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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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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 applications¹.

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 synthesis². 1,4-Oxathiane derivatives possess for instance antitumor³, antibacterial⁴ and antifungal activity^{2a}, and find application as chiral auxiliaries for asymmetric transformations⁵. Replacement of oxygen with sulfur in thiomorpholines allows to obtain compounds with antioxidant and hypolipidemic activity⁶, and to access derivatives that can behave as DPP-IV inhibitors⁷. 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-oxaselenanes⁹ and selenomorpholines¹⁰, 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 heterocycles¹² and 1,2,5-trithiepanes¹³. More recently, we discovered that also selenosilanes were able to react with strained molecules, leading to a selective formation of

β -functionalized selenides, diselenides¹⁴ 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 epoxides¹⁶, were treated with bromo acetate (Scheme 1, X = O), in the presence of Cs₂CO₃/TBAI system¹⁷. 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 HMDST¹², was reacted with the bromo ester under similar conditions, affording the Ts-protected α -thio- δ -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-2H-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 stereoisomers²⁰.

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 toluene²¹ 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, $CDCl_3$), δ (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, $CDCl_3$), δ (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. ^1H 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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