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SYNTHESIS, STRUCTURAL ANALYSIS AND REACTIVITY OF 1,3-OXATHIANE DERIVATIVES

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Abstract – The methods of synthesis, the configurational and conformational aspects of the stereochemistry and the main spectral properties and reactions of 1,3-oxathiane derivatives are reviewed.

1. INTRODUCTION

The stereochemistry and the synthesis of some 1,3-oxathiane derivatives were already the subject of some reviews.[1-4] The interest on the 1,3-oxathiane derivatives is due to the peculiar stereochemistry of this heterocycle, to the versatility of some of these derivatives as reagents in

reactions with carbon-carbon bond formation or as chiral auxiliaries and to the many applications[5-11] as food flavoring agents,[5a,6] perfuming agents,[5b] pesticides and plant growth regulators,[5c,7] drugs[8] and liquid crystal materials.[9-11] Many important investigations on the synthesis, stereochemistry and reactivity of 1,3-oxathiane derivatives were carried out in the last years showing an increased interest for the derivatives of this heterocycle and motivating a complete review of this field.

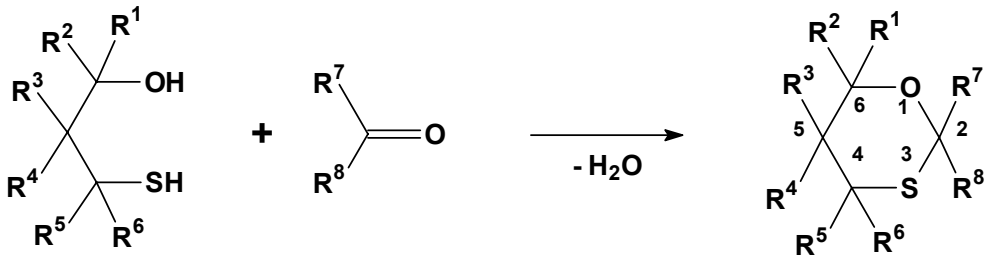
2. SYNTHESIS

1,3-Oxathiane derivatives, despite the large number of known compounds, are obtained by a limited register of methods. The most convenient enclosure of this heterocycle is performed by the direct reaction of carbonyl derivatives with proper γ-thioalcohols.[4] The 1,3-oxathianes obtained this way may be further used to synthesise compounds bearing different substituents at position 2 or on the sulfur atom. [12,13]

2.1. Direct reaction between γ-thioalcohols and carbonyl derivatives

The conditions for the reaction of carbonyl compounds with γ-thioalcohols (Scheme 1) vary a lot and they are correlated with the reactivity, solubility and stability of the starting materials and products as well.

Scheme 1



1-35

The condensation of formaldehyde with γ-thioalcohols (Scheme 1; Table 1, compounds (**1**-**13**)) occurs in very different yields, depending on the nature of the solvent, catalyst and temperature. The best results are obtained at room temperature using water as solvent and sulfuric acid as catalyst (method C, 85-92% yield), while the use of PTSA as catalyst and benzene (method B) or dichloromethane (method A) at reflux for the azeotropic removal of the water formed in the reaction, results into lower yields (14-66%).[14]

Usual aldehydes and ketones react with γ-thioalcohols in dichloromethane (method A) or benzene (method B) at reflux in acidic catalysis (PTSA), the water formed during the reaction being separated by azeotropic distillation[15,18-21] (Scheme 1, Table 1).

Table 1. Results in the synthesis of 1,3-oxathiane derivatives by the direct condensation of aldehydes and ketones with 3-mercapto-1-propanols.

Comp.	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Method	Yield	Ref.
1	H	H	H	H	H	H	H	H	A	20	15
									B	55	16
2	CH_3	H	H	H	H	H	H	H	A	30	15
									B	14	17
3	H	H	CH_3	H	H	H	H	H	A	19	18
4	H	H	H	H	CH_3	H	H	H	A	27	19
5	CH_3	H	H	H	CH_3	H	H	H	A	65	19
6	H	H	CH_3	H	CH_3	H	H	H	A	62	19
7	CH_3	CH_3	H	H	H	H	H	H	A	43	18
									B	51	16
8	H	H	CH_3	CH_3	H	H	H	H	B	43	16
9	H	H	H	H	CH_3	CH_3	H	H	A	53	18
									B	51	16
10	CH_3	H	CH_3	H	CH_3	H	H	H	A	66	18
11	H	H	H	H	C_6H_5	H	H	H	B	24	14
12	CH_3	H	H	H	CH_3	CH_3	H	H	C	92	14
13	CH_3	CH_3	H	H	CH_3	H	H	H	C	85	14
14	H	H	H	H	H	H	CH_3	H	A	77	15
15	H	H	H	H	H	H	C_2H_5	H	A	69	15
16	H	H	H	H	H	H	*i*-C_3H_7	H	A	60	15
17	H	H	H	H	CH_3	H	CH_3	H	A	81	19
18	H	H	CH_3	H	H	H	CH_3	H	A	90	18
19	CH_3	H	H	H	H	H	CH_3	H	A	65	15
20	CH_3	H	H	H	H	H	C_2H_5	H	A	60	15
21	CH_3	H	H	H	H	H	*i*-C_3H_7	H	A	57	15
22	H	H	H	H	CH_3	CH_3	CH_3	H	A	42	18
23	CH_3	H	H	H	CH_3	H	CH_3	H	A	78	19
24	CH_3	CH_3	H	H	H	H	CH_3	H	A	75	19
25	H	H	CH_3	CH_3	H	H	CH_3	H	A	73	19
26	CH_3	H	CH_3	H	H	H	CH_3	H	A	85	19
27	H	H	H	H	CH_3	H	*i*-C_3H_7	H	A	80	19
28	H	H	CH_3	H	H	H	*i*-C_3H_7	H	A	92	20
29	CH_3	H	H	H	H	H	C_6H_5	H	B	8	17
30	H	H	H	H	C_6H_5	H	C_6H_5	H	B	10	17
31	CH_3	H	H	H	H	H	*t*-C_4H_9	H	B	25	17
32	H	H	H	H	C_6H_5	H	*t*-C_4H_9	H	B	11	17
33	H	H	H	H	H	H	CH_3	CH_3	B	65	15
34	H	H	H	H	H	H	CH_3	C_2H_5	B	57	15
35	H	H	H	H	H	H	CH_3	*t*-C_4H_9	B	30	15

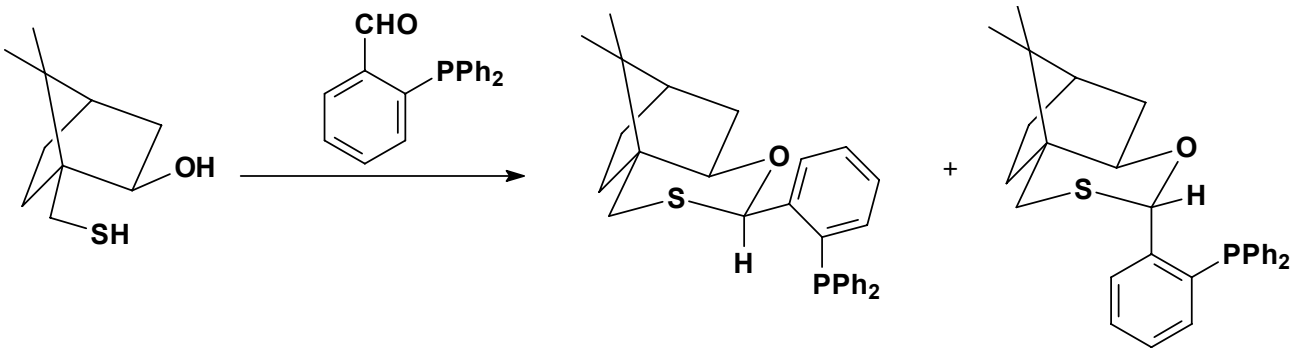
Methods: A (CH_2Cl_2, PTSA, reflux); B (C_6H_6, PTSA, reflux); C(H_2O, H_2SO_4, rt)

The decreasing of the reactivity of aldehydes or ketones lowers the yields (Table 1: compounds (**14**-**16**) and (**33**-**35**)),[15] while the different reactivity of the methylated or dimethylated γ-thioalcohols does not significantly influence the yields of the condensation reaction (Table 1: compounds (**17**-**19**) and (**22**-**26**), respectively).[15,18,19] Higher (**18**) or lower yields (**22**) than usual are measured when peculiar modifications of steric interactions in the transition state of the reaction occur.[18]

The use of other solvents (isopropyl ether or cyclohexane to obtain 2-methyl- or 2,2-disubstituted 4-*n*-propyl-1,3-oxathianes)[22-25] or of another catalyst ($(C_2H_5)_2O{\cdot}BF_3$ complex for the condensation of benzaldehyde with several γ-thioalcohols, compounds (**29**) and (**30**)[17,26] can determine important improvement of the yield.

The efficient synthesis (yield 89 and 92 %)[26] of chiral norbornane-based phosphinooxathianes (Scheme 2, **36a** and **36b**) starting from commercially available (1*S*)-(-)-10-mercaptoisoborneol and 2-(diphenylphosphino)benzaldehyde (method B) shows high stereoselectivity (92 % in benzene and 100 % in toluene) in stereoisomer (**36a**) (exhibiting the aromatic group in equatorial orientation).

Scheme 2



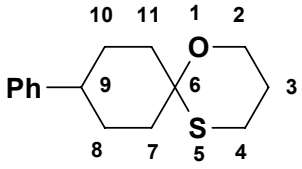
36a **36b**

Spiro-1,3-oxathianes (**37**) and (**38**) are obtained in good yields (54-78 %) starting from variously substituted cyclohexanones and 3-mercapto-1-propanol or 2,2-dimethyl-3-mercapto-1-propanol using PTSA as catalyst and benzene or toluene as solvents (method B).[28,29]

Compounds (**39**) displaying tetrasubstituted rings were synthesised in acidic catalysis without solvent from γ-thioalcohols and various ketones in 75-82% yields.[12]

Derivatives of formaldehyde (**40** and **41**) bearing different substituents at positions 4 and 6 (R^1=CH_3, C_2H_5, *n*-C_3H_7, *i*-C_3H_7, *n*-C_4H_9, *i*-C_4H_9) are obtained starting from the corresponding 1,3-diols (Scheme 3).[30,31] The diols are protected with mesytyl chloride and transformed into the corresponding protected γ-thioalcohols using a salt of thioacetic acid. Besides the two isomeric

mercaptoalcohols a protected dimercapto derivative is also obtained. This mixture of mercapto derivatives in reaction with formaldehyde, using HCl as catalyst at reflux of methanol, leads in good yields (overall up to 90 %) to a mixture of isomeric 1,3-oxathianes (**40**) and (**41**) and of dithiane derivative (**42**). Single compounds are separated from the mixture using chromatographic methods.



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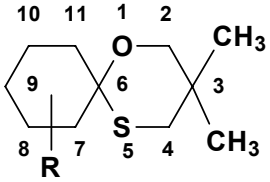

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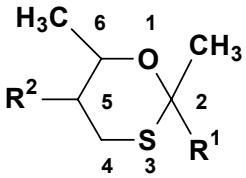
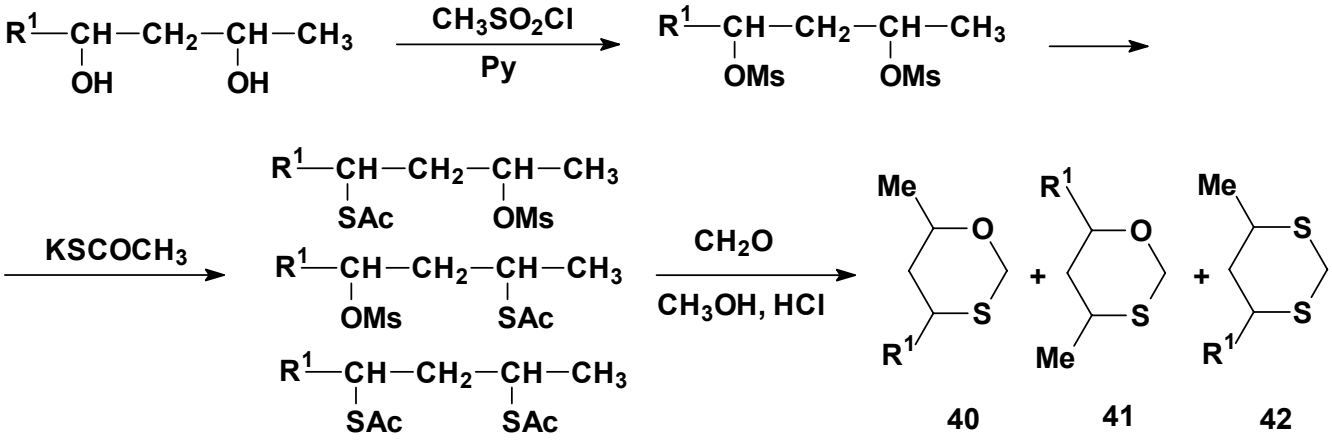


39

R=H (a), 7-CH_3(b),8-CH_3(c), 9-CH_3(d), 9-C_6H_5(e), 9-*t*-C_4H_9(f)

R^1 = CH_3, C_3H_7; R^2 = CH_3, C_3H_7

Scheme 3



40 **41** **42**

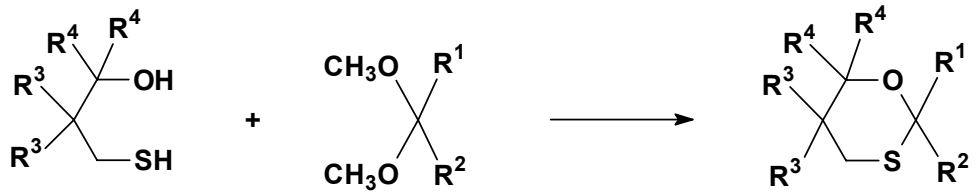
cis and *trans* isomers

2.2. Reaction of acetals with γ-thioalcohols

The reaction of ketals of acetone and DMF with γ-thioalcohols (Scheme 4)[12,16,18] under usual conditions for the transacetalisation reactions[32] (reflux in benzene and PTSA as catalyst or neat with $(C_2H_5)_2O{\cdot}BF_3$ or traces of Dowex 50) leads to substituted-1,3-oxathianes (**43**-**46**; yields 28-72 %).

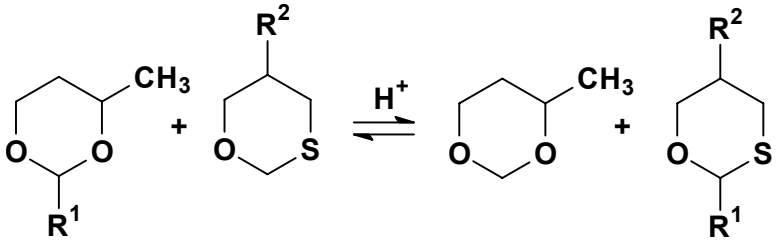
The equilibration of 1,3-dioxane (**47**) and 1,3-oxathiane (**48**) derivatives (Scheme 5) using HCl, H_2SO_4, PTSA or an ion-exchange resin KU-2 as catalysts in xylene at 80-120ºC[33,34] leads in good yields (79-95%) to 2,5-substituted 1,3-oxathianes (**49**).

Scheme 4



R^3=H, R^1=R^2=R^4=CH_3 **43** (28 %)
R^4=H, R^1=R^2=R^3=CH_3 **44** (54 %)
R^3=R^4=H, R^1=R^2=CH_3 **45** (53 %)
R^2=R^3=R^4=H, R^1=$N(CH_3)_2$ **46** (72 %)

Scheme 5



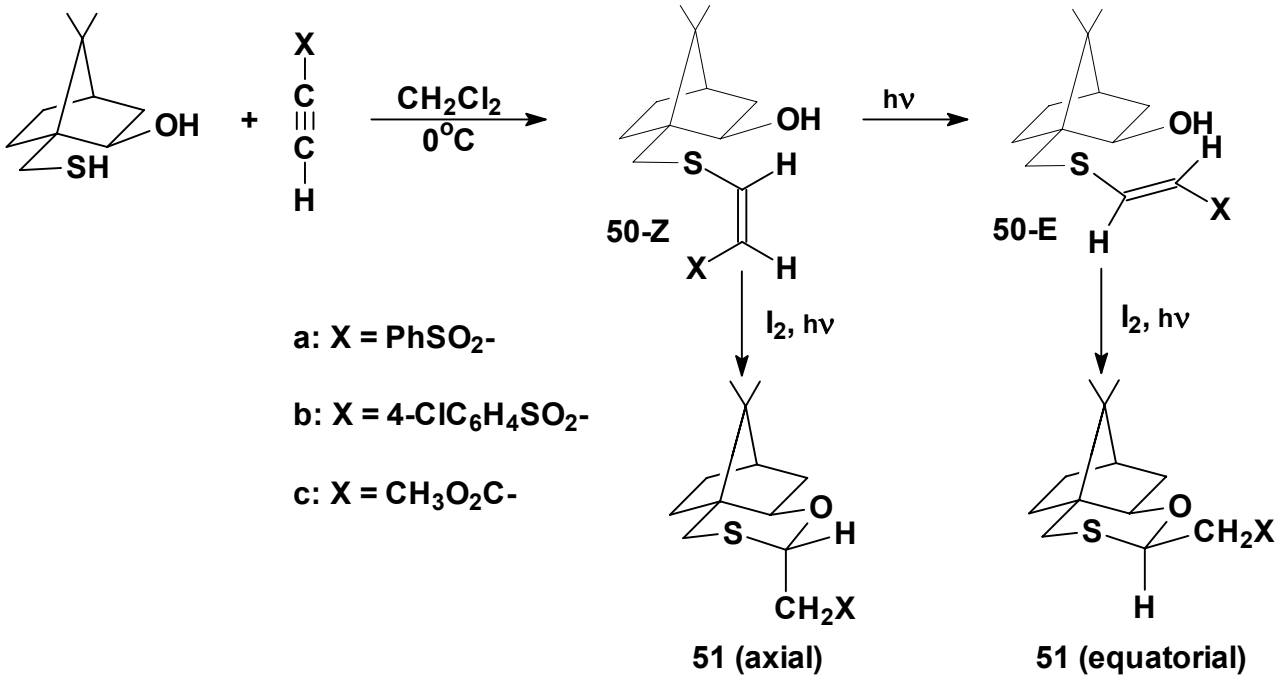
47 **48** **49**

R^1 = CH_3, C_2H_5, *n*-C_3H_7
R^2 = H, CH_3, *i*-C_3H_7, *i*-C_5H_{11}

2.3. Reaction with electron-poor acetylenes

Chiral 1,3-oxathianes (**51**) were obtained *via* nucleophilic addition of hydroxythiols to electron-poor acetylenes, followed by iodine catalysed photoinduced cyclization of the resulted Michael adduct (**50**) (Scheme 6).[35]

Scheme 6



a: X = $PhSO_2$-

b: X = 4-$ClC_6H_4SO_2$-

c: X = CH_3O_2C-

51 (axial) **51 (equatorial)**

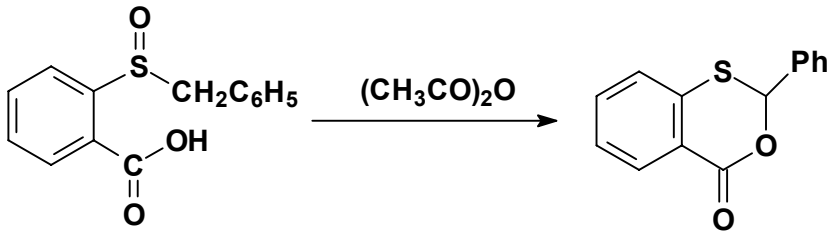
The two diastereomeric 1,3-oxathianes (**51**) have been separated and characterised. The yields and the stereoselectivity of the reaction are influenced by several factors like irradiation source, solvent, temperature, presence of oxygen. The obtained products contain versatile functionalities and they can be further used in asymmetric synthesis.

2.4. 1,3-Oxathiane ring formation through intramolecular rearrangements

The intramolecular condensation reaction of benzyl 2-carboxyphenyl sulfoxide leads to 2-phenyl-1,3-benzoxathian-6-one (**52**, Scheme 7)[36] in the conditions of Pummerer rearrangement (130°C, acetic anhydride).[37]

γ,δ-Unsaturated sulfinyl compounds exhibit Pummerer-type rearrangements into the corresponding 1,3-oxathiane derivatives (*e.g.* compound (**53**-**55**), Scheme 8). The cyclization of *endo*-(alkylsulfinyl)norbornene or 1-(alkylsulfinyl)-2-isopropenylbenzene derivatives occurs in the presence of some protonic acids and, among them, 1 equiv. of PTSA in refluxing xylene was found to be the best (yields up to 96%).[38,39]

Scheme 7



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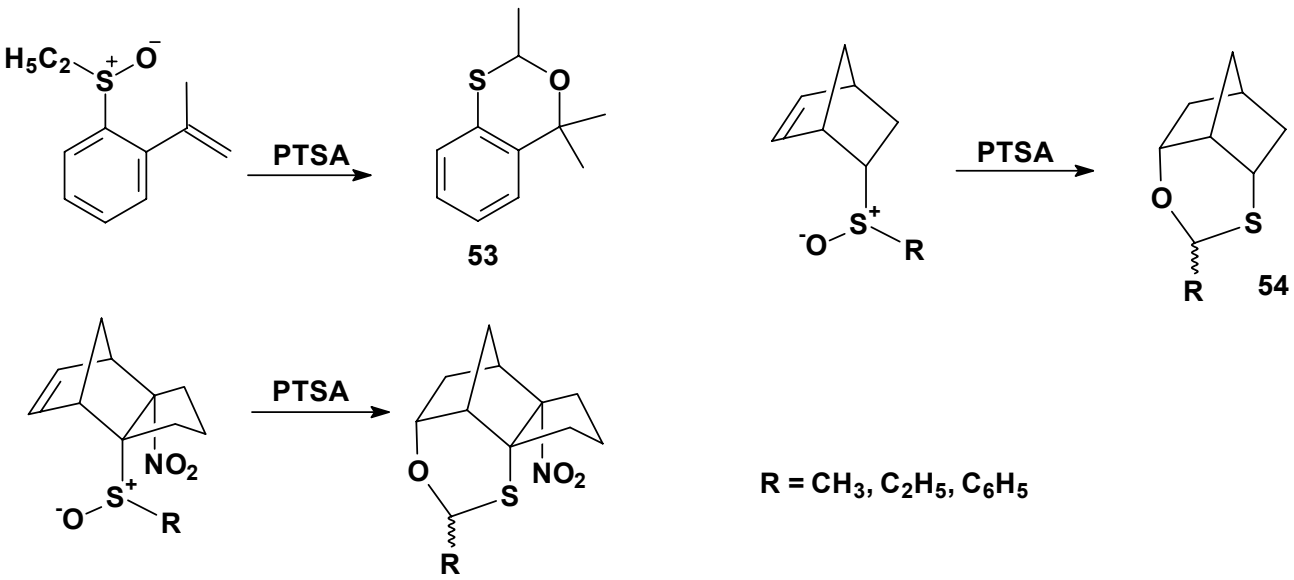
Scheme 8

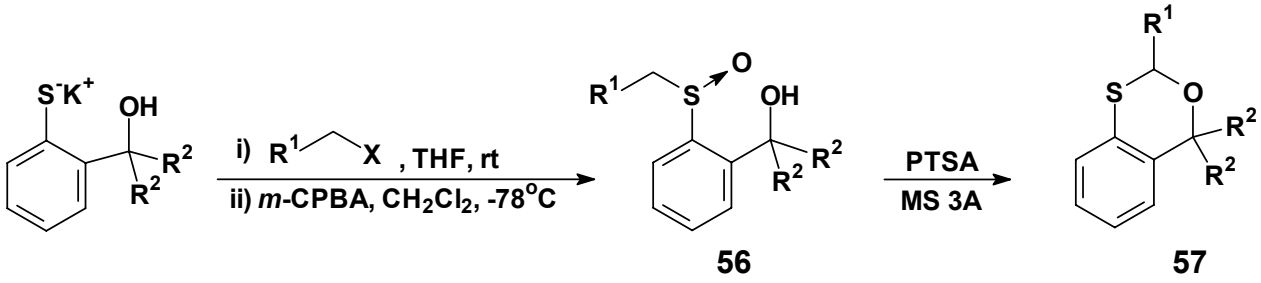


55

A similar intramolecular rearrangement performed in the presence of PTSA and molecular sieves[40] with *ortho*-hydroxymethylphenyl sulfoxides (**56**) yields 1,3-oxathianes (**57**) (Scheme 9). As these, 2-(2-alkyl-sulfinylphenyl)-2-propanols may be obtained from an alkyl halide, a three-step transformation of alkyl halides to 1,3-oxathianes (as masked carbonyl group) can occur using intramolecular Pummerer reaction.

4,6-Substituted 1,3-oxathiane (**58**) can be synthesised by bisalkylation with CH_2Br_2 under phase-transfer catalysis of mercaptoalcohols obtained *via* [2,3]-thia-Wittig rearrangement of α-lithiated sulfides (Scheme 10).[41]

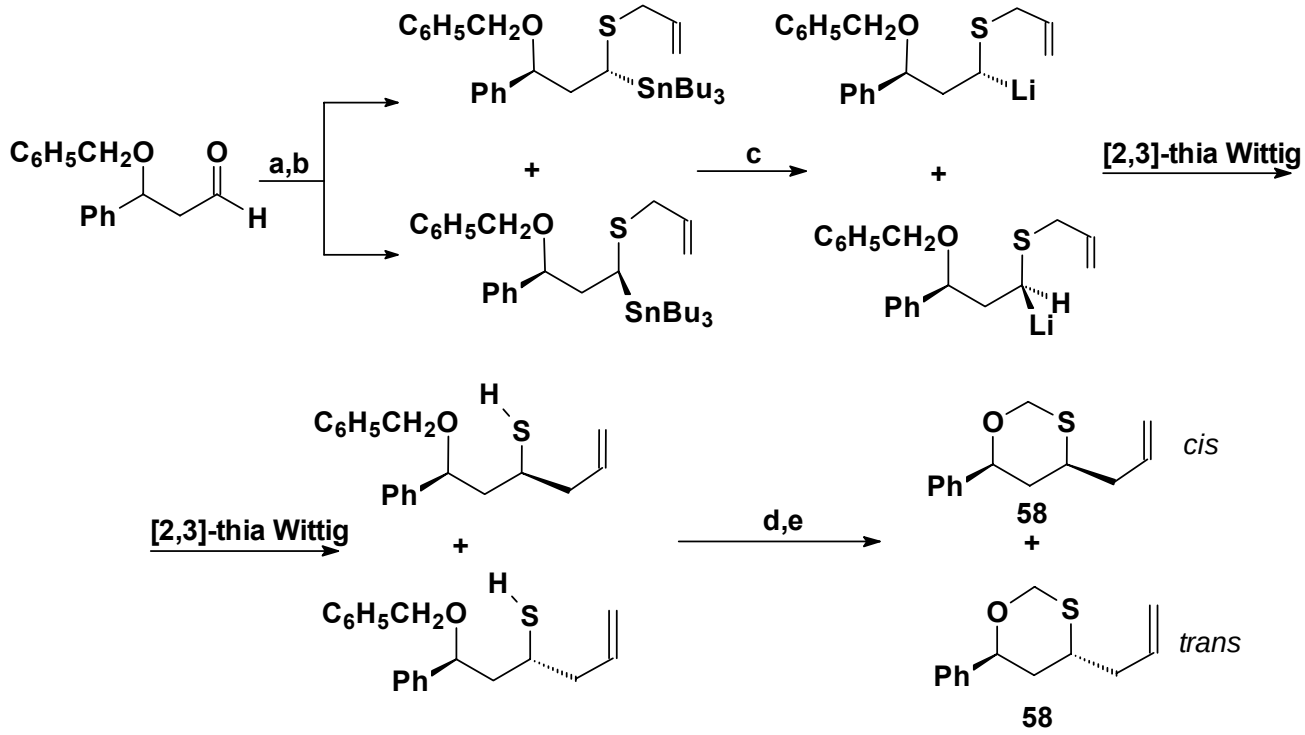
Scheme 9



56 **57**

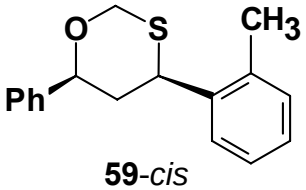
R^1= H, CH_3, C_6H_6, COC_6H_5, CH_2OH, 1,3-dioxolan-2-yl; R^2= H, CH_3

Scheme 10

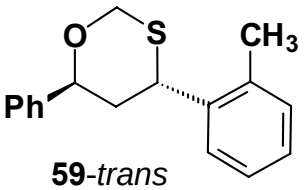


a) $LiSn(C_4H_9)_3$, THF, -78°C, 1 h;→0°C; CBr_4, PPh_3, CH_2Cl_2, rt, 6h, 60%; b) $K^+S^-CH_2CH{=}CH_2$, THF, rt, 12 h, 77%; c) *n*-C_4H_9Li (2.5 equiv.), THF, -78°C, 30 min, 79% *syn*, 89% *anti*; d) $LiC_{10}H_7$ (4 equiv.), THF, -78°C, 5 h, 51% *syn*, 53% *anti*; e) slow addition to a refluxing 5:2 mixture of CH_2Br_2 and 50% aq. KOH with $C_4H_9N(C_2H_5)_3^+Cl^-$ (0.4 equiv.), then reflux 1 h, 53% **58**-*cis*, 49% **58**-*trans.*

Cis and *trans* isomers of **59** are obtained in a similar procedure, but the enclosure of the 1,3-oxathiane ring is performed with HBF_4 in dichloromethane at rt.[42]



59-*cis*

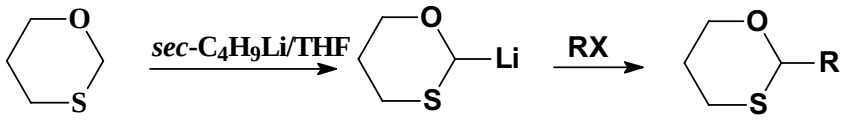


59-*trans*

2.5. Reactions of lithiated 1,3-oxathianes with electrophiles

The hydrogen atom at C(2) in 1,3-oxathiane derivatives is easily removed by usual lithiating agents (*n*-C_4H_9Li, *sec*-C_4H_9Li or LDA). 2-Lithio-1,3-oxathianes (*e.g.* compound (**60**)) can react further with a variety of electrophiles including alkyl halides and carbonyl compounds to afford substitution (*e.g.* **61**) and addition (*e.g.* **62**) products respectively (Schemes 11 and 12).[12,13]

Scheme 11



60 **61**

R=CH_3, C_2H_5, *n*- C_3H_7, *i*- C_3H_7, *n*- C_4H_9, *i*- C_4H_9, $CH_2C_6H_5$

Primary alkyl iodides give an excellent yield of 2-alkylated 1,3-oxathianes (83-99%), while with bromides and isopropyl iodide yields are poor (25-35%), as correlated with the reactivity of the halide in the SN_2 reaction.

Reaction of **60** with carbonyl derivatives leads to 1,3-oxathianes substituted with a secondary or tertiary hydroxy group at position 2 (**62**, Scheme 12). The non-enolizable ketones react in good yields (77-86%), while the enolizable ones provide adducts in about 50% yield due to the competitive enolization of the starting ketone.

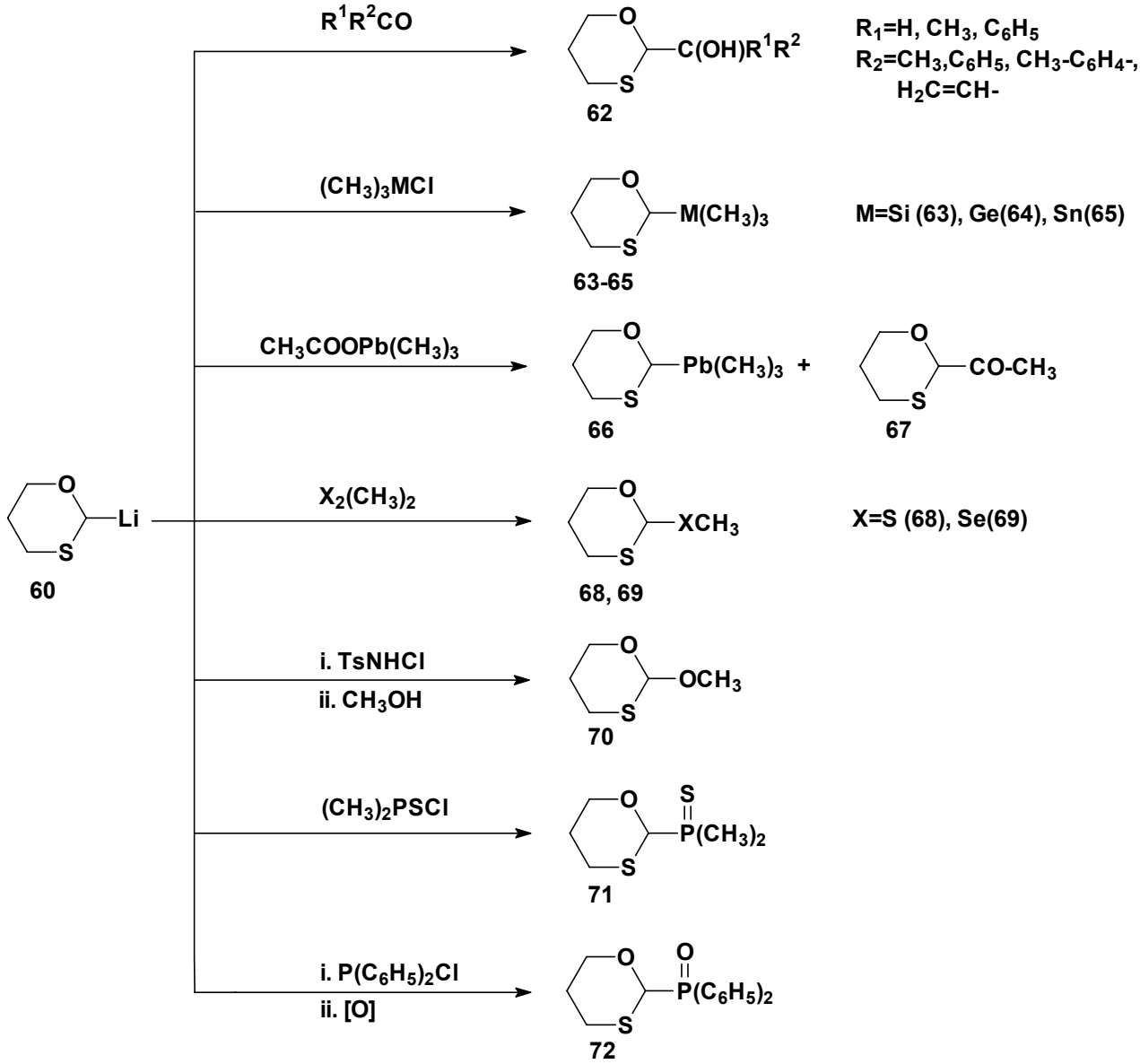
The reaction of **60** with appropriate metal chlorides leads to 1,3-oxathiane derivatives (**63**-**65**) bearing trimethylsillyl, germanyl or stannyl groups at position 2 [$(CH_3)_3M$; M = Si, Ge, Sn)].[12] The reaction of lithiated 1,3-oxathiane (**60**) with trimethyllead acetate gives the expected trimethyllead derivative (**66**) (70 %) and as side product 2-acetyl-1,3-oxathiane **67** (16 %).[12] (Scheme 12)

2-Methylthio- and 2-methylseleno-1,3-oxathianes (**68** and **69**) are obtained by the reaction of lithiated 1,3-oxathiane (**60**) with dimethyl disulfide or dimethyl diselenide, while 2-methoxy-1,3-

oxathiane (**70**) is obtained (overall yield: 31%) in a two-step procedure, including the reaction of lithiated 1,3-oxathiane with chloramine-T followed by the methanolysis of the intermediary *N*-tosylsulfinilimine.[12] (Scheme 12)

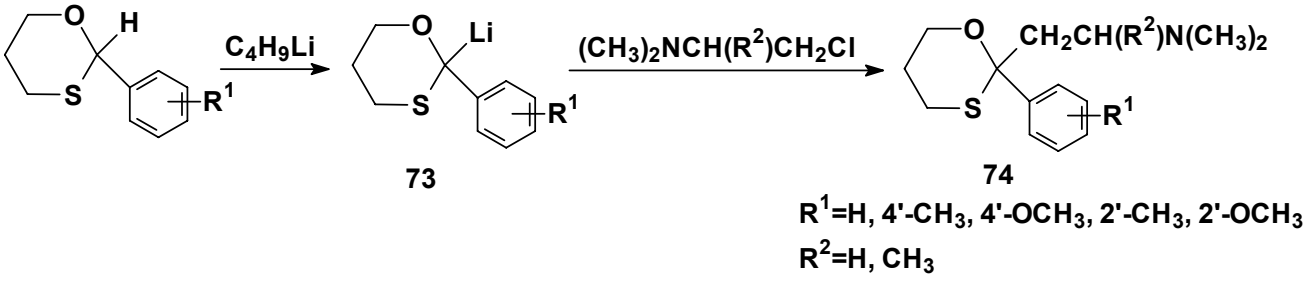
Lithiated derivative (**60**) in reaction with dimethylthiophosphonyl chloride is transformed into 2-dimethylthiophosphinoyl-1,3-oxathiane (**71**). The reaction of the same lithiated compound with chlorodiphenylphosphine produces an unstable derivative, which oxidises spontaneously to 2-diphenylphosphinoyl-1,3-oxathiane (**72**) (Scheme 12).[43]

Scheme 12



2,2-Disubstituted 1,3-oxathianes (**74**) were obtained in the reaction of lithiated 1,3-oxathiane (**73**) with β-chloroalkyldimethylamines (Scheme 13).[8]

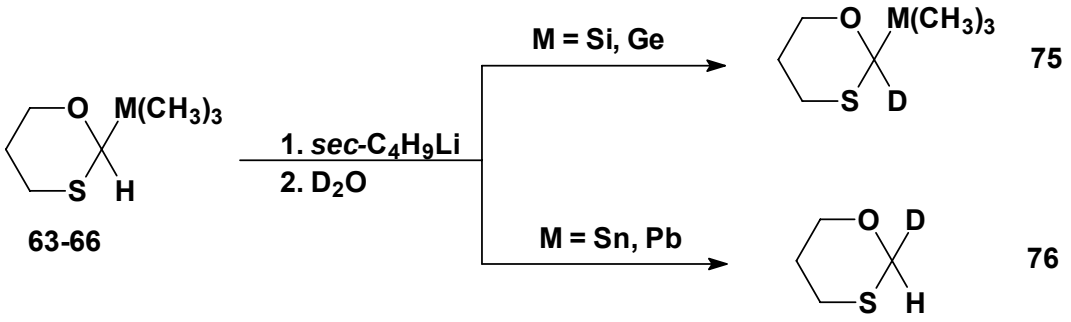
Scheme 13



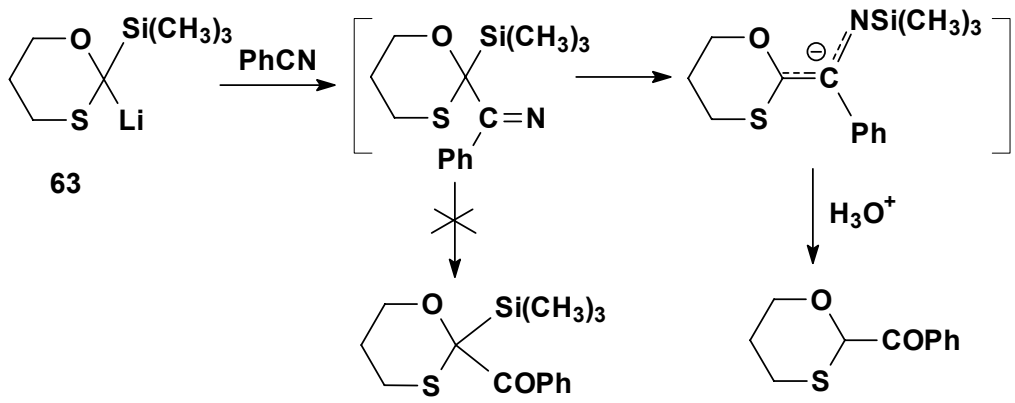
2-Heterosubstituted derivatives of 1,3-oxathianes produced, after the reaction with *sec*-C_4H_9Li as base and quenching with D_2O, 2-deuterio derivatives (**75**) in which the 2-trimethylsilyl and the 2-trimethylgermanyl groups remain unchanged, while for 2-trimethytin and 2-trimethyllead derivatives the nucleophilic attack of *sec*-C_4H_9Li takes place at the heteroatom to produce finally 2-deuterio-1,3-oxathiane (**76**) after the reaction with D_2O (Scheme 14).[44]

The lithiated trimethylsilyl derivative (**63**) in reaction with benzonitrile followed by acid hydrolysis produced to 2-benzoyl-1,3-oxathiane (**77**) in 73% yield instead of the expected 2-benzoyl-2-trimethylsilyl-1,3-oxathiane derivative (Scheme 15).[44]

Scheme 14



Scheme 15



2.6. Synthesis of oxides of 1,3-oxathianes

1,3-Oxathiane oxides (mono and dioxides) are obtained by oxidising the sulfur atom of the corresponding 1,3-oxathiane using different oxidising systems.

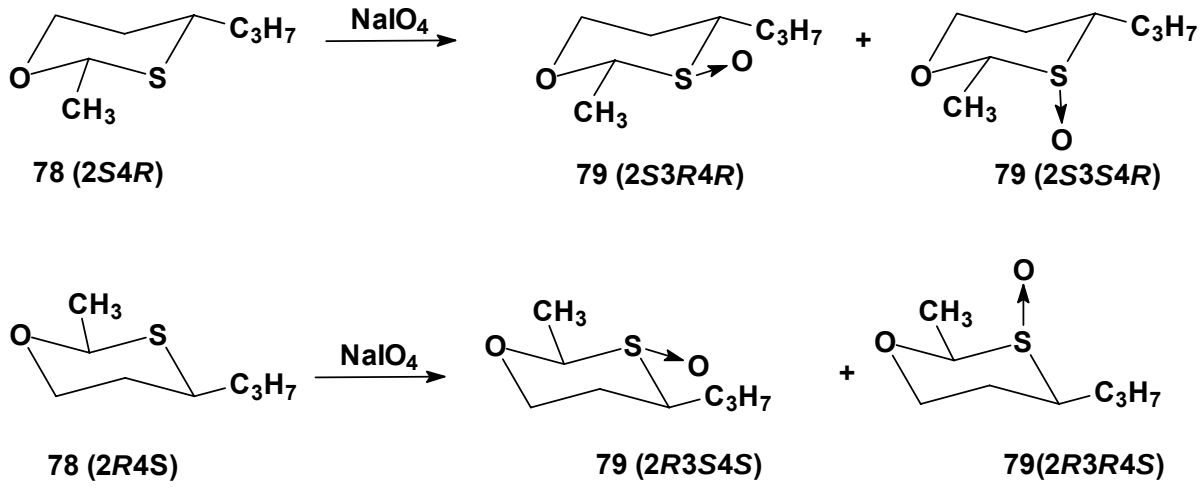
2.6.1. 1,3-Oxathiane-3-oxides

Optically pure (2*R*,4*S*)- and (2*S*,4*R*)-2-methyl-4-propyl-1,3-oxathiane (**78**) enantiomers, by oxidation with $NaIO_4$ (1 equiv.) in a 1:1 methanol-water mixture at 0-5° C in 90% yield are transformed (Scheme 16) into the corresponding equatorial : axial (3:1) sulfoxides (**79**). The axial and equatorial sulfoxides are chromatographically separated.[45,46]

S-Oxides of monomethylated 1,3-oxathianes are similarly obtained by the oxidation of corresponding oxathiane derivatives with sodium metaperiodate in acetonitrile.[47]

Another oxidising method leading to 3-oxides of 1,3-oxathianes uses *m*-chloroperoxybenzoic acid (*m*-CPBA) (1 equiv.) in dichloromethane, reaction conditions (temperature, reaction time) differ with the substrate.[7,45]

Scheme 16



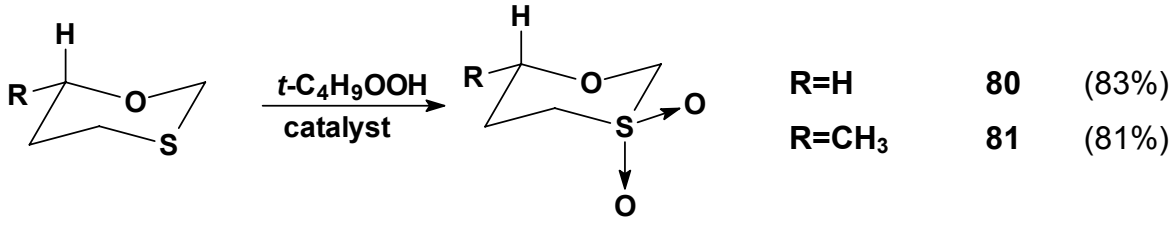
1,3-Oxathiane-3-oxides can also be prepared by the already presented stereoselective addition of hydroxythiols to electron-poor acetylenes followed by oxidation of the sulfides and cyclization of the sulfoxide (Scheme 6).[35]

The diastereoselective cyclization (only one diastereomeric 1,3-oxathiane-3-oxide of equatorial configuration is obtained) does not occur as in the case of the sulfide in the presence of iodine, but on prolonged treatment with silica gel of the sulfoxide, while the corresponding sulfone do not close the ring in either way.

2.6.2. 1,3-Oxathiane-3,3-dioxides

Sulfones (**80** and **81**) can be prepared from 1,3-oxathianes by similar methods with those used for the synthesis of sulfoxides but using 2 equivalents of oxidising substance. Beside the regular oxidants ($NaIO_4$, *m*-CPBA),[7,47-49] the literature also presents the synthesis of sulfones using *t*-butyl hydroperoxide and a catalytic amount of molybdenyl acetylacetonate (Scheme 17).[50]

Scheme 17



3. STEREOCHEMISTRY

3.1. Structure of the main ring

The 1,3-oxathiane ring exhibits a ”schizophrenic” behavior,[51] sometimes it is similar to 1,3-dioxane system and other times similar to 1,3-dithiane one. The geometry of the ring was deduced from data obtained by ^{1}H-NMR spectral investigations and from the several molecular structures determined by X-Ray diffractometry.

The presence of two different heteroatoms in the six-membered ring determines an increased number of boat, twist-boat and half-chair conformations (Scheme 18) compared to cyclohexane (**82**) or 1,3-dioxane (**83**) or 1,3-oxathiane (**84**).

The boat and twist-boat conformers of 1,3-oxathiane are more stable than those of 1,3-dioxane but they exhibit higher energies than the similar conformers of 1,3-dithiane. These data are in agreement with the modifications of the steric interactions across the ring due to the presence in the same cycle of bonds of different lengths: C-O<C-C<C-S. The data reported on the chair-twist-boat energy differences for 1,3-diheterocyclohexanes are not conclusive (Table 2), the differences between the reported data are probably due to the different contributions of the possible twist-boat conformers.

The chair-twist energetic parameters for the unsubstituted 1,3-oxathiane were first estimated[59] and then recalculated[18] by means of chemical equilibration. The compounds used for this purpose were the diastereomeric r-2-*t*-butyl-2,6-dimethyl-1,3-oxathianes (**85**) of which the *trans*

isomer is likely to exist in a twist conformation to avoid the interactions present in the chair conformations (Scheme 19).

Scheme 18

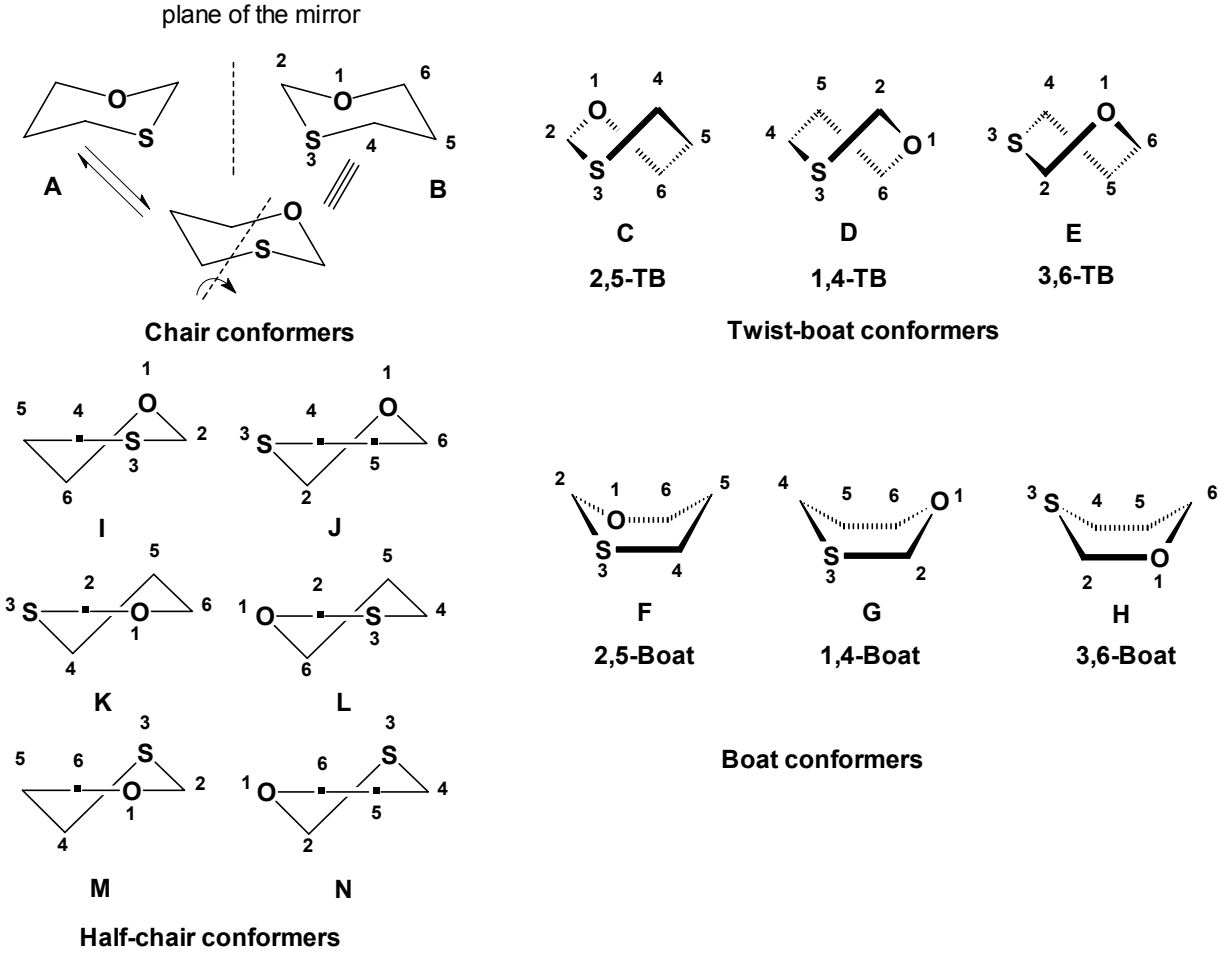


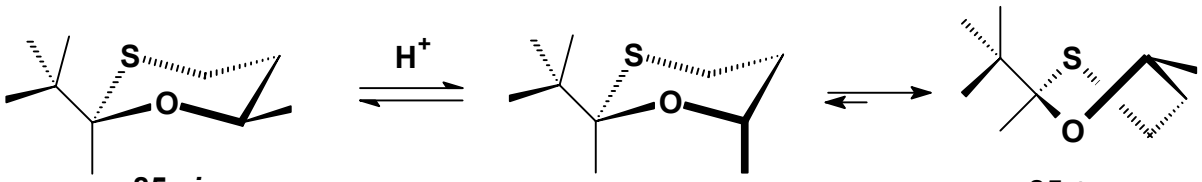
Table 2. Chair – twist-boat* energy and entropy differences in several six-membered rings.

Compound	No	$\Delta G°$ kJmol^{-1}	$\Delta H°$kJmol^{-1}	$\Delta S°$ Jmol^{-1}deg^{-1}	Ref.
cyclohexane	**82**	21.2	25.2	13.4	54
1,3-dioxane	**83**	23.8	29.7	20.1	55
		33.5	35.8	9.1	54
1,3-dithiane	**84**	12.1	17.9	19.5	56
		7.6	14.3	22.3	51
		11.0	16.7	19.0	54
1,3-oxathiane	**1**	23.5	27.0	11.6	18
		23.0	25.2	9.1	52
		-	22.1	-	53

* These values correspond to the 2,5-TB conformers considered of lower energy for the majority of the derivatives

The values determined for the energetic parameters of the chair-2,5-TB equilibrium (Table 2) in this experiment are in good agreement with the values calculated from other experiments in solution[52] or in gaseous state (*i.e.* determinations based on appearance potential measurements).[53] When comparing to the same values for 1,3-dioxane and 1,3-dithiane, a certain addition of the properties of the symmetrical analogues appears.[54,55]

Scheme 19



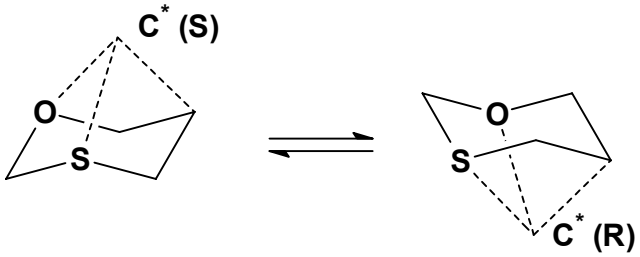
85-*cis* **85-*trans***

All investigations confirmed the general preference of 1,3-oxathiane derivatives for a slightly modified chair conformation (due to the coexistence of oxygen and sulfur atoms in the same ring).

Initially, a supposition was made about 1,3-oxathiane geometry from studying Dreiding molecular models that two deformed structures for the chair conformer of the parent compound - because of the large difference in C-O (1.42 Å) and C-S (1.81 Å) distances - can be constructed *a priori*: in one of these the puckering is largest in the S-side of the ring, in the other one in the O-side.[57,58] This assumption was proven later to be a misinterpretation due to the dissymmetry of the ring, as two enantiomeric chair conformations exist that may be interconverted by a ring inversion process.[51]

The chirality of the 1,3-oxathiane ring is due to a virtual tricoordinated chiral center (Scheme 20)[60] and the configurations of the two enantiomers can be established using the rules of Cahn, Inglog and Prelog.

Scheme 20



The 1,3-oxathiane ring shape can be predicted from NMR spectral data using the Buys-Lambert "R-value" method.[58] For six-membered rings existing in solution as an equilibrium mixture of two

equivalent conformers and having a $–CH_2-CH_2-$ or $–CH_2-CHX-$ moiety (from which two vicinal coupling constants can be extracted), the ratio $R = J_{trans}/J_{cis}$ is related to the ring torsional angle ω in that moiety by $\cos^2\omega=3/(2+4R)$.

In Table 3, R and ω values for some 1,3-oxathianes are presented, along with some results for similar 1,3-dioxane and 1,3-dithiane derivatives for comparison purposes.

Table 3. R and ω values for some 1,3-oxathianes, 1,3-dioxanes and 1,3-dithianes.

Compound	Nr	Side	R	ω	Ref.
1,3-oxathiane	**1**	O	2.29	59	57
		S	2.96	62	
1,3-dioxane	**83**	O	1.76	55	59
1,3-dithiane	**84**	S	3.23	63	59
2-methyl-1,3-oxathiane	**14**	O	2.38	59	18
		S	2.44	60	
2-*t*-butyl-1,3-oxathiane	**86**	O	2.26	59	65
		S	2.65	61	
2-*t*-butyl-1,3-dioxane	**87**	O	1.80	55	65
2-phenyl-1,3-oxathiane	**88**	O	2.41	59	65
		S	2.62	61	
2-phenyl-1,3-dithiane	**89**	S	3.23	63	65
4-methyl-1,3-oxathiane	**4**	O	2.45	60	18
6-methyl-1,3-oxathiane	**2**	S	2.57	60.5	18
cis-2,4-dimethyl-1,3-oxathiane	**17**	O	2.45	60	18
cis-2,6-dimethyl-1,3-oxathiane	**19**	S	2.49	60	18
2,2-dimethyl-1,3-oxathiane	**33**	O	1.94	56	57
		S	2.47	60	
4,4-dimethyl-1,3-oxathiane	**9**	O	2.40	59.5	18, 57
6,6-dimethyl-1,3-oxathiane	**7**	S	2.50	60	18, 57
2-*t*-butyl, 2-methyl-1,3-oxathiane	**35**	O	1.87	56	65
		S	2.32	59	
2-*t*-butyl, 2-methyl-1,3-dioxane	**90**	O	1.76	55	65
2-*t*-butyl, 2-methyl-1,3-dithiane	**91**	S	2.24	58	65
trans-2,2,4,6-tetramethyl-1,3-oxathiane	**92**	O,S	1.65	54	18

These values demonstrate that oxygen-containing rings have the tendency to flatten the C^4-C^5-C^6 moiety (in **83**, **52** and **90**) with $\omega_{4,5} = \omega_{5,6} = 55º$, while in the sulfur-containing rings a more puckered shape is preferred (in **84** and **89**) with $\omega_{4,5} = \omega_{5,6} = 63º$, for a C-S bond is longer then a C-C bond and C^5 is at a super-chair position.[18] But, despite the three different bond lengths (C-O = 1.41 Å, C-C = 1.54 Å, C-S = 1.82 Å), the C^4-C^5-C^6 moiety may attend a fully staggered shape in 1,3-oxathianes. Both $\omega_{4,5}$ and $\omega_{5,6}$ are in most of the cases within 60± 1º and not significantly different from each other, fact that contradicts the previous statement based on

inaccurate ^{1}H-NMR parameters that different heteroatoms of the ring influence the magnitude of $\omega_{4,5}$ and/or $\omega_{5,6}$.[61,62]

The average torsion angles of about 60° obtained by NMR spectral methods are also confirmed in some solid-state studies on 1,3-oxathiane derivatives [2-*p*-nitrophenyl-1,3-oxathiane (**93**), 5,5-dimethyl-2-diphenylphosphinoyl-1,3-oxathiane (**94**)[64] (Figure 1a) and *trans*-3,3-dimethyl-9-phenyl-1-thia-5-oxaspiro[5.5]undecane (**38e**),[29] Figure 1b, Table 4]. In **94** the six-membered ring adopts a slightly deformed chair conformation the differences of torsion angles compared with the values for a normal chair conformation are small, 5.1º for the torsion around the S-C^4 bond and 2.5º for the torsion around the S-C^2 bond. These differences are due to the different bond lengths and bond angles (93.4º and 104.2º for sulfur and oxygen, respectively).

X-Ray studies on several other compounds with 1,3-oxathiane units [*e.g.* S-benzylsulfonium perchlorate (**95**)[66] derived from 5,6,7,8,9,10-hexahydro-4,4,7-trimethyl-4*H*-benzo-1,3-oxathiane or (2*S*,3*R*,4*R*)-2-methyl-4-propyl-1,3-oxathiane-3-oxide (**96**),[44] Figure 1c] confirm that the bond angles and the torsion angles of the 1,3-oxathiane ring remain in the normal range in the sulfur substituted derivatives too (Table 4).

Table 4. Bond angles and torsion angles of the 1,3-oxathiane ring in compounds (**38e**, **93**-**96**) (solid state).

Bond	Compound					Torsion	Compound				
angles	**93**	**94**	**38e**	**95**	**96**	angles	**93**	**94**	**38e**	**95**	**96**
$O^1C^2S^3$	112.3	114.3	109.5	110.0	111.8	$O^1C^2S^3C^4$	-56.4	-60.5	-52.4	53.6	-55.6
$C^2S^3C^4$	95.8	93.4	98.3	99.4	96.2	$C^2S^3C^4C^5$	53.9	57.3	51.0	-44.0	51.0
$S^3C^4C^5$	110.7	114.4	113.9	110.6	110.3	$S^3C^4C^5C^6$	-61.1	-61.4	-55.6	51.2	-59.0
$C^4C^5C^6$	111.7	108.7	109.4	115.0	113.0	$C^4C^5C^6O^1$	62.1	63.2	58.8	-59.2	62.2
$C^5C^6O^1$	112.9	117.7	114.1	111.3	111.9	$C^5C^6O^1C^2$	-64.2	-63.6	-67.4	70.6	-66.5
$C^6O^1C^2$	112.5	104.1	115.6	113.7	113.3	$C^6O^1C^2S^3$	65.4	65.5	65.1	-69.8	67.1

^{1}H NMR ASIS experiments[67,68] on some 1,3-oxathiane derivatives confirmed the geometry of the basic ring.

Full geometry optimisations (*ab initio* calculations) of 1,3-oxathiane (along with other six-membered rings) were carried out using density functional theory (DFT),[69,70] in good agreement with experimental data.

Derivatives exhibiting important steric crowding in their chair forms show lower energy differences between chair and twist-boat conformers, and 1,3-oxathianes with *syn*-axial 2,4- or 2,6- methyl-methyl interactions in the chair conformers prefer to adopt a (2,5-, 1,4- or 3,6-) twist form.[18]

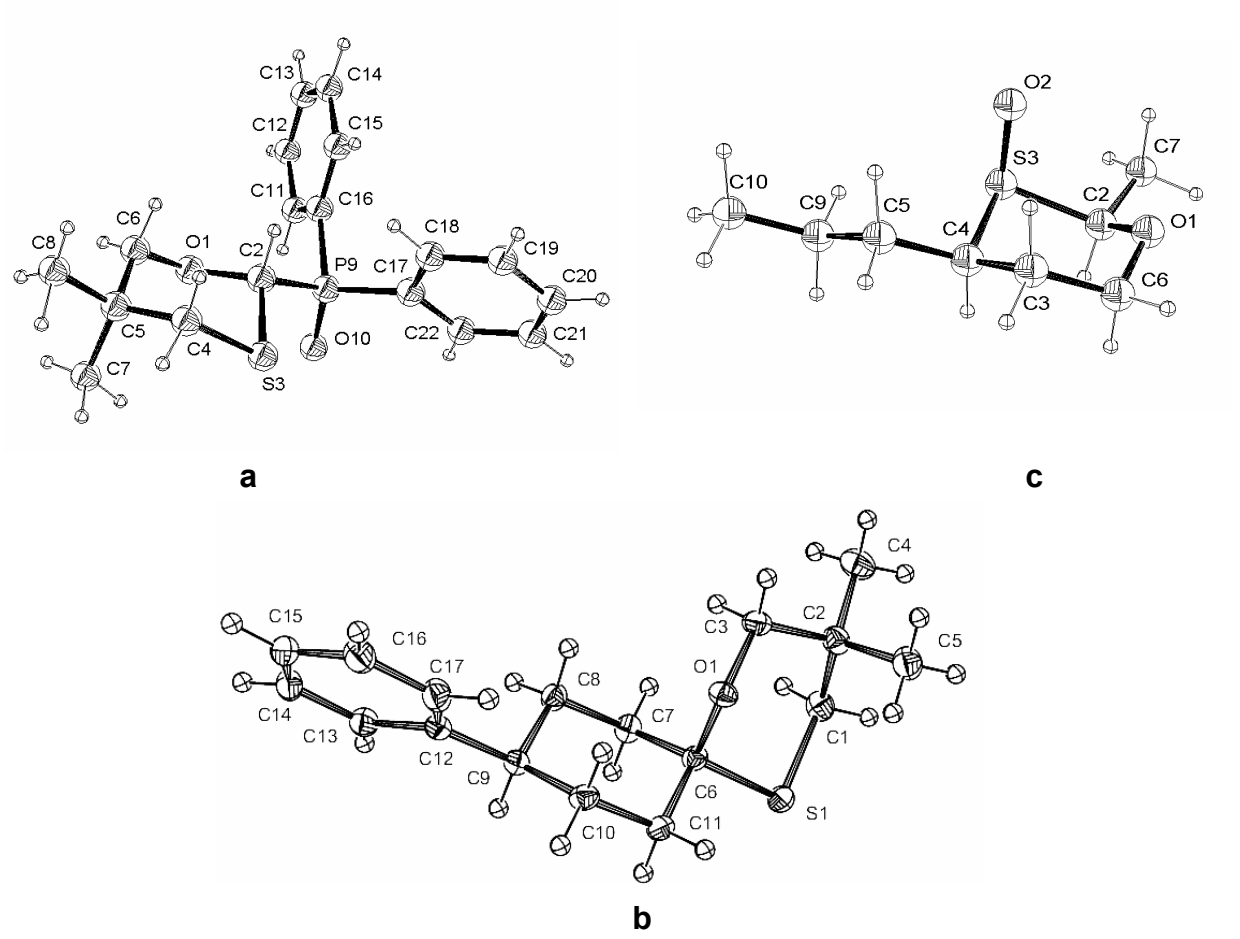
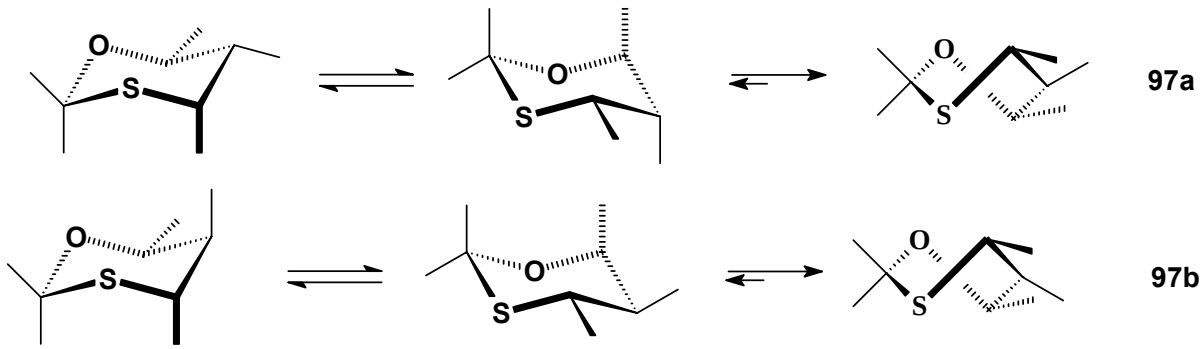


Figure 1. ORTEP diagrams of compounds **94** (a), **38e** (b) and **96** (c).

2,2,r-4,*cis*-5,*trans*-6-Pentamethyl-1,3-oxathiane (**97a**) and 2,2,r-4,*trans*-5,*trans*-6-pentamethyl-1,3-oxathiane derivatives (**97b**) exhibit non-chair conformations and exist mainly in 2,5-TB forms (Scheme 21) in agreement with the observed values for coupling constants. The 2,5-TB conformers of these compounds are at least 8.0 kJ / mol^{-1} more stable than the respective chair forms and so the amounts of the latter conformer do not exceed 5%.[18]

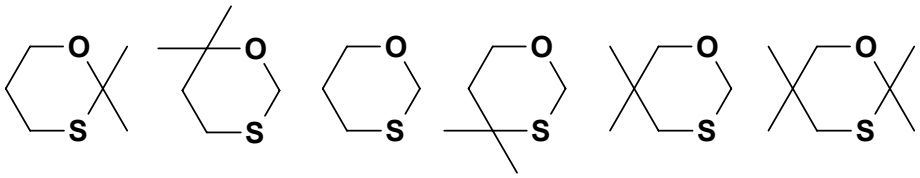
Scheme 21



The free enthalpies of activation (for chair-chair ring inversion) $\Delta G^{\neq}$ were determined by NMR spectrometry for 1,3-oxathiane itself and its methyl derivatives (Table 5). The rate constants *k* of the chair to chair inversion depends on the number and position of the substituents.[16] The value

obtained for the unsubstituted 1,3-oxathiane ($\Delta G^{\neq}$ = 38.9 kJ mol^{-1}) is smaller than the values measured for 1,3-dioxane ($\Delta G^{\neq}$ = 41.4 kJ mol^{-1}) and 1,3-dithiane ($\Delta G^{\neq}$ = 43.1 kJ mol^{-1})[16]

Table 5. Free enthalpies of activation (chair-chair ring inversion) for some 1,3-oxathiane derivatives.[16]

Compound						
	33	**7**	**1**	**9**	**8**	**98**
$\Delta G^{\neq}$ (203 K; kJ / mol)	33.4	38.0	38.9	38.9	43.5	48.5

$\Delta G^{\neq}_{203K}$ exhibits values between 33.4 kJ/mol and 48.5 kJ/mol and the *k* values differ with a 10^3 factor. A pair of geminal methyl groups at position 2 causes an increase of inversion rate; the $\Delta G^{\neq}_{203K}$ value is 33.4 kJ/mol, with 5.5 kJ/mol lower than for the unsubstituted 1,3-oxathiane. The inversion rate is only moderately increased when the geminal methyl groups are at positions 4 or 6. For 5,5-dimethyl-1,3-oxathiane (**8**) the ring inversion is slower ($\Delta G^{\neq}_{203K}$=43.5 kJ/mol). A remarkable difference appears in 2,2,5,5-tetramethyl-1,3-oxathiane (**98**), the barrier of ring inversion is very high ($\Delta G^{\neq}_{203K}$= 48.5 kJ/mol), the expected compensation of geminal substitution at positions 2 and 5 were not observed. The dependence of *k* on the substituents is more difficult to understand in 1,3-oxathianes (comparing to 1,3-dioxanes and 1,3-dithianes) since these molecules are not symmetrical. However, the lower value of $\Delta G^{\neq}_{203K}$ for **33** is due to the more important increasing of the energy of the compound in the ground state compared with the increase of energy of the transition state (half-chair conformers). The opposite result observed for **8** is due to a reversed compensation of the above mentioned effects in agreement with the important A-values differences for a methyl group at positions 2 and 5 ($A_{2\text{-Me}}$ = 13.6 kJ/mol; $A_{5\text{-Me}}$ = 2.8 – 3.1 kJ/mol).[18,20]

3.2. Conformational analysis of the derivatives

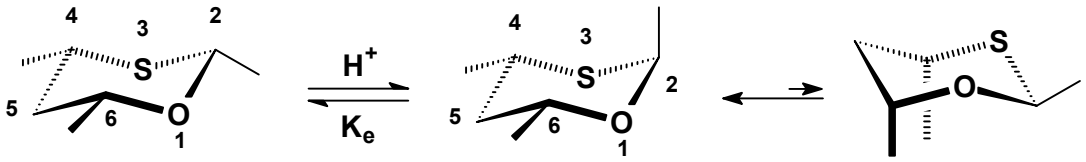
3.2.1. A-values determinations

The majority of A-values determinations on 1,3-oxathiane derivatives were carried out using the method of chemical equilibration of diastereoisomers (*cis* and *trans* structures) under acidic conditions.

The A-value for the methyl group at position 2 was obtained by equilibrating stereomeric 2,4,6-trimethyl-1,3-oxathianes (**23**) (Scheme 22), while from equilibria of similar conveniently

substituted compounds the A values for other substituents (ethyl, *i*-propyl) at position 2 (Table 6) were also determined.[20]

Scheme 22



23 (r-2, 4-*cis*, 6-*cis*) **23 (r-2, 4-*trans*, 6-*trans*)**

The values obtained for 1,3-oxathiane derivatives are somewhat higher than the average of the values obtained for similar 1,3-dioxane and 1,3-dithiane compounds (Table 6).

The diastereoisomeric equilibria of appropriate isomers of **23**, **26** and **10** were used for the determination of A values for methyl groups located at the other positions of the 1,3-oxathiane ring (Table 7)

Table 6. A-values (298 K; kJ mol^{-1}) for several substituents located at position 2 in 1,3-oxathiane, 1,3-dioxane and 1,3-dithiane rings

	Substituent			References
Ring	CH_3	C_2H_5	*i*-C_3H_7	
1,3-oxathiane	13.6	13.6	14.8	20
1,3-dioxane	16.6	16.9	17.4	54
1,3-dithiane	8.0	6.4*	9.3; 9.7	20; 54

* 342 K

Table 7. A-values (298 K; kJ mol^{-1}) for the methyl group in different positions of 1,3-oxathiane, 1,3-dioxane and 1,3-dithiane rings

	Position of methyl group				References
Ring	2	4	5	6	
1,3-oxathiane	13.6	7.4	2.7-3.7	12.3	18, 20
1,3-dioxane	16.6	12.2	3.6	12.2	54
1,3-dithiane	8.0	6.5-7.1	4.9	6.5-7.1	54

Steric demands at C^2 are high and due to the constrained nature of the dissymmetric 1,3-oxathiane ring, the A-value (2-CH_3) is higher than the mean value of the same interactions in 1,3-dioxane and 1,3-dithiane. The A-value for the 6-methyl group is closer to the one for 1,3-dioxane ring, the molecule is behaving in a 1,3-dioxane-like manner, while the A-value for a 4-methyl group is closer to that found in 1,3-dithiane.[71] The unexpectedly low A-value for a 5-

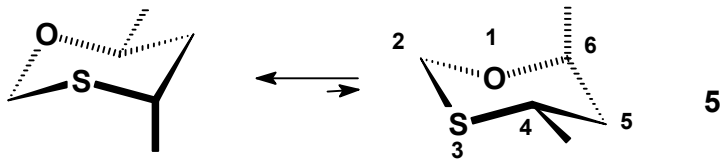
methyl group, even lower than that for 1,3-dioxane, is probably due to a distortion of the 1,3-oxathiane ring.

Similar A-values for methyl groups were also obtained from ^{1}H-NMR coupling constants.[18]

The conformational equilibrium study by ^{1}H-NMR spectra shows that in the case of 4-methyl- and 5-methyl-1,3-oxathianes (**4** and **3**) the equilibrium is shifted towards the conformer with the methyl group in equatorial position. If at position 2 a bulkier alkyl group appears [as in 2-R-5-methyl-1,3-oxathiane, R=CH_3 (**18**), C_2H_5 (**99**), *i*-C_3H_7 (**28**)], the conformer with the methyl group at position 5 in axial orientation is largely favoured for the *cis* isomer [R=CH_3 (2e5a, 98%)],[18] contrary to an earlier study that stated that *cis* isomers are flipping compounds with close ratios of 2e,5a and 2a,5e isomers, and only *trans* isomers are anancomeric.[72]

Some semiquantitative evaluation of steric effects in 1,3-oxathianes can be done by accepting the addition principle. The 1,3-oxathiane ring being dissymetric, an axial group next to the sulfur atom (4-methyl) is less sterically compressed than the one in the ether part. So, the amount of 4-axial isomer (**4a, 6e**) for 4,6-*trans*-dimethyl-1,3-oxathiane (**5**) is of about 85% (ΔG^o = 4.3 kJ/mol) as determined[73] from the vicinal coupling constants in ^{1}H-NMR spectrum, in good agreement with the energy difference ($\Delta G^o_{calc} = A_O - A_S$ = 5.7 kJ/mol) obtained from comparing the A-values of a methyl group located at position 4 of the 1,3-dioxane (A_O = 12.2 kJ/mol) and 1,3-dithiane rings (A_S = 6.5 kJ/mol; Scheme 23).

Scheme 23

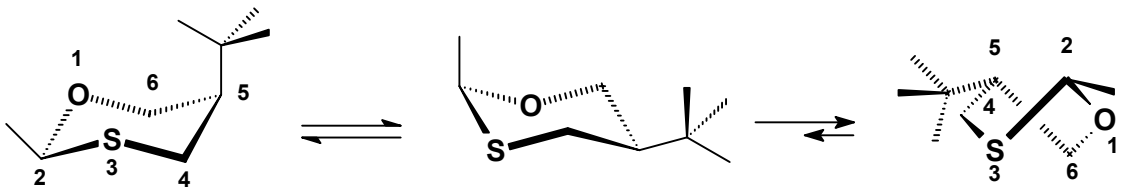


5

4a,6e **4e, 6a**

5-Alkyl-, 2,5-dialkyl- and 2,2,5-trialkyl-1,3-oxathianes exist mainly in chair conformation. As an exception, *cis*-2-methyl-5-*t*-butyl-1,3-oxathiane (**100**) has predominant 1,4-twist conformation with pseudoequatorial orientation of the substituents (Scheme 24).[74-76]

Scheme 24



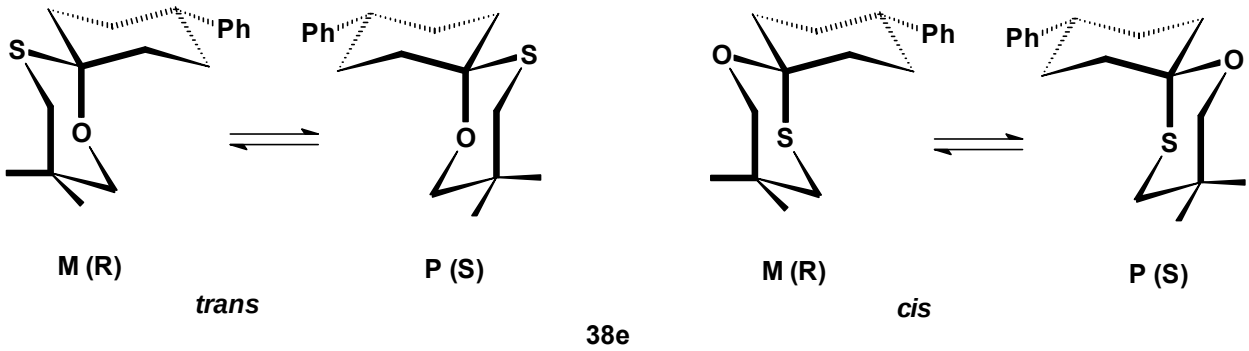
2e, 5a **2a, 5e** **1,4-TB**

100-*cis*

Cis and *trans* isomers of substituted spiro-1,3-oxathianes (*e.g.* 3,3-dimethyl-9-phenyl-1-thia-5-oxaspiro[5.5]undecane (**38e**))[29] and polyspirooxathianes[77] exhibit semiflexible structures, the flipping of the heterocycle (Scheme 25) being an enantiomeric inversion (both the chirality of the oxathiane ring and of the spirane are changed).

The substituent (R= $Si(CH_3)_3$, $Ge(CH_3)_3$, $Sn(CH_3)_3$, $Pb(CH_3)_3$, $N(CH_3)_2$) in 2-R(heterosubstituted)-1,3-oxathianes prefers in most of the cases the equatorial orientation, but in some other cases the conformer with axial orientation of the substituent predominates (R= OCH_3, SCH_3, $SeCH_3$).[30] When R=P(O)R'$_2$ (R'=Ph or OCH_3), the compounds exist as chair forms in solution as well as in solid state with equatorial phosphoryl group (*e.g.* $A_{328K}[P(O)Ph_2]$≈6.0 kJ/mol).[47]

Scheme 25



38e

The axial-equatorial free energy differences of some anancomeric ethyl 1,3-oxathiane-2-carboxylates were obtained by means of chemical equilibration.[78] No equatorial preference of the carboethoxy group in low polar solvents ($A_{COOC2H5}$ = 0.0 kJ / mol in heptane) was noticed and the anomeric effect of the S-C-$COOC_2H_5$ segment was estimated at 5.4 kJ/mol. Following extrapolation of the solvent dependence of $A_{COOC2H5} = A + B(0.5-X)^{1/2}$; $X = (\varepsilon-1)/(2\varepsilon+1)$; ε = dielectric constants of the applied solvents to the vapor state, the anomeric effect of the S-C-$COOC_2H_5$ fragment was found to be of 7.2-7.7 kJ/mol. This leads to the conclusion that, beside the axial-equatorial equilibrium – the equatorial conformer being stabilised by polar solvents -, a second conformational equilibrium is involved – the rotation of the carboethoxy substituent around the exocyclic bond (C^2-C=O) of the heterocyclic ring, also solvent-dependent. Therefore, in nonpolar solvents, there is a decrease in the effective size of the carbethoxy group as a result of the stabilisation of the C=O-inside rotational conformer by $\pi_{C=O} \rightarrow 3d_{(S)}$ orbital interactions and this is in part responsible for the abnormal $A_{COOC2H5}$ value in nonpolar solvents as heptane. At room temperature, there is no preference for the sulfoxide group in 3-oxo-1,3-oxathiane and it is a 1:1 mixture of the SO_{ax} and SO_{eq} chair forms,[47,79] but at low temperature, the axial preference

of the oxygen atom was reported ($A_{175K\ [S\rightarrow O]}$= -2.4 kJ/mol,[80] $A_{178K\ [S\rightarrow O]}$= - 4.8 kJ/mol).[79] More recent studies[47] confirmed the previous results at room temperature but at low temperature a mixture of axial:equatorial conformers of 3:1 corresponding to a smaller $A_{173K\ [S\rightarrow O]}$ (- 1.6 kJ/mol) was observed. Variously substituted [2-methyl- (*trans*:2e,3e only, no *cis* monoxide detected), 4-methyl- (*trans*:3e,4e; *cis*: 3a,4e), 5-methyl-(*trans*:3e,5a; 7% and 3a,5e; 93%; *cis*: 3e,5e) and 6-methyl- (*trans*:3e,6e; *cis*: 3a,6e)] 3-oxo-1,3-oxathianes exhibit anancomeric chair conformation, excepting the 5-methyl derivatives.[47] A totally different preference for the SO group appears in 5,5-dimethyl-1,3-oxathiane-3-oxide: the equatorial disposition is favoured (SO_{ax}:SO_{eq}=1:9, $A_{171K\ [S\rightarrow O]}$= 3.1 kJ/mol).[47] Oxidation of 2-(*p*-bromophenyl)-1,3-oxathiane led to a 3:1 mixture of the *cis* and *trans* sulfoxides respectively.[49] The 3-*p*-chlorophenylimide-1,3-oxathiane has the substituent in equatorial orientation ($A_{[=N\text{-}C6H4\text{-}Cl]}$ = 1.6 kJ/mol), while the 3-tosylimide is again mainly axial ($A_{[=N\text{-}SO2\text{-}C6H4\text{-}Me]}$ = - 1.2 kJ/mol).[81]

The *S*-benzyl group in the *S*-benzyl sulfonium perchlorate[66] derived from Eliel's oxathiane (5,6,7,8,9,10-hexahydro-4,4,7-trimethyl-4*H*-benzo-1,3-oxathiane) is axial both in solution and solid state.

4. NMR SPECTRAL DATA

4.1. H,H coupling constants

The NMR parameters of the 1,3-oxathiane ring were determined from the low temperature spectra of the parent compound and from the spectra of appropriate anancomeric derivatives. The geminal, vicinal and long range coupling constants in the C^4-C^5-C^6 moiety were determined from the ^{1}H NMR spectra of 2-substituted 1,3-oxathianes. The influence of the "holding group" at position 2 on the coupling constants of the aliphatic part of the heterocycle is considered insignificant.

The values of these coupling constants are presented in Table 8 along with the same constants for 1,3-dioxane and 1,3-dithiane rings for comparison.

Table 8. H,H coupling constants (Hz) for 2-*p*-chlorophenyl-1,3-dioxane (**101**),[82] 2-phenyl-1,3-oxathiane (**102**)[59] and 2-phenyl-1,3-dithiane (**103**)[59] (CCl_4, rt).

Com-	^{2}J			^{3}J								^{4}J
pound	4a,4e	5a5e	6a6e	4a5e	4a5a	4e5e	4e5a	5e6e	5e6a	5a6e	5a6a	4e6e
101	-11.5	-13.2	-11.5	2.6	12.3	1.3	4.9	1.3	2.6	4.9	12.3	2.6
102	-13.1	-13.8	-11.9	2.4	12.8	3.2	3.7	2.2	2.2	3.9	12.5	1.9
103	-14.2	-13.9	-11.9	2.3	12.4	4.4	2.9	4.4	2.3	2.9	12.4	0

The geminal H,H coupling constants for 1,3-diheterocyclohexane exhibit different values in correlation with the nature of neighbouring heteroatoms, the expected values being in the normal range:[83-86] – J_{gem} = 11-12.5 Hz in a –CH_2-O- moiety (11.5 Hz in tetrahydropyran), 13-14 Hz in –CH_2-S- moiety (13 Hz in thiane) and 12-15 Hz in –C-CH_2-C- part (13 Hz in cyclohexane). The values of vicinal coupling constants vary on the orientations of the coupled protons, the magnitude of the vicinal axial-axial coupling constant (J_{aa}) varies between 8 and 14 Hz, while the values of the vicinal axial-equatorial (J_{ae}) and equatorial-equatorial (J_{ee}) protons are considerably smaller (0-6 Hz). The long-range coupling constants between the equatorial protons at positions 4 and 6 (W rule) have values of 2-2.5 Hz.[49]

In 1,3-oxathiane ring the geminal coupling constants at C^2 ($-J_{2a2e}$) are in the range of 11.0-11.2 Hz, the $-J_{6a6e}$ value varies from 11.7 to 12.0 Hz, while the $-J_{4e4a}$ value is in the range from 13.1 to 13.4 Hz and the geminal coupling constants at C^5 ($-J_{5e5a}$) vary from 13.4 to 14.0 Hz.

The values of vicinal coupling constants depend on a large number of factors among them the torsion angles and the electronegativity of the heteroatoms of the ring being the most important. In 1,3-oxathiane the axial-axial and equatorial-equatorial coupling constants involving the protons close to the sulfur atom (position 4) are somewhat larger than the similar constants involving the protons close to the oxygen atom (position 6), while the values of axial-equatorial coupling constants are smaller when the axial proton at position 6 is involved (Table 9).[17]

Table 9. Usual range of vicinal coupling constants (Hz) in 1,3-oxathiane derivatives.[17]

Coupling constants	4a5a	5a6a	4e5a	5a6e	4a5e	5e6a	4e5e	5e6e
Values	11.5-11.9	10.5-11.8	3.6-4.2	3.6-3.9	3.1-3.4	2.3-3.0	3.6-3.7	2.3-2.8

Table 10 shows the values of long range couplings (Hz) that appear in 1,3-oxathianes [17,59,87]

Table 10. Usual long-range (^4J and ^5J) coupling constants (Hz) in 1,3-oxathiane derivatives.[17]

Long-range couplings	4e6e	2e4e	2e6e	2e5e	4e6a	2a4e	2a6e
Values of constants	1.9-2.4	1.2-2.1	0.0	0.5	0.3	0.5	0.3

*$^5J_{2e5a}$, $^5J_{2a5e}$, $^5J_{2a5a}$, $^5J_{4a6e}$, $^5J_{4a6a}$, $^4J_{2e4a}$, $^4J_{2a6a}$, $^4J_{2a4a}$ were not observed.

The vicinal exocyclic coupling constants values in the NMR spectra of cyclic products depend on the orientation (axial or equatorial) of the substituents involved. The equatorial ring hydrogen atoms couple with axial exocyclic vicinal nuclei in a larger amount compared to the coupling of the axial protons with equatorial exocyclic vicinal nuclei. Some values for the vicinal exocyclic

constants in variously substituted 1,3-oxathianes summarised by Anteunis[88] are presented in Table 11.

Table 11. Characteristic vicinal exocyclic coupling constants (Hz) of the protons of the 1,3-oxathiane ring.[88]

Coupling constants*	4aRe	4eRa	5aRe	5eRa	6aRe	6eRa	2aRe
Values	6.6-6.8	7.0-7.5	6.9	6.8	5.3-6.2	7.8	6.0-6.6

*R = CH_3, C_2H_5, *n*-C_3H_7, *i*-C_3H_7, *n*-C_4H_9, *i*-C_4H_9

It is worth noticing the difference in the values of the vicinal exocyclic constant for the equatorial or axial methyl group at positions 4 and 6 (ΔJa,e = 0.6-2.0) compared to the same difference that is almost zero at position 5 .

4.2. C,H coupling constants

Correlation between the orientation of the C-H bond and the magnitude of the corresponding ^1J coupling constants have been made starting with Perlin.[89] For example, it has been observed that ^1J for an equatorial C-H bond adjacent to oxygen or nitrogen in a six-membered ring is with 8-10 Hz larger than that for the corresponding axial bond ($^1J_{C\text{-}He} > {}^1J_{C\text{-}Ha}$, normal Perlin effect). For *cis*-4,6-dimethyl-1,3-dioxane $^1J_{C2\text{-}Ha}$ = 157.5 Hz < $^1J_{C2\text{-}He}$ = 167.4 Hz. In the dithiane analogue the situation is reversed $^1J_{C2\text{-}Ha}$ = 154.1 Hz > $^1J_{C2\text{-}He}$ = 144.9 Hz and, in fact, all C-H bond pairs in 1,3-dithiane exhibit a “reverse” Perlin effect when C-H_{eq} bond is antiperiplanar to C-S bonds.[90,91]

The $^1J_{C\text{-}H}$ values for different 1,3-oxathianes are presented in Table 12.[90,91]

Table 12. ^1J coupling constants (Hz) in 1,3-oxathianes

1,3-oxathiane	C2		C4		C5		C6	
derivative	Ha	He	Ha	He	Ha	He	Ha	He
parent compound*	157.5	157.5	142.7	142.7	126.9	129.0	139.0	154.4
cis-4,6-dimethyl	157.5	157.5	142.1	(138.8)#	126.7	126.7	140.7	(145.2)#
trans-4,6-dimethyl	156.4	156.4	138.9	138.9	125.0	125.0	139.9	139.9
2-*t*-butyl	156.0	-	136.2	140.6	128.8	125.7	138.1	146.2
4,4,6-trimethyl	156.5	156.5	-	-	124.5	124.5	142.7	-

*Spectrum run at –90 °C; # estimated values

Proton coupled ^{13}C and high-resolution ^{1}H-NMR spectra of *cis*- and *trans*-4,6-dimethyl-1,3-oxathianes permitted the observation of similar coupling constants $^{1}J_{C\text{-}He} \approx {}^{1}J_{C\text{-}Ha}$ at C^2 and C^5 as a balance of the two opposite effects in these positions. Comparison of the axial with equatorial couplings at positions 4 and 6 leads to the conclusion that C^4 adjacent to the sulfur atom presents a reverse Perlin effect while C^6 shows a normal Perlin effect. However in 2-*t*-butyl-1,3-oxathiane a normal Perlin effect at C^4 was observed.[90] For the unsubstituted 1,3-oxathiane the ring inversion is slowed at –90°C, so ^{1}J values can be determined. An equilibration of the two Perlin effects appears at C^2, C^4 and C^5, while at C^6 a normal Perlin effect is present.

One-bond coupling constants were also calculated by computational methods and these results were in good agreement with those obtained experimentally, although a strong "reversed" Perlin effect is predicted at C^5, contrary to experiment.[69,70]

4.3. ^{1}H-NMR chemical shifts

The chemical shifts for axial and equatorial protons of 1,3-oxathiane itself (Table 13) were determined from the spectrum run at –90°C (CD_2Cl_2).[90,91]

Table 13. ^{1}H NMR chemical shifts for 1,3-oxathiane.[90,91]

Proton	2e	2a	4e	4a	5e	5a	6e	6a
δ, ppm	4.80	4.91	2.75	3.06	1.76	2.01	4.10	3.62

The axial protons at C^2, C^4 and C^5 are more deshielded than the equatorial ones, only at C^6 similarly with 1,3-dioxane the equatorial proton is more deshielded than the axial one. The anomalous chemical shifts ($\delta_a > \delta_e$) at C^2 and C^4 are the result of relevant contributions of $\sigma_{C\text{-}S} \rightarrow \sigma^*_{C\text{-}H}$ two-electron-two-orbital interactions, as well as the $\beta_O W_N \rightarrow C^5\text{-}H_e$ stereoelectronic interactions that are also manifest in 1,3-dioxanes.[92,93]

A special case is that of 1,3-oxathiane derivatives that bear in position 2 substituents containing group 16 elements (O, S, Se): for these, the anomalous chemical shifts ($\delta_a > \delta_e$) are present not only for C^4, but also for C^6.[12]

4.4. ^{13}C-NMR chemical shifts

^{13}C-NMR chemical shifts[66,67] in variously substituted 1,3-oxathianes are gathered in Table 14.

Introducing an alkyl substituent on the 1,3-oxathiane ring produces a downfield shift of up to 17 ppm in the signals of the α-carbon atoms relative to the unsubstituted ring. Changes are also noted in the chemical shifted of the β-carbon atom: the equatorial methyl and isopropyl groups at C^5 have a stronger effect on the chemical shift of the C^4 than of the C^6 carbon atom. The effect of the methyl group at C^5 on the δ-carbon atom.[74,75]

Table 14. ^{13}C-NMR spectral data (ppm) and $\Delta\delta = \delta_{compound}-\delta_{parent\ compound}$ values (ppm) for some 1,3-oxathianes[74,75]

1,3-oxathiane derivative	C^2	Δδ	C^4	Δδ	C^5	Δδ	C^6	Δδ
parent compound[61]	72	-	27.1	-	27.5	-	69.7	-
2-*i*-propyl-	89.0	17.0	27.8	0.7	34.1	6.6	70.2	0.5
5-methyl-	75.2	3.2	30.7	3.6	34.2	6.7	70.6	0.9
5-*i*-propyl-	71.9	-0.1	33.0	5.9	34.8	7.3	73.1	3.4
cis-2,5-dimethyl-	78.4	6.4	29.7	2.6	34.0	6.5	73.9	4.2
trans-2,5-dimethyl-	78.9	6.9	26.4	-0.7	35.0	7.5	75.6	5.9
cis-2-ethyl-5-methyl-	79.2	7.2	32.0	4.9	39.0	11.5	71.2	1.5
trans-2-ethyl-5-methyl-	79.3	7.3	31.3	4.2	39.1	11.6	71.3	1.6

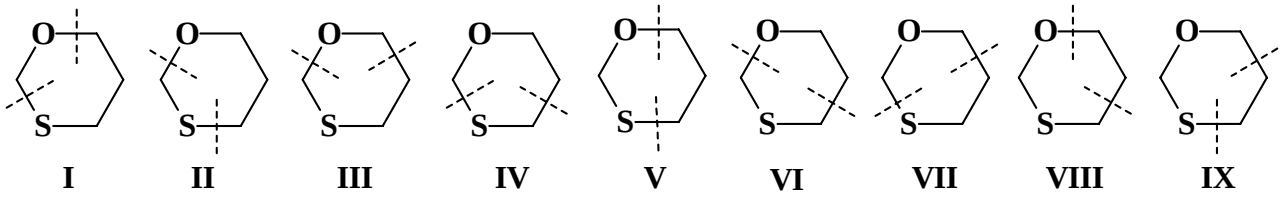
^{13}C-NMR spectral data were also reported for other 2-R-1,3-oxathiane derivatives in which R group contains heteroatoms (R =OCH_3, SCH_3, $SeCH_3$, $Sn(CH_3)_3$, $Ge(CH_3)_3$, $Pb(CH_3)_3$, $Si(CH_3)_3$, $N(CH_3)_2$; $P(O)Ph_2$).[28,40]

5. MS SPECTRAL DATA

Additional data on the structure and the conformational equilibrium of 1,3-oxathianes were obtained from electron impact mass spectrometry studies.

The most intense peaks in the mass spectra of 1,3-oxathianes are mainly due to the sulfur containing fragments, as the heteroatom stabilises the positive charge formed by electron bombardment. The modes of fragmentation differ of those of 1,3-dioxanes, but resemble closely those observed for 1,3-oxathiolanes.[94] Of the nine possible modes of ring cleavage yielding fragments of two to four atoms (Scheme 26), only six modes were actually observed (I, II, VI-IX) and two of these predominate (I and II).[95]

Scheme 26



The ring cleavage of derivatives (R is a substituent on the 1,3-oxathiane ring) follows the formation of the ion $[M]^+$ or $[M\text{-}R]^+$, while only the unsubstituted 1,3-oxathiane gives an appreciable $[M\text{-}1]^+$ fragment. The mode of fragmentation depends on the degree of substitution and on the position of the substituents.

The intensity of the molecular ion decreases with the increasing size of the 2-alkyl group in 2-alkyl-substituted 1,3-oxathianes for which the most intense peak is the $[M\text{-}R]^+$ fragment (R=C_2H_5, *i*-C_3H_7, *t*-C_4H_9). The groups at C^2 are the first to break in the 2-substituted 1,3-oxathianes. When there are two different substituents in position 2, the axial one is more reactive because of its interactions with the *syn*-axial 4 and 6 hydrogen atoms.

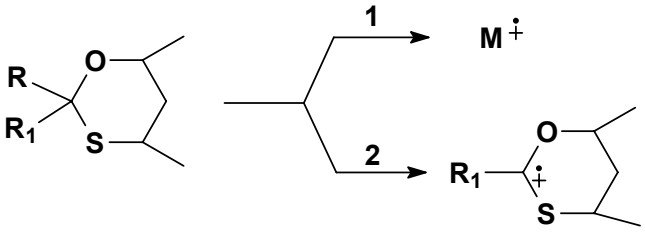
Ionisation and appearance potentials may be successfully applied to the estimation of conformational energies and other non-bonded interactions in gas phase. It is possible to obtain the differences in the ground-state enthalpy of isomers (equations 1 and 2) as sometimes even the formation of the molecular ion$[M]^+$ or of $[M\text{-}R]^+$ fragment (Scheme 27) is sufficient to release the bond energy.[96,97]

$$IP\ ([M]^{+\cdot}) - IP\ ([M_1]^{+\cdot}) = \Delta H_f^o\ (M_1) - \Delta H_f^o\ (M) \qquad (1)$$

$$AP\ ([M\text{-}R]^{+\cdot}) - AP\ ([M_1\text{-}R]^{+\cdot}) = \Delta H_f^o\ (M_1) - \Delta H_f^o\ (M) \qquad (2)$$

where AP is the appearance potential, IP the ionisation potential of the primary fragment and ΔH_f^o is the standard enthalpy of formation of the studied compound.

Scheme 27



route 1: R=R$_1$=H; R=H, R$_1$=CH$_3$; R=R$_1$=CH$_3$
route 2: R=CH$_3$, R$_1$=H; R=R$_1$=CH$_3$

Three series of stereomeric 1,3-oxathianes were studied[63] because the presence of sulfur increases the stability of the $[M]^+$ and $[M\text{-}R]^+$ ions and makes the measurements of IP and AP of these isomer pairs possible.

The less stable compound has always the lowest AP according to the assumption that the energy due to the nonbonding interactions is mainly released in the formation of the first fragmentation. From these data the conformational enthalpies in gas phase at 120°C for axial methyl at 4 and 6 positions were determined as well as the enthalpy for the chair-twist

equilibrium for 2,2-*trans*-4,6-tetramethyl-1,3-oxathiane (**92**) and the values agree well with those obtained by chemical equilibration in liquid state (Table 15).

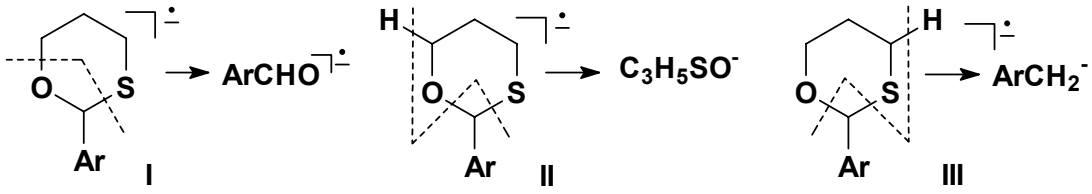
The negative-ion MS spectra of 2-aryl-1,3-oxathianes[98] (aryl = *o-, m-, p*-nitrophenyl) contain pronounced molecular anions together with large fragment ions produced by simple or complex cleavage. These types of compounds may accept electrons in order to produce molecular anions that split later, with or without skeletal rearrangement. Three modes of simple fragmentation are presented (Scheme 28).

Using the deuterated derivatives it was demonstrated that the extent of hydrogen scrambling between the 2-, 4- and 6-positions is specific to each isomer and that a characteristic proximity effect appears for the *o*-nitrophenyl isomer. This behaviour is similar to that of the isomeric 1,3-dithianes,[99] but in contrast with the 1,3-dioxane analogues, which give similar spectra but show no hydrogen scrambling or proximity effects.[98]

Table 15. Conformational enthalpies of methyl-substituted 1,3-oxathianes.

Source of interaction	ΔHº gaseous state (kJ/mol)		ΔHº liquid state[18,20,52] (kJ/mol)
	IP	AP	
Axial 4-methyl	6.5±1.4	9.6±1.1	7.5
Axial 6-methyl	10.9±1.4	13.0±1.1	12.3
Δ(6a-4a)	4.4±0.5	4.0±0.5	4.8
Chair-twist equilibrium (ΔH_{CT})	-	22.5±4.0 (AP)	24-27

Scheme 28



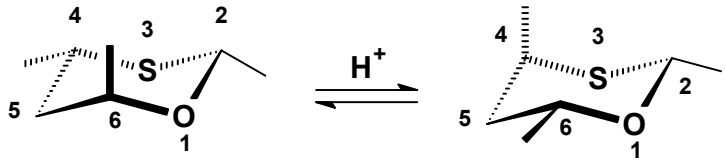
6. RING-CHAIN TAUTOMERISM

Several cases of isomerization of *cis*- and *trans*- 1,3-oxathiane derivatives have been reported. Epimeric 2,4,6-trimethyl-1,3-oxathianes (**23**) (*e.g. r*-2-*cis*-4-*trans*-6- and *r*-2-*trans*-4-*cis*-6-trimethyl-1,3-oxathiane, Scheme 29) were equilibrated in CCl_4 using $BF_3{\cdot}(C_2H_5)_2O$ as catalyst for two to six weeks and the evolution of the reaction was monitored in GC.[20]

Equilibration of ethyl 6-methyl-1,3-oxathiane-2-carboxylate (**104**, Scheme 30) was performed in several solvents using again boron trifluoride etherate as catalyst for 10 days. After working up,

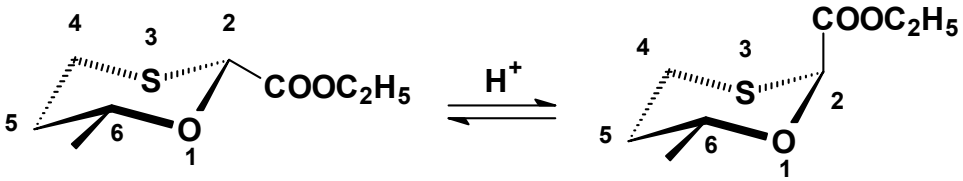
the equilibrated samples were analysed by ^{1}H-NMR spectroscopy to obtain the equilibrium constants by peak area measurement of particular signals.[78]

Scheme 29



23 (r-2, 4-*cis*, 6-*trans*) **23 (r-2, 4-*trans*, 6-*cis*)**

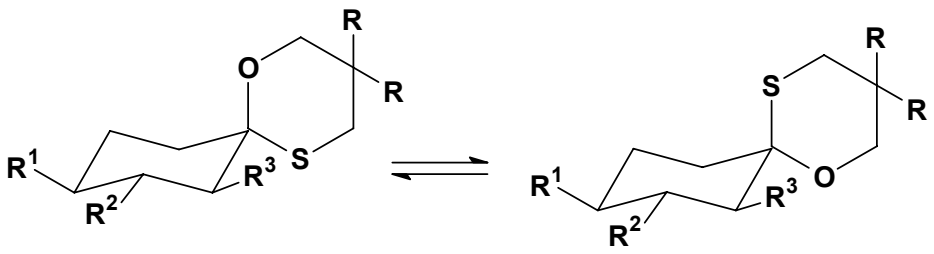
Scheme 30



104-*cis* **104-*trans***

The same technique for analysing the equilibrated mixture was used in the equilibration of spiro-1,3-oxathianes[28,29] (Scheme 31, Table 16) but this time the equilibration was attended in the presence of residual HCl and water in the $CDCl_3$ used in recording the ^{1}H-NMR spectra in matter of hours. Fragments of the spectra (corresponding to the protons at position 6) recorded at several mean times used for the determination of the ratio of *cis* (δ_{cis} = 3.52 ppm) and *trans* (δ_{trans} = 3.45 ppm) isomers of compound (**38e**) are shown in Figure 2. The kinetic parameters were determined using equations 3 and 4.

Scheme 31



trans	R=H; R^1=Ph; R^2=R^3=H,	**37**	*cis*
trans	R=CH_3; R^1=Ph;R^2=R^3=H,	**38e**	*cis*
cis	R=R^2=CH_3;R^1=R^3=H,	**38c**	*trans*
trans	R=R^3=CH_3;R^1=R^2=H,	**38b**	*cis*

In equations (3) and (4) k_1 and k_{-1} are the forward and reverse reaction rate constants, K is the equilibrium constant, x_e is the concentration of the *cis* isomer for **37**, **38b** and **38e** and of *trans* isomer for **38c** at equilibrium and *x* is the concentration of the same isomer at the "*t*" time. The k

values (Table 16) are similar, the rate of the isomerization reaction is not strongly influenced by the position of the substituents.

Table 16. Kinetic parameters (k_1, k_{-1}; min^{-1}) for isomerizations of **37, 38b, 38c** and **38e**.

Compound	Starting isomer	C_i(mol/l) x10^2	K	k_1x10^3	k_{-1}x10^3
37	*trans*	9.7	0.72	8.71	12.0
38e	*trans*	3.4	1.43	4.24	2.96
38c	*cis*	4.3	0.62	7.37	11.8
38b	*trans*	4.8	0.69	2.63	3.81

$$\ln \frac{x_e}{x_e - x} = (k_1 + k_{-1})t \qquad (3) \qquad \frac{k_1}{k_{-1}} = K \qquad (4)$$

The isomerization involves the opening of the heterocycle to give the open-chain form followed by re-closure of the ring and formation of both diastereomers in a ratio determined by the different energies of the two structures. This ring-chain tautomerism is probably reproduced in many substituted 1,3-oxathianes without being observed as the equilibration occurs between homomeric structures with major contribution of the ring form.

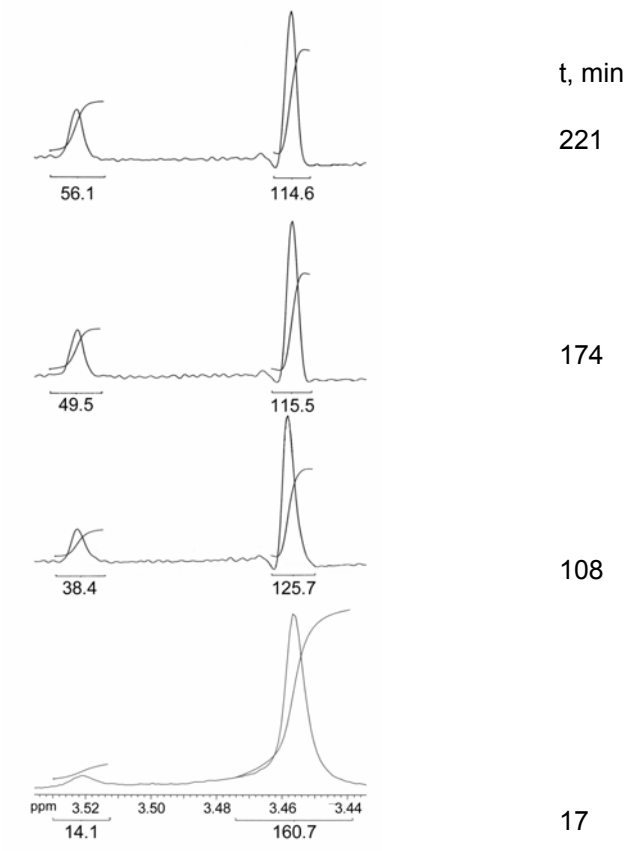


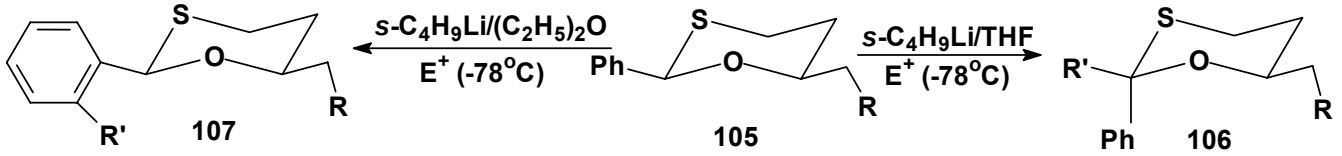
Figure 2. NMR spectra used for the determination of the kinetic parameters for the *trans-cis* isomerization of **38e** by measuring the intensities of the signals belonging to the protons at position 2 of the two isomers (*cis*: δ =3.52 and *trans*: δ = 3.45 ppm) at several mean times.

7. REACTIVITY

7.1 Reaction with lithiated compounds

Lithiation of 1,3-oxathiane derivatives (see 2.5. Schemes 11 and 13) and their further reaction with different electrophiles (Schemes 11-15) is an important synthetic route to many 1,3-oxathiane derivatives. In correlation with the substrates, the electrophiles and reaction conditions these reactions can give simple products or some competitions with other processes can occur. As an example the lithiation of 4-substituted 2-phenyl-1,3-oxathiane (**105**) followed by the reaction with several electrophiles gives in THF the product (**106**) as substitution at position 2 of the heterocycle, while the reaction in ether leads to derivative (**107**) resulted by the substitution at the *ortho* position of the aromatic ring (Scheme 32).[100]

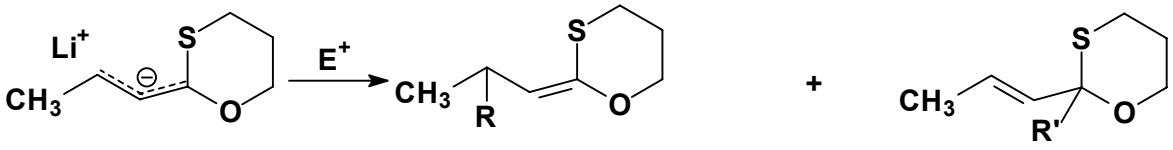
Scheme 32



R = OSiPh$_2$*t*-C$_4$H$_9$, OMOM, N(CH$_3$)$_2$; R' = CH$_3$, PhC(OH)H

The lithiated anion (**108**) [of 2-(1-propenyl)-1,3-oxathiane] reacts with alkyl halides yielding substitution products predominantly at the α terminus **109** and with carbonyl compounds afford addition products at the γ terminus (**110**, Scheme 33).[101]

Scheme 33



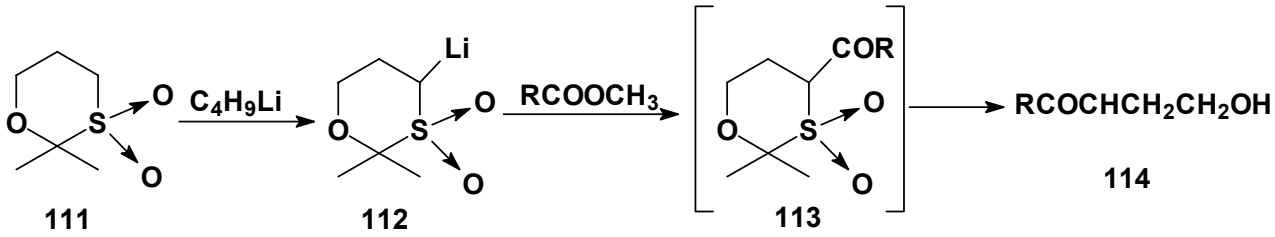
108 **109** **110**

R = D, *n*-C$_3$H$_7$, *n*-C$_4$H$_9$, Si(CH$_3$)$_3$

R' = CH(OH)Ph, CH$_3$C(OH)Ph, CH(OH)CH=CHPh, PhC(OH)Ph

Lithiation of 2,2-disubstituted 1,3-oxathiane-3,3-dioxides (*e.g.* 2,2-dimethyl-1,3-oxathiane-3,3-dioxide (**111**) occurs to the carbon atom adjacent to the sulfone group.[50] Acylation of this lithiated derivative (**112**) provided the labile β-oxosulfone derivative (**113**) that undergoes desulfonation on silica gel to produce the corresponding γ-hydroxy ketone (**114**) (Scheme 34).[48]

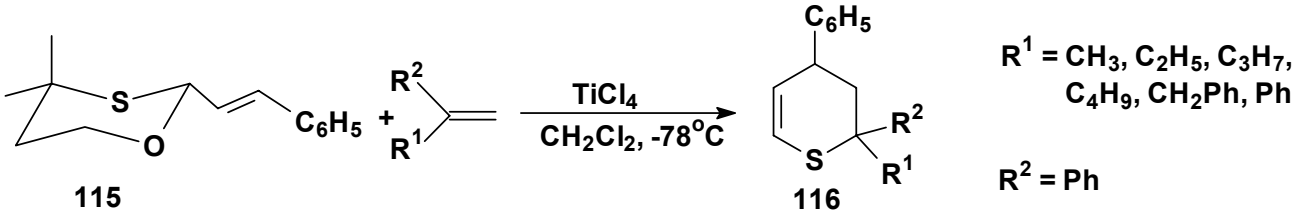
Scheme 34



7.2. Reaction with olefins

Suitably functionalized 1,3-oxathianes such as 4,4-dimethyl-2-styryl-1,3-oxathiane (**115**) can participate in a tandem [4^++2] cycloaddition-elimination reaction with olefins to produce 3,4-dihydro-2*H*-thiopyrans (**116**). They are in fact synthetic equivalents of α,β-unsaturated thioaldehydes that are highly reactive and normally can not undergo hetero Diels-Alder reactions (Scheme 35).[102]

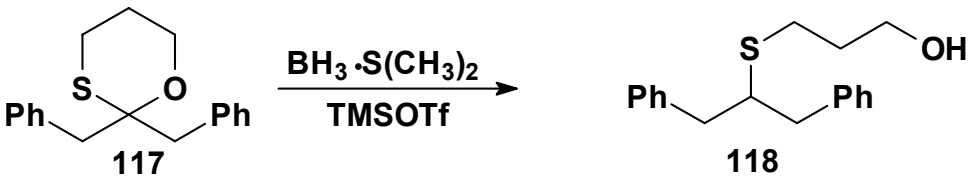
Scheme 35



7.3. Activated reduction with borane dimethyl sulfide

1,3-Oxathianes (*e.g.* 2,2-dibenzyl-1,3-oxathiane (**117**)), as well as other ketals, are reduced in high yields without by-products formation and opened to the corresponding sulfide (**118**, Scheme 36). The reducing agent is borane dimethyl sulfide in conjunction with trimethylsilyl trifluoromethanesulfonate (TMSOTf).[103]

Scheme 36



7.4. Deprotection of 1,3-oxathianes

1,3-Oxathianes (as other ketals) are masked carbonyls and they can react with formation of new C-C bonds, highly efficient methods for their deprotection being established.

Treatment of 1,3-oxathianes with Raney nickel leads to the corresponding ketone in rather low yields (45-72%) along with by-products obtained through desulfurization.[104] Hydrolysis by mineral acids requires drastic conditions to give the ketone in moderate yields.[105,106]

Corey's method[107] with *N*-chlorosuccinimide-silver nitrate was efficient for 2-hydroxyalkyl-1,3-oxathianes.[108,109]

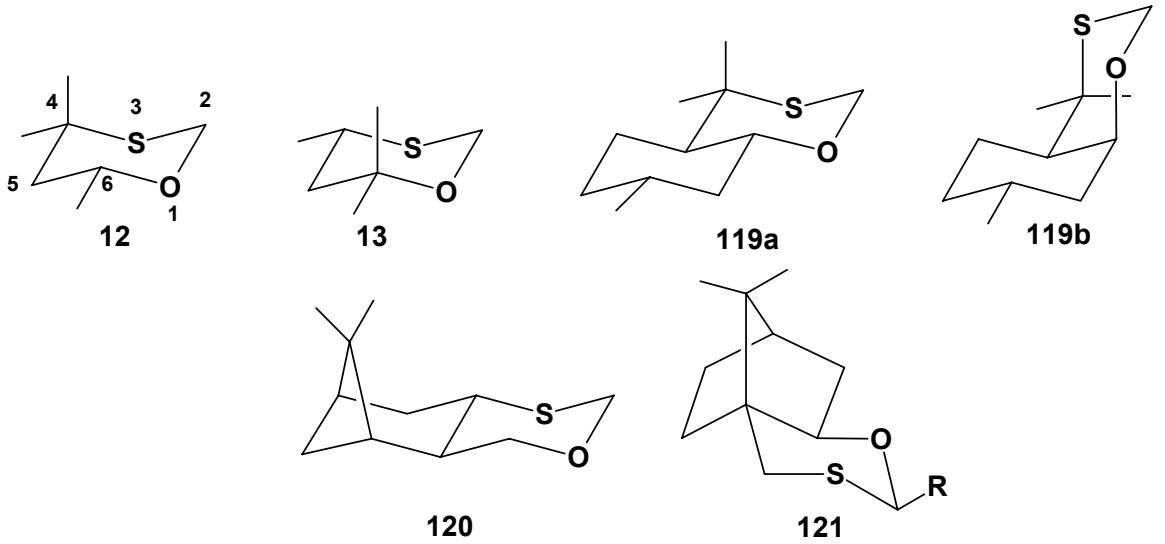
Iodine cation has a stronger affinity to sulfur atom than chlorine cation in Corey's system and it can be generated from iodine by silver cation. High yields (up to 94%) were obtained with the silver nitrite-iodine system.[110,111]

Another deprotection method uses periodic acid under mild nonaqueous conditions and it works also on sensitive aldehydes.[112] The method is chemiospecific, the thioacetal is specifically cleaved in the presence of another acid-sensitive protective group (*e.g.* 1,3-dioxolane) or isomerizable double bonds.

7.5. Asymmetric syntheses based on 1,3-oxathianes

Starting from 1978, when Eliel and his co-workers described the asymmetric synthesis of (*S*)-(+)-atrolactic acid methyl ether in nearly 100% optical yield using (*S*)-(-)-4,6,6-trimethyl-1,3-oxathiane (**13**) and in 92% optical yield from (*R*)-(+)-4,4,6-trimethyl-1,3-oxathiane (**12**) as chiral adjuvants[113] the synthesis of many other 1,3-oxathiane chiral adjuvants was developped. The majority of these chiral derivatives were obtained from suitable natural products (their skeletta are shown in Scheme 37: **119a** (Eliel's 1,3-oxathiane) and **119b** from (*R*)-(+)-pulegone, **120** from (+)-camphor, **121** from (-)-myrtenal).[110,114-116]

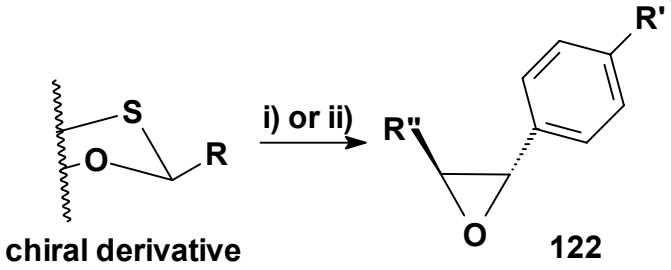
Scheme 37



7.5.1. Asymmetric syntheses of monoaryl, *trans*-diaryl, *trans*-vinylaryl and furyl and pyridyl epoxides based on chiral 1,3-oxathianes

Chiral *trans*-epoxides (**122**) (Scheme 38) are obtained in high yields (up to 100%) and high enantiomeric excess (95-100%) starting from chiral 1,3-oxathianes derived from camphorsulfonic acid[117,118] and (+)-pulegone.[66,118-121]

Scheme 38



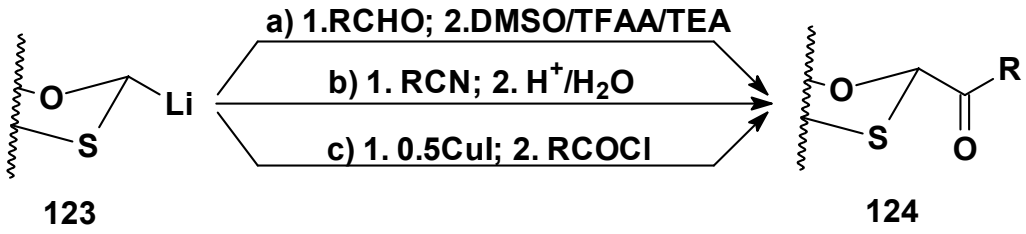
i) $PhCHN_2$, R"CHO, $Cu(acac)_2$; R=alkyl, R'=H, R"=aryl[117,118]; ii) a) R'$C_6H_4CH_2OH/Tf_2O/Py/CH_2Cl_2$ if R'=H; R'$C_6H_4CH_2I/AgOTf/CH_2Cl_2$ if R'=OCH_3; b) $C_2H_5P_2$ (phosphazene base) or NaH, R"CHO; R"= $CH=CH_2$, $CH=C(CH_3)_2$, CH=CH-Ph[119,120]

7.5.2. Asymmetric syntheses of chiral alcohol and aldehydes based on chiral 1,3-oxathianes

A general three-step asymmetric synthesis of compounds of type RR'C(OH)X (X: CHO, COOH, CH_2OH etc.) using 1,3-oxathianes derivatives as chiral auxiliary was designed.

The first step involves the preparation of a 2-acyl-1,3-oxathiane derivative (**124**). The chiral 1,3-oxathiane is deprotonated first at C^2 with lithium compounds and the chiral lithiated compound (**123**) is transformed by several methods in the desired ketone (**124**, Scheme 39).

Scheme 39

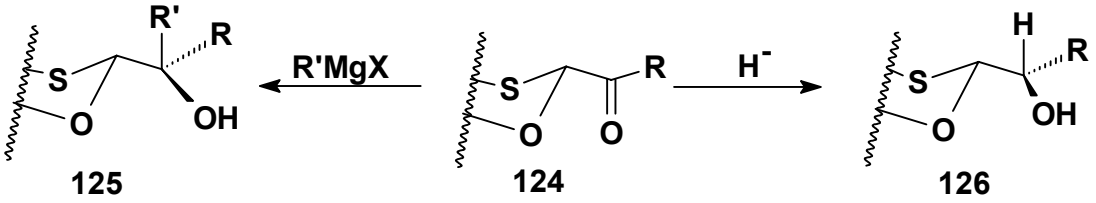


In the first mentioned procedure (a) the lithio derivatives (**123**) are condensed with aldehydes and the obtained isomeric mixture of carbinols by Swern oxidation (dimethyl sulfoxide, trifluoroacetic anhydride and triethylamine) are transformed in good yields in the pure equatorial ketone (**124**).[3] An alternative to this method uses the appropriate nitrile in reaction with the lithio-1,3-oxathiane (**123**) at 0°C in THF followed by acidic hydrolysis (b). Unlike the first mentioned method, this one is not general, it can be used only in obtaining alkyl ketones (**124**)

(except methyl ketones) in 60-82% yield.[122] An improved synthesis of enantioenriched 2-oxathianyl ketones (**124**) uses coupling with cuprate reagents (c). Thus, the 2-lithio-1,3-oxathiane (**123**) is converted to the corresponding lithium cuprate, which is then coupled with acid chlorides to afford the acyl derivative (**124**) in high yields (82-97%) and under stereochemical control (equatorial orientation of the acyl group).[123]

In the second step, the chiral ketone (**124**) reacts with organometallic derivatives[14,109] or a metal hydride[108] to give tertiary and secondary alcohol derivatives (**125**) and (**126**), respectively (Scheme 40).

Scheme 40



125 **124** **126**

Grignard reagents are generally more selective in their addition to 2-acyl-1,3-oxathianes (**124**) than organolithium compounds and alkylmagnesium bromides or iodides are the best. Phenyl ketones are generally more stereoselective than alkyl ketones in reaction with Grignard reagents at reflux. Temperature has a dramatic effect and lowering the temperature from reflux to –78°C causes a marked increase in stereoselectivity to 90% or higher.[14]

The addition of organometallic reagents to the ketone follows Cram's rule. A determinant of the high stereoselectivity is chelation (involving the magnesium atom of the Grignard agent, the carbonyl oxygen of the ketone function and the oxygen from the 1,3-oxathiane ring). If competing chelation occurs, *e.g.* an alkoxy group in the side chain, the stereoselectivity is strongly reduced or even reversed.[124,125] The stereoselectivity is restored if the alkoxy group is replaced by the bulky triisopropylsilyloxy group.[125,126]

Reduction of chiral 2-acyl-1,3-oxathianes (**124**) with various metal hydride combinations proceeds stereoselectively with diastereomeric excess up to 97% as in the case of reduction of phenyl ketones with lithium tri-*sec*-butylborohydride (L-Selectride®, in toluene at –78°C); the stereoselectivity is lower (82% d.e.) for primary or tertiary alkyl ketones. The main product is again the one predicted by Cram's chelate rule. The product ratio is reversed (major product is the diastereomer not favored by chelation) with di-*iso*-butylaluminium hydride (DIBAL) and in the reduction of secondary alkyl ketones with L-Selectride® (but with low stereoselectivity). The results for the chiral ketones (**124a**) obtained using Eliel's 1,3-oxatiane (**119a**) are shown in Scheme 41 and table 17.[108]

Scheme 41

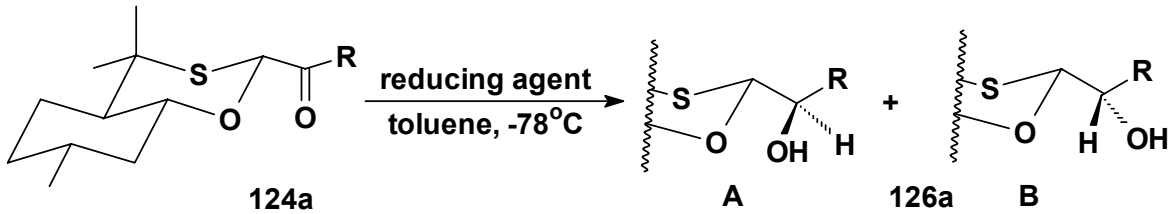


Table 17. Stereoselectivity (A/B) of the reduction of 2-acyl-1,3-oxathianes (**124a**) with L-Selectride® and with DIBAL

Reducing agent	R				
	methyl	*n*-hexyl	*t*-butyl	*i*-propyl	cyclohexyl
L-Selectride®	21/79	11/89	22/78	67/33	52/48
DIBAL	78/22	87/13	81/19	88/12	89/11

There are several methods to inverse the configuration of the obtained product:

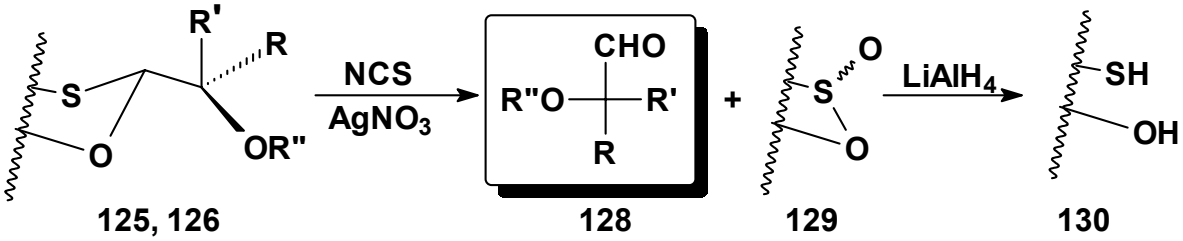
- using as chiral adjuvant the bicyclo-1,3-oxathiane (**119b**) which is diastereoisomer (Scheme 37: the 1,3-oxathiane ring exhibit different configurations) with Eliel's 1,3-oxathiane (**119a**) and it is obtained as side-product in the synthesis of (**119**) from (*R*)-(+)-pulegone.
- reversing the alkyl group in the ketone and the Grignard reagent (using R*COR + R'MgX and then R*COR' + RMgX) when this can be done due to shortage in starting materials.
- an elegant procedure involves lanthanide-mediated reactions with reverses diastereoselectivity when 2-acyl-1,3-oxathianes react with organometallic reagents in the presence of ytterbium salts as opposite face attack of the organometallic species takes place comparing to the reaction with organometallic reagent alone (different chelation).[127] Diastereocontrolled reduction of ketones containing (*R*)-6-methyl–1,3-oxathiane moiety leads to enantiomers of 1,2-alkanediols: reduction with $Zn(BH_4)_2$ selects one diastereoface to give one diastereomer and that with $NaBH_4$-YCl_3 produces another diastereomer selectively.[128] In the same manner, addition of organometallic reagents to imine or hydrazones derived from 2-acyl-1,3-oxathianes proceeds with high diastereoselectivity to obtain enantiomers of chiral β-amino alcohols.[129]

1,4-Addition of organocopper reagents to α,β-unsaturated ketones containing a chiral 1,3-oxathiane proceeds diastereoselectively to give optically active β-substituted ketones in good yields (up to 98%) and addition of ytterbium chloride improves the diastereoselectivity.[130]

The third step in the asymmetric synthesis is the cleavage of the oxathiane and this is usually effected by N-chlorosuccinimide-silver nitrate in CH_3CN-H_2O[107] because the use of this reagent has the advantage that the oxathiane moiety is recovered in high yield in the form of a sultine

that can be then easily reduced with $LiAlH_4$ to the hydroxythiol that the 1,3-oxathiane can be regenerated from (scheme 42).

Scheme 42



125, 126 **128** **129** **130**

The α-hydroxy aldehydes (R"=H) thus obtained are air-sensitive and tend to dimerize so they are further functionalized. There were obtained chiral glycols (by reduction with $NaBH_4$) and then carbinols RR'C(OH)CH_3 (i:TsCl/Py; ii: $LiAlH_4$), α-hydroxy acids ($NaClO_2$), α-hydroxy esthers (I_2/methanol, KOH).[108,109,131]

These compounds may be part of the skeleton of various natural products that can be thus prepared in high diastereomeric and enantiomeric purity using different 1,3-oxathianes as chiral auxiliaries like (*S*)-(+)-atrolactic acid methyl ether,[113,114] (-)-malyngolide (an antibiotic of algal origin) and its stereoisomers (+)-malyngolide and (+)- and (-)-epimalyngolide,[132] (*S*)-(+)-mevalolactone (the biogenetic precursor of steroids and some terpenes),[124] dimethyl (*R*)-(+)- and (*S*)-(-)-2-acetoxycitramalate (as the citramalic acid can be a chiral synthon in prostaglandin synthesis),[133] (*S*)-(+)-linalool,[134] (5*R*6*S*)-6-acetoxy-5-hexadecanolide (the major component of the oviposition attractant pheromone of the mosquito *Culex pipens fatigans*) and two of its stereoisomers,[135] (+)- and (-)-frontalin (the aggregation pheromone of females of the southern bark beetle *Dendroctonus frontalis* and of males of the western pine bark beetle *Dendroctonus brevicomis*),[136] (*R*)-(+)-dodecan-5-olide and (*S*)-(+)- and (*R*)-(-)-5-[(*Z*)-dec-1-enyl]dihydrofuran-2(3*H*)-one (the pheromone of the Japanese beetle),[137,138] (+)-cortisone,[139] 2-methyl-1,2-hexanediol (an intermediate in preparing the ω chain of some modified prostaglandines as the commercially available Misoprostol® and Rioprostil® that have strong gastric antisecretionary activity),[140] (*R*)-(+)-lithium lactate,[141] (*R*)-(+)-γ-caprolactone (a pheromone component of a dermestid beetle *Trogoderma glabrum*),[3] in the preparation of (5*S*)-5-hydroxyoctanoyl *N*-acetylcysteamine thioesther (a substrate in the biosynthesis of oudenone – a metabolite of the fungus *Oudemansiella radicata*- a strong inhibitor of catecholamine biosynthesis).[142,143]

8. CONCLUSIONS

The exhaustive reviewing of literature data on 1,3-oxathiane derivatives offers an useful material for chemists interested in this field. Concerning the synthesis of 1,3-oxathiane derivatives beside the classic condensation synthesis between mercaptopropanols and carbonyl compounds new performed synthetic methods are shown. The presentation of the new aspects concerning the stereochemistry of 1,3-oxathianes and of the NMR and MS spectrometrical data represents a useful tool in the structural analysis of the derivatives of this heterocycle, while the chapters dedicates to the studies on the ring-chain tautomerism and of the reactivity of 1,3-oxathiane derivatives reveal the high chemical potential of the derivatives of the 1,3-oxathiane ring and the high versatility of these compounds in the synthesis of many natural products.

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