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Regio- and Stereoselective Synthesis of (Z,Z)-Bis(3-amino-3-oxo-1-propenyl) Selenides and Diselenides Based on 2-propynamides: A Novel Family of Diselenides with High Glutathione Peroxidase-like Activity

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Abstract: The efficient regio- and stereoselective syntheses of (Z,Z)-bis(3-amino-3-oxo-1-propenyl) selenides and diselenides in high yields based on the nucleophilic addition of sodium selenide to 2-propynamides and sodium diselenide to 3-(trimethylsilyl)-2-propynamides have been developed. The first examples of the addition of a selenium-centered nucleophile to 2-propynamides with a terminal triple bond and diselenide anion to 3-(trimethylsilyl)-2-propynamides have been carried out. Bis(3-amino-3-oxo-1-propenyl) diselenides are a novel family of compounds, none of which has yet been described in the literature. The glutathione peroxidase-like activity of the obtained compounds has been evaluated and products with high activity have been found. It was established that diselenides are superior to selenides with the same substituents in glutathione peroxidase-like activity. The results of the structural studying of products by single-crystal X-ray diffraction analysis and ^{77}Se-NMR data are discussed.

Keywords: divinyl diselenides; divinyl selenides; propynamides; glutathione peroxidase-like activity; selenium; sodium diselenide; sodium selenide

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1. Introduction

Interest in the chemistry of organoselenium compounds has increased significantly in the last few decades due to the discovery of a number of selenoenzymes involved in important physiological processes [1–5]. Selenoenzymes are an important family of mammalian antioxidant biocatalysts that protect cell membranes and other cellular components from oxidative stress. The discovery of the antioxidant enzyme glutathione peroxidase, which contains a selenocysteine fragment in its active site, has made an important contribution to the development of the biochemical role of selenium in the functioning of the mammalian organisms [5–12]. It is worthy to note that the 21st proteinogenic amino acid selenocysteine is the only metalloid-containing biomolecule encoded in human DNA [13].

Organic diselenides represent an important class of organoselenium compounds that are widely used in organic synthesis. Both the electrophilic selenium species and nucleophilic highly reactive selenolates can be generated from organic diselenides and are involved in a variety of further reactions [1–5,14–18] (Figure 1).

Organic diselenides often show glutathione peroxidase-like activity. It is known, for example, that diphenyl diselenide exhibits high glutathione peroxidase-like activity and is used as a standard compound in a series of investigations [19–22].

It is noteworthy that the presence of amide groups is usually very favorable for exhibiting glutathione peroxidase-like activity [1–5,20–24]. Examples of diselenides and organoselenium compounds, which contain amide groups and exhibit high glutathione

peroxidase-like activity, are shown in Figure 2 [20–24]. They include camphor-derived selenenamide [22] and selenazo compounds [25].

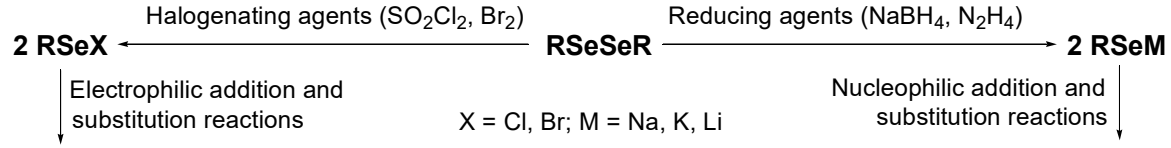


Figure 1. Generation of electrophilic selenium species and nucleophilic highly reactive selenolates from organic diselenides.

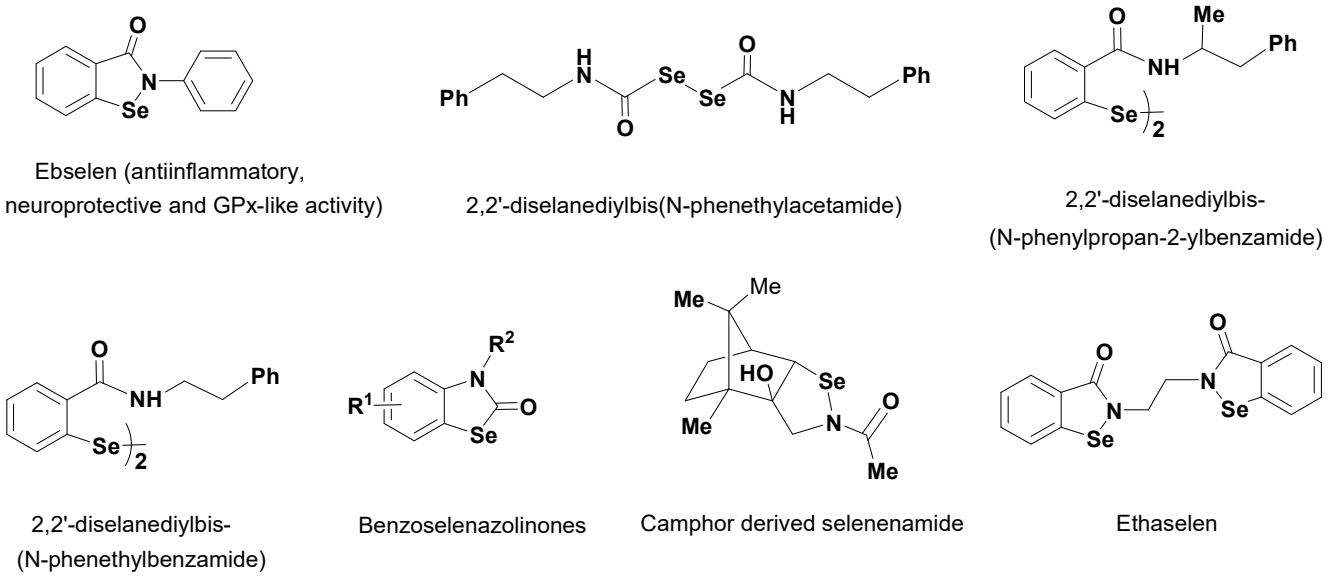


Figure 2. Organoselenium compounds including diselenides, contain amide groups and exhibit glutathione peroxidase-like activity.

Ebselen and its analogue ethaselen contain the selenenamide function in the cycle and exhibit high glutathione peroxidase mimetic properties. Moreover, ebselen shows anti-inflammatory and neuroprotective activity and is also used for the treatment and prevention of cardiovascular diseases and ischemic stroke [20–25]. This compound has found therapeutic application and has undergone evaluation in clinical trials as an anti-inflammatory agent.

Divinyl diselenides are a rare class of organoselenium compounds and there are scarce data in the literature on the synthesis and chemical properties of divinyl diselenides [26–30]. Unsubstituted divinyl diselenide was prepared in a 67% yield by the reaction of vinylmagnesium bromide with elemental selenium followed by oxidation of intermediate vinylselanylmagnesium bromide with bromine [26,27]. Vinyl selanylacetates were cleaved by sodium in HMPA or DMF to give vinyl selenolates, which were oxidized by iodine to yield divinyl diselenides with the retention of a configuration of starting vinylic compounds [28]. The insertion of elemental selenium into the Csp2-Zr bond of alkenylchlorozirconocenes, followed by oxidation in air, affords four divinyl diselenides in 67–75% yields [29].

The synthesis of divinyl selenides by electrophilic addition of selenium dihalides to acetylenes [30], including propargylic alcohols [31], was developed. In the case of the reaction of selenium dichloride with propargylic alcohols, it was noted that the preparation of divinyl selenides was accompanied by the formation of the corresponding divinyl diselenides in low yields as by-products. Two substituted bis[(*Z*)-2-chloro-1-(hydroxymethyl)ethenyl] diselenides were separated from their selenide counterpart by column chromatography. However, the authors of this work were unable to isolate other diselenides by chromatography and their contents were determined by ^{1}H-NMR analysis of the crude reaction

mixture [31]. The diselenide formation was explained by the addition reaction of selenium monochloride, Se_2Cl_2, which was formed via the disproportionation of selenium dichloride [31].

In the last few decades, vinylic selenides have been widely used in organic synthesis as starting materials and versatile intermediates. A number of valuable products have been obtained based on vinylic selenides [32–39]. A representative example is the synthesis of resveratrol and its methoxylated analogues—well-known compounds due to their anti-inflammatory, anticancer, antibacterial and neuroprotective activity [33]. Valuable (*Z*)- and (*E*)-enyne derivatives were obtained in good yields by the cross-coupling reactions of vinyl selenides with terminal alkynes with retention of a stereochemical configuration of starting vinylic selenides [34]. The Grignard reagents were involved in the cross-coupling reaction with vinyl selenides, giving corresponding functionalized alkenes [35].

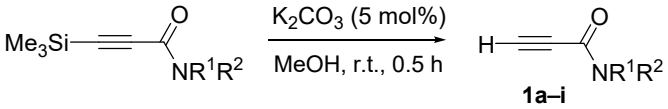
The most useful and atom-economic method for the preparation of vinyl selenides is the addition of selenium-centered nucleophiles to acetylenes [40–45]. The syntheses of unsubstituted divinyl selenide, alkyl vinyl selenides and various functionalized divinyl selenides by the addition reaction of selenide anion to the triple bond were developed in this institute with our participation [45–51].

Furthermore, 2-propynamides are very important reagents for organic synthesis and theoretically can be used for the preparation of vinyl selenides containing amide groups, by nucleophilic addition of selenium-centered nucleophiles to the triple bond. However, 2-propynamides with terminal triple bonds are rarely used in organic synthesis. These compounds are hard to obtain and they are not listed in the catalogs of leading chemical companies. Prior to our research, there were no examples of the addition of selenium-centered nucleophiles to propynamides with terminal triple bonds in the literature.

2. Results and Discussion

The goal of this work is to develop the regio- and stereoselective synthesis of (Z,Z)-bis(3-amino-3-oxo-1-propenyl) selenides and diselenides based on the nucleophilic addition of sodium selenide to 2-propynamides and sodium diselenide to 3-(trimethylsilyl)-2-propynamides.

2-Propynamides **1a–i** with the terminal triple bond were obtained in high yields by desilylation of 3-(trimethylsilyl)-2-propynamides under the action of potassium carbonate in methanol at room temperature (Scheme 1).



$R^1 = R^2 = H$ (**1a**); $R^1 = H$, $R^2 = Me$ (**1b**); $R^1 = H$, $R^2 = Ph$ (**1c**);

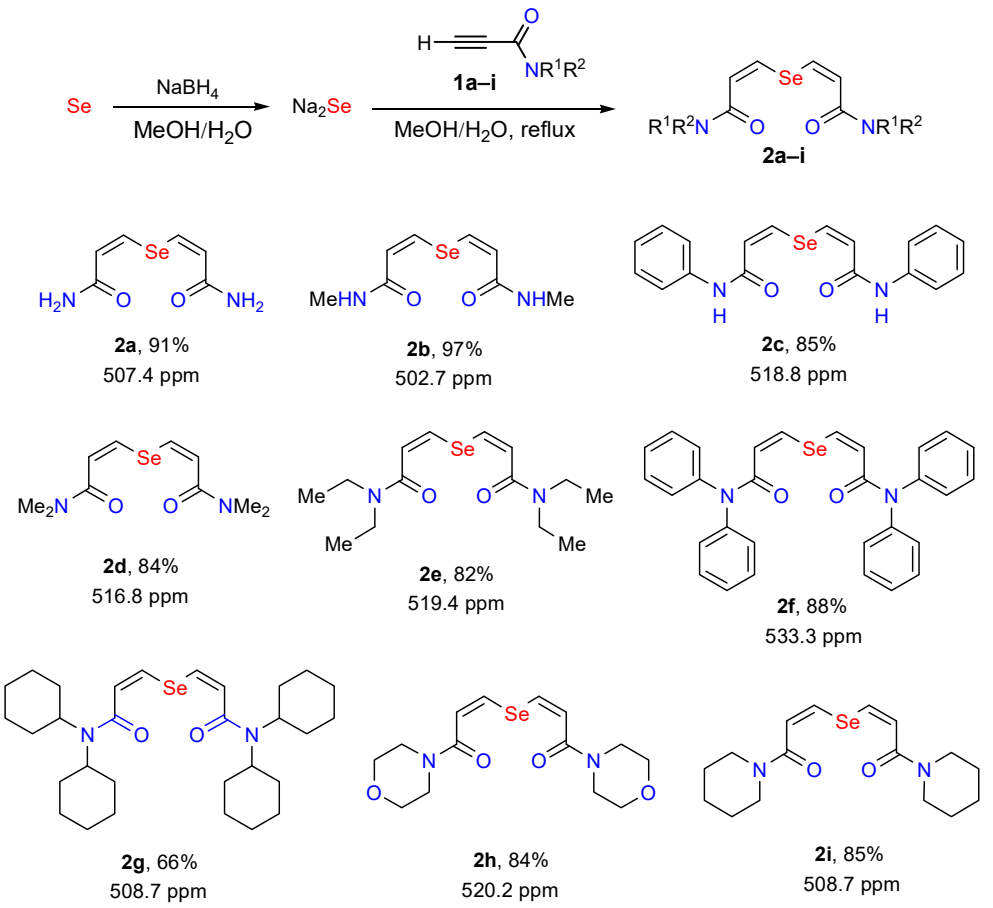
$R^1 = R^2 = Me$ (**1d**); $R^1 = R^2 = Et$ (**1e**); $R^1 = R^2 = Ph$ (**1f**);

$R^1 = R^2$ = c-Hex (**1g**); R^1NR^2 = morpholinyl (**1h**); R^1NR^2 = piperidyl (**1i**)

Scheme 1. Synthesis of 2-propynamides **1a–i** by desilylation of 3-(trimethylsilyl)-2-propynamides.

An efficient and convenient method for the preparation of 3-(trimethylsilyl)-2- propynamides based on propargyl alcohol was previously developed at this institute [52–54] and opened up the possibility of using these reagents in organic synthesis [55–58].

It is noteworthy that one of products **1a–i**, *N*,*N*-dicyclohexyl-2-propynamide **1g** has not been previously described in the literature. The obtained 2-propynamides **1a–i** was used in the synthesis of (Z,Z)-bis(3-amino-3-oxo-1-propenyl) selenides **2a–i**. Reaction conditions, which allowed the process to take place in a regio- and stereoselective manner, giving the target products in high yields, were developed (Scheme 2).



Scheme 2. Regio- and stereoselective synthesis of divinyl selenides **2a**–**i** from 2-propynamides **1a**–**i** and ^{77}Se-NMR data.

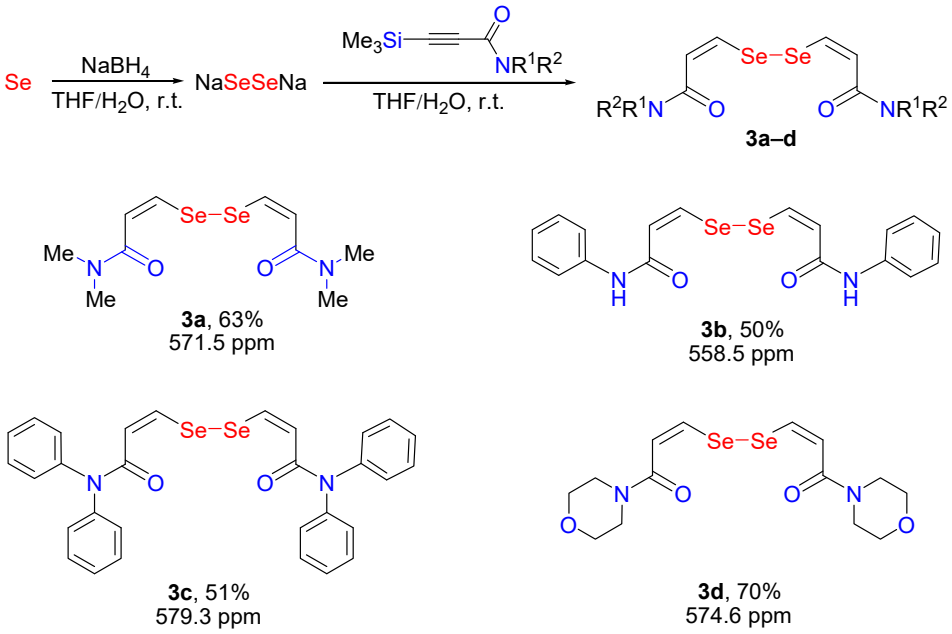
It was found that favorable conditions for the synthesis of selenides **2a**–**i** include the generation of sodium selenide by the action of sodium borohydride on elemental selenium in water on heating (the temperature of the water bath is 80–85 °C), followed by the addition of a solution of 2-propynamides **1a**–**i** in methanol. The reaction mixture was refluxed for 30 min and the target products were isolated in up to 97% yields after extraction. The synthetic procedure is very convenient and efficient and the reaction conditions include the use of green solvents, such as water and methanol. The synthesis of selenides **2a**–**i** represents the first example of the addition of selenium-centered nucleophiles to 2-propynamides with a terminal triple bond.

The synthesis of (Z,Z)-bis(3-amino-3-oxo-1-propenyl) diselenides has not yet been described in the literature. We devoted our efforts to synthesizing the first representatives of this family of compounds based on elemental selenium and alkynes containing the amide group. We found that diselenides **3a**–**d** can be obtained in a 50–70% yield by the nucleophilic addition of diselenide anion to 3-(trimethylsilyl)-2-propynamides, avoiding the stage of desilylation of the latter compounds (Scheme 3).

The nucleophilic addition of diselenide anion to 3-(trimethylsilyl)-2-propynamides was accompanied by desilylation, which occurred in situ under these conditions. Diselenides **3a**–**d** are a novel family of organoselenium compounds.

Some conclusions can be drawn regarding the ^{77}Se-NMR spectral data of selenides **2a**–**i** and diselenides **3a**–**d**. The introduction of the phenyl substituents to the amide group of selenides led to a downfield shift (compounds **2a**, **2c**, and **2f**), whereas the introduction of the cyclohexyl groups does not have a noticeable effect on the chemical shift (compounds **2a** and **2g**). Replacing one carbon atom with an electronegative oxygen atom in the piperidine cycle led to a downfield shift (compounds **2i** and **2h**). Comparing the diselenides **3a**–**d** and

selenides **2c**,**d**,**f**,**h** bearing the same substituents, we can conclude that the selenium atom in diselenides **3a**–**d** resonates in the downfield region (there is an approximately 40–60 ppm difference in the chemical shifts of diselenides **3a**–**d** and selenides **2c**,**d**,**f**,**h**).



Scheme 3. Regio- and stereoselective synthesis of divinyl diselenides **3a**–**d** from 3-(trimethylsilyl)-2-propynamides and ^{77}Se-NMR data.

The structures of four products, **2a**, **2d**, **2f**, and **2i**, were studied by single-crystal X-ray diffraction analysis (Figures 3–10). The amide molecule **2a** is characterized by the presence of *C2* symmetry, the axis passes through the Se atom. However, the C–Se bond lengths in the molecule are slightly different and there is one molecule in the independent part of the cell. The same is typical for the molecules of amides **2d**, **2f**, and **2i**.

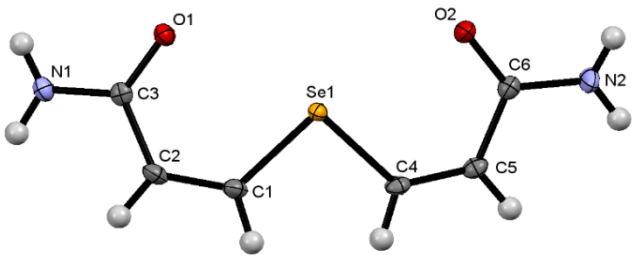


Figure 3. Molecular structure of compound **2a** (ORTEP, 50% probability ellipsoids).

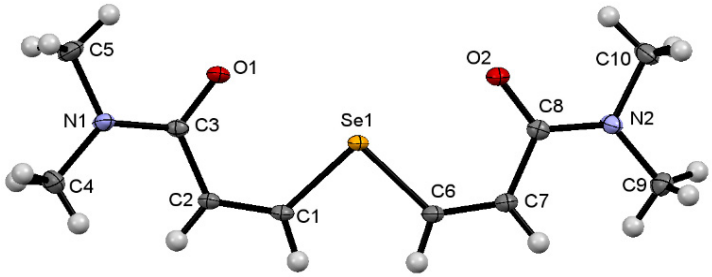


Figure 4. Molecular structure of compound **2d** (ORTEP, 50% probability ellipsoids).

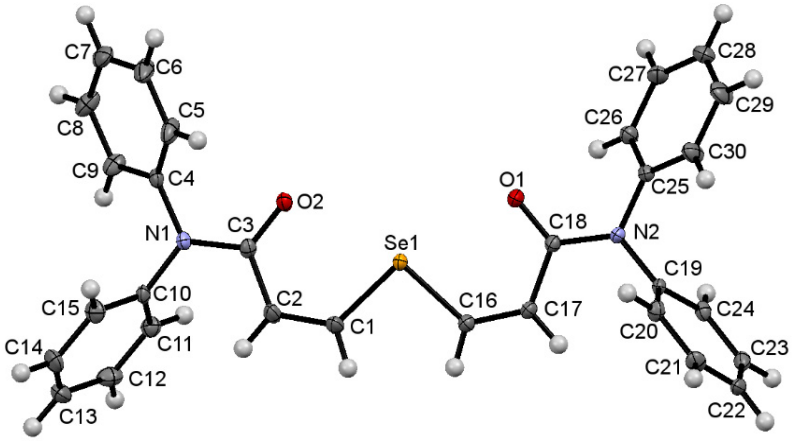


Figure 5. Molecular structure of compound **2f** (ORTEP, 50% probability ellipsoids).

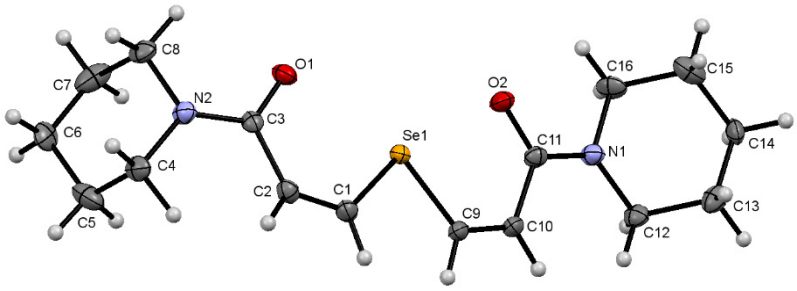


Figure 6. Molecular structure of compound **2i** (ORTEP, 50% probability ellipsoids).

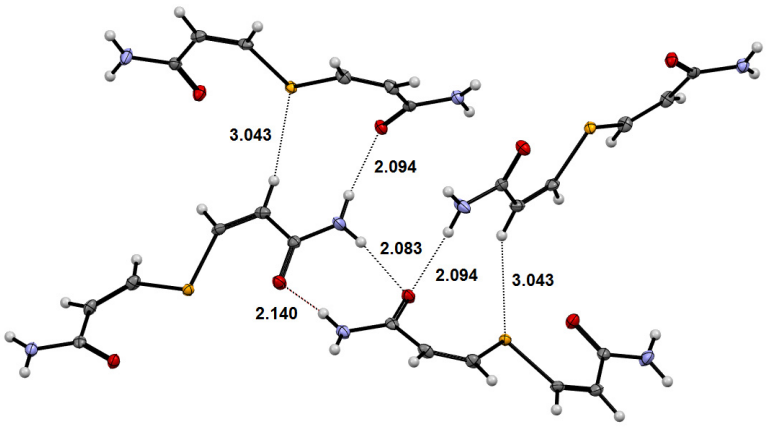


Figure 7. Intermolecular hydrogen bonds NH···O=C in the crystal of amide **2a**.

The C–Se–C angles in compounds **2a**, **2d**, **2f**, and **2i** represent a 'V'-shaped configuration around the selenium atom. The values of the C–Se–C angle in compounds **2a**, **2d**, **2f**, and **2i** are approximately 92–95°, which are close to the value of this angle in other structures containing the C–Se–C fragment [59–63]. The Se–C bond lengths are 1.892–1.900 Å, which are slightly shorter than in previously described molecules [59–63] (1.930–1.940 Å). Such differences are obviously related to the different temperature conditions of the XRD experiment: amides **2a**, **2d**, **2f**, and **2i** were analyzed at the temperature of 100 K, while the known structures [59–63] were determined at room temperature. The Se–C bond length can vary from 1.850–1.920 Å, even in one molecule [62], which is determined by the electronegative properties of substituents at carbon atoms.

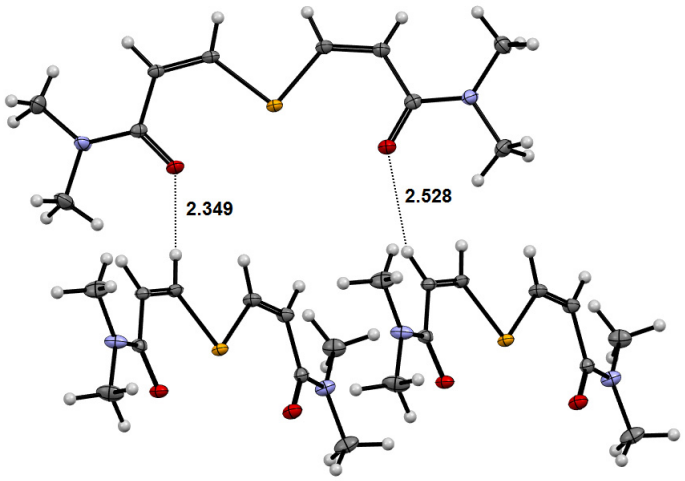


Figure 8. Short CH···O=C contacts in the crystal of compound **2d**.

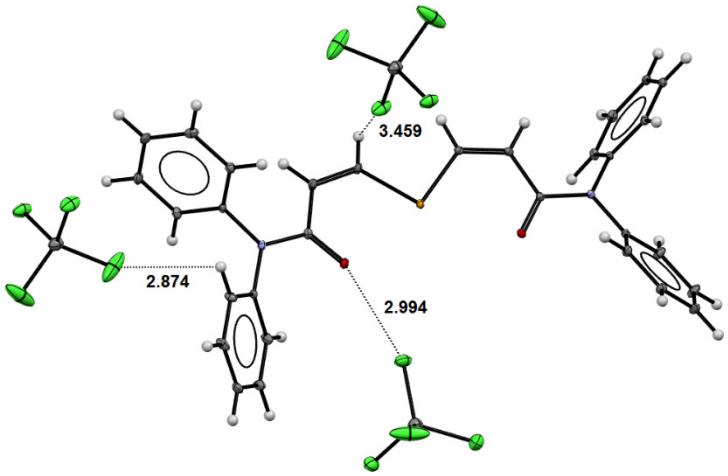


Figure 9. The CH···Cl bonds in the co-crystal of compound **2f** with CCl_4.

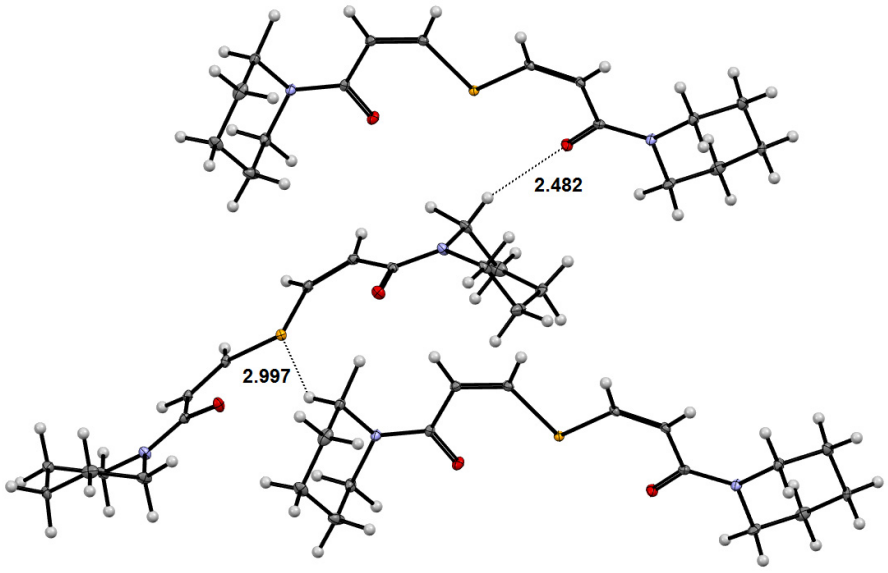


Figure 10. Short CH···O=C and CH···Se contacts in the crystal of compound **2i**.

Molecules of compounds **2a** and **2i** crystallize in the orthorhombic system, space group $P2_12_12_1$, and amides **2d** and **2f** crystallize in the monoclinic system, space group $P2_1/n$ (Figures 3–6).

The crystal structure of compound **2a** is formed due to intermolecular hydrogen bonds NH···O=C with a length of 2.083–2.140 Å (Figure 7), as well as due to short contacts between the unshared electron pair of the selenium atom and the hydrogen atoms of the CH groups of neighboring molecules (3.043 Å). The molecules of amide **2d** in the crystal are interconnected by short CH···O=C contacts approximately 2.3–2.5 Å long (Figure 8).

In contrast to amides **2a**, **2d**, and **2i**, compound **2f**, due to bulky phenyl substituents in the crystal, forms significant voids into which solvent molecules, carbon tetrachloride, are embedded. The crystal structure of such a co-crystal is stabilized by the CH···Cl bonds with solvent molecules ~2.9–3.4 Å long (Figure 9). The crystal structure of compound **2i** is formed due to short contacts CH···O=C and CH···Se (Figure 10).

The presence of amide groups is favorable for exhibiting glutathione peroxidase-like activity [1–5,20–24], and we evaluated this activity for a novel family of organoselenium compounds, diselenides **3a–d**, in comparison with that of selenides **2c**, **2d**, **2f**, and **2h** with the same substituents. The known model reaction of oxidation of phenylmethanethiol by *tert*-butyl hydroperoxide (TBHP) in the presence of the obtained products as catalysts was used, and the progress of this reaction was monitored by ^{1}H NMR spectroscopy [19–23].

It was found that diselenides **3a–d** are superior to analogous selenides **2c**, **2d**, **2f**, and **2h** with the same substituents in glutathione peroxidase-like activity. Diselenide **3d**, containing two morpholine substituents in the amide group, shows the highest glutathione peroxidase-like properties (Figure 11). This compound is superior to other diselenides **3a–c** and selenides **2c**, **2d**, **2f**, and **2h** in activity. To the best of our knowledge, diselenide **3d** is one of the most effective known reagents with glutathione peroxidase-like activity. The second most active product is compound **3c,** bearing four phenyl groups. Compound **3a**, containing four methyl groups, is inferior to diselenides **3b–d**, however, diselenide **3a** surpasses selenide **2d** with the same substituents in activity. When comparing diselenides **3a–c**, the tendency of increasing activity with an increasing number of carbon atoms in the amide moiety is observed.

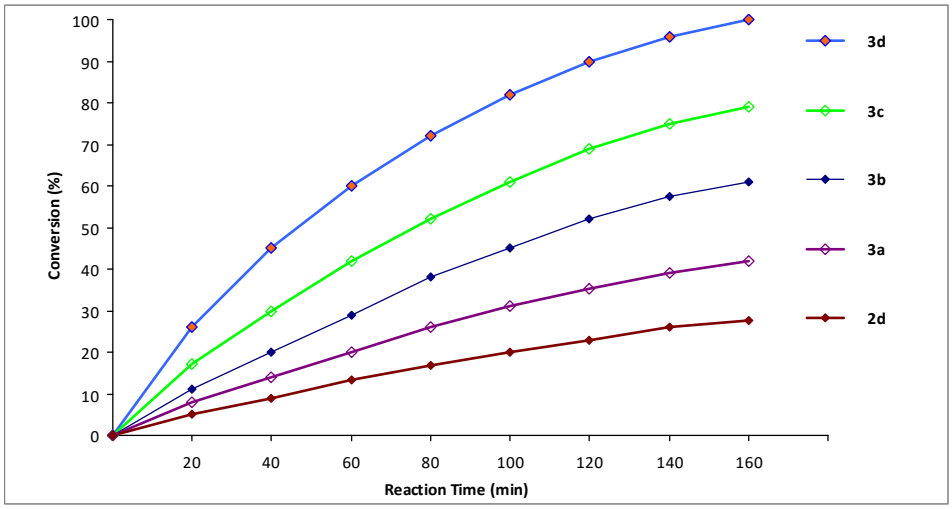


Figure 11. Studying glutathione peroxidase-like activity of compounds **3a–d** and **2d** (TBHP, BnSH, 0.1 mmol, deuterochloroform/CD_3OD = 95/5, 0.5% mol of compounds **3a–d** and **2d**) by ^{1}H-NMR monitoring.

3. Materials and Methods

3.1. General Information

The ^{1}H (400.1 MHz), ^{13}C (100.6 MHz), ^{77}Se (76.3 MHz), and ^{15}N (40.6 MHz) NMR spectra (the spectra can be found in Supplementary Materials) were recorded on a Bruker DPX-400 spectrometer (Bruker BioSpin GmbH, Rheinstetten, Germany) in $CDCl_3$ or DMSO-d_6 5–10% solutions and referred to TMS (^{1}H, ^{13}C), nitromethane (^{15}N) and dimethyl selenide (^{77}Se).

Elemental analysis was performed on a Thermo Scientific Flash 2000 Elemental Analyzer. Melting points were determined on the Kofler apparatus. The organic solvents were dried and distilled according to standard procedures.

Crystal data were collected on a Bruker D8 Venture diffractometer with MoKa radiation (λ = 0.71073) using the φ and ω scans. The structures were solved and refined by direct methods using the SHELX program set [64]. Data were corrected for the absorption effects using the multi-scan method (SADABS). Non-hydrogen atoms were refined anisotropically using the SHELX program set [64]. The Supplementary Materials contain the crystallographic data for compounds CCDC 1,834,087 (**2a**), 1,834,088 (**2d**), 1,834,089 (**2f**) and 1,841,340 (**2i**). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif (accessed on 5 May 2022).

3.2. General Procedure for Synthesis of 2-propynamides **1a–i**

A mixture of 3-trimethylsilyl-2-propynamide (0.48 mmol) and 3.5 mg K_2CO_3 (5 mol%) in MeOH (3.0 mL) was stirred for 0.5 h at room temperature. Then, a solution of 5% HCl (2 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 7 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure, giving products **2a–i**.

N,N-Dicyclohexyl-2-propynamide **1g**. Yield: 103 mg (92%); beige powder; mp 125–127 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.03–1.94 (m, 18H, CH_2), 2.26–2.34 (m, 2H, CH_2), 3.02 (s, 1H, HC≡), 3.10–3.17 (m, 1H, CH), 4.09–4.15 (m, 1H, CH). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 25.1 (CH_2), 25.9 (CH_2), 26.3 (CH_2), 29.5 (CH_2), 31.3 (CH_2), 55.6 (CH), 59.4 (CH), 77.3 (≡CCO), 77.4 (HC≡), 152.6 (C=O).

Anal. calcd for $C_{15}H_{23}NO$ (233.35): C 77.21, H 9.93, N 6.00; found: C 77.17, H 10.05, N 5.91.

3.3. General Procedure for Synthesis of (Z,Z)-bis(3-amino-3-oxo-1-propenyl) Selenides **2a–i**

A mixture of powdered metallic selenium (19 mg, 0.24 mmol) and water (2.0 mL) was heated (the temperature of the water bath was 80–85 °C) and a solution of $NaBH_4$ (28 mg, 0.74 mmol) in water (0.4 mL) was added dropwise under argon. After the dissolution of selenium and forming a colorless solution, a solution of 2-propynamide **1a–i** (0.48 mmol) in MeOH (2.0 mL or 5.0 mL for compounds **1f**,**g**) was added to a hot aqueous solution of sodium selenide. The reaction mixture was refluxed for 30 min on the water bath and cooled with cold water. The mixture was extracted with CH_2Cl_2 (3 × 7 mL) and the organic phase was dried over Na_2SO_4. The solvent was removed under reduced pressure, giving the products **2a–i**. Spectral data for the products **2a–i**, including X-ray analysis data, are given in the Supplementary Materials.

3.4. General Procedure for Synthesis of (Z,Z)-bis(3-amino-3-oxo-1-propenyl) Diselenides **3a–d**

$NaBH_4$ (17 mg, 0.44 mmol) was added portion-wise to a mixture of powdered metallic selenium (34 mg, 0.44 mmol), water (1.0 mL) and THF (5 mL) under argon with stirring. The mixture was stirred at room temperature for 1 h and corresponding 3-trimethylsilyl-2-propynamide (0.44 mmol) was added. The mixture was stirred at room temperature for 5 h and THF was removed by a rotary evaporator. The residue was diluted with water (1.0 mL) and extracted with $CHCl_3$ (3 × 7 mL) and the organic phase was dried over Na_2SO_4. The solvent was removed under reduced pressure, giving diselenides **3a–d**.

(Z,Z)-Bis(N,N-dimethyl-3-amino-3-oxo-1-propenyl) diselenide **3a**. Yield: 63%, yellowish solid; mp 128–130 °C. The pure sample was obtained by dissolving the residue in THF and precipitating by the addition of CCl_4.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.01 (s, 6H, CH_3),, 3.06 (s, 6H, CH_3), 6.61 (d, ^3J = 8.9 Hz, 2H, =CHCO), 7.97 (d, ^3J = 8.9 Hz, 2H, SeCH=). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 35.6, 37.3 (CH_3), 115.7 (=CCO), 151.3 (SeC=, $^1J_{Se-C}$ = 146.1 Hz), 167.7 (C=O). ^{77}Se-NMR (76 MHz, $CDCl_3$): δ 571.5. ^{15}N-NMR (40 MHz, $CDCl_3$): δ –279.9. The 2D ^{15}N-NMR HMBC {^{1}H–

^{15}N} spectrum contains cross-peaks of the nitrogen atom with protons of the CH_3 and =CHCO groups.

Anal. calcd for $C_{10}H_{16}N_2O_2Se_2$ (354.17): C 33.91, H 4.55, N 7.91, Se 44.59; found: C 33.84, H 4.52, N 8.02, Se 44.48.

(Z,Z)-Bis(N-phenyl-3-amino-3-oxo-1-propenyl) diselenide **3b**. Yield: 50%, yellow solid; mp 202–203 °C. The pure sample was obtained by dissolving the residue in THF and precipitating by the addition of CCl_4.

^{1}H-NMR (400 MHz, d_6-DMSO): δ 6.59 (d, ^3J = 8.9 Hz, 2H, =CHCO), 7.08 (t, ^3J = 7.8 Hz, 2H, H^p), 7.33 (dd, ^3J = 7.8 Hz, 4H, H^m), 7.63 (d, ^3J = 7.8 Hz, 4H, H^o), 8.01 (d, ^3J = 8.9 Hz, 2H, SeCH=) 10.36 (s, 2H, NH). ^{13}C-NMR (100 MHz, d_6-DMSO): δ 119.2 (=C̲CO), 121.0 (C^o), 123.7 (C^p), 128.9 (C^m), 138.8 (C^i), 148.3 (SeC=, $^1J_{Se–C}$ = 144.2 Hz), 165.2 (C=O). ^{77}Se-NMR (76 MHz, d_6-DMSO): δ 558.5. ^{15}N-NMR (40 MHz, d_6-DMSO): δ –243.7 ($^1J_{N–H}$ = 88.7 Hz). The 2D ^{15}N-NMR HMBC {^{1}H–^{15}N} spectrum contains cross-peaks of the nitrogen atom with H^m, H^o and NH protons.

Anal. calcd for $C_{18}H_{16}N_2O_2Se_2$ (450.25): C 48.02, H 3.58, N 6.22, Se 35.07; found: C 48.00, H 3.44, N 6.01, Se 35.31.

(Z,Z)-Bis(N,N-diphenyl-3-amino-3-oxo-1-propenyl) diselenide **3c**. Yield: 51%, yellow solid; mp 197–198 °C. The pure sample was obtained by dissolving the residue in dichloromethane and precipitating by the addition of cold hexane.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.26 (d, ^3J = 9.1 Hz, 2H, =CHCO), 7.17–7.30 (m, 12H, H^{o,p}), 7.30–7.44 (m, 8H, H^m), 7.99 (d, ^3J = 9.1 Hz, 2H, SeCH=). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 118.3 (=C̲CO), 125.1–130.6 (C^{o,p,m}), 142.1 (C^i), 152.3 (SeC=, $^1J_{Se–C}$ = 148.2 Hz), 167.2 (C=O). ^{77}Se-NMR (76 MHz, $CDCl_3$): δ 579.3.

Anal. calcd for $C_{30}H_{24}N_2O_2Se_2$ (602.44): C 59.81, H 4.02, N 4.65, Se 26.21; found: C 59.91, H 4.05, N 4.59, Se 26.09.

(Z,Z)-Bis(3-morpholino-3-oxo-1-propenyl) diselenide **3d**. Yield: 70%, yellow solid; mp 193–195 °C. The pure sample was obtained by dissolving the residue in chloroform and precipitating by the addition of cold ether.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.46–3.61 (m, 4H, NCH_2), 3.62–3.79 (m, 12H, NCH_2, OCH_2), 6.61 (d, ^3J = 9.1 Hz, 2H, =CHCO), 8.07 (d, ^3J = 9.1 Hz, 2H, SeCH=). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 42.3, 46.1 (NCH_2), 66.8 (OCH_2), 114.7 (=C̲CO), 152.7 (SeC=, $^1J_{Se–C}$ = 147.4 Hz), 166.5 (C=O). ^{77}Se-NMR (76 MHz, $CDCl_3$): δ 574.6. ^{15}N-NMR (40 MHz, $CDCl_3$): δ –264.7. The 2D ^{15}N-NMR HMBC {^{1}H–^{15}N} spectrum contains cross-peaks of the nitrogen atom with proton of the =CHCO group.

Anal. calcd for $C_{14}H_{20}N_2O_4Se_2$ (438.24): C 38.37, H 4.60, N 6.39, Se 36.04; found: C 38.34, H 4.50, N 6.32, Se 35.80.

4. Conclusions

With the goal to obtain previously unknown divinyl diselenides, containing amide groups, the reaction of sodium diselenide with 3-trimethylsilyl-2-propynamides was studied and the conditions for regio- and stereoselective addition were found. The reaction proceeded in a THF-water system at room temperature and was accompanied by desilylation.

The efficient regio- and stereoselective syntheses of (Z,Z)-bis(3-amino-3-oxo-1-propenyl) selenides **2a–i** in up to 97% yields based on the nucleophilic addition of sodium selenide to 2-propynamides were developed. These are the first examples of the addition of a selenium-centered nucleophile to 2-propynamides with a terminal triple bond. The glutathione peroxidase-like activity of the obtained compounds was evaluated and the activity of selenides and diselenides was compared. It was found that diselenides **3a–d** are superior to the analogous selenides **2c**, **2d**, **2f**, and **2h** with the same substituents in glutathione peroxidase-like activity. Diselenide **3d**, containing two morpholine substituents in the amide group, shows the highest glutathione peroxidase-like properties. To the best of our knowledge, diselenide **3d** is one of the most effective known reagents with glutathione peroxidase-like activity. When comparing diselenides **3a–c**, the tendency of increasing activity with an increase in the number of carbon atoms in the amide moiety is observed.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/inorganics10060074/s1, Spectral data for the products **2a–i**, including X-ray analysis data and examples of NMR spectra of the obtained compounds.

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