

A STUDY OF THE ALKYLATION AND REARRANGEMENT PRODUCTS OF CHIRAL 1,3-OXAZOLIDINE- AND THIAZOLIDINE-2-THIONES

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Abstract – Homochiral 1,3-oxazolidine-2-thiones and 1,3-thiazolidine-2-thiones are useful chiral auxiliaries in asymmetric synthesis. Our interest in chiral amino dienes drove us to consider the preparation of dienes (**1a**) and (**1b**) bearing those auxiliaries. Trying to synthesize such dienes by alkylation of the corresponding heterocycles with 1,4-dihalogeno-2-butenes, we found several rearrangement reactions leading to new compounds that we fully characterized. In particular, we found a new access towards 4-vinyl-1,3-thiazolidin-2-ones.

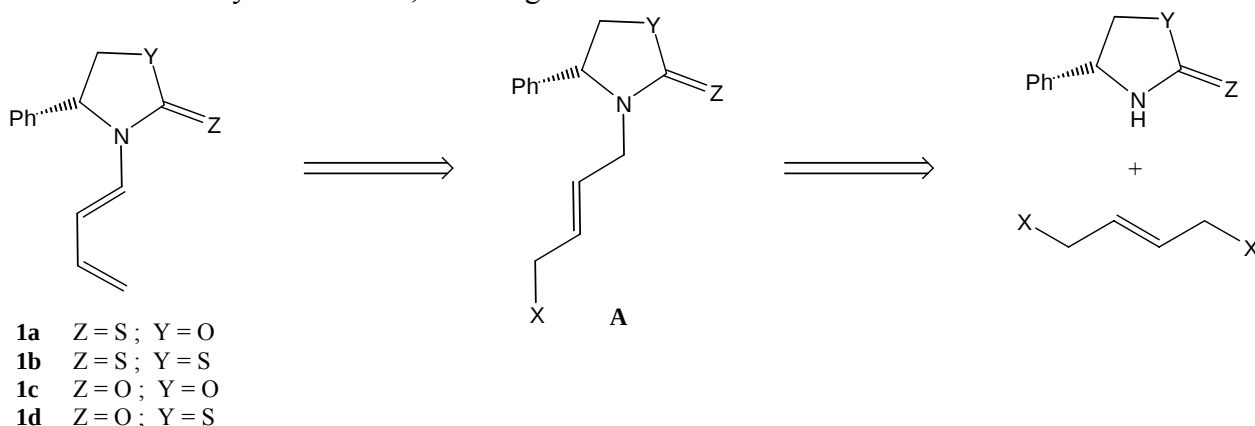
Introduction

Homochiral 1,3-oxazolidine-2-thiones and 1,3-thiazolidine-2-thiones emerged recently as useful chiral auxiliaries in the design of enantioselective syntheses;¹ comparatively to the very popular 1,3-oxazolidin-2-ones, they appeared to be more efficient in aldol-type reactions.^{2,3} The usual way to fix these chiral auxiliaries on substrates made use of *N*-acylation reactions;^{1,4-6} *N*-alkylation processes were less operated and, to our knowledge, applied exclusively to reactions with Michael acceptors.⁶

Chiral 1-amino-1,3-butadiene derivatives, such as oxazolidinone (**1c**) (Scheme 1) were prepared and successfully used in Diels-Alder cycloaddition reactions.^{7,8} Our interest in amino dienes as reagents towards phosphono-dienophiles⁹ drove us to consider the preparation of homochiral dienes (**1a**) and (**1b**) derived from (*R*)-4-phenyl-1,3-oxazolidine-2-thione and (*R*)-4-phenyl-1,3-thiazolidine-2-thione,¹⁰ respectively (Scheme 1).

When trying to apply the strategy outlined in Scheme 1, we found several rearrangement reactions

leading to new compounds. This paper summarizes our results in the field of oxazolidinethione and thiazolidinethione alkylation with 1,4-dihalogeno-2-butenes.



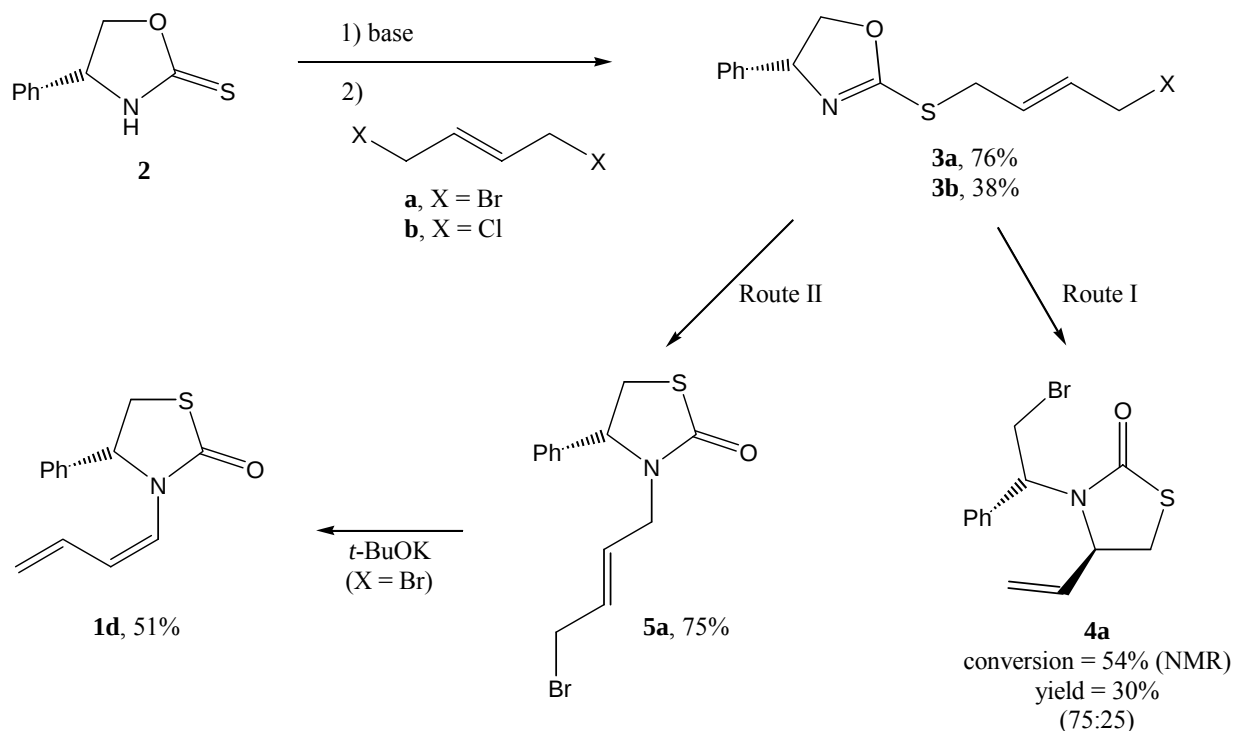
Scheme 1

Results

By heating oxazolidinethione (**2**)¹⁰ with crotonaldehyde in the presence of a catalytic amount of *p*-toluenesulfonic acid, we could not isolate the desired amino diene (**1a**); an intractable mixture was obtained. We considered thus the alkylation of **2** with 1,4-dibromo-2-butene and a subsequent dehydrobromination reaction (Scheme 1). Treatment of **2** with various bases (LiHMDS, NaH, KF-Al₂O₃) in THF solution followed by addition of 1,4-dibromo-2-butene furnished the *S*-alkylation product (**3a**) as the only product (Scheme 2); the Δ^2 -1,3-oxazoline structure (**3a**) was characterized in ¹⁵N NMR spectroscopy by a signal at 220.3 ppm. Attempts to rearrange **3a** into *N*-substituted oxazolidinethione (Scheme 1; intermediate **A**; Z=S, Y=O) failed; the products recovered by heating **3a** in acetonitrile solution (reflux, 48 h) were the *N*-alkylthiazolidinones (**4a**) and (**5a**). In diluted solution (0.01 g/mL), the rearrangement product (**4a**) (route I) was the major compound isolated by chromatography; it appeared as a 75:25 mixture of diastereoisomers from ¹H NMR spectral and gas chromatography analyses. The thiazolidinone moiety gave a typical signal at 125.6 ppm in ¹⁵N NMR spectroscopy. In more concentrated solution (0.1 g/mL), the rearrangement product (**5a**) was the only isolated compound after column chromatography (route II). The ¹⁵N NMR spectrum of **5a** showed a signal at 120.8 ppm. Further treatment of **5a** with potassium *tert*-butoxide furnished the diene (**1d**), the structure of which was unambiguously confirmed by X-Ray diffraction analysis of a monocystal (see EXPERIMENTAL). Other solvents than acetonitrile (and catalysts) were tested to perform the rearrangement of **3a**: no reaction occurred in acetone-water (1:1, LiCl, 20°C, 3 days) and in acetone-methanol (1:1, LiBr, 20°C, 2 days); the reaction was very slow in toluene (80°C, 2 days), leading to traces of **4a**; lastly, a mixture of **4a** and **5a** was recovered in *i*-propanol-acetonitrile (1:1, KBr, 80°C, 2 days).

The *S*-alkylation product (**3b**) was similarly obtained, in modest yield, by deprotonation of **2** with

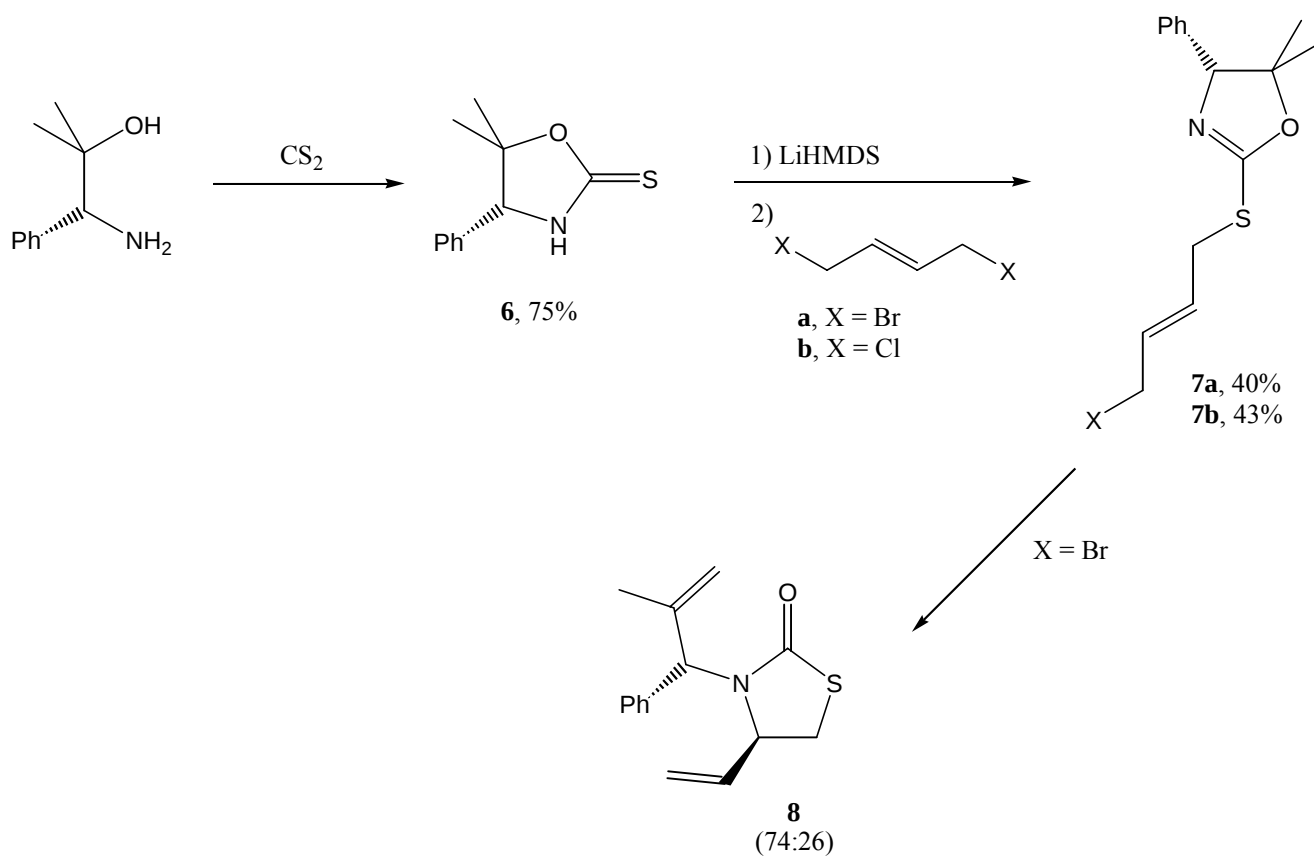
LiHMDS followed by addition of 1,4-dichloro-2-butene (Scheme 2). This chloro derivative (**3b**) appeared however to be stable under thermal conditions (MeCN, reflux) and failed to rearrange into *N*-substituted thiazolidin-2-one or oxazolidine-2-thione. Nevertheless, reflux of **3b** in acetonitrile in the presence of 2 equivalents of 1,4-dibromo-2-butene furnished **5a** as the only rearrangement product. Thus diene (**1a**) was not accessible according to the strategy outlined in Scheme 1.



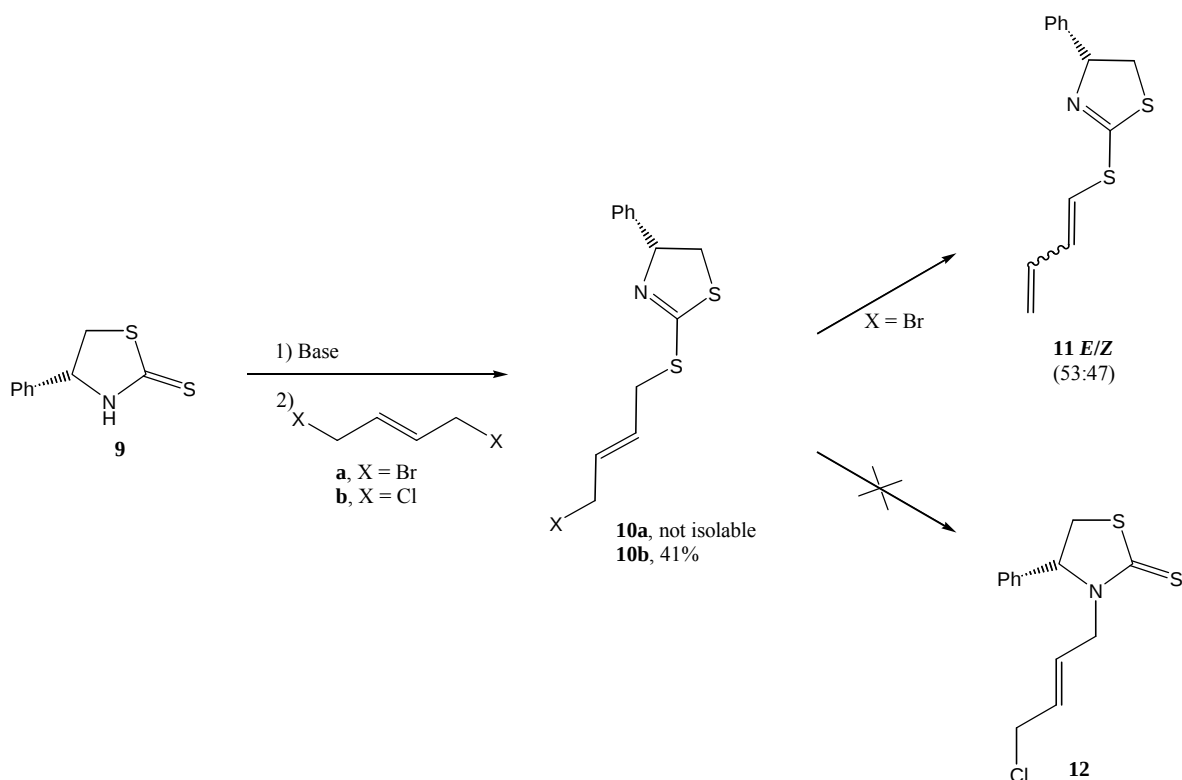
Scheme 2

These results drove us to examine the influence of steric effect (by blocking the C5 position) on the rearrangement of 2-thioalkyl- Δ^2 -1,3-oxazoline. Indeed, Le Corre¹⁰ reported that bulky substituents at the C5 position prevent ring opening and then further rearrangement of the heterocycle. Accordingly, we prepared (*R*)-4-phenyl-5,5-dimethyl-1,3-oxazolidine-2-thione (**6**) by cyclization of the corresponding amino alcohol with carbon disulfide (Scheme 3). Treatment of **6** with LiHMDS and 1,4-dibromo- or 1,4-dichloro-2-butene gave the corresponding *S*-alkyloxazolines (**7a**) and (**7b**) ($\delta^{15}\text{N} = 217.9$ ppm). The chloro derivative (**7b**) was again thermally stable (MeCN, reflux), and provided an intractable mixture in those conditions in the presence of 1,4-dibromo-2-butene. Treatment of compound (**7a**) in refluxing acetonitrile gave a complex mixture in which the desired *N*-substituted oxazolidine-2-thione could not be detected; the ^1H NMR spectral analyses let us to tentatively attribute the structure (**8**) to the major product.

In order to avoid the undesired rearrangement of 1,3-oxazolidine-2-thione into 1,3-thiazolidin-2-one, we then further examined the reaction of thiazolidinethione (**9**)¹⁰ with 1,4-dihalogeno-2-butenes (Scheme 4).



Scheme 3



Scheme 4

All attempts to isolate or to react the initially formed *S*-alkylation product (**10a**) failed because a rapid degradation by dehydrobromination occurred to furnish the diene (**11**), as a 53:47 mixture of respectively

E and *Z* isomers from ^1H NMR spectroscopy; its Δ^2 -1,3-thiazoline moiety gave a typical signal at 291.7 ppm in ^{15}N NMR spectroscopy. The corresponding chloro derivative (**10b**) was nevertheless stable and recovered by column chromatography ($\delta^{15}\text{N} = 289.7$ ppm). However, again, all attempts to rearrange the chloro derivative into (**12**) (intermediate **A** of Scheme 1; $\text{Y}=\text{Z}=\text{S}$, $\text{X}=\text{Cl}$) failed; no reaction was observed under various experimental conditions (reflux in MeCN, or methanol-acetone; catalysis with H_2SO_4 or LiCl), and an intractable mixture was obtained by heating **10b** in the presence of 1,4-dibromo-2-butene. Thus diene (**1b**), as diene (**1a**), appeared to be inaccessible following the Scheme 1.

All new compounds were characterized by IR and ^1H , ^{13}C and ^{15}N NMR spectroscopies (see experimental); indication on the structural differentiation between *exo-S*-substituted Δ^2 -1,3-oxazolines (**3**, **7**) or thiazolines (**10**, **11**) and *N*-substituted 1,3-thiazolidin-2-ones (**4**, **5**, **1d**, **8**) could be obtained on the basis of ^{13}C NMR spectral data, as previously described by Fujita *et al.*,¹¹ but ^{15}N NMR spectral values confirmed more clearly and unequivocally the assigned structures. Some typical spectroscopic features are summarized in Table 1.

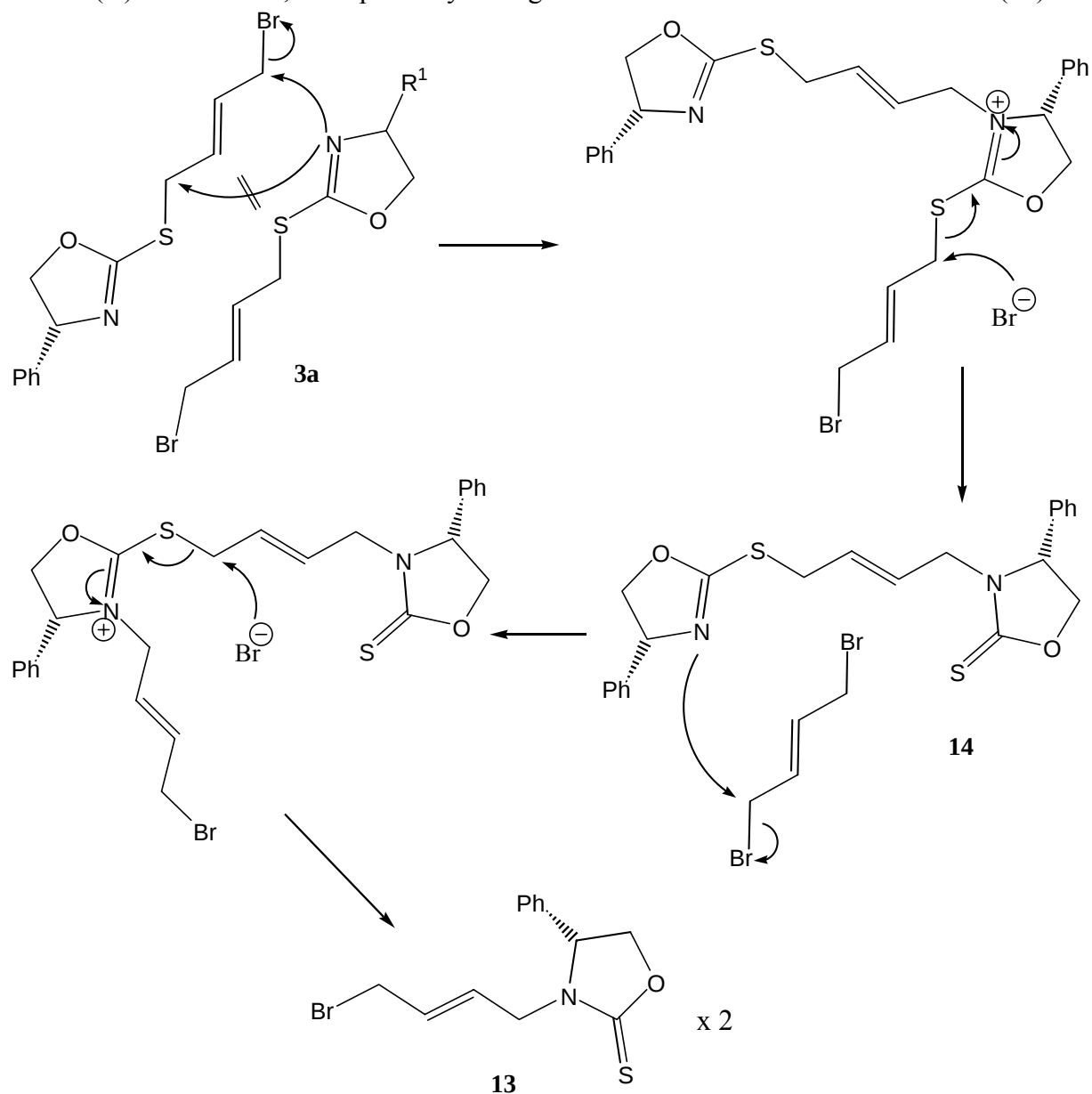
Table 1. ^{13}C and ^{15}N NMR (ppm), and IR (cm^{-1}) spectral data.

Compound	^{13}C (C2)	^{15}N	IR (C=X)
3a	166.2	220.3	1606
3b	165.6	220.3	1605
4a	172.4	125.6	1671
5a	172.2	120.8	1671
1d	171.4	134.7	1671
6	189.1	/	1507
7a	164.4	217.9	1601
7b	164.3	217.9	1598
10b	164.9	289.7	1563
11	164.2 (<i>E</i>) 164.9 (<i>Z</i>)	291.7	1562

Discussion

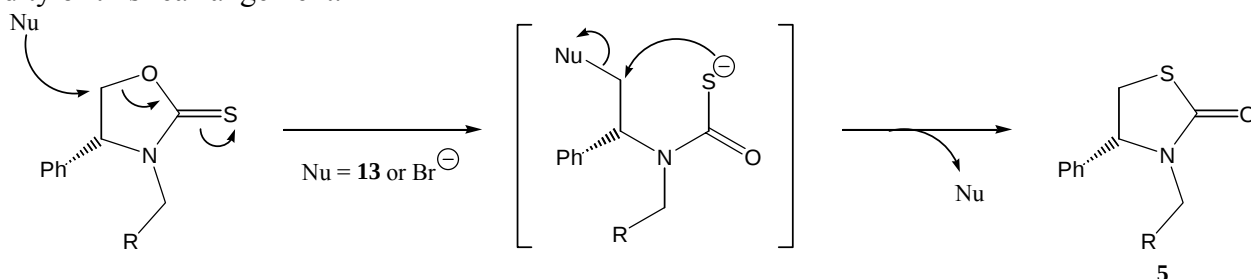
N-Alkyl-1,3-oxazolidine(or thiazolidine)-2-thiones are commonly obtained by condensation of carbondisulfide with *N*-alkylated β -amino alcohols.¹⁰ *N*-alkylation of preformed NH-oxazolidinethiones (or thiazolidinethiones) are limited to the reaction of Michael acceptors ($\text{CH}_2=\text{CH}$ -EWG) in the presence of triethylamine.⁶ On the other hand, alkyl halides (being more soft electrophilic reagents) give *S*-alkylation products independently of the nature of the added base (Et_3N , NaH, LiHMDS, $\text{KF}\cdot\text{Al}_2\text{O}_3$).^{6,11-13}

The resulting *S*-alkyl- Δ^2 -1,3-oxazolines(or thiazolines) can be rearranged into *N*-alkyl-1,3-oxazolidine(or thiazolidine)-2-thiones, by heating with a trace of R-Br.¹¹ This transposition is related to the conversion of *O*-alkyl thionocarbamates into *S*-alkyl thiolcarbamates which is catalyzed by I₂, BF₃·Et₂O, *p*-TsOH or H₂SO₄.¹⁴ It has been experimentally demonstrated that such rearrangement proceeds by an intermolecular alkylating mechanism.¹⁵ In our case, the stability of the chloro derivatives (**3b**, **7b** and **10b**) indicated moreover that the first step of the rearrangement consists in an alkylation reaction and that in those process the alkylating reagent can not be the *S*-alkyl moiety of Δ^2 -1,3-oxazoline(or thiazoline) itself (nor R-Cl). Thus, the mechanism outlined in Schemes 5 and 6 could rationalize the rearrangement of **3a** (*S*-alkyl- Δ^2 -1,3-oxazoline) into **5a** (*N*-alkyl-1,3-thiazolidin-2-one) observed in relatively concentrated solution: the first step (Scheme 5) is a bimolecular *N*-alkylation of **3a** leading to **13**, which is the desired intermediate (**A**) of Scheme 1, most probably through the formation of another intermediate (**14**).



Scheme 5

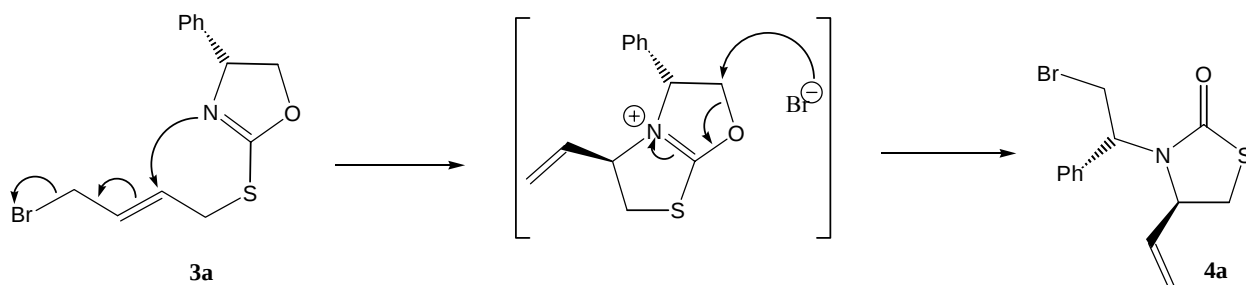
These compound (**13**) further isomerizes rapidly into **5a** (**13** has never been observed by following the reaction in ^1H NMR) in a second step (Scheme 6), *via* ring opening and intramolecular S-alkylation, as already described by Ishikawa.¹⁵ This author mentioned nevertheless the requirement of an acid catalyst as boron trifluoride etherate or *p*-toluenesulfonic acid. In our case, no acid catalysis was needed (the reaction occurred even in basic washed vessel). This is probably due to the presence of bromide in the medium which could catalyze the process (Scheme 6). This catalysis by bromide would also explain the rapidity of this rearrangement.



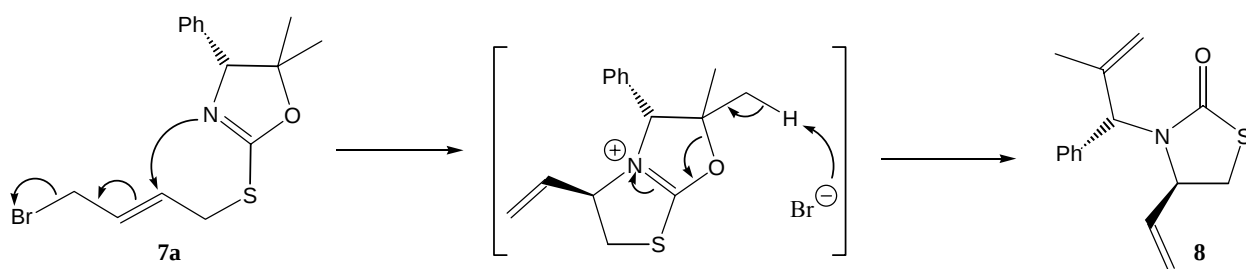
Scheme 6

In diluted solution, on the other hand, **3a** rearranges into **4a**, most probably *via* an intramolecular N-alkylation reaction as depicted in Scheme 7 (Part 1).

Part 1:



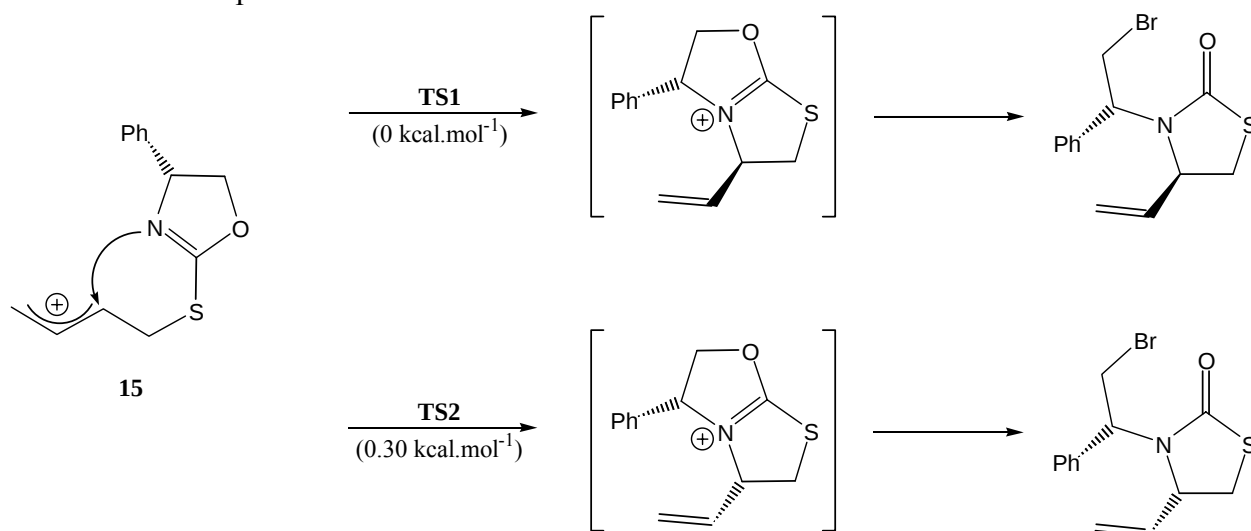
Part 2:



Scheme 7

This nucleophilic substitution process is diastereoselective, giving a major stereoisomer in the ratio of 75:25. The selectivity of this new reaction has been examined from a theoretical point of view, considering the allyl cation (**15**) as model of the reactive intermediate (Scheme 8). *Ab initio* calculations

(see EXPERIMENTAL) of the energy of the two relevant transition states indicated a relative difference of 0.30 kcal in favor of the transition state leading to the diastereoisomer C4(*R*)-C1'(*R*); a value in good agreement with the experimental ratio of isomers.



Scheme 8

When the C5 position of the 2-thioalkyl- Δ^2 -1,3-oxazoline precursor is sterically hindered, such as in compound (**7a**), only the second type of rearrangement (intramolecular nucleophilic substitution reaction) was observed (Scheme 7, Part 2), but in this case, the final product (**8**) resulted of hydrogen abstraction from a methyl group (elimination) instead of nucleophilic substitution of bromide at position C5.

In conclusion, we found that dienes (**1a**) and (**1b**) (see Scheme 1) could not be prepared by alkylation of oxazolidinethione (**2**) and thiazolidinethione (**10**) respectively. Interestingly, the unexpected rearrangement of **3** (and **7**) into **4** (and **8**) provided a new diastereoselective route towards chiral 4-vinyl-1,3-thiazolidin-2-one derivatives (Scheme 7). This structural feature is found in a wide range of biologically active products,¹⁶ and could be considered as a bioisoster of the corresponding 4-vinyl-oxazolidinone.¹⁷

EXPERIMENTAL

General

Reagents and solvents were purchased from Across or Aldrich. The IR spectra were taken with a Perkin-Elmer 1710 instrument and calibrated with polystyrene. The ¹H, ¹³C and ¹⁵N NMR spectra were recorded on Bruker AM-500 and Varian-Gemini 300 spectrometers, in CDCl₃ solution; chemical shifts are reported in ppm (δ) downfield from internal Me₄Si (*J* in Hz) for ¹H and ¹³C NMR and from NH₃ for ¹⁵N NMR. The HRMS were performed in the laboratory of Prof. R. Flammang (Université Mons-Hainaut, Belgium). GC analyses were realized on a OPTIMA-5 column (l = 30 m, d = 0.25 mm). Optical rotation values, given in deg mL dm⁻¹ g⁻¹, were taken on a Perkin-Elmer 241MC apparatus. Column

chromatographies were preformed on a silica gel (MERCK 60, 40-63 μm).

(R)-2-(4'-Bromobut-2'-enylthio)-4-phenyl- Δ^2 -1,3-oxazoline (3a):

(R)-4-Phenyloxazolidine-2-thione (**2**) (0.5 g, 2.79 mmol) in THF (3 mL) was added to a solution of LiHMDS (0.49 g, 2.93 mmol) in THF (7 mL), at -78°C . The mixture was stirred at this temperature for 30 min and 1,4-dibromo-2-butene (2.38 g, 11.16 mmol) was added in one portion. The mixture was gradually warmed to rt and stirred for 15 h. After concentration under reduced pressure, the residue was diluted in ether and washed with water. The organic layer was dried over magnesium sulfate and evaporated in vacuo. The residue was purified by chromatography (eluent: ether/cyclohexane = 1/1) to provide compound (**3a**) (0.58 g, 76%) as an oil : $[\alpha]_{\text{D}}^{20} +34.12^\circ$ ($c = 1.65$ in CHCl_3); IR (NaCl) $\nu(\text{cm}^{-1})$: 3029, 2962, 2897 (C-H), 1606 (C=N); ^1H NMR δ : 3.73 (m, 2H, CH_2S), 3.94 (dd, $J_{4',3'} = 7.7$, $J_{4',2'} = 1.9$, 2H, CH_2Br), 4.19 (dd, $J_{5a,5b} = J_{5a,4} = 8.0$, 1H, $H_a\text{CHO}$), 4.72 (dd, $J_{5b,5a} = 8.0$, $J_{5b,4} = 9.7$, 1H, $H_b\text{CHO}$), 5.22 (dd, $J_{4,5a} = 8.0$, $J_{4,5b} = 9.7$, 1H, CHPh), 5.95 (m, 2H, $\text{HC}=\text{CH}$), 7.20-7.40 (m, 5H, Ph); ^{13}C NMR δ : 32.2 (CH_2Br), 33.5 (CH_2S), 70.3 (CHPh), 76.8 (CH_2O), 127.0, 128.2, 129.2, 130.4, 131.2, 142.3, 166.2 (C=N); ^{15}N NMR δ : 220.3; HRMS : calcd for $\text{C}_{13}\text{H}_{14}\text{NOS}$ (232.0796), found (232.0784).

(R)-2-(4'-Chlorobut-2'-enylthio)-4-phenyl- Δ^2 -1,3-oxazoline (3b):

(R)-4-Phenyloxazolidine-2-thione (**2**) (0.4 g, 2.23 mmol) in THF (3mL) was added to a solution of LiHMDS (0.39 g, 2.34 mmol) in THF (7 mL), at -78°C . The mixture was stirred at this temperature for 30 min and 1,4-dichloro-2-butene (1.11 g, 8.93 mmol) was added in one portion. The mixture was gradually warmed to rt and stirred for 15 h. After concentration under reduced pressure, the residue was diluted in ether and washed with water. The organic layer was dried over magnesium sulfate and evaporated in vacuo. The residue was purified by chromatography (eluent: ether/cyclohexane = 1/1) to provide compound (**3b**) (230 mg, 38%) as an oil : $[\alpha]_{\text{D}}^{20} -81.4^\circ$ ($c = 1.5$ in CHCl_3); IR (NaCl) $\nu(\text{cm}^{-1})$: 3030, 2961, 2880 (C-H), 1605 (C=N); ^1H NMR δ : 3.71 (m, 2H, CH_2S), 4.03 (d, $J = 5.7$, 2H, CH_2Cl), 4.18 (dd, $J_{5a,5b} = J_{5a,4} = 7.5$, 1H, $H_a\text{CHO}$), 4.71 (dd, $J_{5b,5a} = 7.5$, $J_{5b,4} = 9.6$, 1H, $H_b\text{CHO}$), 5.21 (dd, $J_{4,5a} = 7.5$, $J_{4,5b} = 9.6$, 1H, CHPh), 5.91 (m, 2H, $\text{HC}=\text{CH}$), 7.20-7.40 (m, 5H, Ph); ^{13}C NMR δ : 33.0 (CH_2S), 44.1 (CH_2Cl), 69.8 (CHPh), 76.3 (CH_2O), 127.0, 127.5, 128.6, 129.3, 129.4, 141.7, 165.6 (C=N); ^{15}N NMR δ : 220.2; HRMS : calcd for $\text{C}_{13}\text{H}_{14}\text{NO}^{35}\text{ClS}$ (268.0563), found (268.0570).

(R,S)-3-((1'R)-2'-Bromo-1'-phenyl-ethyl)-4-vinylthiazolidin-2-one (4a):

A solution of (R)-2-(4'-bromobut-2'-enylthio)-4-phenyl- Δ^2 -1,3-oxazoline (**3a**) (816 mg, 2.6 mmol) in acetonitrile (80 mL) was heated at reflux for 48 h. The mixture was concentrated in vacuo and the residue was purified by chromatography (eluent: dichloromethane/cyclohexane = 1/1) to provide compound (**4a**) (245 mg, 30%) as a colorless oil : IR (NaCl) $\nu(\text{cm}^{-1})$: 3148 (C-H), 1671 (C=O); ^1H NMR δ : 3.12 (dd, $J_{5a,5b} = 11.0$, $J_{5a,4} = 8.5$, 1H, $H_a\text{CHS}$), 3.33 (dd, $J_{5b,5a} = 11.0$, $J_{5b,4} = 7.0$, 1H, $H_b\text{CHS}$), 3.91 (dd, $J_{2a',2b'}$ =

10.5, $J_{2a',1'} = 5.5$, 1H, $H_a\text{CHBr}$), 4.24 (ddd, $J_{4,5a} = 8.5$, $J_{4,5b} = 7.0$, $J_{4,6} = 16.0$, 1H, $\text{CHCH}=\text{CH}_2$), 4.54 (dd, $J_{2b',2a'} = J_{2b',1'} = 10.5$, 1H, $H_b\text{CHBr}$), 4.76 (dd, $J_{1',2a'} = 5.5$, $J_{1',2b'} = 10.5$, 1H, CHPh), 5.29 (m, 2H, $\text{CH}_2=\text{CH}$), 5.81 (ddd, $J_{6,4} = 16.0$, $J_{6,7\text{cis}} = 9.0$, $J_{6,7\text{trans}} = 18.0$, 1H, $\text{CH}=\text{CH}_2$), 7.30-7.40 (m, 5H, Ph); ^{13}C NMR δ : 31.2 (CH_2Br), 32.0 (CH_2S), 61.2 (CHPh), 63.3 ($\text{CHCH}=\text{CH}_2$), 120.2 ($\text{CH}_2=\text{CH}$), 127.9-128.5-128.8 (Ph), 136.2 ($\text{CH}=\text{CH}_2$), 137.3 (Ph), 172.4 ($\text{C}=\text{O}$); ^{15}N NMR δ : 125.6; GC (150°C→250°C at 3°C min⁻¹): 29.8 min (major, 75%), 30.0 min (minor, 25%); HRMS : calcd for $\text{C}_{13}\text{H}_{14}\text{NO}^{80}\text{BrS}$ (312.0058), found (312.0062).

(R)-3-(4'-Bromobut-2'-en-1'-yl)-4-phenylthiazolidin-2-one (5a):

A solution of (R)-2-(4'-bromobut-2'-enylthio)-4-phenyl- Δ^2 -1,3-oxazoline (**3a**) (179 mg, 0.6 mmol) in acetonitrile (2 mL) was heated at reflux for 72 h. The mixture was concentrated in vacuo and the residue was purified by chromatography (eluent: ethyl acetate/cyclohexane = 12/88) to provide compound (**5a**) (134 mg, 75%) as an oil : $[\alpha]_D^{20} -220.5^\circ$ ($c = 1.1$ in CHCl_3); IR (NaCl) ν (cm⁻¹) : 3063, 3032, 2926, 2850 (C-H), 1671 (C=O); ^1H NMR δ : 3.17 (m, 1H, $H_a\text{CHN}$), 3.22 (m, 1H, $H_b\text{CHS}$), 3.61 (dd, $J_{5a,5b} = 8.1$, $J_{5a,4} = 7.8$, 1H, $H_a\text{CHS}$), 3.88 (m, 2H, CH_2Br), 4.33 (m, 1H, $H_b\text{CHN}$), 4.80 (dd, $J_{4,5a} = J_{4,5b} = 7.8$, 1H, CHPh), 5.63 (m, 2H, $\text{CH}=\text{CH}$), 7.30-7.45 (m, 5H, Ph); ^{13}C NMR δ : 31.3, 33.8, 44.1 (CH_2S), 62.8 (CHPh), 127.0, 128.3, 129.0, 129.2, 130.7, 138.5, 172.2 (C=O); ^{15}N NMR δ : 120.8; HRMS : calcd for $\text{C}_{13}\text{H}_{15}\text{NO}^{80}\text{BrS}$ (312.0058), found (312.0053).

(R)-3-(1',3'-Butadienyl)-4-phenylthiazolidin-2-one (1d):

Potassium *tert*-butoxide (135 mg, 1.2 mmol) was added to a solution of (R)-3-(4'-bromobut-2'-en-1'-yl)-4-phenylthiazolidine-2-one (**5a**) (375 mg, 1.2 mmol) in THF (4 mL) and the mixture was stirred for 15 h. After dilution with ether the solution was washed with water, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by chromatography (eluent: ethyl acetate/cyclohexane = 15/85) to provide compound (**1d**) (143 mg, 51%) as a white solid which can be recrystallized from toluene to give white crystals: mp 92-93°C; $[\alpha]_D^{20} +202.75^\circ$ ($c = 2.9$ in CHCl_3); IR (NaCl) ν (cm⁻¹) : 3148 (C-H), 1671 (C=O); ^1H NMR δ : 3.21 (dd, $J_{5a,5b} = 11.0$, $J_{5a,4} = 4.5$, 1H, $H_a\text{-CHS}$), 3.81 (dd, $J_{5b,5a} = 11.0$, $J_{5b,4} = 8.0$, 1H, $H_b\text{-CHS}$), 5.10 (d, $J_{4',\text{cis},3'} = 10.0$, 1H, $H_{\text{cis}}\text{CH}=\text{CH}$), 5.20 (d, $J_{4',\text{trans},3'} = 17.0$, 1H, $H_{\text{trans}}\text{CH}=\text{CH}$), 5.22 (dd, $J_{4,5a} = 4.5$, $J_{4,5b} = 8.0$, 1H, CHPh), 5.66 (dd, $J_{2',1'} = J_{2',3'} = 10.5$, 1H, $\text{CH}=\text{CHN}$), 5.91 (d, $J_{1',2'} = 10.5$, 1H, $\text{NCH}=\text{CH}$), 6.41 (ddd, $J_{3',2'} = 10.5$, $J_{3',4',\text{cis}} = 10.0$, $J_{3',4',\text{trans}} = 17.0$, 1H, $\text{CH}=\text{CH}_2$), 7.25-7.45 (m, 5H, Ph); ^{13}C NMR δ : 34.8 (CH_2S), 63.9 (CHPh), 119.1 ($\text{CH}_2=\text{CH}$), 120.5, 122.3, 126.1, 128.6, 129.0, 130.8, 138.6, 171.4 (C=O); ^{15}N NMR δ : 134.7; HRMS : calcd for $\text{C}_{13}\text{H}_{13}\text{NOS}$ (231.0718), found (231.0707); X-Ray analysis (Figure 1) : wavelength = 0.71069, crystal system monoclinic, unit cell dimensions : $a = 6.144 \text{ \AA}$ ($\alpha = 90^\circ$), $b = 12.398 \text{ \AA}$ ($\beta = 97^\circ$), $c = 8.160 \text{ \AA}$ ($\gamma = 90^\circ$).

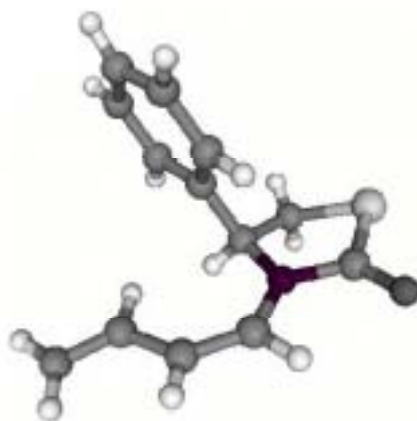


Figure 1

(*R*)-4-Phenyl-5,5-dimethyl-1,3-oxazolidine-2-thione (6):

To a solution of (*R*)-1-amino-2-methyl-1-phenyl-2-propanol (1.35 g, 8.2 mmol) in aqueous 1N sodium carbonate (40 mL) was added carbon disulfide (0.73 mL, 12.3 mmol). The reaction mixture was stirred at 100°C for 15 min. After cooling to rt, the solution was extracted with dichloromethane (2x20 mL). The combined organic layers were dried over magnesium sulfate, and then the solvent was removed under reduced pressure to afford **6** (1.28 g, 75%) as a yellow solid : mp 110-112°C; $[\alpha]_D^{20} +45.6^\circ$ ($c = 0.1$ in CHCl_3); IR (NaCl) ν (cm^{-1}) : 3229 (N-H), 3023, 2930 (C-H), 1507 (C=S), 1453, 1276, 1211, 1125; ^1H NMR δ : 0.99 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 4.75 (s, 1H, CHPh), 7.20-7.45 (m, 5H, Ph), 8.18 (s, 1H, NH); ^{13}C NMR δ : 23.3 (CH_3), 28.0 (CH_3), 69.1 (CHPh), 91.4 (CMe_2), 126.6-129.0-129.1-135.4 (Ph), 189.1 (C=S); HRMS : calcd for $\text{C}_{11}\text{H}_{13}\text{NOS}$ (207.0718), found (207.0718).

(*R*)-2-(4'-Bromobut-2'-enylthio)-4-phenyl-5,5-dimethyl- Δ^2 -1,3-oxazoline (7a):

(*R*)-4-Phenyl-5,5-dimethyl-1,3-oxazolidine-2-thione (**6**) (0.98 g, 4.73 mmol) in THF (5 mL) was added to a solution of LiHMDS (0.83 g, 4.96 mmol) in THF (15 mL), at -78°C . The mixture was stirred at this temperature for 30 min and 1,4-dibromo-2-butene (4.0 g, 18.91 mmol) was added in one portion. The mixture was gradually warmed to rt and stirred for 15 h. After concentration under reduced pressure, the residue was diluted in ether and washed with water. The organic layer was dried over magnesium sulfate and evaporated in vacuo. The residue was purified by chromatography (eluent: ethyl acetate/cyclohexane = 1/3) to provide compound (**7a**) (0.64 g, 40%) as a dark oil : IR (NaCl) ν (cm^{-1}) : 2981 (C-H), 1601 (C=N), 1457, 1207, 1112; ^1H NMR δ : 0.88 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 3.73 (m, 2H, CH_2S), 3.95 (d, $J_{4',3'} = 6.6$, 2H, CH_2Br), 4.86 (s, 1H, CHPh), 5.98 (m, 2H, HC=CH), 7.15-7.45 (m, 5H, Ph); ^{13}C NMR δ : 23.6 (CH_3), 28.6 (CH_3), 31.8, 32.8, 77.8 (CHPh), 90.0 (CMe_2), 126.9, 127.5, 128.1, 129.6, 130.0, 138.3, 164.4 (C=N); ^{15}N NMR δ : 217.9; HRMS : calcd for $\text{C}_{15}\text{H}_{19}\text{NO}^{80}\text{BrS}$ (340.0371), found (340.0339).

(*R*)-2-(4'-Chlorobut-2'-enylthio)-4-phenyl-5,5-dimethyl- Δ^2 -1,3-oxazoline (7b):

(*R*)-4-Phenyl-5,5-dimethyl-1,3-oxazolidine-2-thione (**6**) (0.58 g, 2.80 mmol) in THF (5 mL) was added to

a solution of LiHMDS (0.49 g, 2.94 mmol) in THF (15 mL), at -78°C . The mixture was stirred at this temperature for 30 min and 1,4-dichloro-2-butene (1.18 g, 11.19 mmol) was added in one portion. The mixture was gradually warmed to rt and stirred for 15 h. After concentration under reduced pressure, the residue was diluted in ether and washed with water. The organic layer was dried over magnesium sulfate and evaporated in vacuo. The residue was purified by chromatography (eluent: ethyl acetate/cyclohexane = 1/3) to provide compound (**7b**) (0.36 g, 43%) as a dark oil : IR (NaCl) $\nu(\text{cm}^{-1})$: 3067, 3030, 2976, 2922, 2957 (C-H), 1598 (C=N), 1448, 1200, 1114; ^1H NMR δ : 0.88 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 3.73 (m, 2H, CH_2S), 4.06 (d, $J_{4',3'} = 6.0$, 2H, CH_2Cl), 4.86 (s, 1H, CHPh), 5.94 (m, 2H, $\text{HC}=\text{CH}$), 7.15-7.40 (m, 5H, Ph); ^{13}C NMR δ : 23.5 (CH_3), 28.6 (CH_3), 32.7 (CH_2S), 44.0 (CH_2Cl), 77.9 (CHPh), 90.2 (CMe_2), 126.9, 127.5, 128.1, 128.9, 129.7, 138.5, 164.3 (C=N); ^{15}N NMR δ : 217.9; HRMS : calcd for $\text{C}_{15}\text{H}_{19}\text{NO}^{35}\text{ClS}$ (296.0876), found (296.0885).

(R)-2-(4'-Chlorobut-2'-enylthio)-4-phenyl- Δ^2 -1,3-thiazolidine-2-thione (10b):

(R)-4-Phenylthiazolidine-2-thione (**9**) (0.87 g, 4.45 mmol) in THF (5 mL) was added to a solution of LiHMDS (0.74 g, 4.45 mmol) in THF (10 mL), at -78°C . The mixture was stirred at this temperature for 30 min and 1,4-dichloro-2-butene (1.37 g, 12.36 mmol) was added in one portion. The mixture was gradually warmed to rt and stirred for 15 h. After concentration under reduced pressure, the residue was diluted in ether and washed with a solution 1N HCl and water. The organic layer was dried over magnesium sulfate and evaporated in vacuo. The residue was purified by chromatography (eluent: ether/cyclohexane = 5/95) to provide compound (**10b**) (0.52 g, 41%) as an oil : $[\alpha]_{\text{D}}^{20} -127.9^{\circ}$ ($c = 5.5$ in CHCl_3); IR (NaCl) $\nu(\text{cm}^{-1})$: 3028, 2929 (C-H), 1563 (C=N), 1452, 1274, 1253, 979, 961; ^1H NMR δ : 3.29 (dd, $J_{5a,5b} = 11.1$, $J_{5a,4} = 8.7$, 1H, $H_a\text{CHCHPh}$), 3.80 (m, 3H, $H_b\text{CHCHPh}$ and $\text{SCH}_2\text{CH}=\text{CH}$), 4.03 (d, $J_{4',3'} = 5.7$, 2H, CH_2Cl), 5.48 (dd, $J_{4,5a} = J_{4,5b} = 8.7$, 1H, CHPh), 5.89 (m, 2H, $\text{CH}=\text{CH}$), 7.36 (m, 5H, Ph); ^{13}C NMR δ : 33.8 ($\text{SCH}_2\text{CH}=\text{CH}$), 42.8 (CH_2CHPh), 44.2 (CH_2Cl), 79.4 (CHPh), 126.3-127.5-128.4 (Ph), 129.3-129.5 ($\text{CH}=\text{CH}$), 141.3 (Ph), 164.9 (C=N); ^{15}N NMR δ : 289.7; HRMS : calcd for $\text{C}_{13}\text{H}_{15}\text{N}^{35}\text{ClS}_2$ (284.0334), found (284.0343).

Characterization of (R)-2-butadienyl-4-phenyl- Δ^2 -1,3-thiazolidine-2-thione (11):

E isomer (53%): ^1H NMR δ : 3.32 (m, 1H, $H_a\text{CHCHPh}$), 3.80 (m, 1H, $H_b\text{CHCHPh}$), 5.18 (d, $J_{4',\text{cis},3'} = 10.5$, 1H, $H_{\text{cis}}\text{CH}=\text{CH}$), 5.26 (d, $J_{4',\text{trans},3'} = 16.5$, 1H, $H_{\text{trans}}\text{CH}=\text{CH}$), 5.54 (dd, $J_{4,5a} = J_{4,5b} = 9.0$, 1H, CHPh), 6.43 (m, 1H, $\text{HC}=\text{CH}_2$), 6.50 (m, 1H, $\text{HC}=\text{CHS}$), 6.89 (d, $J_{1',2'} = 15.0$, 1H, $\text{HCS}=\text{CH}$), 7.36 (m, 5H, Ph); ^{13}C NMR δ : 42.4 (CH_2S), 79.8 (CHPh), 118.5 ($\text{CH}_2=\text{CH}$), 121.6 ($\text{CHS}=\text{CH}$), 134.2 ($\text{CH}=\text{CHS}$), 135.0 ($\text{CH}=\text{CH}_2$), 126.3-127.5-128.4-141.2 (Ph), 164.9 (C=N); ^{15}N NMR δ : 291.7.

Z isomer (47%): ^1H NMR δ : 3.32 (m, 1H, $H_a\text{CHCHPh}$), 3.80 (m, 1H, $H_b\text{CHCHPh}$), 5.31 (d, $J_{4',\text{cis},3'} = 10.5$, 1H, $H_{\text{cis}}\text{CH}=\text{CH}$), 5.37 (d, $J_{4',\text{trans},3'} = 16.5$, 1H, $H_{\text{trans}}\text{CH}=\text{CH}$), 5.54 (dd, $J_{4,5a} = J_{4,5b} = 9.0$, 1H,

CHPh), 6.35 (m, 1H, HC=CH₂), 6.62 (ddd, $J_{3',4'}_{trans} = 16.5$, $J_{3',4'}_{cis} = J_{3',2'} = 9.5$, 1H, HC=CHS), 6.81 (d, $J_{1',2'} = 9.5$, 1H, HCS=CH), 7.36 (m, 5H, Ph); ¹³C NMR δ : 42.4 (CH₂S), 79.7 (CHPh), 119.6 (CH₂=CH), 120.4 (CHS=CH), 131.3 (CH=CHS), 131.7 (CH=CH₂), 126.3-127.5-128.4-141.2 (Ph), 164.2 (C=N); ¹⁵N NMR δ : 291.7.

Theoretical methods

Calculations were performed using Gaussian 98 program package.¹⁸ The structure of the transition states under investigation have been studied at the B3LYP level using the 6-31G* basis set. Analytical normal mode frequency calculations were performed for all of the optimized structures. The correctness of the curvature and their eigenvector were checked in order to guarantee the quality of the obtained results. Intrinsic reaction coordinate (IRC) calculations were performed on both transition states to insure that the identified transition structures lie along the correct reaction coordinates and connect effectively the reactants to the products.

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