspiro[4.5]decanes (**9**)

N-Phenyl-C-aryl-nitrones **8** (2.18 mmol) and 4,4-methylene-thiacyclohexane (**1**) (4.39 mmol) in dry benzene (10 ml) were heated under reflux for 4 days. Concentration under reduced pressure gave the corresponding cycloadducts after purification by crystallization from methanol.

2,3-Diphenyl-1-oxa-8-thia-2-azaspiro[4.5]decane (**9a**; $C_{19}H_{21}NOS$)

Yield 72%; m.p. 95–96 °C; ^1H NMR: 1.76–2.13 (m, 3H), 2.20 (dd, 1H, H_B-4, $J_{AB} = 12.9$ Hz, $J_{3,4B} = 9.4$ Hz), 2.30–2.61 (m, 3H), 2.70 (dd, 1H, H_A-4, $J_{3,4A} = 9.4$ Hz), 3.10 (m, 2H), 4.66 (dd, 1H, H-3), 6.90–7.00 (m, 2H), 7.15–7.50 (m, 8H, aromat. H); ^{13}C NMR: 25.50, 25.74 (t, C-6, C-10), 36.47, 37.37 (t, C-7, C-9), 52.29 (t, C-4), 68.44 (d, C-3), 80.55 (s, C-5), 114.71, 121.16, 126.35, 127.41, 128.46, 128.83, 141.68, 151.30 (aromat. C).

2-Phenyl-3-(4-chlorophenyl)-1-oxa-8-thia-2-azaspiro[4.5]decane (**9b**; $C_{19}H_{20}ClNOS$)

Yield 91%; m.p. 121–122 °C; ^1H NMR: 1.80–2.08 (m, 3H), 2.50 (dd, 1H, H_B-4, $J_{AB} = 12.9$ Hz, $J_{3,4B} = 9.3$ Hz), 2.20–2.40 (m, 1H), 2.40–2.60 (m, 2H), 2.68 (dd, 1H, H_A-4, $J_{3,4A} = 9.3$ Hz), 3.10 (m, 2H), 4.60 (dd, 1H, H-3), 6.88–7.45 (m, 9H, aromat. H); ^{13}C NMR: 25.51, 25.67 (t, C-6, C-10), 36.99, 37.62 (t, C-7, C-9), 52.03 (t, C-4), 67.79 (d, C-3), 80.47 (s, C-5), 115.14, 121.49, 127.80, 128.36, 128.86, 133.16, 140.24, 150.78 (aromat. C).

2-Phenyl-3-(2,4-dichlorophenyl)-1-oxa-8-thia-2-azaspiro[4.5]decane (**9c**; $C_{19}H_{20}Cl_2NOS$)

Yield 94%; m.p. 102–103 °C; ^1H NMR: 1.72–2.10 (m, 4H), 2.05 (dd, 1H, H_B-4, $J_{AB} = 12.9$ Hz, $J_{3,4B} = 9.3$ Hz), 2.15–2.30 (m, 1H), 2.39–2.60 (m, 2H), 2.89 (dd, 1H, H_A-4, $J_{3,4A} = 9.3$ Hz), 2.95–3.18 (m, 2H), 5.02 (dd, 1H, H-3), 6.80–7.68 (m, 8H, aromat. H); ^{13}C NMR: 25.51, 25.65 (t, C-6, C-10), 36.23, 37.23 (t, C-7, C-9), 49.52 (t, C-4), 64.36 (d, C-3), 81.37 (s, C-5), 114.02, 121.16, 127.82, 128.67, 128.75, 129.27, 132.38, 133.48, 138.07, 150.59 (aromat. C).

4-Hydroxy-4-(2'-phenyl-2'-aminoethyl)-thiacyclohexane (**11**; $C_{13}H_{19}NOS$)

To a suspension of $LiAlH_4$ (2.0 g, 52.6 mmol) in 100 ml of dry tetrahydrofuran a solution of isoxazoline **4a** (3.1 g, 12.97 mmol) in 25 ml of dry tetrahydrofuran was added dropwise. The reaction mixture was

refluxed for 18 h and the excess of hydride was subsequently destroyed by addition of 50 ml water and 20 ml of 20% NaOH to the stirred reaction mixture until the precipitate bleached white. The precipitate was filtered off and washed with 2 × 20 ml of ether. The aqueous layer was extracted with ether and the combined organic layers were concentrated *in vacuo*. Yield: 2.81 g (91%); m.p. 86–88 °C; ^{1}H NMR: 1.58–1.98 (m, 5H), 2.15–2.56 (m, 3H), 3.00–3.20 (m, 2H), 4.20 (dd, 1H, H-1′, J = 9.0 and 6.5 Hz), 7.15–7.42 (m, 5H, aromat. H); ^{13}C NMR: 23.84 and 24.00 (t, C-3 and C-5), 37.40 and 41.15 (t, C-2 and C-6), 48.14 (t, CH_2), 52.03 (d, C-2′), 69.17 (s, C-4), 125.21, 127.13, 128.77, 146.63 (aromat. C).

2-(4-Nitrophenyl)-4-phenyl-1-oxa-9-thia-3-azaspiro[5.5]undecane (**12**; $C_{20}H_{22}N_2O_3S$)

To a solution of γ-amino-alcohol **11** (400 mg, 1.65 mmol) in 20 ml dry chloroform a solution of 4-nitrobenzaldehyde (248 mg, 1.65 mmol) in 10 ml of dry chloroform was added, followed by the addition of *p*-toluenesulfonic acid (20 mg dissolved in 5 ml dry chloroform). Finally, 1.0 g of molecular sieve (4 Å) was added, the reaction mixture was refluxed for 1 d, filtered through a short column filled with sodium carbonate, washed with dry chloroform, and worked up as usual. Yield: 480 mg (79%); m.p. 138–140 °C, ^{1}H NMR: 1.46–1.65 (d, 2H), 1.70–2.12 (m, 4H), 2.37–2.60 (m, 2H), 2.80–3.10 (m, 2H), 3.30 (m, 1H, NH), 4.39 (dd, 1H, H-4, J = 10.0 Hz and 1.0 Hz), 5.60 (s, 1H, H-2), 7.30–8.35 (m, 9H, aromat. H); ^{13}C NMR: 23.17 (t), 23.21 (t), 31.64 (t), 41.74 (t), 43.46 (t), 53.28 (d, C-4), 71.70 (s, C-6), 80.12 (d, C-2), 123.22, 126.01, 127.10, 127.46, 128.56, 142.14, 147.53, 147.70 (aromat. C).

4-Phenyl-1-oxa-9-thia-3-azaspiro[5.5]undecane-2-one (**13**; $C_{14}H_{17}NO_2S$)

To a solution of γ-amino-alcohol **11** (400 mg, 1.69 mmol) in 20 ml dry tetrahydrofuran *CDI* (1040 mg, 6.4 mmol) was added under nitrogen and the mixture was heated for 18 h under reflux. After pouring onto water, extraction with chloroform, drying (Na_2SO_4) and concentrating the combined organic layers under reduced pressure, product **13** was purified by crystallization from diisopropylether/isopropanol. Yield: 210 mg (74%); m.p. 210–213 °C; ^{1}H NMR: 1.60–2.00 (m, 3H), 2.05–2.18 (m, 2H), 2.36–2.60 (m, 3H), 2.98–3.29 (m, 2H), 4.68 (dd, 1H, H-4, J = 12.9 Hz and 6.5 Hz), 5.70 (s, 1H, NH), 7.20–7.48 (m, 5H, aromat. H); ^{13}C NMR: 22.49 (t), 22.83 (t), 34.25 (t), 38.14(t), 40.86 (t), 50.73 (d, C-4), 76.42 (s, C-6), 125.49, 127.46, 128.13, 140.47 (aromat. carbons).

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