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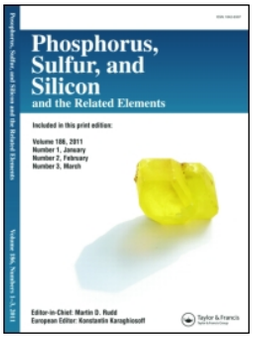

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Novel sulfur and selenium-containing antioxidants: Synthesis and evaluation of their GPx-like activity

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ABSTRACT
New linear and cyclic chalcogen-containing compounds have been synthesized exploiting the reactivity of bis(trimethylsilyl)selenide with strained heterocycles. A simple and efficient procedure allowed a selective access to β-functionalized selenides, diselenides, and dithiaselenepanes under mild conditions. Antioxidant catalytic activity of these compounds was investigated in the reaction of hydrogen peroxide with dithiothreitol (DTT^{red}). According to this assay, some of the synthesized structures exhibited a remarkable glutathione peroxidase (GPx)-like activity.

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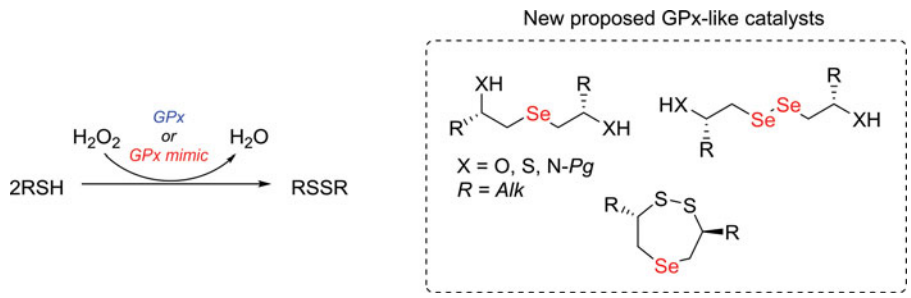
GRAPHICAL ABSTRACT



Introduction

Glutathione peroxidase (GPx), a thoroughly studied antioxidant selenoenzyme, protects cells against oxidative damage catalyzing the reduction of hydroperoxides at the expense of two molecules of glutathione (GSH).[1,2]

Several human diseases such as cancer, neurodegenerative pathologies, inflammation, immune disorders, atherosclerosis, cystic fibrosis have been correlated with a altered intracellular redox balance and oxidative stress.[3,4] In this regard, the synthesis of novel small molecules able to reproduce the antioxidant activity of glutathione peroxidase is highly sought after.

For their redox chemistry, organochalcogen compounds such as selenides, have been widely applied as synthetic mimics of GPx.[2,5,6]

Our longtime interest in the study of the reactivity of silylchalcogenides led us to discover synthetic routes to access several classes of novel sulfur- and selenium-containing organic compounds.[7] More recently we became interested in the synthesis and evaluation of the properties of new antioxidant molecules.[8] As a part of our growing interest in the design of new antioxidant systems, we report herein the synthesis and the preliminary results on the assessment of the GPx-like activity of novel chalcogen-containing small molecules.

Results and discussion

Synthesis of cyclic and open chain selenides and diselenides

Bis(trimethylsilyl)sulfide (Me_3Si-S-$SiMe_3$, HMDST) behaves as an efficient reagent in the delivery of sulfur functionalities. A number of sulfur containing molecules, such as 1,2,5-trithiepanes, β-hydroxy-, β-amino-thiols, 1,2-dithiols and thiocarbonyl compounds can be conveniently synthesized through the reaction of HMDST with different electrophiles.[7a,b,9] More recently, we investigated the reactivity of bis(trimethylsilyl)selenide (Me_3Si-Se-$SiMe_3$, HMDSS) with strained heterocycles, disclosing a mild and straightforward access to cyclic and acyclic selenides and diselenides.[7c,d]

Thus, treatment of substituted epoxides with an excess of HMDSS in the presence of a catalytic amount of TBAF led smoothly to the formation of substituted β-hydroxy-diselenides **1**, arising from a clear regioselective attack of the selenated

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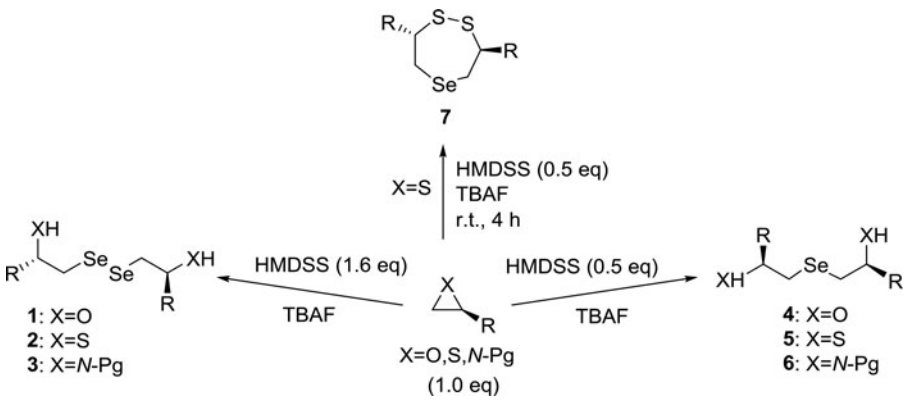

Scheme 1. Synthesis of β-functionalized diselenides, selenides, and 1,2,5-dithiaselenepanes through reaction of HMDSS with strained heterocycles.

nucleophile on the less substituted side of the oxirane. The reaction scope proved to be broad and β-mercapto- and β-amino-diselenides (**2** and **3**) were obtained under similar conditions from thiiranes and aziridines, respectively (Scheme 1).[7c]

Furthermore, a selective formation of β-functionalized selenides was conveniently achieved tuning the HMDSS/electrophile molar ratio. Indeed, reacting HMDSS (1.0 eq) with an excess of differently substituted epoxides (2.0 eq) under TBAF catalysis, the corresponding substituted β-hydroxy-selenides **4** were isolated in good yields.[7c] The scope of the reaction was then enlarged to the synthesis of β-mercapto- and β-amino-selenides (**5** and **6**), exploiting the reactivity of thiiranes and aziridines under similar conditions (Scheme 1).

Interestingly, to avoid -SH oxidation in the products **2** and **5**, controlled reaction time and temperature are required (20–30 min, 0°C). As shown in the Scheme 1, when HMDSS and episulfides were reacted at ambient temperature for a longer time (4 h), the corresponding 3,7-disubstituted 1,2,5-dithiaselenepanes **7** were selectively obtained in good yield (Scheme 1).[7d]

Evaluation of GPx-like antioxidative activity

Having in our hands a robust procedure for the synthesis of new chalcogen-containing organic molecules, we preliminary investigated their antioxidant activity as glutathione peroxidase catalytic mimics.

Several spectrophotometrical[10] and NMR-based[11] methods for the assessment of the GPx-like activity have been reported. The activity of compounds reported in Figure 1 was evaluated according to a literature procedure in catalyzing the reaction between hydrogen peroxide (H_2O_2) and dithiothreitol

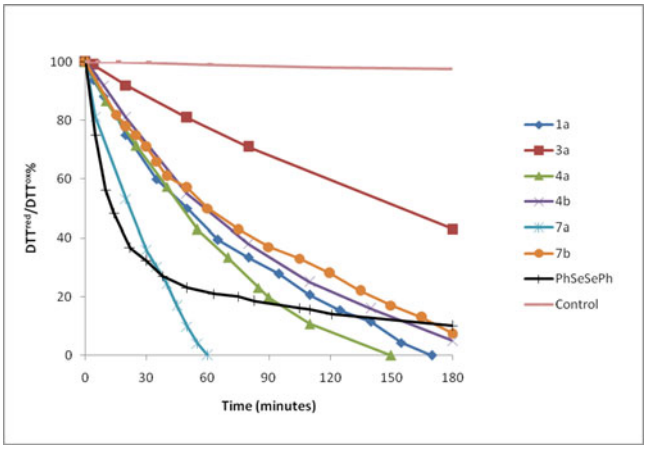

Figure 2. GPx-like behavior of compounds **1a**, **3a**, **4a**,**b**, **7a**,**b** as catalysts in the oxidation of DTT^{red} with H_2O_2. In the control experiment, the reaction was run with no catalyst.

(DTT^{red}).[5e,11b] The oxidation of the substrate was monitored by the mean of ^1H NMR in CD_3OD.[12] A control experiment was performed in the absence of catalyst. The catalytic activity of diphenyldiselenide against DTT^{red} under these conditions was also determined, to compare the activity of title compounds with $(PhSe)_2$, commonly used as standard material for the GPx assays.[13]

As depicted in Figure 2, when the reaction was performed in the absence of any catalyst, 96% of DTT^{red} remained unreacted after 200 min. On the contrary, the addition of 10% of the Se-containing compounds reported in Figure 1 caused an increasing of the DTT^{ox} formation rate with respect to the control experiment. Indeed, when β-hydroxy-diselenide **1a** was used as the catalyst, complete oxidation of DTT^{red} was achieved within

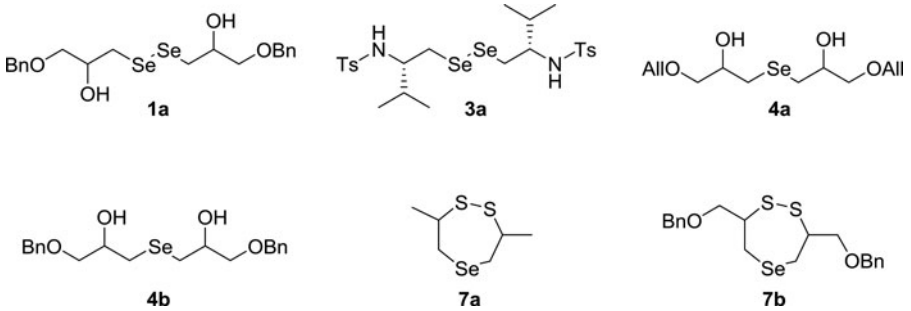

Figure 1. New chalcogen-containing GPx mimics.

170 min. On the other hand, β-amino-diselenide **3a** behaved as poor catalyst under these conditions, being almost 50% of DTT^{red} unreacted after 160 min (Fig. 2).

To investigate the GPx-like catalytic activity of a different class of organoselenium compounds, β-hydroxy-selenides **4a**,**b** were tested. As can be noticed in Figure 2, no significant differences were found among kinetic profiles of **1a** and **4a**,**b**.

Having analyzed the GPx-like activity of linear selenides and diselenides, we then turned to evaluate the efficiency of dithiaselenepanes **7** in catalyzing the DTT^{red} oxidation. According to this assay 3,7-dimethyl-1,2,5-dithiaselenepane **7a** proved to be an effective mimic of GPx: 50% of DTT was indeed oxidized in ca. 20 min and complete substrate consumption was observed within 60 min (Figure 2). Noticeably, when $(PhSe)_2$ was used as the catalyst, 10% of DTT^{red} was still unreacted after 180 min, whereas in the presence of catalysts **1**,**4**,**7** complete DTT oxidation was observed within 180 min. Intriguingly, the more hindered dithiaselenepane **7b** showed a lower catalytic efficiency than **7a**.

Conclusions

In conclusion, we have reported a convenient and simple procedure to access new chalcogen-containing small molecules under rather mild conditions. Preliminary results on the evaluation of the GPx-like activity of selected compounds have also been presented, showing interesting results. The synthesis and the study of other Se-containing antioxidant catalysts is currently under investigation.

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12. *Typical procedure*: DTT^{red} (0.15 mmol) and Se-catalyst (0.015 mmol) were dissolved in CD_3OD (1.1 mL), and the solution was added to 35% H_2O_2 (15 μL, 0.15 mmol) to start the reaction. ^1H NMR spectra were measured at a variable reaction time at 25 °C. The relative populations of DTT^{red} and DTT^{ox} were determined by integration of the ^1H NMR signals.
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