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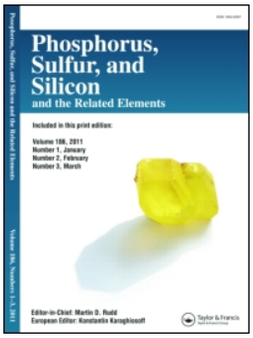

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Selective access to sulfurated and selenated heterocycles by intramolecular cyclization of β-substituted sulfides and selenides

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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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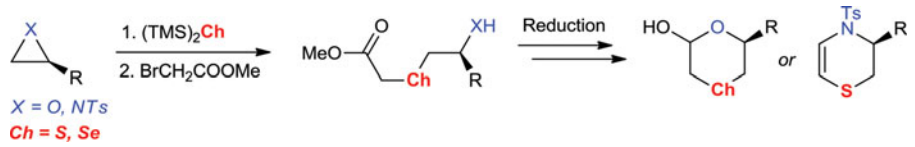
GRAPHICAL ABSTRACT



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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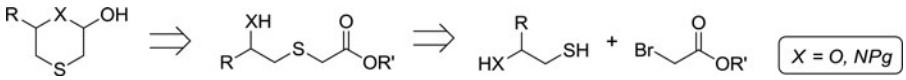
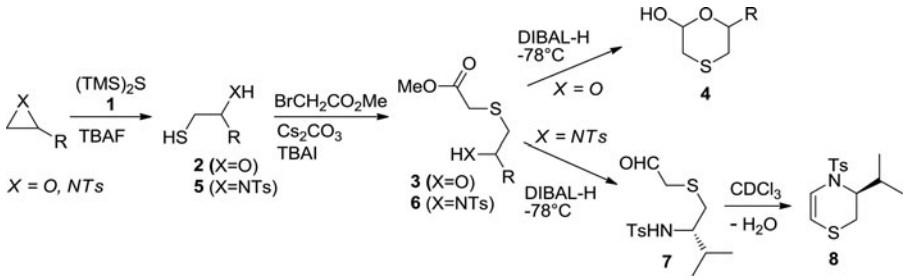
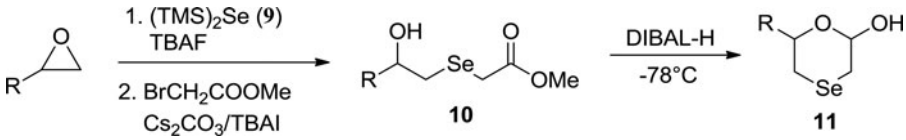


Figure 1. Retrosyntetic approach to six-membered 1,4-heterocycles.



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.

References

1. Inter alia: a) Mugesh, G.; du Mont, W.-W.; Sies, H. *Chem. Rev.* **2001**, 101, 2125-2179. b) Tiecco, M.; Testaferri, L.; Bagnoli, L.; Marini, F.; Santi, C.; Temperini, A.; Sternativo, S.; Terlizzi, R.; Tomassini, C. *Arkivoc.* **2006**, vii, 186-206. c) J. Młochowski, J.; Kloc, K.; Lisiak, R.; Potaczek, P.; Wójtowicz, H. *Arkivoc.* **2007**, vi, 14-46.
2. a) Cook, M. J. *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R.; Rees, C. W., Eds.; Pergamon Press: Oxford, **1984**, Vol. 3, 943-994. b) Matlock, J. V.; Svejstrup, T. D.; Songara, P.; Overington, S.; McGarrigle, E. M.; Aggarwal, V. K. *Org. Lett.* **2015**, 17, 5044-5047 and references cited therein.
3. Miyauchi, H.; Tanio, T.; Ohashi, N. *Bioorg. Med. Chem. Lett.* **1996**, 6, 2377-2380.
4. Kim, J. W.; Park, H. B.; Chung, B. Y. *Bull. Korean Chem. Soc.* **2006**, 27, 1164-1170.
5. Gharpure, S. J.; Anuradha, D.; Prasad, J. V. K.; Rao, P. S. *Eur. J. Org. Chem.* **2015**, 86–90, and references cited therein.
6. Tooulia, K.-K.; Theodosis-Nobelos, P.; Rekka *Arch. Pharm. Chem. Life Sci.* **2015**, 348, 629–634, and references cited therein.
7. a) Han, B.; Liu, J. L.; Huan, Y.; Li, P.; Wu, Q.; Lin, Z. Y.; Shen, Z. F.; Yin, D. L.; Huang, H. H. *Chin. Chem. Lett.* **2012**, 23, 297-300. b) Li, S.; Zhong, W.; Xiao, J.; Ma, X.; Wang, L.; Liu, H.; Zheng, P. PCT Int. Appl. (**2008**), WO 2008119208 A1 20081009.
8. Samzadeh-Kermani, A. *Synlett.* **2014**, 1839–1842, and references cited therein.
9. Potapov, V. A.; Musalov, M. V.; Abramova, E. V.; Musalova, M. V.; Rusakov, Y. Y.; Amosova, S. V. *Chem. Heterocycl. Compd.* **2014**, 49, 1821-1826.
10. a) Martynov, A. V.; Makhaeva, N. A.; Amosova, S. V. *J. Sulfur. Chem.* **2014**, 35, 502-511. b) Xi, L.; Yi, L.; Jun, W.; Songsheng, Q. *Thermochim. Acta.* **2001**, 375, 109-113.
11. Xi, L.; Yi, L.; Ruming, Z.; Jun, W.; Xuesong, S.; Songsheng, Q. *Biol. Trace Elem. Res.* **2000**, 75, 167-175.
12. Degl'Innocenti, A.; Pollicino, S.; Capperucci, A. *Chem. Commun.* **2006**, 4881-4893, and references cited therein.
13. Capperucci, A.; Tanini, D.; Borgogni, C.; Degl'Innocenti, A. *Heteroatom Chem.* **2014**, 678-683.
14. Tanini, D.; Degl'Innocenti, A.; Capperucci, A. *Eur. J. Org. Chem.* **2015**, 357-369.
15. Capperucci, A.; Tanini, D. *Phosphorus Sulfur Silicon Relat. Elem.* **2015**, 190, 1320-1338.
16. Degl'Innocenti, A.; Capperucci, A.; Cerreti, A.; Pollicino, S.; Scapecchi, S.; Malesci, I.; Castagnoli, G. *Synlett* **2005**, 3063-3066.
17. Salvatore, R. N.; Smith, R. A.; Nischwitza, A. K.; Gavin, T. *Tetrahedron Lett.* **2005**, 46, 8931-8935.
18. Treatment of methyl 2-(3-(allyloxy)-2-hydroxypropylthio)acetate (R = CH_2OAll) (0.4 mmol) with DIBAL-H (0.48 mmol) in dry toluene[21] for 3 h, at −78°C, led to 6-(allyloxymethyl)-1,4-oxathian-2-ol **3a** (63%). Diastereomeric ratio = 65:35. ^{1}H 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) [$M^{+\cdot}$], 188 (8), 147 (3), 119 (10), 89 (28), 73 (20), 61 (30), 41 (100).

19. Tanini, D.; Barchielli, G.; Benelli, F.; Degl'Innocenti, A.; Capperucci, A. *Phosphorus Sulfur Silicon Relat. Elem.* **2015**, 190, 1265-1270.
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.
21. Tiecco, M.; Testaferri, L.; Marini, F.; Sternativo, S.; Santi, C.; Bagnoli, L.; Temperini, A. *Tetrahedron.* **2007**, 63, 5482-5489.