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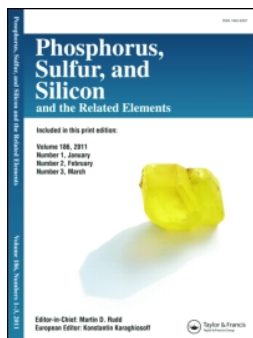
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## Selective access to sulfurated and selenated heterocycles by intramolecular cyclization of $\beta$ -substituted sulfides and selenides

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### ABSTRACT

$\delta$ -Hydroxy- and  $\delta$ -amino  $\alpha$ -thio-esters, easily obtainable through S-alkylation of  $\beta$ -mercapto alcohols and  $\beta$ -amino thiols with bromo acetate, behave as suitable starting compounds to obtain various 2-hydroxy-1,4-oxathianes and (S)-3,4-dihydro-2H-1,4-thiazines via a reductive ring closure. Under similar conditions, selenated heterocycles are also synthesized.

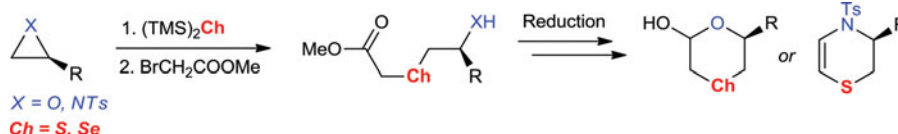
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2-Hydroxy-1,4-oxathianes;  
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2-hydroxy-1,4-selenanes;  
3,4-dihydro-2H-1,4-selenazines;  
ring closure

### GRAPHICAL ABSTRACT



### Introduction

A variety of sulfur containing heterocyclic compounds are contained in natural products, drug molecules, and food flavors. Also, selenated heterocycles represent a very interesting class of molecules due to their useful reactivity in organic synthesis and their potential biological applications<sup>1</sup>.

Among the various heterocyclic compounds, six-membered 1,4-heterocycles have attracted considerable attention for their properties in medicinal and biological field, and for their use in organic synthesis<sup>2</sup>. 1,4-Oxathiane derivatives possess for instance antitumor<sup>3</sup>, antibacterial<sup>4</sup> and antifungal activity<sup>2a</sup>, and find application as chiral auxiliaries for asymmetric transformations<sup>5</sup>. Replacement of oxygen with sulfur in thiomorpholines allows to obtain compounds with antioxidant and hypolipidemic activity<sup>6</sup>, and to access derivatives that can behave as DPP-IV inhibitors<sup>7</sup>. Several methods are reported for obtaining 1,4-oxathianes<sup>5,8</sup> and thiomorpholines<sup>6,8</sup>. On the contrary, to the best of our knowledge, few examples are described for obtaining the seleno-analogues 1,4-oxaselenanes<sup>9</sup> and selenomorpholines<sup>10</sup>, the latter showing an interesting antibiotic activity<sup>10b,11</sup>.

Our interest in the chemistry of thiosilanes led us to disclose a selective and general methodology to access  $\beta$ -substituted thiols, which were demonstrated as useful reagents for the synthesis of 2-silyl five-membered heterocycles<sup>12</sup> and 1,2,5-trithiepanes<sup>13</sup>. More recently, we discovered that also selenosilanes were able to react with strained molecules, leading to a selective formation of

$\beta$ -functionalized selenides, diselenides<sup>14</sup> and various five- and seven-membered thia(seleno) heterocycles<sup>13,15</sup>.

On the basis of these results, we then moved to explore the behavior of  $\beta$ -substituted sulfides and selenides to synthesize sulfurated and selenated six-membered 1,4-heterocycles.

### Results and discussion

We reasoned that a convenient access to chalcogen containing hexaatomic heterocycles could be the functionalization of suitable substituted  $\delta$ -hydroxy or  $\delta$ -amino  $\alpha$ -thio-esters (Figure 1). The latter could be obtained through reaction of  $\beta$ -substituted thiols with a  $\alpha$ -bromo ester.

Thus,  $\beta$ -mercapto alcohols **2**, easily obtained through reaction of bis(trimethylsilyl)sulfide (HMDST) **1** and variously substituted epoxides<sup>16</sup>, were treated with bromo acetate (Scheme 1,  $X = O$ ), in the presence of  $CS_2/CO_3/TBAI$  system<sup>17</sup>. Under these conditions, a clean S-alkylation occurred, leading to the corresponding  $\delta$ -hydroxy- $\alpha$ -thioesters **3** in good yields. Reduction with DIBAL-H allowed the formation of differently 6-substituted 2-hydroxy-1,4-oxathianes **4** as equimolar mixture of diastereoisomers, *via* a spontaneous intramolecular cyclization of the intermediate aldehyde (Scheme 1,  $X = O$ )<sup>18</sup>.

In order to evaluate the scope of this procedure, a chiral  $\beta$ -amino thiol **5**, obtained from aziridine and HMDST<sup>12</sup>, was reacted with the bromo ester under similar conditions, affording the Ts-protected  $\alpha$ -thio- $\delta$ -amino esters **6** (Scheme 1,

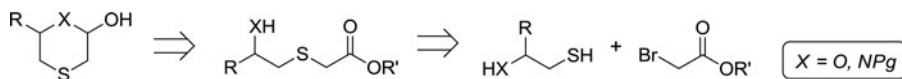
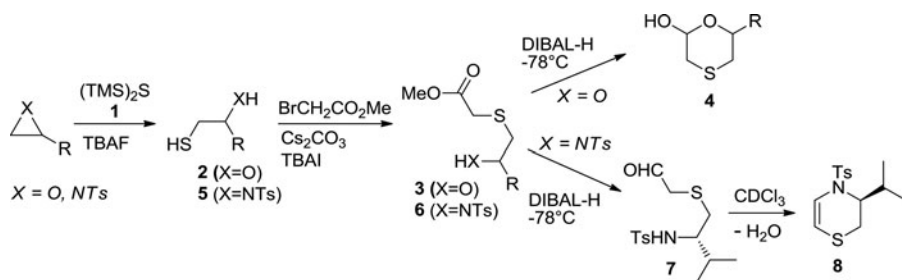
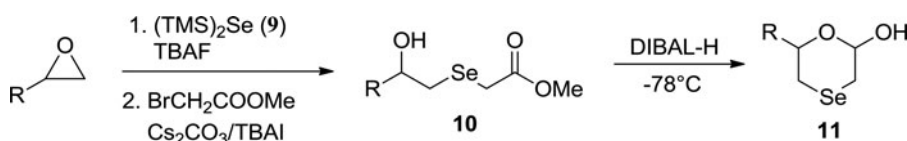


Figure 1. Retrosynthetic approach to six-membered 1,4-heterocycles.



Scheme 1. Synthesis of thiaheterocycles.



Scheme 2. Synthesis of Se-containing heterocycles.

$X = NTs$ ). Treatment under reducing conditions led this time to the isolation of the corresponding aldehyde **7**. The aldehyde undergoes cyclization in *d*-chloroform, while recording NMR spectra, leading to (*S*)-3-isopropyl-4-tosyl-3,4-dihydro-2*H*-1,4-thiazine **8**, after water elimination.

Expanding the scope of this procedure to seleno analogues, we found that the precursor  $\beta$ -hydroxy selenide **10** could be achieved by treatment of selenol (obtained from the epoxide and  $(TMS)_2Se$  **9**)<sup>19</sup> with the bromo ester (Scheme 2) under  $Cs_2CO_3/TBAI$  activation. Treatment with DIBAL-H directly afforded differently 6-substituted 2-hydroxy 1,4-oxaselenolanes **11** as mixture of stereoisomers<sup>20</sup>.

## Conclusions

This approach represents a convenient method for the preparation of six-membered chalcogen-containing heterocycles. Further work to extend this methodology to differently functionalized sulfur and seleno heterocycles is now in progress in our laboratory.

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- Treatment of methyl 2-(3-(allyloxy)-2-hydroxypropylthio)acetate ( $R = CH_2OAl$ ) (0.4 mmol) with DIBAL-H (0.48 mmol) in dry toluene<sup>21</sup> for 3 h, at  $-78^\circ C$ , led to 6-(allyloxymethyl)-1,4-oxathian-2-ol **3a** (63%). Diastereomeric ratio = 65:35.  $^1H$  NMR (400 MHz,  $CDCl_3$ ),  $\delta$  (ppm): 2.27–2.40 (1 H, m), 2.45–2.6 (2 H, m), 2.72 (1 H, dd,  $J = 11.2, 13.4$  Hz), 2.88–2.96 (1 H, m), 3.0 (1 H, dd,  $J = 3.1, 12.5$  Hz), 3.09 (1 H, dd,  $J = 2.1, 13.4$  Hz), 3.23 (1 H, ap d,  $ls = 15.0$  Hz), 3.37 (1 H, dd,  $J = 5.4, 10.0$  Hz), 3.43 (1 H, dd,  $J = 4.2, 5.8$  Hz), 3.46 (1 H, dd,  $J = 3.7, 5.8$  Hz), 3.61 (1 H, dd,  $J = 5.4, 10.3$  Hz), 3.71 (1 H, dd,  $J = 4.9, 10.3$  Hz), 4.0–4.07 (4 H, m), 4.29–4.35 (1 H, m), 4.59–4.66 (1 H, m), 4.97 (1 H, dd,  $J = 3.5, 7.6$  Hz), 5.18–5.32 (5 H, m), 5.84–5.96 (2 H, m).  $^{13}C$  NMR (100 MHz,  $CDCl_3$ ),  $\delta$  (ppm): = 27.4, 28.5, 31.4, 32.5, 67.4, 70.7, 72.3, 72.5, 72.6, 78.0, 87.9, 95.8, 117.4, 117.6, 134.3, 134.4. MS  $m/z$  (%): 190 (2) [ $M^+$ ], 188 (8), 147 (3), 119 (10), 89 (28), 73 (20), 61 (30), 41 (100).

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20. *Characteristic data*: Diastereomeric ratio = 60:40.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 2.43–2.56 (4 H, m), 2.70–2.72 (4 H, m), 3.42–3.67 (4 H, m), 4.11–4.16 (1 H, m,  $\text{CHCH}_2\text{Cl}$ ), 4.41–4.44 (1 H, m,  $\text{CHCH}_2\text{Cl}$ ), 5.08 (1 H, bd,  $J = 9.3$  Hz,  $\text{CHOH}$ ), 5.21 (1 H, bd,  $J = 7.7$  Hz,  $\text{CHOH}$ ).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): = 18.5, 21.5, 29.6, 30.3, 47.2, 47.3, 78.4, 80.6, 96.9, 99.8.
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