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Stereospecific Synthesis of 2,3-Dimethyl-1,4-Thiamorpholines by Cyclization of β-*N*-Methoxycarbonylaminoalkyl Vinyl Sulfoxides and Related Compounds

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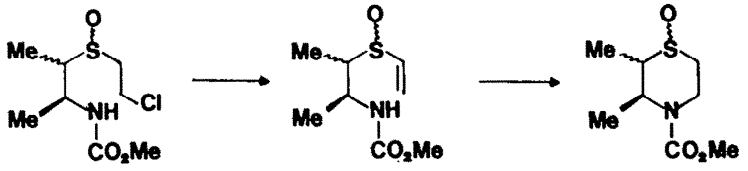
Abstract. Synthesis of *cis*- and *trans*-*N*-methoxycarbonyl-2,3-dimethyl-1,4-thiamorpholine and their *S*-oxides and *S,S*-dioxides by intramolecular reaction of the corresponding 2-methoxycarbonylaminoalkyl-2′-chloroethyl thioethers, sulfoxides and sulfones with sodium hydride in dimethylformamide at room temperature is reported. Cyclization of chlorothioethers and -sulfones is stereospecific although, in the case of sulfones, the formed 1,4-thiamorpholines *S,S*-dioxides epimerize at C(2) after long reaction times. In chlorosulfoxides, elimination of HCl is previous to cyclization which also resulted stereospecific except in the case of the acyclic starting material of R*$_S$,S*$_1$,S*$_2$ configuration, where epimerization at sulfur takes place.

INTRODUCTION

In previous work we have reported on the synthesis and conformational analysis of thianes and oxanes with exocyclic β-heteroatomic functions.[1] We are now interested in the corresponding 1,4-diheteracyclohexanes[2] of which there are no examples in the literature concerning the preparation of 2,3-dialkyl-1,4-thiamorpholines.[3] Despite the usefulness of the *inter*molecular nucleophilic addition to vinyl sulfoxides,[4] the corresponding *intra*molecular reaction has scarcely been used to build sulfur-containing heterocyclic rings. For instance, cyclization of *S*-(1-alkenyl)-L-cysteine *S*-oxide gave the corresponding 3-(5-alkyl-1,4-thiamorpholin)carboxylic acids but yields were low and the stereochemistry of the reaction was not studied in detail.[5] In contrast, we cyclized β-hydroxyalkyl β′-haloalkyl sulfoxides to give 2,3-dimethyl-1,4-oxathianes in good yield.[6] This reaction resulted stereospecific except in the case of the starting material of R*$_S$,S*$_1$,S*$_2$ configuration in which epimerization at sulfur was somewhat surprisingly observed.[6] We were interested in extending this method to the synthesis of other sulfur-containing heterocycles as well as checking whether epimerization at sulfur was nucleophile

dependent. Thus, we have carried out, and hereby report, the preparation of 1,4-thiamorpholine *S*-oxides **8** shown in Scheme I by cyclization of β-chlorosulfoxides **3**, via the vinyl sulfoxides **6**. Cyclization of the corresponding vinyl sulfides and sulfones is also discussed. Configuration and preferred conformation of the resulting 1,4-thiamorpholines is determined by ^1H- and ^{13}C-nmr spectroscopy.

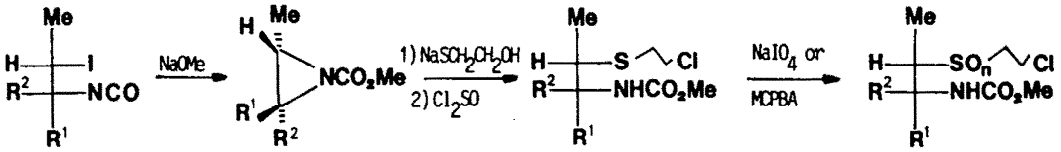


3 **6** **8**

Scheme I

RESULTS AND DISCUSSION

Preparation of starting materials **2**, **3** and **4** is outlined in Scheme II. Aziridines 1-*cis* and 1-*trans* were stereospecifically obtained in high yield from *threo*- and *erythro*-1-methyl-2-iodopropyl isocyanate, respectively, by treatment with sodium methoxide.[7] Reaction of sodium 2-hydroxyethylsulfide with aziridines 1-*cis* and 1-*trans*, followed by treatment of the resulting alcohol with thionyl chloride at 0°C, yielded respectively compounds 2*t* and 2*e*.[8] The structures of these compounds were assigned assuming a S_N2 process for the opening of the three-membered ring. Chlorosulfides 2*e* and 2*t* were oxidized to a mixture of diastereomeric chlorosulfoxides epimers at sulfur [3*e*(α) + 3*e*(β) and 3*t*(α) + 3*t*(β)[9]] or to sulfones **4***e* and **4***t* by treatment, respectively, with one mole of sodium metaperiodate or excess of *m*-chloroperbenzoic acid (MCPBA). The *erythro*-sulfoxides [3*e*(α) + 3*e*(β)] were separated and purified by crystallization and flash chromatography. However, we were only able to purify 3*t*(α) from the corresponding mixture of *threo* isomers (see Experimental Section).



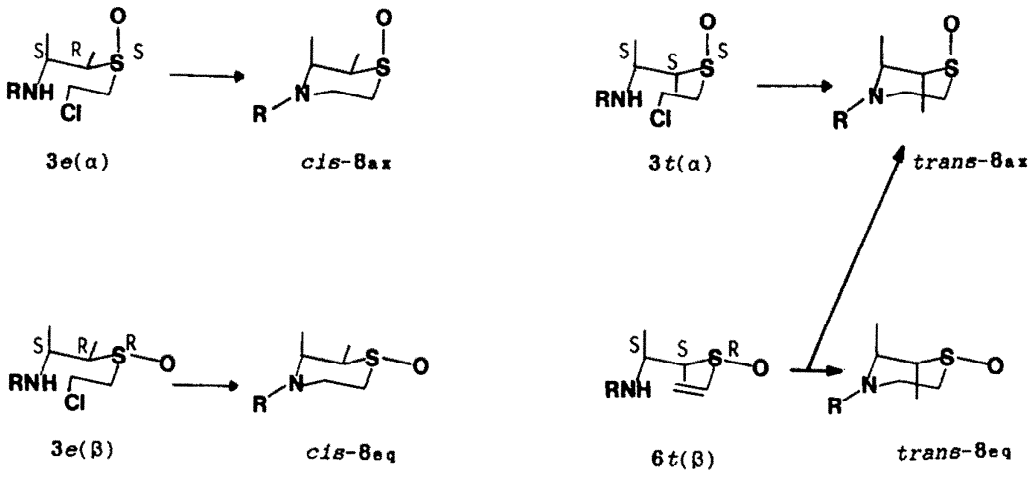
1 **2** **3** (n=1), **4** (n=2)

R^1 = H, R^2 = Me: 1-*cis*, 2*t*, 3*t* (α + β), **4***t*
R^1 = Me, R^2 = H: 1-*trans*, 2*e*, 3*e* (α + β), **4***e*

Scheme II

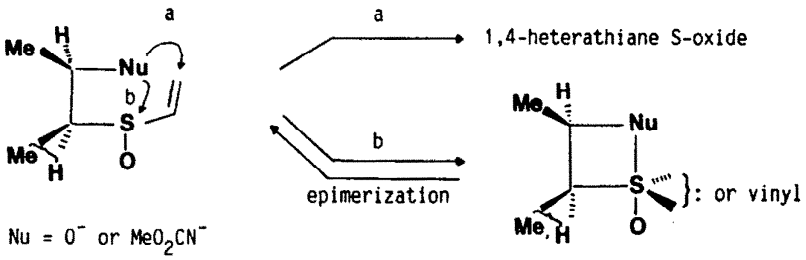
Chlorosulfoxides 3*e*(α), 3*e*(β) and 3*t*(α) - which were obtained pure - and the mixture 3*t*(α) + 3*t*(β) react at room temperature with sodium hydride in dimethylformamide (NaH/DMF) to give, respectively, *cis*-**8**$_{ax}$, *cis*-**8**$_{eq}$, *trans*-**8**$_{ax}$ and (*trans*-**8**$_{ax}$ + *trans*-**8**$_{eq}$)[10] (Scheme III) whose relative configurations and

preferred conformation were determined from their ^1H- and ^{13}C-nmr spectra (Table I; see below). The reaction was therefore stereospecific for 3*e*(α), 3*e*(β) and 3*t*(α) suggesting that no epimerization takes place in these cases. Under this assumption, we have assigned back relative configurations of the starting chlorosulfoxides (Scheme III) which were consistent, concerning the stereocenters C(2) and C(3), with the assumed S_N2 opening of aziridines (see above).



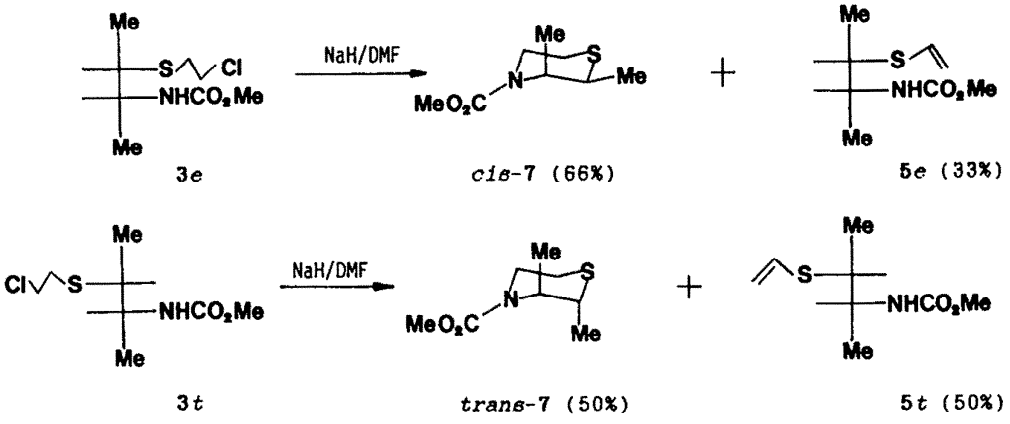
Scheme III (R = CO_2Me)

We were unable to follow the stereochemical course of 3*t*(β) since this isomer could not be purified in our hands. Nevertheless, if the cyclization reaction is quenched after a certain period of time (10 and 60 min respectively for the *erythro* and *threo* isomers), we observed by ^1H-NMR that the major constituent of the resulting mixtures are vinyl sulfoxides **6** suggesting that the latter compounds are intermediates as shown in Scheme I. Fortunately, the mixture 6*t*(α) + 6*t*(β) could be resolved by flash chromatography and a small amount of pure 6*t*(β) was thus obtained and finally cyclized in NaH/DMF yielding a 6:1 mixture of *trans*-8eq + *trans*-8ax. This shows that sulfur does in fact epimerize in the isomer of R**s*,S**1*,S**2* configuration regardless of nucleophile, MeO_2C-N- or O-, since a 1:1 mixture of 2,3-dimethyl-1,4-oxathiane *S*-oxides epimers at sulfur was obtained from the corresponding hydroxyalkylvinyl sulfoxide.[6] A plausible explanation for this behavior may be competition between attack of nucleophile to the double bond or to sulfinyl sulfur (Scheme IV). Epimerization of the latter atom would take place in the sulfurane-like intermediate (Scheme IV) whose formation appears to be only favorable starting from 6*t*(β), presumably due to steric reasons. We are gathering more evidence concerning this point which will be the subject of a future paper.



Scheme IV

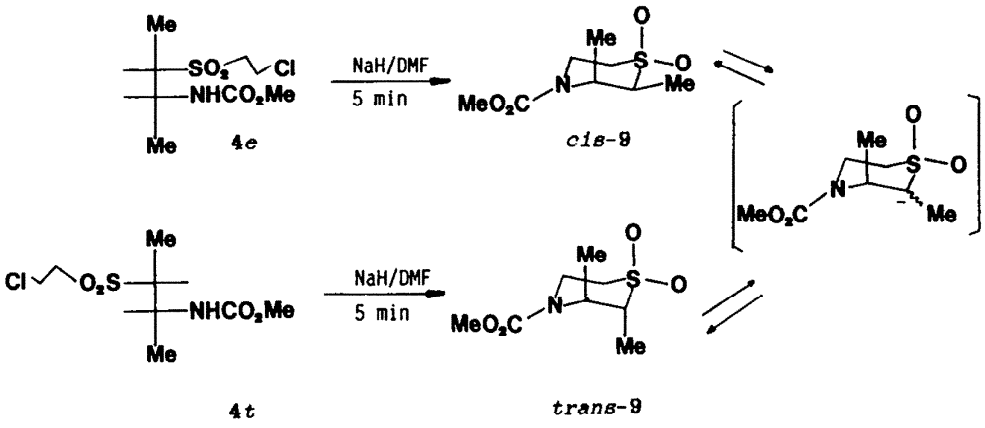
Thioethers **2** in NaH/DMF give a mixture of 2,3-dimethyl-1,4-thiamorpholine (**7**) and the corresponding vinylsulfide **5** (Scheme V). NMR spectra of the final products (see below) indicate that the stereocenters remained unchanged after cyclization. It should be noted that the sulfides of similar structure and configuration with hydroxyl instead of $NHCO_2Me$ group did not cyclize at all in similar conditions and quantitatively afforded vinylsulfides.[6] This different behavior suggests that the elimination of HCl on one hand, and the substitution of the halogen on the other, should be two *intra*molecular processes in competition, and that the vinyl thioether, once it is formed, cannot evolve into the cyclic substrate. The lower basicity and higher nucleophility of R-N⁻-CO_2Me compared to RO⁻ may explain why the carbamates are able to cyclize, at least in part, and why the hydroxyderivatives are not.



Scheme V

Finally, treatment of sulfones **4***e* and **4***t* (Scheme VI) with NaH/DMF at room temperature gave respectively the desired cyclic sulfones *cis*-**9** and *trans*-**9**. We were unable to find out whether the corresponding vinyl sulfones are intermediates for the reaction is much faster than in the case of sulfoxides **3** (see above).. On the other hand, if the reaction is not quickly quenched, a mixture of *cis*- and *trans*-**9** is obtained whose composition after a long time (2 h

for **4*t*** and *ca.* 10 h for **4*e***) is *ca.* 1:1. Cyclization is therefore stereospecific but, once it has proceeded, the resulting cyclic *cis*- and *trans*-sulfones equilibrate presumably by epimerization at C(2), the 1:1 ratio resulting from the similar stability of *cis*-**9** and *trans*-**9** which has been deduced from the conformational analysis of *N*-alkoxycarbonyl-2-methyl-1,4-thiamorpholine *S,S*-dioxide.[11] In this compound, the methyl group at C(2) prefers to be equatorial by 0.74 kcal/mol in a number of solvents (CD_2Cl_2, acetone-d_6 or methanol-d_4).

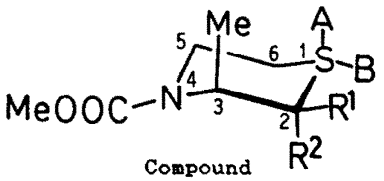


Scheme VI

However, this equatorial preference of Me-C(2) should be almost exactly counterpoised in *cis*-**9** by the [Me-C(2)/Me-C(3)]$_{gauche}$ interaction (0.87 kcal/mol[12]). ΔG^0 for the equilibrium *cis*-**9**/*trans*-**9** is therefore estimated to be 0.13 kcal/mol which gives a 1:1.2 *cis*/*trans* ratio at room temperature, in reasonable agreement with the observed one (1:1; see above). On the other hand, we have mentioned that the *cis*-**9**/*trans*-**9** equilibrium is reached faster when one starts from **4*t*** (*ca.* 2 h) than from **4*e*** (*ca.* 10 h), suggesting that *trans*-**9** epimerizes faster than its *cis*-isomer and that C(2)-H is thus more acidic in equatorial than axial arrangement. In order to check these assumptions, the cyclic sulfones were independently treated with NaH/DMF at room temperature and the evolution followed by ^{1}H-NMR. Compound *trans*-**9** transformed in *ca.* 2 h in a 1:1 mixture of *trans*-**9** + *cis*-**9** whereas a much longer reaction time (*ca.* 8 h) was necessary to obtain the same result starting from *cis*-**9**.

Configurational assignment of sulfoxides **8** and the preferred conformation of all cyclic substrates have been established from their ^{1}H- and ^{13}C-nmr parameters (Table I) of which we discuss the most important ones for the sake of brevity. The finding of a high coupling constant (10.5-13.0 Hz) in the C(5)-C(6) fragment, assigned to $J_{5a,6a}$ in Table I, suggests that the studied compounds are conformationally homogeneous. On the other hand, the chemical shifts displayed

Table I.- First-order proton chemical shifts (ppm), proton-proton coupling constants (Hz) and carbon-13 chemical shifts (ppm) of thiamorpholines 7-9.



Compound

Param.	*cis*-7	*cis*-8ax	*cis*-8eq	*cis*-9	*trans*-7	*trans*-8ax	*trans*-8eq	*trans*-9
R^1	Me	Me	Me	Me	H	H	H	H
R^2	H	H	H	H	Me	Me	Me	Me
A	:	O	:	O	:	O	:	O
B	:	:	O	O	:	:	O	O
$\delta_{H(2)}$	3.14	2.38	2.76	3.20	2.54	2.98	3.20	2.85
$\delta_{H(3)}$	4.43	4.52	4.67	4.72	4.35	4.46	4.69	4.66
$\delta_{H(5e)}$	4.19	4.20	4.44	4.47	4.20	4.20	4.39	4.42
$\delta_{H(5a)}$	3.09	3.86	3.26	3.62	3.19	3.93	3.25	3.63
$\delta_{H(6e)}$	2.38	3.02	3.42	3.02	2.23	2.72	3.02	2.80
$\delta_{H(6a)}$	2.75	2.65	2.68	3.10	2.93	2.84	2.82	3.14
$\delta_{H(10)}$	3.70	3.74	3.74	3.75	3.71	3.74	3.74	3.75
$\delta_{Me(2)}$	1.11	1.46	1.48	1.38	1.47	1.15	1.33	1.44
$\delta_{Me(3)}$	1.22	1.49	1.23	1.37	1.40	1.63	1.39	1.53
$J_{2,Me(2)}$	7.1	7.3	7.1	7.1	7.0	7.4	7.0	7.2
$J_{3,Me(3)}$	6.8	7.3	7.3	7.2	6.8	7.2	7.3	7.2
$J_{2,3}$	3.4	4.9	3.8	5.0	2.6	2.1	3.3	2.6
$J_{5a,6e}$	2.6	2.1	2.0	4.5	2.7	3.4	2.7	2.6
$J_{5e,6a}$	3.0	4.0	3.7	3.9	3.3	4.2	4.0	4.4
$J_{5e,6e}$	2.7	3.0	3.7	3.3	2.6	3.4	4.0	3.3
$J_{3,5e}$	-	-	1.4	1.9	-	1.5	1.4	-
$J_{2,6e}$	-	-	-	-	0.8	-	1.5	1.8
$J_{5a,6a}$	12.5	12.5	13.0	10.5	12.5	11.4	12.5	12.3
$-J_{5,5}$	13.8	14.7	15.1	15.0	13.7	14.8	15.2	14.9
$-J_{6,6}$	13.3	14.2	12.0	13.9	13.2	14.2	12.5	14.1
$\delta_{C(2)}$	40.2	50.3	61.2	58.2	38.2	51.6	53.2	59.5
$\delta_{C(3)}$	51.0	50.9	52.5	51.9	52.0	51.2	51.9	53.2
$\delta_{C(5)}$	38.8	27.9	36.0	37.1	39.1	28.6	35.7	37.5
$\delta_{C(6)}$	28.8	45.6	51.4	51.4	22.5	40.6	43.3	47.6
$\delta_{Me(2)}$	18.0	14.2	13.1	7.4	20.0	13.5	7.0	14.6
$\delta_{Me(3)}$	10.3	13.7	12.9	10.8	17.3	18.0	17.0	16.9
δ_{MeO}	52.6	52.9	53.1	53.3	52.6	52.9	53.1	53.3
δ_{CO}	155.7	155.4	155.2	155.0	156.5	156.2	155.9	155.9

by H(3) (4.35-4.72 ppm; *cf.* Table I), very similar to those of H(5e) (4.19-4.47 ppm; *cf.* Table I), suggest that H(3) is equatorial, and hence, Me-C(3) is axial in all compounds. This is not surprising since Me-C(2) of *N*-acyl-2-methylpiperidines has been also reported to be axial,[13] a finding which was explained assuming an allylic-strain-like effect of acyl group on Me-C(2).[14] Nontheless, the magnitude of this effect is unexpectedly high since Me-C(3) remains axial in the *trans* isomers of **8ax** and **9** even though these compounds share strong steric interactions.[15] The *trans* (axial) or *cis* (equatorial) arrangement of Me-C(2) is, in turn, easily confirmed by ^{13}C-nmr. *Trans* isomers display a value of $\delta_{C(6)}$ 3.8 to 6.9 ppm (see Table I) lower than that of their *cis* counterparts, which is in agreement with the expected effect of steric compression of axial Me-C(2) on C(6). Arrangement of sulfinyl oxygen may be determined by the shielding[16] and deshielding[17] effects exerted, respectively, on $\delta_{C(5)}$ and $\delta_{H(5a)}$ by axial S-O. Thus, the **8ax** isomers display values for $\delta_{C(5)}$ and $\delta_{H(5a)}$ (Table I) which are, respectively, lower [by 8.1 (*cis*-**8ax**) or 7.1 ppm (*trans*-**8ax**)] and higher [by 0.60 (*cis*-**8ax**) or 0.68 ppm (*trans*-**8ax**)] than their **8eq** epimers.

EXPERIMENTAL SECTION

^{1}H- (200 MHz) and ^{13}C-NMR (50 MHz) spectra (CDCl$_3$ solutions) were recorded in the FT mode on a Bruker WP-200-SY instrument coupled to an ASPECT 2000 computer, transforming 16K data points. Double resonance, DEPT and/or ^{1}H/^{13}C 2D experiments were performed to assigning proton and carbon signals of the studied 1,4-thiamorpholines. The NMR spectra of the latter compounds were recorded at *ca.* 50°C in order to simplify them by averaging the restricted rotation around the N-CO bond which causes line broadening at room temperature. Both chemical shifts (ppm downfield from internal tetramethylsilane) and coupling constants (Hz) were obtained by first order analysis of spin patterns. Mass spectra were recorded on a Hewlett-Packard 5985 spectrometer at electron impact (70 eV). Mass data are reported in mass units (m/z) and the values in brackets regard the relative intensity from base peak (as 100%). IR spectra were recorded on a Nicolet FT-5DX spectrometer. Microanalyses were performed by the *Instituto de Química Orgánica del CSIC* (Madrid, Spain) with a Perkin-Elmer 240 analyzer. Melting points are uncorrected. The silica-gel used in chromatography was Merck PR-254 (TLC) or Kieselgel 60 (flash).

***Cis*- and *trans*-*N*-methoxycarbonyl-2,3-dimethylaziridine (1).** To a suspension of 0.54 g (10 mmol) of sodium methoxide in 10 mL of dry acetone was added dropwise at 0°C 2.25 g (10 mmol) of *erythro*- or *threo*-1-methyl-2-iodopropyl isocyanate[18] in 25 mL of acetonitrile. The mixture was stirred for 30 m at 0°C and 1 h at room temperature, quenched with 50 mL of water and the resulting solution extracted with methylene chloride. Usual work-up of the extracts yielded a yellow oil which was used without further purification. Yields 85% for *trans*-**1** (from *erythro*-isocyanate) and 77% for *cis*-**1** (from *threo*-isocyanate). Their spectroscopic data agreed with those previously reported.[19]

***Erythro*- and *threo*-1,2-dimethyl-2-methoxycarbonylaminoethyl-2'-chloroethyl sulfide (2).** To a suspension of 0.49 g (17 mmol) of sodium hydride in 5 mL of acetonitrile was added dropwise 1.0 g (13 mmol) of 2-mercaptoethanol (Aldrich Co.) in 10 mL of acetonitrile at 0°C under N$_2$ and the mixture was stirred for 30 m at room temperature. It was then added 1.29 g (10 mmol) of *cis*- or *trans*-*N*-methoxycarbonyl-2,3-dimethylaziridine (**1**) in 20 mL of acetonitrile and the solution was refluxed for 3 h. The reaction was quenched with 50 mL of water and extracted with chloroform. Work up of the extracts afforded the crude product

which, after purification by flash chromatography (ethyl acetate/hexane 1:1), was dissolved in chloroform and treated with 1.2 g (10 mmol) of thionyl chloride in 25 mL of chloroform for 30 min at room temperature. The solution was dried (anh. $MgSO_4$), the solvent removed and the resulting oil distilled at reduced pressure. Yield 75%. Compound **2*e*** (bp 118°C/0.5 mm Hg) and **2*t*** (116°C/0.5 mm Hg) were respectively obtained from *trans*-**1** and *cis*-**1**. IR **2*e*** (film) 3325, 1710, 1521, 1248, 1092, 755, 698 cm^{-1}; IR **2*t*** (film) 3311, 1699, 1527, 1250, 1078, 780, 698 cm^{-1}; ^1H NMR **2*e*** ($CDCl_3$) δ 1.13 (d, 3H, J=6.8 Hz, C*H*$_3$CN), 1.32 (d, 3H, J=7.1 Hz, C*H*$_3$CS), 2.90 (m, 2H, C*H*$_2$S), 2.98 (dq, 1H, J's=3.7, 7.1 Hz, C*H*S), 3.60 (m, 2H, C*H*$_2$Cl), 3.67 (s, 3H, C*H*$_3$O), 3.87 (m broad, 1H, C*H*N), 5.30 (d broad, 1H, N*H*); ^1H NMR **2*t*** ($CDCl_3$) δ 1.20 (d, 3H, J=6.8 Hz, C*H*$_3$CN), 1.24 (d, 3H, J=7.0 Hz, C*H*$_3$CS), 2.93 (m, 2H, C*H*$_2$S), 2.99 (dq, 1H, J's=3.3, 7.0 Hz, C*H*S), 3.66 (m, 2H, C*H*$_2$Cl), 3.67 (s, 3H, C*H*$_3$O), 3.89 (m broad, 1H, C*H*N), 4.85 (d broad, 1H, N*H*); MS (**2*e***) 210 M+-15 (2.5), 123 (21.5), 102 (100), 59 (19.7); MS (**2*t***) 189 M+-36 (11.5), 123 (3.5), 102 (100), 59 (14.8).

Erythro*- and *threo*-1,2-dimethyl-2-methoxycarbonylaminoethyl-2'-chloroethyl sulfoxide (3).** To a solution of 1.28 g (6 mmol) of sodium metaperiodate in 20 mL of water was added 1.35 g (6 mmol) of **2*e or **2*t*** in 15 mL of ethanol at 0°C. The reaction mixture was stirred for 2 h at 0°C and overnight at room temperature. Ethanol was then added and the solid filtered. The solvent was removed and the solid cake extracted several times with chloroform. Usual work up of the extracts afforded sulfoxides **3*e*** (from **2*e***) and **3*t*** (from **2*t***) as a mixture of diastereoisomers (α + β). Yield 90%. **3*e*(β)** (mp. 128-130°C) and **3*t*(α)** (mp. 95-97°C) crystallized from their respective mixtures from benzene-hexane and **3*e*(α)** was purified from the corresponding mother liquors by flash chromatography (CH_2Cl_2/CH_3OH 40:1) as a colorless oil. **3*t*(β)** could not be purified in our hands and was always contaminated with *ca.* 20% of **3*t*(α)**. IR **3*e*(α)** (film) 3297, 1716, 1534, 1253, 1025, 778, 665 cm^{-1}; IR **3*e*(β)** (KBr) 3318, 1687, 1550, 1272, 1022, 647 cm^{-1}; IR **3*t*(α)** (KBr) 3248, 1715, 1559, 1278, 1028, 868 cm^{-1}; ^1H NMR **3*e*(α)** 1.16 (d, 3H, J=7.1 Hz, C*H*$_3$CS), 1.43 (d, 3H, J=7.0 Hz, C*H*$_3$CN), 3.10 (m, 3H, C*H*$_2$SO, C*H*SO), 3.66 (s, 3H, CH_3O), 3.97 (m, 2H, C*H*$_2$Cl), 4.21 (dq, 1H, J=2.7, 7.0 Hz, C*H*N), 6.09 (d broad, 1H, N*H*); ^1H NMR **3*e*(β)** 1.32 (d, 3H, J=7.0 Hz, C*H*$_3$CN), 1.33 (d, 3H, J=7.1 Hz, C*H*$_3$CS), 2.92 (m, 1H, C*H*SO), 3.09 (m, 2H, C*H*$_2$SO), 3.68 (s, 3H, CH_3O), 4.05 (m, 2H, C*H*$_2$Cl), 4.06 (dq, 1H, J=4.0, 7.0 Hz, C*H*N), 4.92 (d broad, 1H, N*H*); ^1H NMR **3*t*(α)** 1.34 (d, 3H, J=6.9 Hz, C*H*$_3$CS), 1.37 (d, 3H, J=7.1 Hz, C*H*$_3$CN), 2.86 (dq, 1H, J=5.0, 6.9 Hz, C*H*SO), 3.05 (m, 2H, C*H*$_2$SO), 3.66 (s, 3H, CH_3O), 3.91 (m, 2H, C*H*$_2$Cl), 4.07 (m, 1H, C*H*N), 5.46 (d broad, 1H, N*H*); ^1H NMR **3*t*(β)** 1.24 (d, 3H, J=7.0 Hz, C*H*$_3$CN), 1.32 (d, 3H, J=6.8 Hz, C*H*$_3$CS), 2.85 (m, 1H, C*H*SO), 3.10 (m, 2H, C*H*$_2$SO), 3.67 (s, 3H, CH_3O), 3.90 (m, 2H, C*H*$_2$Cl), 4.05 (m, 1H, C*H*N), 5.25 (d broad, 1H, N*H*); MS [**3*e*(α)**] 241 M+ (0.1), 130 (100), 102 (33.5), 98 (34.8), 71 (32.7), 59 (41.3); Anal. Calcd. for $C_8H_{16}ClO_3NS$: C, 39.75, H, 6.63, Cl, 14.70, N, 5.80, S, 13.25. Found [**3*e*(β)**]: C, 40.00, H, 6.57, Cl, 14.60, N, 6.00, S, 13.10; [**3*t*(α)**]: C, 39.70, H, 6.67, Cl, 14.47, N, 5.92, S, 13.20.

Erythro*- and *threo*-1,2-dimethyl-2-methoxycarbonylaminoethyl-2'-chloroethyl sulfone (4).** To a solution of 2.30 g (12 mmol) of *m*-chloroperbenzoic acid in 20 mL of chloroform was slowly added 1.35 g (6 mmol) of **2*e or **2*t*** in 10 mL of chloroform. The mixture was stirred at room temperature for 12 h and washed with saturated solution of $NaCO_3H$. Work up of the organic layer afforded crude sulfones in 90-92% yield, which were purified by flash chromatography (**4*e***, colorless oil, obtained from **2*e***) or recrystallized from hexane (**4*t***, mp. 93-95°C, obtained from **2*t***). IR **4*e*** (film) 3354, 1706, 1550, 1360, 1120, 940 cm^{-1}; IR **4*t*** (KBr) 3360, 1699, 1539, 1253, 1116, 827 cm^{-1}; ^1H NMR **4*e*** ($CDCl_3$) δ 1.37 (d, 3H, J=7.1 Hz, C*H*$_3$CN), 1.44 (d, 3H, J=7.2 Hz, C*H*$_3$CS), 3.34 (dq, 1H, J=3.1, 7.2 Hz, C*H*SO_2), 3.45 (m, 2H, C*H*$_2SO_2$), 3.68 (s, 3H, CH_3O), 3.89 (m, 2H, CH_2Cl), 4.25 (m, 1H, C*H*N), 5.46 (d broad, 1H, N*H*). ^1H NMR **4*t*** ($CDCl_3$) δ 1.34 (d, 3H, J=7.0 Hz, C*H*$_3$CN), 1.39 (d, 3H, J=7.2 Hz, C*H*$_3$CS), 3.48 (dq, 1H, J=3.2, 7.2 Hz, C*H*SO_2), 3.52 (m, 2H, C*H*$_2SO_2$), 3.68 (s, 3H, CH_3O), 3.95 (m, 2H, CH_2Cl), 4.26 (dq, 1H, J=3.2, 7.0 Hz, C*H*N), 5.07 (d broad, 1H, N*H*). Anal. Calcd. for $C_8H_{16}ClO_4NS$: C, 37.28, H, 6.21, Cl, 13.79, N, 5.44, S, 12.43. Found (**4*t***): C, 37.50, H, 6.25, Cl, 13.57, N, 5.39, S, 12.23.

Reaction of compounds 2-4 with NaH/DMF. General procedure. To a suspension of sodium hydride in 1 mL of dry DMF was slowly added a solution of 1 mmol of compounds **2**, **3** or **4** in 10 mL of dry DMF at room temperature under N_2. The reaction mixture was stirred at room temperature for a variable time and quenched with 10 mL of water. The solvent was removed to dryness and the residue treated with chloroform (3 x 50 mL). Usual work-up of the extracts yielded the crude product.

***Erythro*- and *threo*-1,2-dimethyl-2-methoxycarbonylaminoethylvinyl sulfoxides (6).** They were obtained by treatment of chlorosulfoxides **3** with NaH (60 mg, 2.5 mmol) in DMF following the general procedure described above (reaction times: *erythro* isomers, 10 min; *threo* isomers, 1 h). The mixture of compounds **3*t*(α)** + **3*t*(β)** yielded a mixture of diastereoisomers **6*t*(α)** + **6*t*(β)** which were separated by crystallization from hexane [**6*t*(α)**, mp. 117-119°C] or flash chromatography

(CH_2Cl_2/CH_3OH 40:1) [**6***t*(β), colorless oil]. IR **6***t*(α) (KBr) 3304, 1700, 1541, 1062, 1041, 669 cm^{-1}; IR **6***t*(β) (film) 3287, 1699, 1536, 1261, 1038, 978 cm^{-1}; ^1H NMR **6***t*(α) ($CDCl_3$) δ 1.20 (d, 3H, J=6.9 Hz, C*H*$_3$CS), 1.45 (d, 3H, J=6.8 Hz, C*H*$_3$CN), 2.74 (m, 1H, J=4.7 Hz, C*H*SO), 3.66 (s, 3H, CH_3O), 4.15 (m, 1H, C*H*N), 5.52 (d broad, 1H, N*H*), 6.06 (d, 1H, J=9.4 Hz), 6.07 (d, 1H, J=16.8 Hz), 6.46 (dd, 1H, J=9.4, 16.8 Hz). ^1H NMR **6***t*(β) ($CDCl_3$) δ 1.19 (d, 3H, J=7.1 Hz, C*H*$_3$CSO), 1.29 (d, 3H, J=6.8 Hz, C*H*$_3$CN), 2.95 (q, 1H, J=7.1, 7.2 Hz, C*H*SO), 3.68 (s, 3H, CH_3O), 3.93 (m, 1H, C*H*N), 4.94 (d broad, 1H, N*H*), 6.07 (d, 1H, J=9.9 Hz), 6.11 (d, 1H, J=16.5 Hz), 6.75 (dd, 1H, J=9.9, 16.5 Hz). MS [**6***t*(β)]: 205 M^+ (3.6), 130 (100), 98 (20.4), 87 (16.0), 71 (18.0), 59 (25.6). Anal. Calcd. for $C_8H_{15}O_3NS$: C, 46.83, H, 7.32, N, 6.83, S, 15.61. Found [**6***t*(α)]: C, 46.68, H, 7.42, N, 6.94, S, 15.45.

N*-Methoxycarbonyl-2,3-dimethyl-1,4-thiamorpholine *S*-oxides (8).** They were prepared from **3** folowing the general procedure described above and purified by flash chromatography (CH_2Cl_2/CH_3OH 40:1) as colorless oils. The *cis*-**8**$_{eq}$ isomer (R**s*,R**1*,S**2*) was obtained from **3e*(β). Reaction time 2 h. Yield 80%. The *cis*-**8**$_{ax}$ isomer (S**s*,R**1*,S**2*) was obtained from **3***e*(α). Reaction time 4 h. Yield 72%. The *trans*-**8**$_{ax}$ isomer (S**s*,S**1*,S**2*) was obtained from **3***t*(α). Reaction time 4 h. Yield 78%. The *trans*-**8**$_{eq}$ isomer (S**s*,R**1*,S**2*) was obtained from **6***t*(β) as a 6:1 mixture of *trans*-**8**$_{eq}$ + *trans*-**8**$_{ax}$. Reaction time 24 h. Yield 50% after separation of the isomers by flash chromatography. IR (*cis*-**8**$_{eq}$) (film): 1694, 1292, 1193, 1034, 885 cm^{-1}; IR (*cis*-**8**$_{ax}$) (film): 1697, 1294, 1187, 1019, 881 cm^{-1}; IR (*trans*-**8**$_{eq}$) (film): 1698, 1190, 1041, 891 cm^{-1}; IR (*trans*-**8**$_{ax}$) (film): 1696, 1187, 1029, 887 cm^{-1}; ^1H NMR (see Table I); MS (*cis*-**8**$_{eq}$) 205 M^+ (100), 188 (51.5), 142 (48.1), 128 (49.9), 114 (49.1), 70 (61.6); MS (*cis*-**8**$_{ax}$) 205 M^+ (88.1), 188 (40.9), 149 (100), 128 (62.9), 114 (61.1), 70 (77.7), 56 (90.2); MS (*trans*-**8**$_{eq}$) 205 M^+ (100), 188 (33.7), 142 (47.0), 128 (65.9), 114 (50.8), 70 (69.2); MS (*trans*-**8**$_{ax}$) 205 M^+ (75.9), 188 (15.8), 142 (27.7), 128 (42.5), 114 (27.8), 59 (100). Anal. Calcd. for $C_8H_{15}O_3NS$: C, 46.83, H, 7.32, N, 6.83. Found (*trans*-**8**$_{ax}$): C, 46.58, H, 7.60, N, 6.70.

N*-Methoxycarbonyl-2,3-dimethyl-1,4-thiamorpholines (7) and 1,2-dimethyl-2-methoxycarbonylaminoethylvinyl sulfides (5)** were obtained together when chlorosulfides **2** were treated with NaH (36 mg, 1.5 mmol) in DMF following the general procedure described above. Reaction time 4 h. In the case of **2t*, a 1:2 mixture of **5***e* + *cis*-**7** was obtained, whereas in the case of **2***e* the composition of the **5***t* + *trans*-**7** mixture was 1:1. Compounds **5** and **7** were separated from the corresponding mixtures by flash chromatography (ethyl acetate/hexane 1:5). IR (*cis*-**7**) (film) 1702, 1196, 1105, 884 cm^{-1}; IR (*trans*-**7**) (film) 1701, 1194, 1099, 892 cm^{-1}; IR (**5***e*) (film) 3325, 1699, 1528, 1246, 1194, 1090, 965 cm^{-1}; IR (**5***t*) (film) 3310, 1699, 1528, 1254, 1187, 1098, 1009 cm^{-1}; ^1H NMR (*cis*- and *trans*-**7**) see Table I; ^1H NMR (**5***e*) ($CDCl_3$) δ 1.16 (d, 3H, J=6.8 Hz, C*H*$_3$CN), 1.33 (d, 3H, J=7.1 Hz, C*H*$_3$CS), 3.25 (dq, 1H, J=4.1, 7.1 Hz, C*H*S), 3.67 (s, 3H, CH_3O), 3.93 (m, 1H, CH*N*), 5.05 (d broad, 1H, N*H*), 5.23 (d, 1H, J=9.9 Hz), 5.27 (d, 1H, J=16.7 Hz), 6.38 (dd, 1H, J=9.9, 16.7 Hz); ^1H NMR (**5***t*) ($CDCl_3$) δ 1.20 (d, 3H, J=6.8 Hz, C*H*$_3$CN), 1.27 (d, 3H, J=7.1 Hz, C*H*$_3$CS), 3.20 (dq, 1H, J=3.7, 7.1 Hz, C*H*S), 3.67 (s, 3H, CH_3O), 3.96 (m, 1H, CH*N*), 4.76 (d broad, 1H, N*H*), 5.24 (d, 1H, J=9.9 Hz), 5.34 (d, 1H, J=16.7 Hz), 6.39 (dd, 1H, J=9.9, 16.7 Hz); MS (*cis*-**7**) 189 M^+ (7.7), 160 (15.7), 129 (11.6), 114 (30.7), 102 (17.3), 88 (32.1), 70 (94.0), 59 (67.0), 42 (100); MS (*trans*-**7**) 189 M^+ (53.2), 160 (95.1), 129 (47.7), 114 (83.0), 102 (39.2), 88 (59.0), 70 (100), 59 (40.1), 42 (55.3); MS (**5***e*) 189 M^+ (25.9), 102 (100), 87 (22.4), 59 (17.6); MS (**5***t*) 189 M^+ (6.1), 102 (100), 87 (9.3), 59 (46.4); Anal. Calcd. for $C_8H_{15}O_3NS$: C, 50.79, H, 7.94, N, 7.41. Found (*trans*-**7**): C, 50.58, H, 7.64, N, 7.60.

N*-Methoxycarbonyl-2,3-dimethyl-1,4-thiamorpholine *S,S*-dioxides (9)** were obtained in 80% yield by treatment of chlorosulfones **4** with NaH (60 mg, 2.5 mmol) in DMF following the general procedure described above. Reaction time 5 min (see Results and Discussion). The crude products *cis*-**9** (from **4e*) and *trans*-**9** (from **4***t*) were purified as colorless oils by flash chromatography (ethyl acetate/hexane 1:2). IR (*cis*-**9**) (film) 2959, 1697, 1456, 1322, 1128, 900, 769 cm^{-1}; IR (*trans*-**9**) (film) 2946, 1699, 1450, 1342, 1137, 897, 768 cm^{-1}; ^1H HMR (see Table I); MS (*cis*-**9**) 221 M^+ (6.0), 206 (16.6), 142 (23.7), 127 (10.8), 114 (18.3), 84 (22.7), 70 (51.8), 59 (50.4), 56 (65.9), 42 (100); MS (*trans*-**9**) 221 M^+ (35.2), 206 (100), 162 (20.9), 142 (70.3), 127 (40.6), 114 (45.2), 101 (31.4), 82 (35.7), 70 (91.7), 56 (68.8), 42 (97.9); Anal. Calcd. for $C_8H_{15}O_4NS$: C, 43.44, H, 6.79, N, 6.33. Found (*cis*-**9**): C, 43.18, H, 6.93, N, 6.11.

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