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Thio- and Seleno-Michael Addition: an Efficient Tool for the Delivery of Sulfur and Selenium Functionalities

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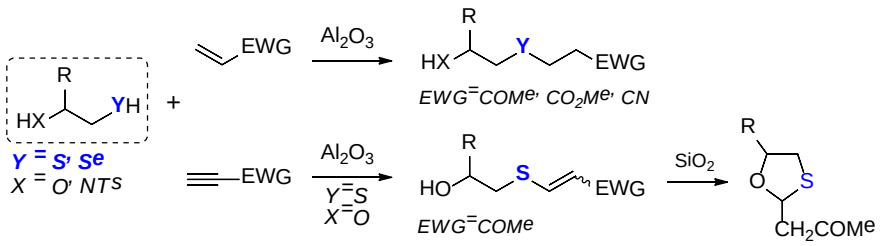
ABSTRACT *1,2-Mercapto alcohols and 1,2-mercapto amines proved to be useful reagents towards Michael acceptors, such as α,β-ethylenic ketones, esters and nitriles leading to variously polyfunctionalized unsymmetric sulfides. Reaction of 1,2-mercapto alcohols with electron-deficient alkynes allowed to obtain β-hydroxy vinyl sulfides as valuable precursors of 1,3-oxathiolane derivatives. Extension to β-hydroxy selenols resulted in the isolation of unsymmetric selenides, formed through a Se-alkylation on*

GRAPHICAL ABSTRACT



KEYWORDS 1,2-Mercapto alcohols; 1,2-mercapto amines; β-hydroxy selenols; Michael addition.

INTRODUCTION

The Michael reaction is one of the most powerful and widely used methods to form carbon-carbon and carbon-heteroatom bonds.[1] In this context, the Michael addition of sulfurated nucleophiles to α,β-unsaturated derivatives represents an useful strategy for carbon-sulfur bond formation.[2] The reaction constitutes a key step in organic synthesis to achieve more complex sulfurated molecules, which find application in various fields, as pharmaceutical chemistry, food chemistry, agrochemistry and material science. More recently, also the conjugate addition of nucleophilic selenium species, such as selenolates, to α,β-unsaturated carbonyl compounds was applied in different organic transformations.[3]

Our long dated interest in the chemistry of thiosilanes led us to develop a general procedure to access bifunctionalized

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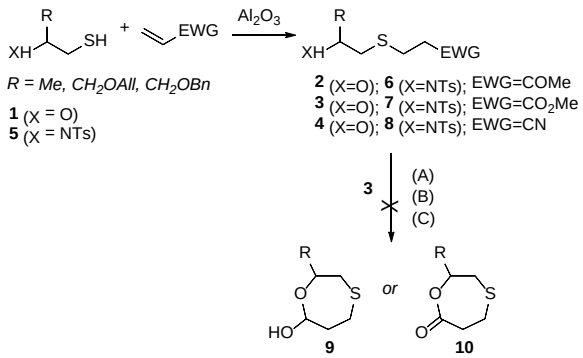
derivatives, namely 1,2-dithiols, β-hydroxy- and β-amino-thiols,[4] which proved to be efficient reagents to prepare sulfurated compounds, including heterocycles of different ring size, by exploiting the reactivity of the two functional groups with suitable electrophiles. More recently, we found that the reaction of 2-hydroxy- and 2-amino-thiols with suitable electrophiles led to substituted 1,4-oxathianes and 3,4-dihydro-1,4-thiazines through *S*-alkylation of the ester, followed by a reductive ring closure.[5] This reaction was also extended to the selenated analogues, allowing a mild access to 6-substituted 1,4-oxaselenan-2-ols under mild conditions.[5,6] Interestingly, some of the so obtained sulfurated and selenated structures were able to act as antioxidants and enzymes inhibitors.[6,7]

As a continuation of our research in this field, we turned our attention to explore the behaviour of the β-functionalized-thiols and selenols as Michael donors with electron-deficient compounds, to prepare polyfunctionalized chalcogen containing derivatives.

RESULTS AND DISCUSSION

When β-hydroxy thiols **1**, smoothly obtained by reaction of epoxides with bis(trimethylsilyl)sulfide (HMDST),[4c] were treated with unsaturated derivatives, such as methyl vinyl ketone, methyl acrylate and acrylonitrile, in the presence of Al_2O_3, a clean conjugated addition occurred, leading to the synthesis of differently substituted β-hydroxy unsymmetric sulfides **2-4** in good yields (Scheme 1).[8] This behaviour was efficiently extended to β-amino thiols **5**, prepared through ring opening of (*S*)-aziridines with HMDST.[4b] Their reaction with enones allowed a direct access to functionalized enantioenriched β-amino sulfides **6-8** (Scheme 1).



Scheme 1. Thio-Michael addition of β-hydroxy-thiols **1** and β-amino-thiols **5** to α,β-unsaturated systems and functionalization of β-hydroxy sulfides (Reagents: (A) = DIBAL-H; (B) = $BF_3{\cdot}Et_2O$; (C) = NaOH or NaH)

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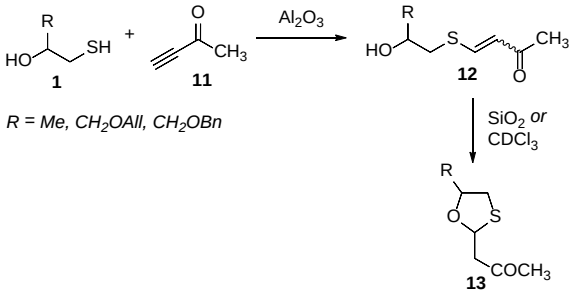
In order to assess whether compounds **3** could behave as precursors of heterocyclic systems, they were subjected to reduction with DIBAL-H to obtain the corresponding aldehydes. Differently from what previously obtained with the lower homologues δ-hydroxy-α-thioesters,[5b] which underwent to intramolecular cyclization, this time no trace of the seven-membered sulfurated hemiacetal **9** was evidenced (Scheme 1, Conditions A). The reaction was carried out also under different conditions, using either a Lewis acid or a base to promote the cyclization, with the aim to obtain the sulfurated lactone **10** (Scheme 1, Conditions B, C). However, the formation of the heterocycle was not achieved even under these conditions.

2-Substituted thiols were then reacted with electron deficient alkynes as Michael acceptors. Treatment of β-mercaptoalcohols **1** with the α,β-acetylenic ketone **11** led to the synthesis of functionalized β-hydroxy-vinyl sulfides **12** (Scheme 2).

Interestingly, after purification on silica gel or in $CDCl_3$, during the acquisition of NMR spectra, an easy cyclization occurred. This allowed to isolate 1,3-oxathiolan derivatives



Scheme 2. Thio-Michael addition of β-hydroxy-thiols **1** on electron-deficient alkyne **11**.

13, arising from an intramolecular oxa-Michael addition on the β-thio-α,β-ethylenic ketone **12**.

Then, we moved to consider the selenated analogues in order to develop a novel strategy to prepare organoselenated derivatives. Taking advantage of our recent results to access stable β-functionalized alkyl-selenols,[9] an initial investigation was carried out to establish the behaviour of the so obtained selenols as nucleophilic species towards different electrophiles. Therefore, 2-hydroxy selenols **14** were reacted with methyl 2-bromoacetate and propylene oxide, as well as with methyl vinyl ketone, in the presence of different catalysts, such as cesium carbonate/TBAI and aluminium oxide (Scheme 3).

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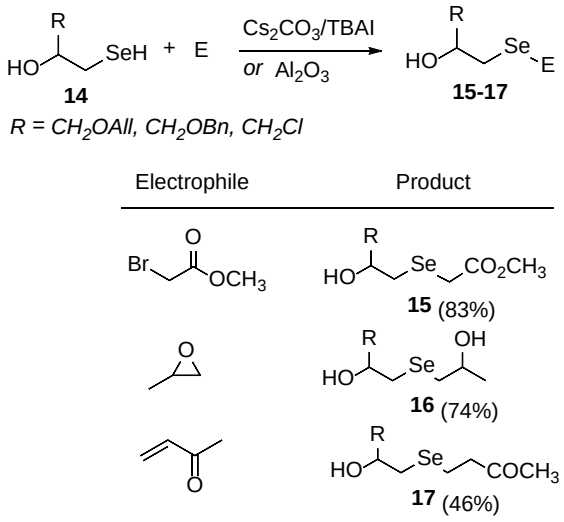

Scheme 3. Reaction of selenols with electrophiles.

We found that a Se-alkylation occurred, leading, respectively, to functionalized β-selenoesters **15** and to unsymmetric dihydroxy selenides **16** in good yields. When selenols were reacted with the unsaturated ketone, we were pleased to observe the formation of the corresponding β-hydroxy-γ-keto selenides **17**, arising from a seleno-Michael addition. These results show that, under these mild conditions, selenols are stable enough to react with electrophiles, leading to variously functionalized organoselenides.

CONCLUSIONS

β-Hydroxy- and β-amino-thiols behaved as useful nucleophiles towards Michael acceptors, such as α,β-ethylenic carbonyl compounds and nitriles. The reaction of β-mercapto alcohols with electron-deficient alkynes allowed the synthesis of β-hydroxy vinyl sulfides, which undergo cyclization under mild acidic conditions to yield 1,3-oxathiolane derivatives. Also β-hydroxy selenols were able to react with electrophiles, including methyl vinyl ketone, leading to variously functionalized selenides. Extension to different Michael acceptors and to differently substituted thiols and selenols is nowadays under investigation, as well as the evaluation of the properties of the obtained compounds.

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8. Typical procedure: Neutral Al_2O_3 (30 mg, 0.30 mmol, 3.0 eq.) was added under inert atmosphere (N_2) to a stirred solution of the β-hydroxy thiol **1a** [1-(allyloxy)-3-mercaptopropan-2-ol, R=CH_2OAll] (0.10 mmol, 1.0 eq.) and methyl acrylate (0.12 mmol, 1.2 eq) in dry toluene (2 mL) at room temperature. The reaction mixture was stirred for 4 h, then diluted with Et_2O (5 mL) and filtered through a short pad of Celite. Flash column chromatography (petroleum ether/Et_2O 5:1) afforded methyl 3-[(3-(allyloxy)-2-hydroxypropyl)thio]propanoate **3a** (R=CH_2OAll) (16 mg, 64%) as a yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 2.42 (1H, bs, OH), 2.60-2.65 (3H, m), 2.71-2.85 (3H, m), 3.46 (1H, dd, J=6.2 Hz, 9.6 Hz, C*Ha*HbO), 3.52 (1H, dd, J=4.2 Hz, 9.6 Hz; CHa*Hb*O), 3.69 (3H, s), 3.87-3.93 (1H, C*H*OH), 4.01-4.03 (2H, m), 5.18-5.29 (2H, m), 5.84-5.94 (1H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 27.5, 34.6, 35.9, 51.8, 69.4, 72.3, 72.6, 117.4, 134.4, 172.3. MS (ESI, positive), m/z (%): 234 (100, M^+).
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