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Asymmetric synthesis of 3-methylthio alcohols by intramolecular Michael addition reactions

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Abstract—Chiral 3-methylthio alcohols have been synthesized through a known intramolecular sulfur transfer reaction that has been carried out in di- and trisubstituted α,β-unsaturated *N*-enoyl oxazolidinethiones as substrates, giving rise to *syn*/*anti*-diastereomers. The *anti*-diastereomer is favored and obtained via a highly diastereoselective protonation step.

The introduction of a thiol group in the α and β-positions of carboxylic acid derivatives, has been subject of extensive researches. S_N2 substitution has been the method employed to prepare α-mercapto derivatives from α-hydroxy or α-halo acids with (RS^-) as nucleophile.[1] On the other hand nucleophilic addition reactions, such as the Michael addition, have provided β-mercapto derivatives through the addition of thiols to achiral[2] or chiral[3] α,β-unsaturated carboxylic acid derivatives.[2] Both methodologies used different kinds of thiols, which after their addition, were cleavaged for different reactions carried out in an atmosphere of dry, oxygen-free nitrogen.[1]

A highly diastereoselective Michael addition of a thiol to α-substituted α,β-unsaturated derivatives has been described based on asymmetric protonation.[4] On the other hand it has also been described that the addition of thiols to trisubstituted *E* and *Z* α,β-unsaturated carboxylic acid derivatives produces stereospecifically *erythro* and *threo* adducts, respectively.[2]

Palomo et al. have described highly diastereoselective preparation of such compounds through intramolecular sulfur transfer in *N*-enoyl oxazolidinethiones.[5] Recently, this methodology has been applied in the construction of C–S bonds with a quaternary stereocenter.[6]

We describe herein the preparation of a series of chiral methylthio alcohols, which are shown in Figure 1. Their synthesis was achieved by the intramolecular sulfur transfer reaction in di- and trisubstituted α,β-unsaturated *N*-enoyl oxazolidinethiones, followed by protection of the thiol and removal of the oxazolidinone by reduction with $LiAlH_4$.

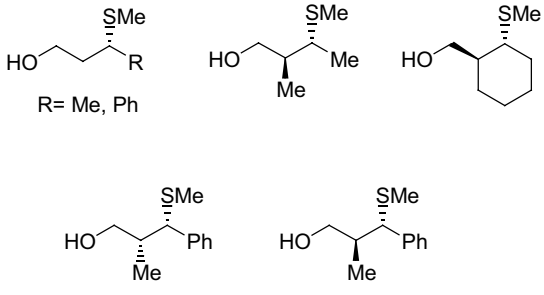

Figure 1.

The chiral auxiliary oxazolidinethione employed was prepared from (*S*)-valine[7] and the *N*-enoyl oxazolidinethiones (**1a**–**c**) were prepared as previously described[5,7] in yields of 70–79%, all of them as *E*-isomers. The

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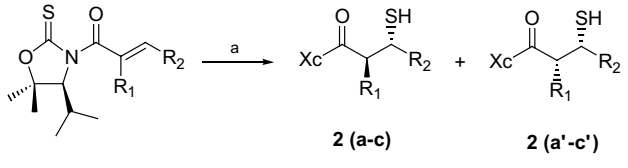
intramolecular sulfur transfer reaction of these *N*-enoyl oxazolidinethiones was performed using $SnCl_4$ and $NbCl_5$, as promoters, to afford the desired β-mercapto adducts (**2a–c**) as shown in Scheme 1. The results and reaction conditions are listed in Table 1.



1a R_1=CH_3 R_2=CH_3
1b R_1=CH_3 R_2=Ph
1c R_1= R_2= -$(CH_2)_4$

2a=2a' R_1=CH_3 R_2=CH_3
2b=2b' R_1=CH_3 R_2=Ph
2c=2c' R_1= R_2= -$(CH_2)_4$

Scheme 1. Reagents: (a) $SnCl_4$ or $NbCl_5$, CH_2Cl_2, H_2O.

Table 1. Intramolecular sulfur transfer reaction of the *N*-enoyl oxazolidinethiones

Products	Promoter	*T* (°C)/*t* (h)[a]	Yield[b] (%)	*anti*/*syn*[d]
2a/**2a′**	$SnCl_4$	−78/14	40	98:2
2b/**2b′**	$NbCl_5$	−30/72	93[c]	84:16[e]
2b/**2b′**	$SnCl_4$	0/60	70[c]	84:16[e]
2c/**2c′**	$SnCl_4$	−78/14	52	96:4

[a] *T* = temperature, *t* = time.
[b] Purified yield.
[c] Yield of the diastereomeric mixture.
[d] Diastereomeric isomer ratios were determined by HPLC on the crude products.
[e] Ratio determined by NMR.

From the data in Table 1, for adducts **2b** and **2b′** the use of different reaction conditions provides the same diastereomeric ratio. This reaction at −78 °C and large reaction times provided starting material. The formation of new chiral centers in compounds **2a** and **2c** is highly diastereoselective and the *E*-isomers (**1a–c**) provide the *anti*-diastereomers (**2a–c**) mainly.

The configuration at the newly formed stereogenic centers (C-12, C-13) are *S* and *R*, respectively, for both compound **2a**, and **2c** as established by X-ray analysis (Figs. 2 and 3).[8,9]

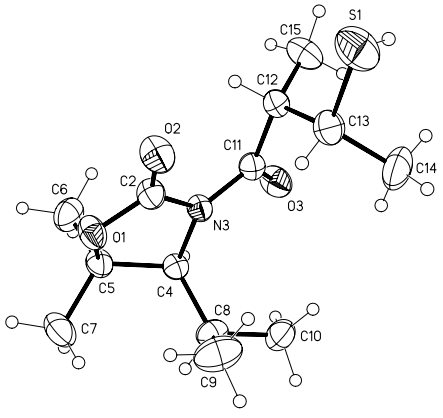


Figure 2. Molecular structure of the β-mercapto compound **2a**.

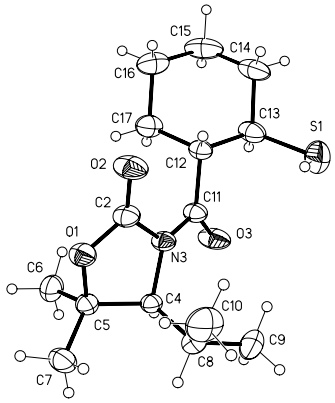


Figure 3. Molecular structure of the β-mercapto compound **2c**.

The intramolecular sulfur transfer reaction in **1b** provides an *anti*/*syn*-diastereomeric mixture in a ratio 84/16 for adducts **2b**/**2b′**. Their isolation gives *anti*-diastereomer **2b** as a liquid compound and *syn*-diastereomer **2b′** as a solid compound. For **2b′** the absolute configuration at the newly formed stereogenic centers (C-12, C-13) are *R* and *S*, respectively, as established by X-ray analysis (Fig. 4).[11]

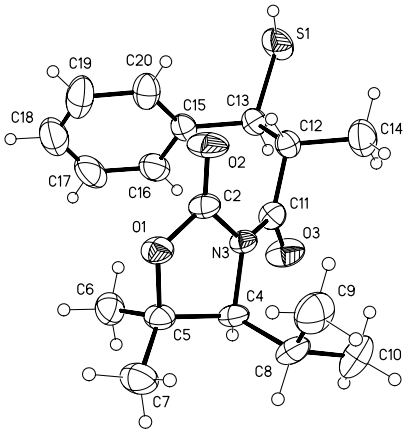


Figure 4. Molecular structure of the β-mercapto compound **2b′**.

The sense of stereodirection is the same for principal compounds as shown in Table 2.

Table 2. Physical properties of the β-mercapto compounds

Compound	Mp (°C)	$[\alpha]_D$ (*c*)[a]
2a-(*S*,*R*)	70–72	−43.2 (1.25)
2b-(*S*,*S*)	—	−58.1 (1.60)
2b′-(*R*,*S*)	145	+14.1 (1.05)
2c-(*S*,*R*)	92–93	−65.2 (1.10)

[a] Determined in $CHCl_3$ at 25 °C.

This diastereoselective can be explained by cyclization between the sulfur atom and the C(β) atom of the α,β-unsaturated system, to form a six-membered ring as shown in Figure 5. A posterior diastereoselective protonation gave the *anti*-diastereomer mainly.

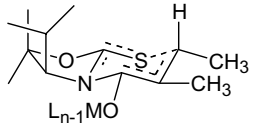
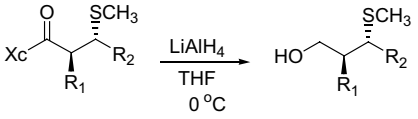


Figure 5.

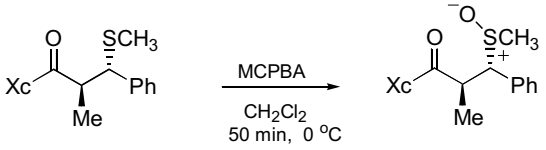
Subsequently, the compounds **2(a–c)** and **2(d–e)**[7] were treated with CH_3I and Et_3N in MeOH to provide the methylthio adducts **3(a–e)** in excellent yields (93–99%). The removal of the oxazolidinone moiety was carried out with $LiAlH_4$[3a] in THF at 0 °C, to give the chiral methylthioalcohols **4(a–e)** in good yields and to recover the oxazolidinone in yields of 80–82% as shown in Scheme 2.



3a	R_1=CH_3	R_2=CH_3	**4a**	R_1=CH_3	R_2=CH_3
3b	R_1=CH_3	R_2=Ph (*S*, *S*)	**4b**	R_1=CH_3	R_2=Ph (*S*, *S*)
3b´	R_1=CH_3	R_2=Ph (*R*, *S*)	**4b´**	R_1=CH_3	R_2=Ph (*R*, *S*)
3c	R_1= R_2=	$-(CH_2)_4$	**4c**	R_1= R_2=	$-(CH_2)_4$
3d	R_1=H	R_2=CH_3	**4d**	R_1=H	R_2=CH_3
3e	R_1=H	R_2= Ph	**4e**	R_1=H	R_2= Ph

Scheme 2.

The sulfoxide **5b** was prepared from *anti*-diastereomer **3b** as described elsewhere[12] using MCPBA to afford a diastereomeric mixture of **5b** as shown in Scheme 3. It was possible to isolate crystals of this mixture. X-ray crystallographic analysis permitted the assignment of absolute configuration at the newly formed stereogenic centers (C-12, C-13) as *S* and *S*, respectively, to compound **5b** (Fig. 6).[13]



3b **5b**

Scheme 3.

In conclusion we have applied the intramolecular sulfur transfer reaction to trisubstituted α,β-unsaturated *N*-enoyl oxazolidine-2-thiones. This study shows that the *anti*-diastereomer is favored and obtained via a highly diastereoselective protonation step. Furthermore this methodology was applied to synthesize 3-methylthio alcohols. The absolute configuration to compound **2b** was confirmed from compound **5b**.

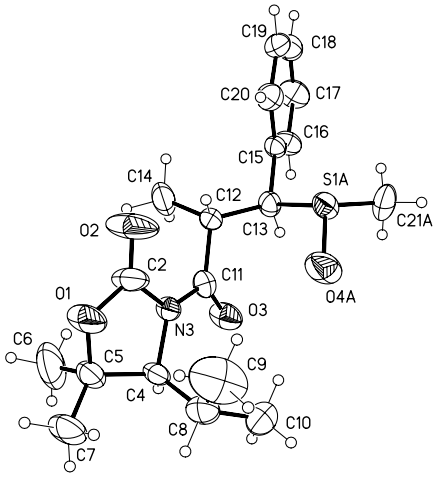


Figure 6. Molecular structure of the sulfoxide compound **5b**.

Acknowledgements

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8. *Crystal data for* **2a**: $C_{13}H_{23}NO_3S$, M = 273.38, colorless irregular block, $0.65 \times 0.60 \times 0.36$ mm^3, space group $P2_12_12_1$, cell parameters a = 7.2713 (7), b = 11.4320 (7), c = 18.4288 (12) Å, Z = 4, D_c = 1.185 g cm^{-3}. Reflections (4683) collected on a Bruker P4 diffractometer at room temp, with the Mo-Kα radiation (λ = 0.71073 Å) in the range 2θ = 4.20–59.98°, of which 4019 are unique (R_{int} = 0.0192). Variables (163) refined:[10] R_1 = 0.0679 [2731 data with $I > 2\sigma(I)$] and wR_2 = 0.2197 [all data]. Absolute configuration was determined starting from

the known configuration at C4 and confirmed by the refinement of a Flack parameter, $x = -0.22$ (18), 1470 Friedel pairs measured. Complete data have been deposited with the CCDC, reference 257397. Structure factors and raw files are available on request to authors.

9. *Crystal data for* **2c**: $C_{15}H_{25}NO_3S$, $M = 299.42$, colorless block, $0.60 \times 0.40 \times 0.28$ mm^3, space group $P2_1$, cell parameters $a = 6.7361$ (4), $b = 8.3096$ (5), $c = 15.2470$ (10) Å, $\beta = 95.207$ (6)°, $Z = 2$, $D_c = 1.170$ g cm^{-3}. Reflections (5907) collected on a Bruker P4 diffractometer at room temp, with the Mo-Kα radiation ($\lambda = 0.71073$ Å) in the range $2\theta = 5.36$–59.96°, of which 2956 are unique ($R_{int} = 0.0194$). Variables (182) refined: [10] $R_1 = 0.0413$ [2290 data with $I > 2\sigma(I)$] and $wR_2 = 0.1224$ [all data]. Absolute configuration was determined starting from the known configuration at C4 and confirmed by the refinement of a Flack parameter, $x = 0.22$ (13), 317 Friedel pairs measured. Complete data have been deposited with the CCDC, reference 257398. Structure factors and raw files are available on request to authors.
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11. *Crystal data for* **2b′**: $C_{18}H_{25}NO_3S$, $M = 335.45$, colorless plate, $0.40 \times 0.20 \times 0.08$ mm^3, space group $C2$, cell parameters $a = 19.831$ (3), $b = 6.4460$ (10), $c = 16.786$ (2) Å $\beta = 117.522$ (9)°, $Z = 4$, $D_c = 1.171$ g cm^{-3}. Reflections (3400) collected on a Bruker P4 diffractometer at room temp, with the Mo-Kα radiation ($\lambda = 0.71073$ Å) in the range $2\theta = 4.16$–50.00°, of which 2753 are unique ($R_{int} = 0.0194$). Variables (211) refined:[10] $R_1 = 0.0455$ [2034 data with $I > 2\sigma(I)$] and $wR_2 = 0.1094$ [all data]. Absolute configuration was determined starting from the known configuration at C4 and confirmed by the refinement of a Flack parameter, $x = 0.09$ (12), 903 Friedel pairs measured. Complete data have been deposited with the CCDC, reference 257399. Structure factors and raw files are available on request to authors.
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13. *Crystal data for* **5b**: Crystallization of this compound revealed to be problematic. After several attempts, we only produced poor-quality single-crystals, which were however suitable for a low resolution (1.0 Å) X-ray study, allowing the determination of the absolute configuration for chiral centers with a good level of confidence. $C_{19}H_{27}NO_4S$, $M = 365.48$, colorless irregular, $0.42 \times 0.40 \times 0.08$ mm^3, space group $P2_12_12_1$, cell parameters $a = 7.0592$ (16), $b = 11.460$ (4), $c = 24.972$ (10) Å, $Z = 4$, $D_c = 1.202$ g cm^{-3}. Reflections (3559) collected on a Bruker P4 diffractometer at room temp, with the Mo-Kα radiation ($\lambda = 0.71073$ Å) in the range $2\theta = 3.92$–42.06°, of which 2174 are unique ($R_{int} = 0.0573$). Variables (255) refined:[10] $R_1 = 0.0546$ [1547 data with $I > 2\sigma(I)$] and $wR_2 = 0.1353$ [all data]. Absolute configuration was determined starting from the known configuration at C4 and confirmed by the refinement of a Flack parameter,[14] $x = -0.2$ (2), 881 Friedel pairs measured. Complete data have been deposited with the CCDC, reference 257400. Structure factors and raw files are available on request to authors.
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