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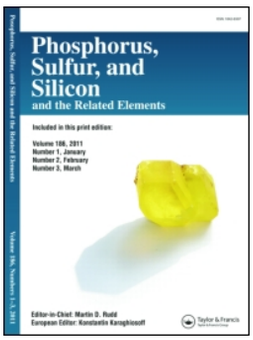

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Selective access to sulfurated and selenated heterocycles by intramolecular cyclization of β-substituted sulfides and selenides

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ABSTRACT

δ-Hydroxy- and δ-amino α-thio-esters, easily obtainable through S-alkylation of β-mercapto alcohols and β-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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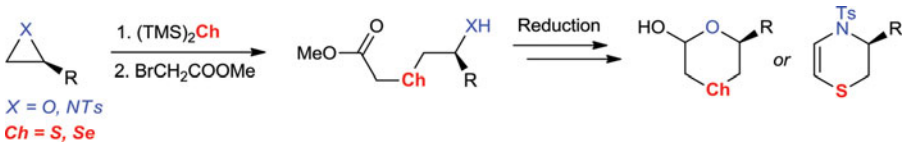
GRAPHICAL ABSTRACT



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[1].

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[2]. 1,4-Oxathiane derivatives possess for instance antitumor[3], antibacterial[4] and antifungal activity[2a], and find application as chiral auxiliaries for asymmetric transformations[5]. Replacement of oxygen with sulfur in thiomorpholines allows to obtain compounds with antioxidant and hypolipidemic activity[6], and to access derivatives that can behave as DPP-IV inhibitors[7]. Several methods are reported for obtaining 1,4-oxathianes[5,8] and thiomorpholines[6,8]. On the contrary, to the best of our knowledge, few examples are described for obtaining the seleno-analogues 1,4-oxaselenanes[9] and selenomorpholines[10], the latter showing an interesting antibiotic activity[10b,11].

Our interest in the chemistry of thiosilanes led us to disclose a selective and general methodology to access β-substituted thiols, which were demonstrated as useful reagents for the synthesis of 2-silyl five-membered heterocycles[12] and 1,2,5-trithiepanes[13]. More recently, we discovered that also selenosilanes were able to react with strained molecules, leading to a selective formation of β-functionalized selenides, diselenides[14] and various five- and seven-membered thia(seleno) heterocycles[13,15].

On the basis of these results, we then moved to explore the behavior of β-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 δ-hydroxy or δ-amino α-thio-esters (Figure 1). The latter could be obtained through reaction of β-substituted thiols with a α-bromo ester.

Thus, β-mercapto alcohols **2**, easily obtained through reaction of bis(trimethylsilyl)sulfide (HMDST) **1** and variously substituted epoxides[16], were treated with bromo acetate (Scheme 1, $X = O$), in the presence of Cs_2CO_3/TBAI system[17]. Under these conditions, a clean S-alkylation occurred, leading to the corresponding δ-hydroxy-α-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, $X = O$)[18].

In order to evaluate the scope of this procedure, a chiral β-amino thiol **5**, obtained from aziridine and HMDST[12], was reacted with the bromo ester under similar conditions, affording the Ts-protected α-thio-δ-amino esters **6** (Scheme 1,

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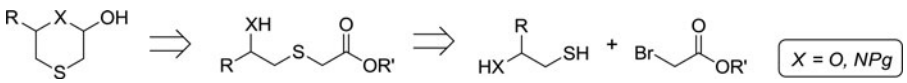
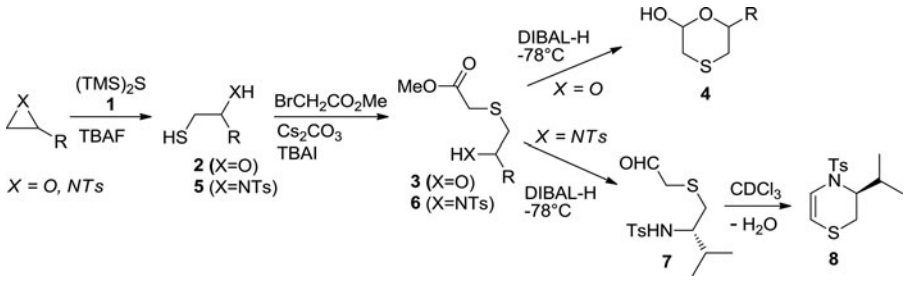
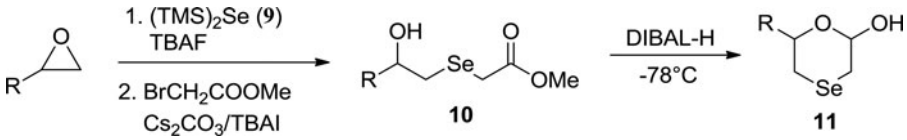


Figure 1. Retrosyntetic approach to six-membered 1,4-heterocycles.



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 β-hydroxy selenide **10** could be achieved by treatment of selenol (obtained from the epoxide and $(TMS)_2Se$ **9**)[19] 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[20].

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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20. *Characteristic data*: Diastereomeric ratio = 60:40. ^{1}H NMR (400 MHz, $CDCl_3$), δ (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, $CHCH_2Cl$), 4.41–4.44 (1 H, m, $CHCH_2Cl$), 5.08 (1 H, bd, J = 9.3 Hz, CHOH), 5.21 (1 H, bd, J = 7.7 Hz, CHOH). ^{13}C NMR (100 MHz, $CDCl_3$), δ (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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