Synthesis of Water-Soluble Vinyl Selenides and Their High Glutathione Peroxidase (GPx)-Like Antioxidant Activity

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Received: 25.08.2013; Accepted after revision: 10.10.2013

Abstract: A convenient procedure for the synthesis of novel bis-(1-hydroxymethyl-2-halo-3-hydroxy-1-propylene) selenides has been developed. On oxidation these compounds form novel seleno-spiro compounds and their glutathione peroxidase mimetic activity has been studied. They promote the hydrogen peroxide oxidation of phenylmethanethiol to the corresponding disulfide via a catalytic cycle.

Key words: alkenes, selenium, oxidation, spiro compounds, diols

Glutathione peroxidase (GPx) is a selenoenzyme that protects cells by catalyzing the reduction of peroxides with the stoichiometric reductant glutathione.1 The enzyme catalytic site includes a selenocysteine residue in which the selenium undergoes a redox cycle involving the selenolate anion as the active form, which reduces hydroperoxides. The selenol is first oxidized to a selenenic acid EnzSeOH, which reacts with reduced glutathione GSH to form the selenyl sulfide EnzSeSG. A second glutathione then regenerates the active form of the enzyme by attacking the EnzSeSG to form the oxidized glutathione GSSG. The overall catalytic cycle is depicted in Figure 1.2

Figure 1 Catalytic cycle for the reduction of peroxides

Inspired by the above findings, we applied our regio- and stereospecific SeCl₂ addition protocol in the planned preparation of novel GPx-mimetics of spirodioxaselenurane type.8 Those divinyl selenides formed by syn-addition of SeCl₂ to the triple bond, which do not bear a vicinal hydrogen capable of cis elimination, gave stable selenoxides 2a,b and selenone 3 in good yield upon oxidation with tert-butyl hydroperoxide or with 2 equivalents of MCPBA, respectively (Scheme 2). The divinyl selenoxides 2c,d derived from the unsubstituted or monosubstituted propargyl alcohols are relatively unstable, presumably due to syn-elimination. The divinyl selenoxides 2a and 2b do not cyclize to spiro compounds (see below) presumably because of ring strain of four-membered rings.
In contrast to the above, were our findings in the reaction of selenium dihalides with homopropargyl alcohol. Although some loss of stereo- and regioselectivity was observed, Z-anti-Markovnikov adducts were chromatographically isolated as major products and underwent oxidation with H₂O₂ to the corresponding five-membered spiroseelenuranes with exocyclic double bonds (Scheme 3).

In an alternative approach to the preparation of spirodioxaselenuranes, we have found that but-2-yn-1,4-diol smoothly reacts with selenium dihalides in a completely stereospecific manner and affords the corresponding water-soluble tetrahydroxymethyldivinyl selenides in high yields. Noteworthy is the fact that unlike the syn-addition of SeX₂ to the triple bond of propargyl alcohols containing a single hydroxymethyl functionality, but-2-yn-1,4-diol gives under the similar conditions exclusively 1,2-anti-adducts. The mechanistic explanation of this striking difference is still under investigation. However, in general anti-addition of electrophilic selenium reagents to multiple bonds is the expected stereochennical result. Compounds upon oxidation with 30% hydrogen peroxide in aqueous solution produce the spiroselenurane compounds with the endocyclic double bonds in excellent yields (Scheme 4). Spiroselenurane compounds precipitated from the reaction mixture as white needles within 15 minutes, and were recrystallized from water and fully characterized by spectroscopic methods. The structure of the chloro-substituted compound 7a was confirmed by X-ray crystallography (Figure 2).

The reaction of substituted alkyne diols with selenium dihalogenides was used for the preparation of a series of spirodioxaselenuranes. However, in the case of 2,5-dimethylhex-3-yne-2,5-diol the reaction with SeCl₂ proceeded slowly and produced, not a divinyl selenide, but the seleninate ester 9, presumably via 8 (Scheme 5). Steric hindrance of the four methyl groups precluded addition to the triple bond.
Recently, we have shown that the addition of commercially available selenium tetrachloride to the triple bond of propargyl alcohols proceeded easily with the same regio- and stereochemistry as selenium dichloride and produces unstable divinylselenium dichloride intermediates. The latter underwent hydrolysis to the corresponding divinyl selenoxides during basic workup. In the case in hand, but-2-yn-1,4-diol reacted stereospecifically with selenium tetrachloride in anhydrous acetonitrile and afforded the expected spiroseleuran compound in a one-pot manner and in good yield (Scheme 6).

Even the sterically hindered 2,5-dimethylhex-3-yne-2,5-diol reacted easily with SeCl₄ and produced, in an almost 1:1 ratio, two products, and , which were separated by column chromatography (Scheme 7). The first product, selenium-bridged dihydrofuran derivative , presumably was formed via syn-addition of SeCl₄ to the triple bond followed by double intramolecular dehydrative cyclization. The second one , was identified as a chlorinated analogue of the seleninate ester . Dicyclic selenide upon oxidation with hydrogen peroxide gave the expected stable selenoxide (Scheme 8). The structure of the latter was unambiguously confirmed by X-ray crystallography (Figure 3).

An interesting result was obtained using ethyl 4-hydroxybut-2-ynoate (13) as a hydroxyalkyne substrate. Whereas selenium dichloride does not react with this alcohol, selenium tetrachloride undergoes smooth 1,2-addition to the deactivated triple bond of this propargyl alcohol. However, the regiochemistry differ from the one observed in a ‘normal’ SeCl₂ addition (see, Scheme 1) and produces, after hydrolysis of the intermediate, the divinyl selenium oxide with the geometry that permits its subsequent cyclization to the spiro derivative (Scheme 9).
The novel selenium-containing spiro compounds 5a, b and 7a, b were found to exhibit higher glutathione peroxidase mimetic activity than the widely studied compound ebselen (in nonenzymic conditions). To examine the glutathione peroxidase-like (GPx) catalytic activity of the spiroseleuranone compounds, 30% H2O2 and benzylthiol (BnSH) were chosen as the oxidant and stoichiometric reductant, respectively. The oxidation of BnSH to the disulfide BnSSBn was monitored by 1H NMR spectroscopy. When 10 mol% of the catalyst 6a or 7a was used in the presence of excess 30% H2O2, 75% of BnSH was converted into BnSSBn after 1.5 hours. (3Z)-4-Chloro-1-{[(Z)-2-chloro-1-(1-hydroxy-1-methylethyl)vinyl]selanyl}-2-methylbut-3-en-2-ol (1a) exhibits a similar GPx-like catalytic activity. In the control experiment in the absence of the catalyst under the same reaction condition after 24 hours, only 4% of BnSSBn was observed in the reaction mixture according to 1H NMR spectrum. The suggested catalytic cycle of compounds 6 and 7 is shown on Scheme 10.

Thus, an easy and efficient synthesis of the water-soluble divinyl selenides has been achieved. These divinyl selenides perform as glutathione peroxidase mimetics with high efficacy. Spiroseleuranone 7a also showed some antifungal activity in preliminary experiments.

The THF solution of SeCl4 was prepared by the known procedure14 and used immediately. All solvents and reagents were obtained from Aldrich or Fluka and used without further purification with the following exception: THF was distilled from sodium benzophenone dianion just before use and CHCl3 was distilled from P2O5. All reactions were carried out under dry argon atmosphere using oven-dried glassware. Reagents and solvents were handled by using standard syringe-septum cap techniques. Column chromatography was performed with Merck silica gel 60 (230–400 mesh), and TLC was run on precoated Merck silica gel plates 60 F254 (2.00 mm). Preparative TLC was carried out in glass sheets precoated with Merck silica gel 60 F254 (0.25 mm). All new compounds have satisfactory analytical and spectroscopic data.

Melting points were obtained on a Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Bruker Tensor 27 FTIR instrument. 1H NMR and 13C NMR were recorded on Bruker DPX-300, DMX-600 or Avance-III-700 spectrometers in either CDCl3 or other deuterated solvents, using TMS as internal standard. Chemical shifts are reported in δ units, and coupling constants in Hz. COSY and NOSY experiments have been carried out in order to assign 1H and 13C spectra and confirmed the structures of new compounds. Mass spectra were obtained on Auto flex ToF/ToF Bruker MALDI (matrix assisted laser desorption ionization) instrument with graphite matrix. High-resolution mass spectra were obtained on a VG-Fison Autospec instrument. Elemental analyses were performed on Thermo CHNS Analyzer FlashEA instrument.

Divinyl selenides 1a–d were prepared according to our reported procedure.15,16 Ethyl 4-hydroxybut-2-ynoate (13) was prepared by the known procedure.30

Oxidation of Divinyl Selenides with TBHP: General Procedure
An excess of TBHP (0.90 mL, 5 mmol, ~5.5 M solution in nonane) was added to divinyl selenide 1a–d (1 mmol) dissolved in CH2Cl2 (10 mL) and the solution was stirred at r.t. for 18 h. After completion of the reaction (TLC, eluent: hexanes–EtOAc, 4:1), the solvent was evaporated to dryness under reduced pressure. All selenoxides 2a–d were purified by removing the excess of TBHP overnight under vacuum. In the case of stable compounds, further purification can be done by column chromatography, if required, using EtOAc–MeOH (4:1) as eluent.

(3Z)-4-Chloro-3-{[(Z)-2-chloro-1-(1-hydroxy-1-methylethyl)vinyl]selanyl}-2-methylbut-3-en-2-ol (2a)

Yield: 0.294 g (88%); white solid; mp 126 °C.

IR (KBr): 3355, 2936, 2560, 1604, 1466, 1426, 1370, 1305, 1173, 1149, 981, 901, 821, 786 cm–1.

1H NMR (300 MHz, CDCl3): δ = 1.51 (s, 6 H), 1.73 (s, 6 H), 5.67 (br s, 2 H), 6.73 (s, 2 H).

13C NMR (75 MHz, CDCl3): δ = 27.8 (CH3), 28.4 (CH3), 73.6 (J CSe = 12.2 Hz, (CH3)2C), 122.4 (=CCl), 157.1 (J CSe = 123.6 Hz, =CSe).

HRMS: m/z [M + H] calcd for C10H16Cl2O3Se: C, 35.95; H, 4.83; O, 14.37. Found: C, 35.56; H, 4.76; O, 14.35.

(3Z)-4-Bromo-3-{[(Z)-2-bromo-1-(1-hydroxy-1-methylethyl)vinyl]selanyl}-2-methylbut-3-en-2-ol (2b)

Yield: 0.368 g (87%); white solid; mp 112 °C.

IR (KBr): 3102, 1623, 1434, 1373, 1131, 1007, 806 cm–1.

1H NMR (300 MHz, CDCl3): δ = 1.54 (s, 6 H), 1.75 (s, 6 H), 6.31 (br s, 2 H), 6.74 (s, 2 H).

13C NMR (75 MHz, CDCl3): δ = 27.7 (CH3), 28.4 (CH3), 74.3 (C), 110.3 (C–Se), 158.8 (C–Se).

(2Z)-3-Chloro-2-{[(Z)-2-chloro-1-(hydroxymethyl)prop-1enyl]selanyl}but-2-en-1-ol (2c)

Eluent EtOAc–MeOH (4:1); yield: 0.260 g (85%); white solid; mp 81–83 °C.

IR (KBr): 3102, 1623, 1434, 1373, 1131, 1007, 806 cm–1.

1H NMR (300 MHz, CDCl3): δ = 2.42 (s, 6 H), 4.68 (br s, 2 H), 4.58 (d, J = 15.4 Hz, 2 H), 4.70 (d, J = 15.4 Hz, 2 H).

13C NMR (75 MHz, CDCl3): δ = 25.03 (CH3), 58.06 (CH3), 137.02 (C–Se), 140.43 (C–Se).

(2Z)-3-Chloro-2-{[(Z)-2-chloro-1-(hydroxymethyl)vinyl]seleninyl}prop-2-en-1-ol (2d)

Yield: 0.228 g (82%); viscous liquid.
1H NMR (300 MHz, acetone-d6): δ = 4.22 (s, 2 H), ABq: 4.53 (dd, J = 14.3, 1.5 Hz, 2 H), 4.73 (dd, J = 14.3, 1.5 Hz, 2 H), 7.02 (t, 1.5 Hz, 2 H).

13C NMR (75 MHz, acetone-d6): δ = 57.4 (CH3), 123.6 (CH=), 146.4 (\(J_{CC} = 162.3\) Hz, C=).

((1Z,2,2-Z)-Selenenylibis-(3-chloroprop-2-ene-1,2-diyi))bis(oxi)bis(methylene) dibenzene (2e)

Eluent: EtOAc–hexane (1:1); yield: 0.504 g (93%); viscos liquid.

1H NMR (300 MHz, CDCl3): δ = 1.80 (s, 2 H), 4.31 (s, 2 H), 6.73 (s, 2 H), 7.02 (td, 9.6, 7.5 Hz, 2 H), 7.17 (t, 9.6 Hz, 2 H).

HRMS: \([M + H]^+\) calcd for C10H17Cl2O4Se: 288.9356; found: 288.9356.

Oxidation of Divinyl Selenide 1a with MCPBA; Preparation of Compounds 2a and 3

4-Chloro-3-[2-chloro-1-[1-hydroxy-1-methylthyl(vinylselenyl)-2-methylbut-3-en-2-ol (1a) (3.18 g, 1 mmol) was dissolved in CHCl3 (10 mL) and a CHCl3 solution (15 mL) of MCPBA (77%), 491 mg, 2.2 mmol) was added slowly. The reaction mixture was then stirred for 24 h at r.t. TLC (eluent: EtOAc–MeOH, 4:1) indicated the formation of two products. The products were then quenched with sat. aq Na2SO3 (10 mL) under ice cold conditions. The product was extracted with CH2Cl2 (30 mL), and the CH2Cl2 layer was washed with sat. aq NaHCO3 (5 mL), H2O (10 mL), and brine (10 mL). Drying (MgSO4) and evaporation of the solvent un-

1H NMR (75 MHz, CDCl3): δ = 63.80 (\(J_{CC} = 6.8\) Hz, CH2Se), 72.98 (CH=Ph), 125.81 (\(J_{CC} = 21\) Hz, CH=), 127.67 (CH), 128.28 (CH), 136.67 (C-ipso), 142.17 (\(J_{CC} = 125.4\) Hz, C=).

HRMS (DCI + CH4): m/z [M + H]+ = 459.0033; found: 459.0071.

Bis(1-butyl-1H-4,4-dioxo-5,5-dimethyl-5H-thiophene-3-yl)selenone (4a[4]nonane (5b)

Eluent: EtOAc–MeOH (8:1); yield: 0.18 g (89%); white solid; mp 65−67 °C.

1H NMR (700 MHz, CDCl3): δ = 2.77 (m, 4 H), 4.02 (ddd, J = 9.6, 7.5, 6.0 Hz, 2 H) 4.18 (ddd, J = 9.6, 7.5, 6.0, 0.14 Hz, 2 H), 7.40 (t, J = 2.5 Hz, 2 H).

13C NMR (175 MHz, CDCl3): δ = 33.6 (CH3), 64.2 (CH2O), 114.1 (\(J_{CC} = 22.6\) Hz, CH), 140.0 (\(J_{CC} = 103.0\) Hz, Cq).

MS (Cl/CH3): m/z (%) = 378.8 (88), 296.9 (13), 227.8 (100), 118.9 (8).

HRMS: m/z [M + H]+ calcd for C18H26Cl2O8Se: 375.8213; found: 375.8251.

Bis(4-chloro-2,2,5,5-tetramethyl-2,5-dihydrofurran-3-yl)selenenel (12)

Eluent: EtOAc–hexane (1:3); yield: 0.115 g (51%); colorless plates; mp 96–97 °C (CHCl3–hexane).

1H NMR (CDCl3, 600 MHz): δ = 1.40 (s, 6 H), 1.44 (s, 6 H), 1.62 (s, 12 H).

13C NMR (CDCl3, 150 MHz): δ = 27.3 (CH3), 27.4 (CH2), 29.0 (CH3), 30.4 (CH2), 86.1 (MeC=), 88.9 (MeCH3), 134.3 (\(J_{CC} = 150.6\) Hz, =CSe), 143.02 (\(J_{CC} = 16.5\) Hz, =CSCI).

MS (DCI): m/z (%) = 415.0 (100, [M + H]+), 399.0 (26), 381 (93.7), 159.1 (13.3), 85.0 (48.7).

HRMS: m/z [M + H]+ calcd for C11H20O5Cl3Se: 415.0324; found: 415.0317.

Anal. Calcd for C11H20O5Cl3Se: C, 46.39; H, 5.84. Found: C, 46.67; H, 5.89.

Divinyltetrahydroxy Seleneids 6a,b

The THF solution of SeCl3 (1 mmol) prepared by the known procedure was added dropwise to a solution of but-2-yn-1,4-diol (172 mg, 2 mmol) in anhydrous THF (2 mL) at 0 °C. The reaction mixture was then stirred at r.t. for 45 min. After completion of the reaction (TLC, eluent: EtOAc), the mixture was extracted with EtOAc (20 mL) and the EtOAc layer was washed with brine (2 × 5 mL) and dried (MgSO4). After evaporation of the solvent, a crude product containing some black gummy materials and selenide compounds was obtained. This crude product was dissolved in a mixture of CH2Cl2 (5 mL) and dried (MgSO4). After evaporation of the solvent. The corresponding bromo derivative 6b was prepared by the same procedure using SeBr2 instead of SeCl3.

2-Chloro-3-(2-chloro-3-hydroxy-1-hydroxymethylpropenylsel-

1H NMR (700 MHz, CDCl3): δ = 2.79 (m, 4 H), 4.02 (dt, J = 9.6, 6.1 Hz, 2 H), 4.17 (dt, J = 9.6, 6.1 Hz, 2 H), 7.17 (t, J = 2.5 Hz, 2 H).

13C NMR (175 MHz, CDCl3): δ = 31.6 (CH3), 64.3 (CH2), 125.6 (\(J_{CC} = 25\) Hz, Cq–Se), 138.5 (\(J_{CC} = 101.5\) Hz, Cq–Se).

MS (DCI/CH2): m/z (%) = 288.9 (78), 252.9 (26), 236.9 (14), 206.9 (17), 183.9 (79), 168.9 (14), 123.0 (15), 83.9 (100).

HRMS: m/z [M + H]+ calcd for C16H10Br2O2Se: 282.9032; found: 282.9032.

(4Z,9)-4,9-Bis(bromomethylene)-1,6-dioxo-5,5-selenospi-

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2-Bromo-3-(2-bromo-3-hydroxy-1-hydroxymethylpropenylselenanyl)but-2-ene-1,4-diol (6b)

Yield: 0.37 g (90%); colorless solid; mp 103–105 °C.

IR (KBr): 3392 (br), 2914, 1641, 1422, 1284, 1227, 1094, 1022, 952 cm–1.

Yield: 0.16 g (93%); colorless needles; mp 151 °C (H2O).

MS (DCI): m/z (%) 322.9306; found: 322.9356.

Spiroselenurane 7a,b

The corresponding divinyl selenide 6a or 6b (0.545 mmol) was dissolved in H2O (10 mL) and 30% aq H2SO4 (0.05 mL, 1.635 mmol) was added. The mixture was stirred for 15 min at r.t. whereupon a colorless solid precipitated. The solid was collected by filtration, washed with distilled H2O (5 mL), and dried under vacuum overnight to obtain the pure product 7a or 7b, respectively.

Spiroselenurane 15

Prepared from ethyl 4-hydroxybut-2-ynoate (13; 170 mg, 1.35 mmol) and SeCl4 (150 mg, 0.675 mmol) following the above procedure for the preparation of 10 and 11, with the exception that the mixture was stirred at r.t. for 18 h.

Yield: 8.2 mg (30%); yellow oil; Rf = 0.78 (hexane–EtOAc, 2:1).

1H NMR (CDCl3, 700 MHz): δ = 1.37 (t, J = 7 Hz, 6 H), 4.37 (ABq of q, J = 7, 11.2 Hz, 4 H), 5.33 (d, J = 17.5 Hz, 2 H), 5.68 (d, J = 17.5 Hz, 2 H).

13C NMR (CDCl3, 175 MHz, DMSO-d6): δ = 27.7 (CH2), 28.9 (CH2), 86.3 (CMe2), 124.8 (1/JSe = 132 Hz, =CSe), 141.8 (=C(Cl)).

Acknowledgment

This research was supported by The Israel Science Foundation (grant No 919-05). One of the authors (Y. K.) gratefully acknowledges The Israel Ministry of Science, Technology, and Space for a Ph.D. fellowship.

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(18) Crystallographic data for compounds 7a and 12 have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 956314 and CCDC 956315, respectively. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033.

