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

Original Citation:
Selective access to sulfurated and selenated heterocycles by intramolecular cyclization of -substituted sulfides and selenides / Capperucci, Antonella; Salles, Cynthia; Scarpelli, Simone; Tanini, Damiano. - In: PHOSPHORUS, SULFUR, AND SILICON AND THE RELATED ELEMENTS. - ISSN 1563-5325. - ELETTRONICO. - 192:(2017), pp. 172-174. [DOI: 10.1080/10426507.2016.1252364]

Availability:
This version is available at: 2158/1071744 since: 2017-01-20T11:34:34Z

Published version:
DOI: DOI: 10.1080/10426507.2016.1252364

Terms of use:
Open Access
La pubblicazione è resa disponibile sotto le norme e i termini della licenza di deposito, secondo quanto stabilito dalla Policy per l'accesso aperto dell'Università degli Studi di Firenze (https://www.sba.unifi.it/upload/policy-oa-2016-1.pdf)

Publisher copyright claim:
Selective access to sulfurred and selenated heterocycles by intramolecular cyclization of β-substituted sulfides and selenides

Antonella Capperucci, Cynthia Salles, Simone Scarpelli & Damiano Tanini

To cite this article: Antonella Capperucci, Cynthia Salles, Simone Scarpelli & Damiano Tanini (2017) Selective access to sulfurred and selenated heterocycles by intramolecular cyclization of β-substituted sulfides and selenides, Phosphorus, Sulfur, and Silicon and the Related Elements, 192:2, 172-174, DOI: 10.1080/10426507.2016.1252364

To link to this article: http://dx.doi.org/10.1080/10426507.2016.1252364

Accepted author version posted online: 26 Oct 2016.
Published online: 26 Oct 2016.
Selective access to sulfurated and selenated heterocycles by intramolecular cyclization of \( \beta \)-substituted sulfides and selenides

Antonella Capperucci, Cynthia Salles, Simone Scarpelli, and Damiano Tanini

Dipartimento di Chimica "Ugo Schiff", Università di Firenze, Sesto Fiorentino, Firenze, Italy

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.

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.

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. 1,4-Oxathiane derivatives possess for instance antitumor, antibacterial and antifungal activity, and find application as chiral auxiliaries for asymmetric transformations. Replacement of oxygen with sulfur in thiomorpholines allows to obtain compounds with antioxidant and hypolipidemic activity, and to access derivatives that can behave as DPP-IV inhibitors. On the contrary, the best of our knowledge, few examples are described for obtaining the seleno-analogues 1,4-oxaselenanes and selenomorpholines, the latter showing an interesting antibiotic activity.

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 and 1,2,5-trithiepanes. More recently, we discovered that also selenosilanes were able to react with strained molecules, leading to a selective formation of \( \beta \)-functionalized selenides, diselenides and various five- and seven-membered thia(seleno) 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. The latter could be obtained through reaction of \( \beta \)-substituted thiols with a \( \alpha \)-bromo ester.

Thus, \( \beta \)-mercapto alcohols, easily obtained through reaction of bis(trimethylsilyl)sulfide (HMDST) and variously substituted epoxides, were treated with bromo acetate, in the presence of \( \text{Cs}_2\text{CO}_3/\text{TBAI} \) system. Under these conditions, a clean \( S \)-alkylation occurred, leading to the corresponding \( \delta \)-hydroxy-\( \alpha \)-thioesters in good yields. Reduction with DIBAL-H allowed the formation of differently 6-substituted 2-hydroxy-1,4-oxathianes as equimolar mixture of diastereoisomers, via a spontaneous intramolecular cyclization of the intermediate aldehyde.

In order to evaluate the scope of this procedure, a chiral \( \beta \)-amino thiol was reacted with the bromo ester under similar conditions, affording the \( \text{Ts} \)-protected \( \alpha \)-thio-\( \delta \)-amino esters 6.

CONTACT

Antonella Capperucci, antonella.capperucci@unifi.it

Dipartimento di Chimica “Ugo Schiff”, Università di Firenze, Via della Lastruccia 3-13, 50019 Sesto Fiorentino (Firenze), Italy.

Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/gpss.

© 2017 Taylor & Francis Group, LLC
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)\(^\text{19}\) with the bromo ester (Scheme 2) under Cs_2CO_3/TBAI activation. Treatment with DIBAL-H directly afforded differently substituted 2-hydroxy 1,4-oxasedelenolanes \(\text{11}\) as mixture of stereoisomers\(^\text{20}\).

**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**


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\(^\text{i}\) 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, \(J_{13.4} = 2.1, 13.4\) Hz), 3.23 (1 H, ap d, ls, \(J_{13.4} = 3.37(1H, d d, J = 3.37, 7.6 Hz), 3.61 (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).

19. \(^{13}C\) 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).

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

**Scheme 1.** Synthesis of thia heterocycles.

\[ X = \text{NTs} \]

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)\(^\text{19}\) with the bromo ester (Scheme 2) under Cs_2CO_3/TBAI activation. Treatment with DIBAL-H directly afforded differently substituted 2-hydroxy 1,4-oxasedelenolanes \(\text{11}\) as mixture of stereoisomers\(^\text{20}\).

**Scheme 2.** Synthesis of Se-containing heterocycles.

\( X = \text{NTs} \)

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