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(*S*)-4-Isopropyl-5,5-dimethyl-1,3-oxazolidinethione as chiral auxiliary for the intramolecular sulfur transfer in α,β-unsaturated *N*-acylimides, promoted by $NbCl_5$

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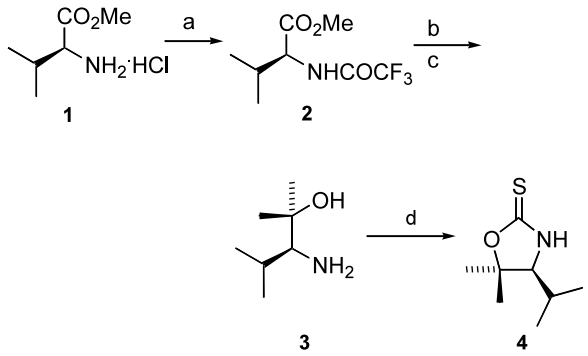
Abstract—The 1,3-oxazolidinethione **4** has been synthesized from (*S*)-valine and used in the intramolecular sulfur transfer in its *N*-enoyl derivatives in the presence of $NbCl_5$ as catalyst, which, moreover, works as an indicator of the course of the reaction. The adducts have subsequently been transformed into the corresponding β-mercapto esters by action of $Sm(OTf)_3$ in methanol.

Recently, a novel strategy for asymmetric synthesis, based on the principle of intramolecular atom transfer, has been described by Palomo and co-workers in which they report a Lewis acid-promoted sulfur transfer reaction with *N*-enoyl oxazolidine-2-thiones to yield β-mercapto carboxylic acid derivatives.[1] Our interest in finding other promoters for this reaction led us to use $NbCl_5$ as a new Lewis acid, different to the traditional type, it is a stable solid, easy to handle and soluble in organic solvents, but its use in organic syntheses has been limited.[2]

In this paper we describe the synthesis of a new oxazolidine-2-thione chiral auxiliary **4** and its application to the asymmetric synthesis of β-mercapto methyl ester compounds. Chiral auxiliary **4** was prepared from the commercially available *S*-valine through a series of transformations,[3,4] as shown in Scheme 1. In order to optimize the yield and avoid racemization of the stereogenic center by use of excess Grignard reagent, the amino group in **1** was protected as its trifluoracetamide using trifluoroacetic anhydride and triethylamine to give *N*-trifluoroacetyl *S*-valine methyl ester **2** in quantitative yield.[5] The condensation of the β-amino alcohol **3** with CS_2 was carried out by a modification of previously described method.[6] Firstly, the β-amino alcohol **3** was treated with 4 equiv. of CS_2 in 100 mL of an aqueous solution of Na_2CO_3 and refluxed for 16 h. After this time, to totally consume the starting material, added was 2 equiv. of CS_2 and refluxed for 4 h to afford **4** in 80% yield, mp 118–120°C, $[\alpha]_D^{25} = -14.3$, $c = 2$, $CHCl_3$.[7]



Scheme 1. *Reagents and conditions*: (a) Et_3N (2 equiv.), $(CF_3CO)_2O$, −78°C→rt, 3 h, THF, 99.8%; (b) MeMgI (5 equiv.), Et_2O, 0°C rt, →12 h; (c) KOH, rt, 78%; (d) CS_2 (4 equiv.), Na_2CO_3 1N, reflux, 16 h, $+CS_2$ (2 equiv.), reflux, 4 h.

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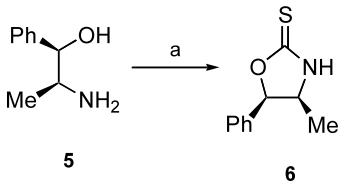
Table 1. Synthesis of chiral 1,3-oxazolidine-2-thione **6**

Compound	Yield (%)	Mp (°C)	$[\alpha]_D$ (c, t °C)	Reference
(4*R*,5*S*)-**6**	73.1	81–82	+219.2 (0.4, 20)[a]	8
rac-**6**	87.0	91–92	*rac*	6
(4*S*,5*R*)-**6**	100	83.4–83.9	–	9
(4*S*,5*R*)-**6**	93	80–81	−218.0 (2, 25)[a]	Our study

[a] Determined in $CHCl_3$.

On the other hand, the chiral auxiliary **6** has been widely studied and prepared by different methods. The results and its physical properties are shown in Table 1.

The chiral auxiliary **6** was prepared from (1*R*,2*S*) norephedrine **5**. It was treated under the same reaction conditions described above to give the desired chiral auxiliary **6** in 93% yield (Scheme 2). In both cases, under these reaction conditions, the formation of thiazolidinethione was undetected.[6,10]



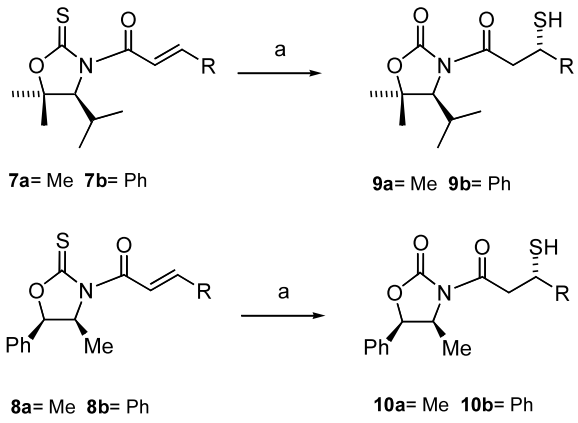
5 **6**

Scheme 2. *Reagents and conditions*: (a) CS_2 (4 equiv.), Na_2CO_3 1N, reflux, 16 h, $+CS_2$ (2 equiv.), reflux, 4 h.

The *N*-enoyl oxazolidinethiones **7a**, **7b**, **8a** and **8b** were then prepared from **4** and **6** as previously described.[1] Deprotonation of compounds **4** and **6** with NaH in THF followed by acylation with either crotonyl or cinnamoyl chloride yielded the desired *N*-enoyl oxazolidinethiones **7a**, **7b** and **8a**, **8b** in a range of 73–91%, all of them as white solid, after purification by flash column chromatography using silica gel that had been previously treated with an aqueous solution of $NaHCO_3$.[11]

The asymmetric intramolecular sulfur transfer reaction of the *N*-enoyl oxazolidinethiones **7a**, **7b**, **8a** and **8b** was investigated using three Lewis acids, $NbCl_5$, TMSCl and $SnCl_4$ to afford the desired β-mercapto products **9a**, **9b**, **10a**, **10b**. The results of these reactions are shown in Table 2. In all cases 2 equiv. of the respective Lewis acid were used in 300 mL of methylene chloride. It was found that $SnCl_4$ at −78°C in 3 h gave β-mercapto product in 40% yield, moreover when $SnCl_4$ was added to the *N*-enoyl oxazolidinethiones, a precipitate was formed that was soluble at −78°C when R = Me, for R = Ph it was insolvable at the same temperature. $SnCl_4$ was not the most desirable Lewis acid for this reaction because it gave one of the lowest yields for the desired β-mercapto product. When the reaction was carried out with TMSCl at 0°C it very slowly gave the β-mercapto product in 72% yield. The addition to the *N*-enoyl oxazolidinethiones did not form the precipitate. TMSCl was also not the Lewis acid of choice because it required an exceedingly long reaction time to form the product in good yield.

In the case of $NbCl_5$, it gave β-mercapto products in the mayor yields and its addition did not form the precipitate in any reactions. $NbCl_5$ has the advantage of being highly soluble and easy to handle. An additional improvement of the methodology comes from the fact that the reaction course is readily followed by the color change, from red to yellow. All of these advantages make $NbCl_5$ the most desirable Lewis acid for this reaction.[12] Scheme 3 shows the reaction conditions to provide the adducts (**9a**, **9b**, **10a**, **10b**) with $NbCl_5$. The typical reaction procedure is described for obtention of **10a**.[13]



7a= Me **7b**= Ph **9a**= Me **9b**= Ph

8a= Me **8b**= Ph **10a**= Me **10b**= Ph

Scheme 3. *Reagents and conditions*: (a) $NbCl_5$, CH_2Cl_2, −78°C, H_2O.

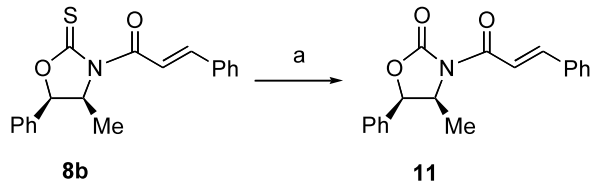
Table 2. Intramolecular sulfur transfer reaction of the *N*-enoyl oxazolidinethiones

Products	Catalyst	T (°C)/t (h)[a]	Yield (%)[b]	Diastereomeric ratio[d]
9a	$NbCl_5$	−78/6	50	98:2
10a	$NbCl_5$	−78/10	76	97:3
9b	$NbCl_5$	−50/12	95	96:4
10b	$NbCl_5$	−50/24	57[c]	63:37
10a	$SnCl_4$	−78/3	40	96:4
10a	TMSCl	0/336	72	98:2

[a] T = temperature, t = time.
[b] Purified yield.
[c] Diastereomeric mixture yield.
[d] Diastereomeric isomer ratios were determined by HPLC on the crude products.

From the data in Table 2, it was observed that in the case of products **9b** and **10b** there is a notable difference both in the yield and in the diastereomeric ratio. The presence of the aromatic groups in **7b** and **8b** has an important influence in the reaction to give products **9b** and **10b**. These compounds were obtained at −50°C in comparison with products **9a** and **10a**. When compound **8b** was treated with $SnCl_4$ and the mixture was

warmed close to room temperature, the elimination product **11** was obtained in 80% yield as a crystalline solid. The structure of **11** was determined by X-ray crystallography[14] showing a five-membered ring for the 1,3-oxazolidinone moiety and the carbonyl group at C-13 *anti* to carbonyl group at C-2, a conformation which was previously described for another *N*-acylimides[15] (Scheme 4).



Scheme 4. *Reagents and conditions*: (a) $SnCl_4$, CH_2Cl_2, −78→ 25°C, H_2O.

The configuration at the newly formed stereogenic center (C-15) is *R*, as established by X-ray analysis[16] of compound **10a**, derived from norephedrine (Fig. 1). The X-ray structure of **10a** shows the expected five-membered ring for the 1,3-oxazolidinone as evidenced by ^{13}C NMR analysis.[17]

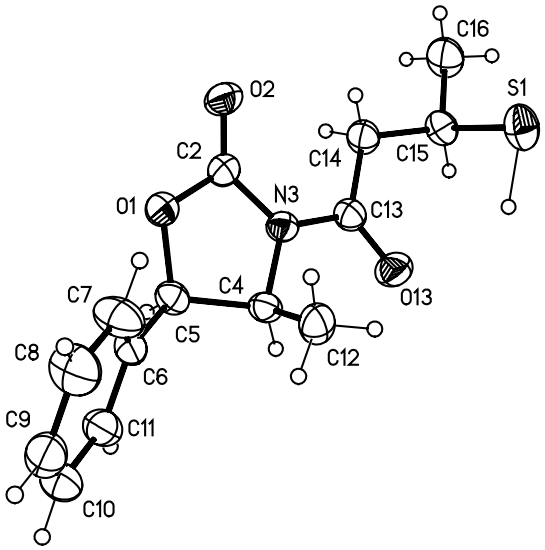
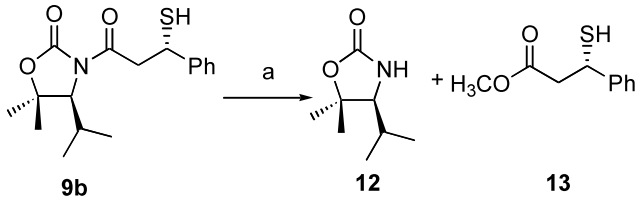


Figure 1. Molecular structure of the β-mercapto adduct **10a**, the first structure obtained by X-ray without blocking the thiol group. Displacement ellipsoids are drawn at the 30% probability level.

Our subsequent work focused on finding the conditions for the cleavage of the adduct **9b**. The treatment of **9b** with aqueous lithium hydroxide[18] provided the recovery of oxazolidinone **12** in 85% yield and as elimination product *trans*-cinnamic acid instead of the desired product **13**. Therefore, was employed an efficient method[19] for the conversion of **9b** to **13** with samarium-(III) triflate in methanol (10 mL) at room temperature to provide methyl ester **13** in 75% yield as a dense liquid, $[\alpha]_D^{25} = -46$ (*c* 1.3, $CHCl_3$) and the oxazolidinone **12** in 80% yield (Scheme 5).



Scheme 5. *Reagents and conditions*: (a) $Sm(OTf)_3$ (1.5 equiv.), MeOH, rt, 24 h.

In conclusion, we have prepared a new chiral auxiliary 1,3-oxazolidinethione **4** that was utilized in the asymmetric intramolecular sulfur transfer reaction to the *N*-enoyl oxazolidinethiones using $NbCl_5$ as a promoting reagent, furthermore this Lewis acid is easy to handle and makes it possible to follow the course of the reaction. On the other hand, we applied an esterification to remove the modified chiral auxiliary using $Sm(OTf)_3$ as Lewis acid and CH_3OH to produce (*R*)-methyl-3-phenyl-3-mercaptopropionate **13**.

Acknowledgements

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7. Compound **4**: ^1H NMR (400 MHz, $CDCl_3$): δ 8.27 (br s, 1H, NH), 3.37 (d, 1H, $J=8.0$, CH-N), 1.90 (m, 1H, CH–CH_3), 1.56 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.04 (d, 3H, $J=6.6$, CH_3–CH), 0.95 (d, 3H, $J=6.6$, CH_3–CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.1 (C=S), 90.4 (C–O), 71.2 (C–N), 28.2 (CH_3), 28.0 (CH_3), 21.0 (CH–CH_3), 19.8 ($2CH_3$). Anal. calcd for $C_8H_{15}NOS$: C, 55.45; H, 8.73. Found: C, 55.48; H, 8.69%.
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11. The *N*-enoyl oxazolidinethiones (**7a**, **7b**, **8a**, **8b**) are unstable in acid media. The purification of these by flash column chromatography using normal silica gel gave **4** or **6** as deacylation products.

12. $NbCl_5$ is a solid, and highly soluble in CH_2Cl_2 and none of the reactions produced a precipitate when it was added to the solution of *N*-enoyl oxazolidinethiones.
13. A typical reaction procedure for the asymmetric sulfur transfer reaction is described. To a solution of **8a** (0.3 g, 1.14 mmol) in CH_2Cl_2 (300 mL) was added $NbCl_5$ (0.62 g, 2.28 mmol) at −78°C under a nitrogen atmosphere. The reaction mixture was stirred at −78°C until the red solution turned yellowish (10 h, TLC monitoring). The reaction was quenched with water, extracted with CH_2Cl_2 (3×30 mL) and the combined organic extracts were washed with brine and dried over Na_2SO_4. After removal of solvent, analysis by ^1H NMR showed the formation of β-mercapto adduct **10a** as a (97:3) diastereomeric mixture (by HPLC). The crude was purified by flash column chromatography (10% ethylacetate in hexane as eluent) to give **10a** (0.243 g, 76% yield) as a white solid mp 108°C, $[\alpha]_D^{25}=-42.03$ (*c* 1.5, $CHCl_3$).
14. *Crystal data for* **11**: $C_{19}H_{17}NO_3$, $M=307.34$, colorless block, 0.70×0.34×0.18 mm^3, space group $P2_12_12_1$, cell parameters $a=6.4224(9)$, $b=12.4092(11)$, $c=20.386(2)$ Å, $Z=4$, $D_{calcd}=1.256$ g cm^{-3}. 2296 reflections collected on a Bruker P4 diffractometer at rt, with the Mo Kα radiation ($\lambda=0.71073$ Å) in the range $2\theta=4$–50°, of which 2105 are unique ($R_{int}=0.0235$). 209 variables refined: $R_1=0.0522$ [1102 data with $I>2\sigma(I)$] and $wR_2=0.1456$ [all data]. Complete data have been deposited with the CCDC, reference 197369. Structure factors and raw files are available on request to authors. Supplementary Material available: Tables of atomic coordinates, thermal parameters, bond lengths and angles and observed and calculated structure factors have been deposited at the Cambridge Crystallographic Data Centre.
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16. *Crystal data for* **10a**: $C_{14}H_{17}NO_3S$, $M=279.35$, colorless plate, 0.38×0.26×0.14 mm^3, space group $P2_12_12_1$, cell parameters $a=10.0428(10)$, $b=10.6011(10)$, $c=13.3494(8)$ Å, $Z=4$, $D_{calcd}=1.306$ g cm^{-3}. 2442 reflections collected on a Bruker P4 diffractometer at rt, with the Mo Kα radiation ($\lambda=0.71073$ Å) in the range $2\theta=3$–50°, of which 2115 are unique ($R_{int}=0.0513$). 173 variables refined: $R_1=0.0429$ [1374 data with $I>2\sigma(I)$] and $wR_2=0.1088$ [all data]. Complete data have been deposited with the CCDC, reference 197368. Structure factors and raw files are available on request to authors.
17. The ^{13}C NMR spectrum of **10a** showed a signal at δ 153 ppm due to carbonyl group (C-2), in agreement with ^{13}C NMR analysis spectrum of **8a** which showed a signal at δ 185.3 ppm for the thiocarbonyl group (C-2).
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