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# Triple-Click Chemistry of Selenium Dihalides: Catalytic Regioselective and Highly Efficient Synthesis of Bis-1,2,3-Triazole Derivatives of 9-Selenabicyclo[3.3.1]nonane

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**Abstract:** The catalytic regioselective and highly efficient synthesis of bis-1,2,3-triazole derivatives of 9-selenabicyclo[3.3.1]nonane was developed. The 1,3-dipolar cycloaddition reaction of 2,6-diazido-9-selenabicyclo[3.3.1]nonane with a variety of terminal acetylenes catalyzed by a copper acetate/sodium ascorbate system proceeded in a regioselective fashion, affording 2,6-bis(4-organyl-1,2,3-triazole)-9-selenabicyclo[3.3.1]nonanes in high yields (93–98%). The reaction of 2,6-diazido-9-selenabicyclo[3.3.1]nonane with dimethyl and diethyl acetylenedicarboxylates was carried out as thermal 1,3-dipolar Huisgen cycloaddition giving the corresponding 4,5-disubstituted 1,2,3-triazole derivatives of 9-selenabicyclo[3.3.1]nonane in high yields. The obtained products are potentially bioactive compounds and first representatives of selenium heterocycles combined with two 1,2,3-triazole moieties. 2.6-Diazido-9-selenabicyclo[3.3.1]nonane was obtained in quantitative yield via the reaction of sodium azide with 2,6-dibromo-9-selenabicyclo[3.3.1]nonane at room temperature. The latter compound was synthesized by stereoselective transannular addition of selenium dibromide to cis, cis-1,5-cyclooctadiene.

**Keywords:** acetylenes; 1,3-dipolar cycloaddition; 9-selenabicyclo[3.3.1]nonane derivatives; copper-catalyzed reactions; regioselective synthesis



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## 1. Introduction

Heterocycles can be regarded as the most common and important structural components of pharmaceuticals [1]. Nitrogen heterocycles are integral parts of the vast majority of modern widely used drugs [2], and 1,2,3-trizoles are among the most useful heterocyclic scaffolds for pharmaceutical application [3–5].

Compounds containing the 1,2,3-trizole moiety exhibit a variety of biological activities: antifungal, anticancer, antivirus (including anti-HIV), antibacterial, antihypertensive, antimalarial, anti-tubercular, and hypocholesterolemic activities; they also show properties of NMDA receptor antagonists, VEGF receptor tyrosine kinase inhibitors, and α-glucosidase inhibitors [3–20]. Some examples of 1,2,3-trizoles with biological activity are presented in Figure 1.

Some potential pharmaceuticals based on 1,2,3-triazoles (the cephalosporine Cefatrizine, β-lactum antibiotic Tazobactum, anticancer compound carboxyamidotriazole and the non-nucloside reverse transcriptase inhibitor tert-butyldimethylsilylspiroaminooxathiol edioxide) are undergoing clinical trials [3].

Since the discovery of the copper-catalyzed 1,3-dipolar cycloadditions of azides to alkynes independently by Sharpless et al. [20] and Meldal et al. [21], research on the synthesis and application of 1,4-substituted 1,2,3-triazoles has been intensively developed. The reaction is termed the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC). This reaction represents one example of click chemistry, a term introduced in 2001 by Sharpless [22]. The modified CuAAC version of this reaction is completely regioselective and provides

only one regioisomer in contrast with the mixture of regioisomers usually obtained under classical thermal conditions [23]. The application of this methodology has made great contribution to the fields of drug discovery, pharmaceutical chemistry, polymer chemistry, medicinal, biological and materials sciences [24–27].

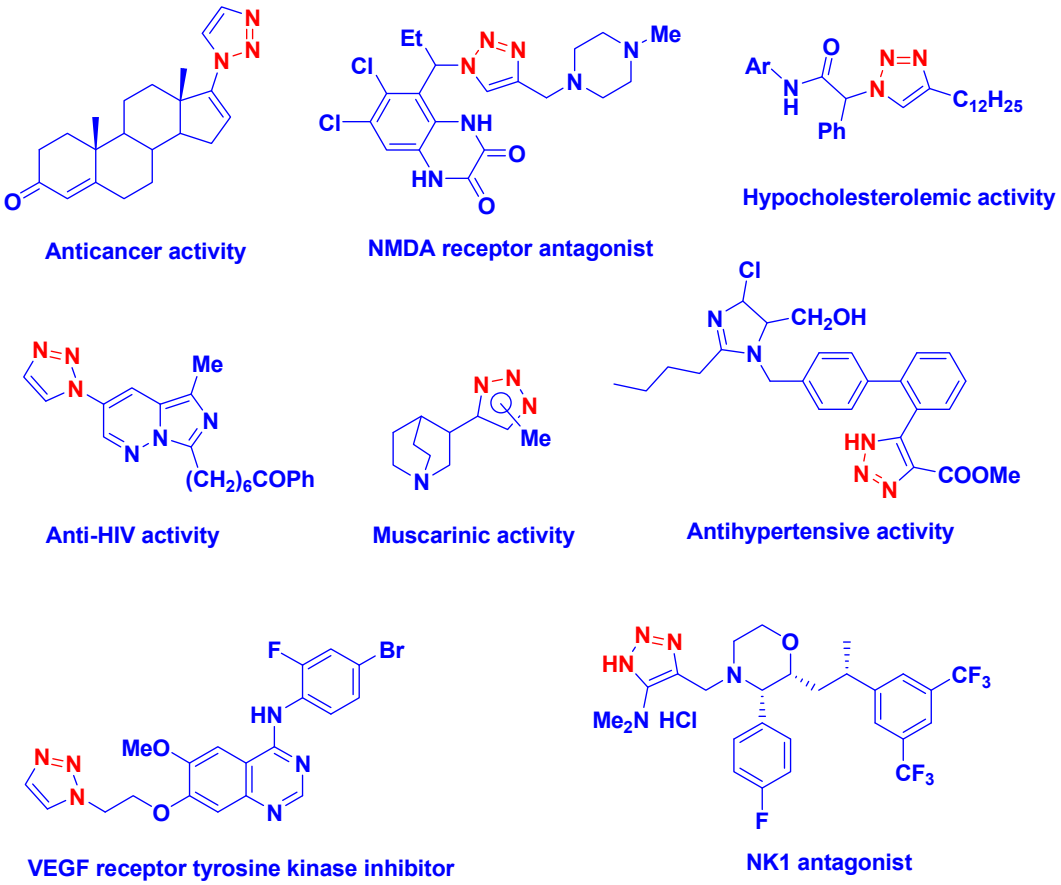



**Figure 1.** Examples of 1,2,3-trizoles with biological activity.

Recent publications and comprehensive reviews discussed different aspects of the CuAAC reactions [28–35] including reaction conditions, catalytic systems, ligands, mechanistic features and the nature of the Cu-intermediates [28], recoverable and recyclable catalytic systems [29], and systems under continuous flow conditions [30]. The catalytic Cu(I) species may either be introduced as preformed complexes, or otherwise generated in situ from various copper sources. Although some reactions can be carried out using usual copper(I) sources such as copper iodide or copper bromide, the CuAAC process often proceeds much better using a mixture of copper(II) salt and a reducing agent for in situ generation of Cu(I) intermediates [31]. Many modifications to this Cu-based protocol were developed by using copper(II) acetate/sodium ascorbate, CuI/$Et_3N$, $CuSO_4$/sodium ascorbate, Cu(II) salts/Cu wire, CuI/sodium ascorbate, ionic liquids, polymers as copper support, or alternative energy sources, such as microwave or ultrasounds irradiation [28–35].

Organoselenium chemistry began to develop rapidly after the discovery of the important biological role of selenium [36]. Currently, selenium is recognized as an essential micronutrient and organoselenium compounds, especially selenium heterocycles, exhibit various types of biological activity including antibacterial, antifungal, anti-inflammatory, antitumor, antiviral, antiproliferative and glutathione peroxidase-like properties [37–53]. Ebselen was used the cardiovascular disease treatment, as well as for prevention of ischemic stroke and overcoming acute stroke [42–44]. This selenium heterocycle is a novel anti-inflammatory drug with neuroprotective and glutathione peroxidase-like effects. Ebse-

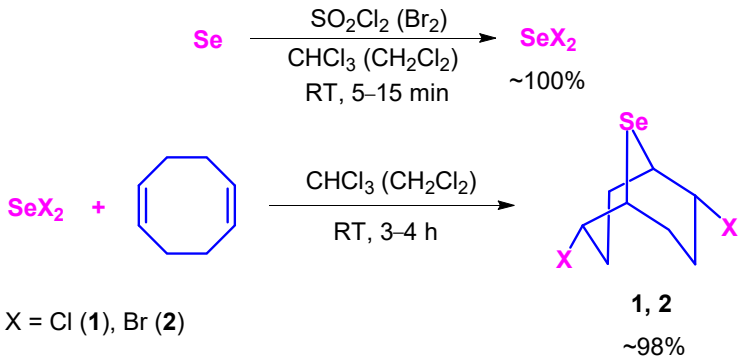
len has been also found to inhibit CoV2 activity and viral replication, and this drug has recently been in clinical trials in COVID-19 patients [42–44].

To date, a number of works on the synthesis of selenium-containing 1,2,3-triazole derivatives have been described in the literature. These works include cycloadditions of azides and selenium-containing acetylenes [54,55], reactions of selenium-containing azides to alkynes [56,57], and introduction of elemental selenium into the 1,2,3-triazole system [58,59]. The three-component reaction of ribosyl azides, terminal alkynes, and phenylselanyl bromide in the presence of CuI and N, N-diisopropylethylamine should be noted [60]. The interesting reaction of benzyl azide, terminal alkynes, and phenylselanyl benzenesulfonate in the presence of CuI and t-BuOLi has been carried out [61]. It is important that 5-arylselanyl-1,2,3-triazoles exhibit anticancer activity [54].

One of the most important trends of the last years in the field of organoselenium chemistry is the widespread development of novel electrophilic reagents, selenium dihalides: selenium dichloride and selenium dibromide, in the synthesis of organoselenium compounds [53,62–71]. We were the first to use selenium dihalides in the synthesis of organoselenium compounds, including selenium heterocycles, by annulation, transannular addition, cyclization, annulation-methoxylation and selenocyclofunctionalization reactions; these electrophilic reagents demonstrated high efficiency and selectivity [66–71].

The synthesis of various derivatives of 9-thiabicyclo[3.3.1]nonane based on 2,6-dichloro-9-thiabicyclo[3.3.1]nonane was developed by Sharpless [72,73], one of the founders of click chemistry, and his colleague Finn [72–74]. They considered 2,6-dichloro-9-thiabicyclo[3.3.1]nonane as a click chemistry reagent and a starting compound for the preparation of products with biological activity. This includes fragmentable oligocationic materials, which can be used for drug delivery or gene delivery into cells [74].

We synthesized selenium analogs of 2,6-dichloro-9-thiabicyclo[3.3.1]nonane, 2,6-dichloro-9-selenabicyclo[3.3.1]nonane (**1**) and 2,6-dibromo-9-selenabicyclo[3.3.1]nonane (**2**) via the transannular addition of selenium dichloride to cis,cis-1,5-cyclooctadiene (Scheme 1) [75,76]. These compounds, as well as 2,6-dichloro-9-thiabicyclo[3.3.1]nonane, were used in joint studies of anchimeric assistance with Finn's group. The anchimeric assistance effect of the selenium and sulfur atoms was quantitatively estimated based on of the rates of nucleophilic substitution reactions in 2,6-dichloro-9-thia- and -9-selenabicyclo[3.3.1]nonanes. It was found that the anchimeric assistance effect of the selenium atom is about two orders of magnitude higher than the anchimeric assistance effect of the sulfur atom [76]. Thus, compounds **1** and **2** are substantially more reactive in nucleophilic substitution reactions compared to 2,6-dichloro-9-thiabicyclo[3.3.1]nonane, and can be considered as click chemistry reagents.



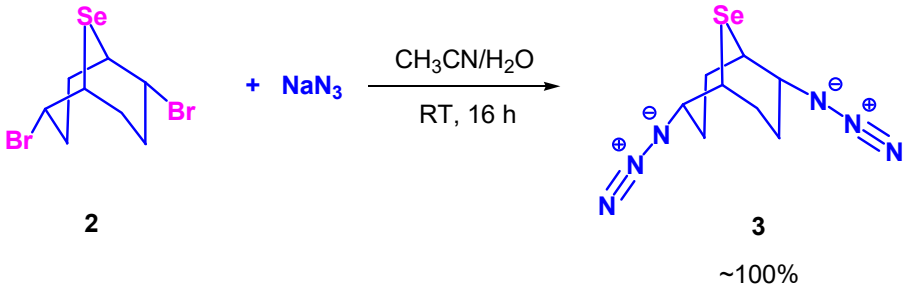

**Scheme 1.** The synthesis of 2,6-dichloro- and 2,6-dibromo-9-selenabicyclo[3.3.1]nonane **1** and **2**.

Selenabicyclo[3.3.1]nonane **2** was used as a starting compound in the present research on synthesis of bis-1,2,3-triazole derivatives of 9-selenabicyclo[3.3.1]nonane based on catalytic 1,3-dipolar cycloaddition reactions.

## 2. Results and Discussion

The aim of this work is to develop the efficient regioselective synthesis of novel functionalized 9-selenabicyclo[3.3.1]nonane derivatives, containing two triazole heterocycles, based on cycloaddition reaction of 2,6-diazido-9-selenabicyclo[3.3.1]nonane (**3**) with various acetylenes.

Diazido derivative **3** was obtained in quantitative yield by the nucleophilic substitution reaction of 2,6-dibromo-9-selenabicyclo[3.3.1]nonane (**2**) with sodium azide (Scheme 2). This is the second step (the second efficient "click") of the triple-click chemistry of selenium dihalides.




**Scheme 2.** Synthesis of 2,6-diazido-9-selenabicyclo[3.3.1]nonane (**3**) by the nucleophilic substitution reaction of 2,6-dibromo-9-selenabicyclo[3.3.1]nonane (**2**) with sodium azide.

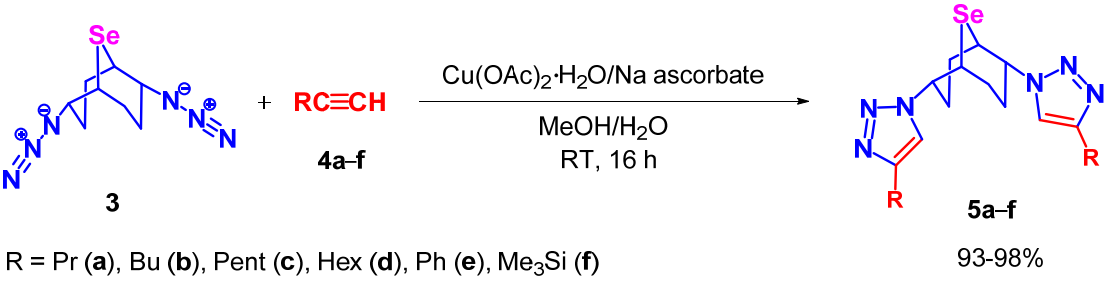
It was found that the reaction of dibromo derivative **2** with sodium azide proceeded efficiently in a mixture of acetonitrile and water, and the excess of sodium azide was necessary to use. A solution of sodium azide was added dropwise to a mixture of compound **2** and acetonitrile (20 mL), with stirring at room temperature, and the reaction mixture was stirred overnight at room temperature. After removing acetonitrile by a rotary evaporator, the residue was extracted with methylene chloride. Pure product **3** in quantitative yield was obtained by removing methylene chloride from the extract, and drying the residue under a vacuum. It is important that the product **3** did not require additional purification.

Compound **3** was also obtained in 91% yield from dichloro derivative **1** and sodium azide under similar conditions.

The prepared diazido derivative **3** was used in cycloaddition reactions with various acetylenes: 1-pentyne (**4a**), 1-hexyne (**4b**), 1-heptyne (**4c**), 1-octyne (**4d**), phenylacetylene (**4e**), trimethylethynylsilane (**4f**), dimethylethynylcarbinol (**4g**), phenylpropargyl ether (**4h**), methyl and ethyl propiolates (**4i**,**j**), dimethyl and diethyl acetylenedicarboxilates (**6a**,**b**) in order to synthesize novel 2,6-functionalized 9-selenabicyclo[3.3.1]nonane derivatives containing two triazole rings.

It is known that the cycloaddition reaction often proceeds much better using a mixture of copper(II) salt and a reducing agent (e.g., sodium ascorbate) for in situ generation of Cu(I) intermediates [31]. The catalytic system of $Cu(OAc)_2 \cdot H_2O$ and sodium ascorbate was chosen to carry out cycloaddition reactions. This system was found to be very efficient in the reactions of selenium-containing organic azides with terminal acetylenes [56,57]. In this case, the active Cu(I) catalyst was generated in situ from the Cu(II) salt via reduction of copper acetate with sodium ascorbate. Addition of a slight excess of sodium ascorbate prevents the formation of oxidative homocoupling products. It was also shown that increasing the loading of copper acetate in the reaction from 0.5 to 5 mol % led to a significant increase in the yield of target 1,2,3-triazoles [56].

The 1,3-dipolar cycloaddition reaction of diazido, derivative **3** with acetylenes **4af**, proceeded efficiently in a methanol–water mixture of solvents in the presence of the copper acetate/sodium ascorbate catalytic system at room temperature for 16 h affording 2,6-bis(4-organyl-1*H*-1,2,3-triazol-1-yl)-9-selenabicyclo[3.3.1]nonanes **5a**–**f** in high yields (Scheme 3).

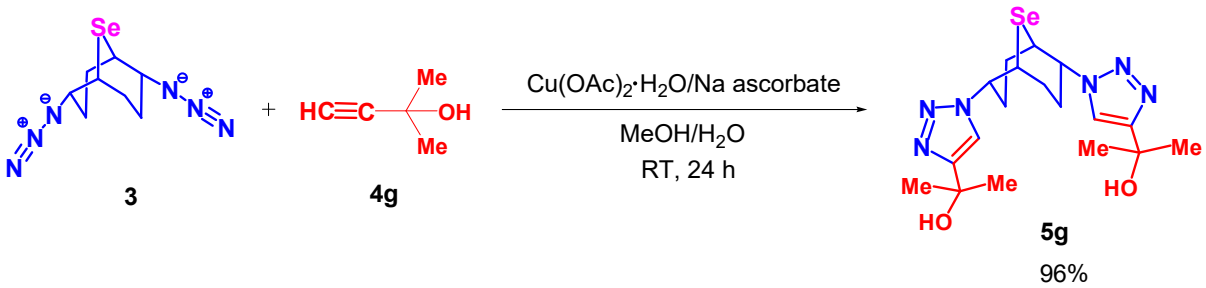



**Scheme 3.** Synthesis of 2,6-bis(4-organyl-1*H*-1,2,3-triazol-1-yl)-9-selenabicyclo[3.3.1]nonanes **5a–f** by the 1,3-dipolar cycloaddition reaction of diazido derivative **3** with 1-alkynes **4a–f** (1-pentyne, 1-hexyne, 1-heptyne, 1-octyne), phenylacetylene (**4e**), and trimethylethynylsilane (**4f**).

The amounts of the catalytic system reactants, sodium ascorbate and copper acetate (20% mol in respect to compound **3**), were used taking into account the presence of two diazide groups in compound **3**. A slight excess of alkynes **4a–f** compared to the stoichiometric amount of these acetylenes was found to help obtaining high yields of the desired products.

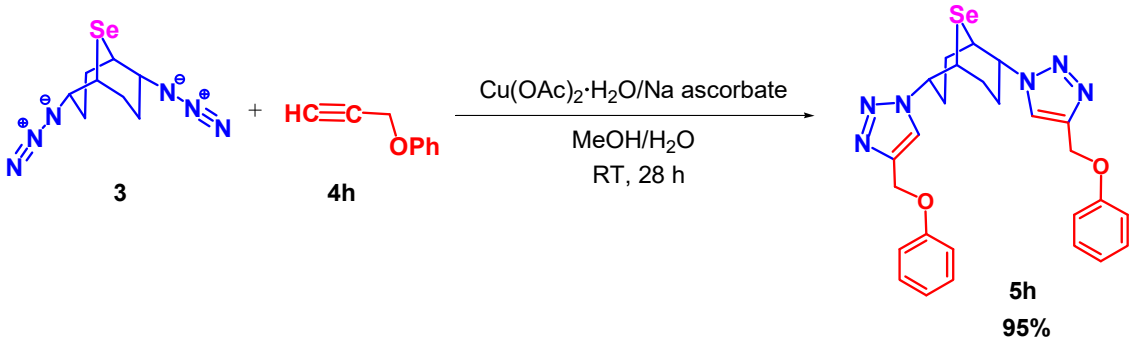
Acetylene, containing heteroatom at the triple bond, trimethylethynylsilane was involved in the 1,3-dipolar cycloaddition reaction with diazido derivative **3**. A specific feature of this compound is that it can be hydrolyzed in the presence of water with the rupture of the carbon–silicon bond. However, the formation of side products by hydrolysis was not observed under these reaction conditions. The target product, 2,6-bis(4-trimethylsilyl-1*H*-1,2,3-triazol-1-yl)-9-selenabicyclo[3.3.1]nonane (**5f**), was obtained in 93% yield as white flakes.

When the 1,3-dipolar cycloaddition of diazido derivative **3** with dimethylethynylcarbinol (**4g**) and phenylpropargyl ether (**4h**) was studied under the same conditions, it was found that the reactions proceeded more slowly compared to the processes presented in Scheme 3. The higher amounts of the catalyst, copper acetate and sodium ascorbate, were taken, as well as the reaction duration was increased in order to obtain the product in high yield. Also, when the reaction with dimethylethynylcarbinol was finished, first it was necessary to distill off methanol from the reaction mixture and then to carry out the extraction of the residue with methylene chloride in order to avoid the loss of the product, containing the hydroxyl groups, and to obtain compound **5g** in 96% yield (Scheme 4).




**Scheme 4.** Synthesis of compound **10** by the 1,3-dipolar cycloaddition reaction of diazido derivative **3** with dimethylethynylcarbinol.

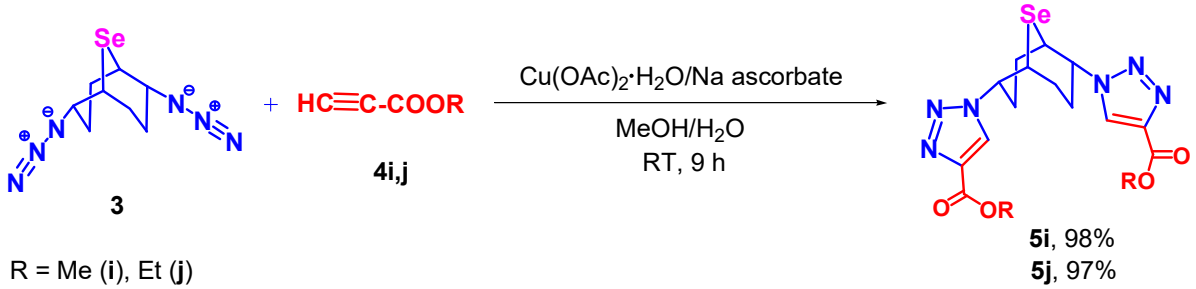
Phenylpropargyl ether **4h** has a relatively high boiling point (~202 °C) and it is difficult to remove an excess of this reagent under the reduced pressure after finishing the reaction. Therefore, stoichiometric amounts of the reagents were used in the reaction, but the reaction duration was increased to 28 h in order to obtain the high yield (95%) of 2,6-bis(4-phenyloxymethyl-1*H*-1,2,3-triazol-1-yl)-9-selenabicyclo[3.3.1]nonane (**5h**) (Scheme 5).




**3** **4h** **5h**
**95%**

**Scheme 5.** Synthesis of compound **5h** by the 1,3-dipolar cycloaddition reaction of diazido derivative **3** with phenylpropargyl ether **4h**.

Finally, methyl and ethyl propiolates **4i,j** were involved in the copper-catalyzed 1,3-dipolar cycloaddition reaction with diazido derivative **3**. The propiolates were found to react faster than dimethylethynylcarbinol and phenylpropargyl ether and also than 1-alkynes, phenylacetylene and trimethylethynylsilane. The experiments showed that the 9 h duration is sufficient for the reaction to be completed and to obtain 2,6-bis(4-alkoxycarbonyl)-1*H*-1,2,3-triazol-1-yl)-9-selenabicyclo[3.3.1]nonanes (**5i,j**) in 97–98% yields (Scheme 6).




**3** **4i,j**

R = Me (**i**), Et (**j**)

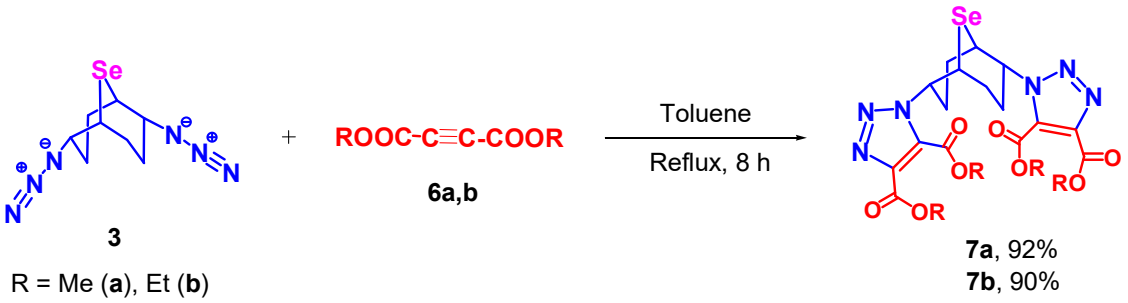
**5i**, 98%
**5j**, 97%

**Scheme 6.** Synthesis of compound **5i,j** by the 1,3-dipolar cycloaddition reaction of diazido derivative **3** with methyl and ethyl propiolates **4i,j**.

It is worthy to note that all reaction with terminal acetylenes proceeded in a regioselective manner with the formation of only one regioisomer: 1,4-substituted 1,2,3-triazole.

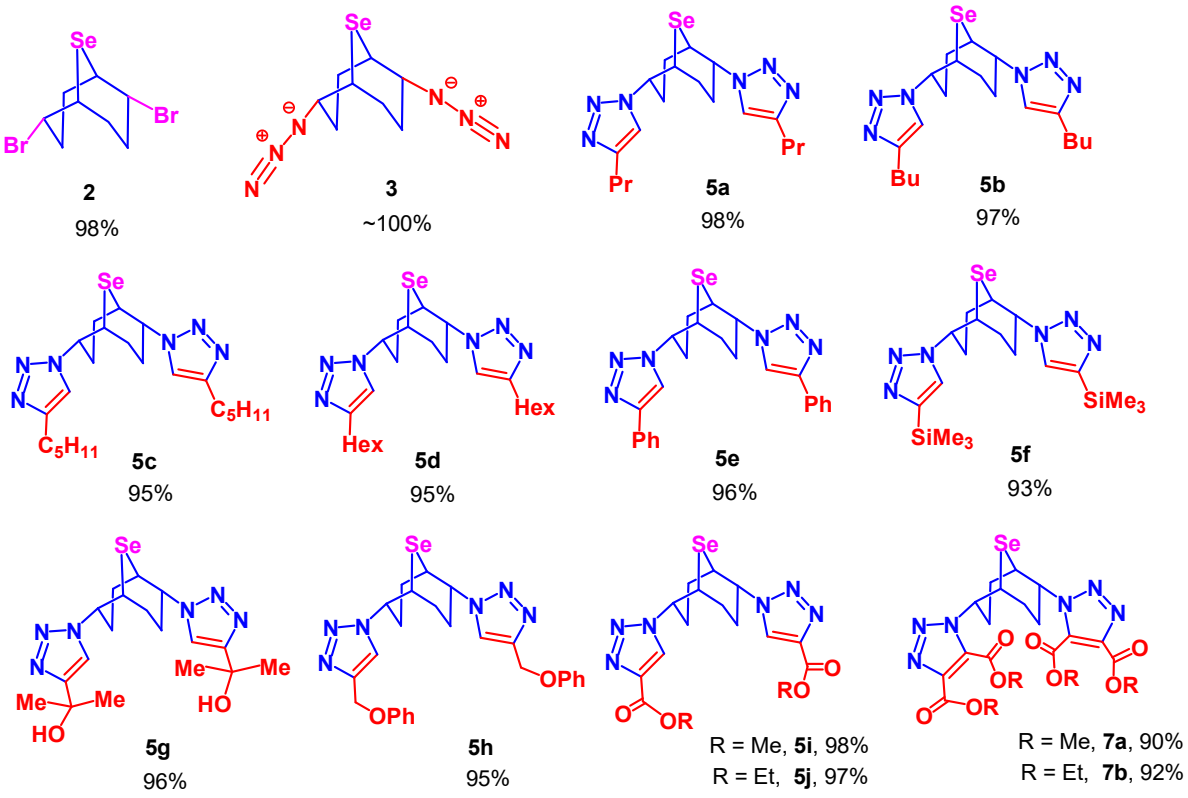
Dimethyl and diethyl acetylenedicarboxilates **6a,b** have no the terminal CH group, which is able to coordinate with the formation of intermediate acetylide species. In order to carry out the 1,3-dipolar cycloaddition reaction of diazido derivative **3** with acetylenedicarboxilates **6a,b**, the thermal conditions were used without the copper catalyst.

The heating dimethyl and diethyl acetylenedicarboxilates **6a,b** with diazido derivative **3** in toluene solution up to reflux for 8 h afforded the target products **7a** and **7b** in 92% and 90% yields, respectively (Scheme 7). The thermal reaction is less efficient compared to the copper-catalyzed process (Schemes 3–6).



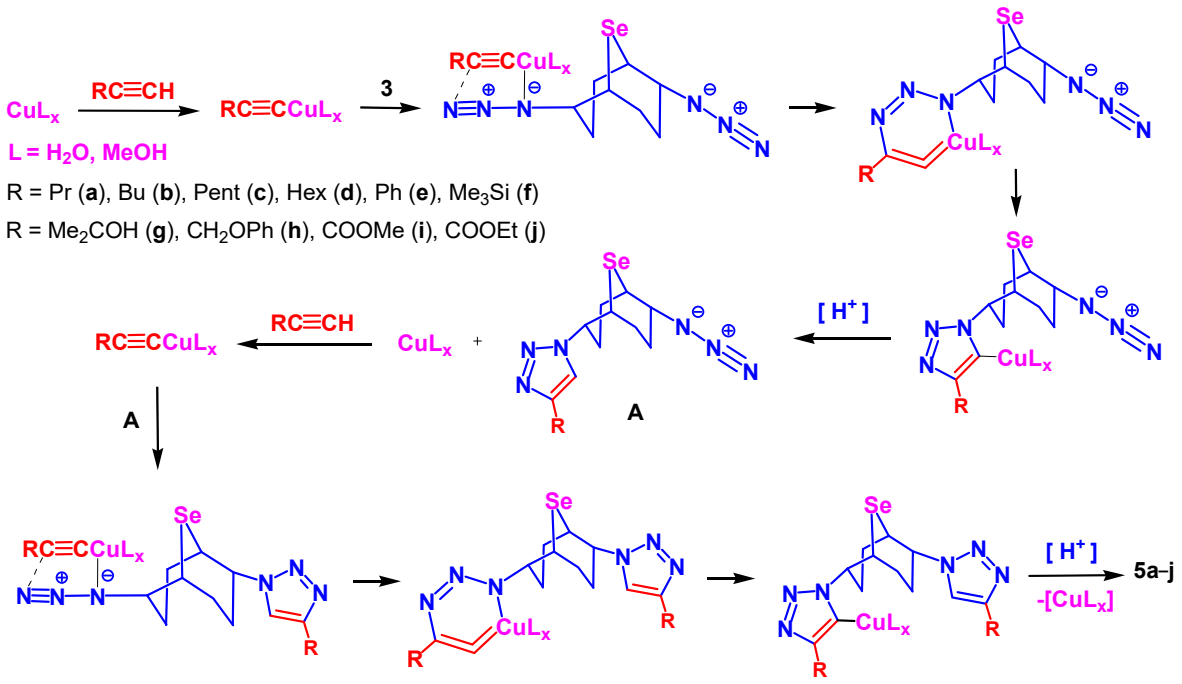

**Scheme 7.** Synthesis of compound **7a**,**b** by the 1,3-dipolar cycloaddition reaction of diazido derivative **3** with dimethyl and diethyl acetylenedicarboxilates **6a**,**b**.

Thus, the regioselective and highly efficient synthesis of bis-1,2,3-triazole derivatives of 9-selenabicyclo[3.3.1]nonane **5a–j** (93–98% yields) and **7a**,**b** (90–92% yields) was developed by the cycloaddition reaction of 2,6-diazido-9-selenabicyclo[3.3.1]nonane with a variety of acetylenes (Scheme 8).




**Scheme 8.** The obtained products **2**, **3**, **5a–j**, and **7a**,**b**.

A mechanistic scheme that includes the interaction of two copper centers, with one or two alkyne/acetylide units and one azide, has been proposed based on kinetics measurements of the Cu-catalyzed cycloaddition reaction of 1,3-diazidoalkyl derivatives [77]. We suppose that the two azide groups in compound **3** are further apart than in ordinary 1,3-diazidoalkyl derivatives and interaction between the two centers is less possible. The possible reaction pathway of the Cu-catalyzed formation of the products **5a–j** is outlined in Scheme 9. Water and methanol may play the role of ligands in this catalytic reaction.




**Scheme 9.** The possible reaction pathway of the Cu-catalyzed formation of the products **5a**–**j**.

The structural assignments of synthesized compounds were made using $^{1}$H and $^{13}$C-NMR spectroscopy including two-dimensional experiments and confirmed by elemental analysis.

The signals of the carbon atoms of the CH group, which is bonded to the nitrogen atom, are observed in the 61–64 ppm region in the $^{13}$C-NMR spectra of the obtained compounds. The carbon atoms of the SeCH group exhibit the direct spin–spin coupling constants ($^{1}J_{Se–C}$), which are about 51–56 Hz in the $^{13}$C-NMR spectra of the obtained compounds.

The NMR spectra of the products **5a**–**e** contains singlets at 7.38−7.43 ppm ($^{1}$H-NMR) and signals at 119.4–119.8 ppm ($^{13}$C-NMR spectra) corresponding to the olefinic CH= group of the triazole ring. The signals of the olefinic CH= group of compounds **5i** and **5j** are observed at lower field at 8.23−8.25 ppm in the $^{1}$H-NMR spectra and at 126.4–126.9 ppm in the $^{13}$C-NMR spectra due to high electron-withdrawing effect of the alkoxycarbonyl group.

Compounds **5g**,**h**, obtained from propargyl alcohol **4g** and propargyl ether **4h**, are poorly soluble in $CDCl_3$ and their spectra are recorded in DMSO-$d_6$.

## 3. Materials and Methods

### *3.1. General Information*

The $^{1}$H (400.1 MHz) and $^{13}$C (100.6 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-$d_6$ solutions and referred to the residual solvent peaks of $CDCl_3$ (δ = 7.27 and 77.16 ppm) and DMSO-$d_6$ (δ = 2.50 and 39.50 ppm) for $^{1}$H- and $^{13}$C-NMR, respectively.

Elemental analysis was performed on a Thermo Scientific Flash 2000 Elemental Analyzer (Thermo Fisher Scientific Inc., Milan, Italy). Melting points were determined on a Kofler Hot-Stage Microscope PolyTherm A apparatus Wagner & Munz GmbH, München, Germany). The distilled organic solvents and degassed water were used in syntheses.

### *3.2. Synthesis of Starting Compound* **3**

*2,6-Diazido-9-selenabicyclo[3.3.1]nonane* (**3**). A solution of sodium azide (1.5 g, 23 mmol) in water (12 mL) was added dropwise to a mixture of compound **2** (0.75 g, 2.16 mmol) and acetonitrile (20 mL) with stirring at room temperature. The reaction mixture was stirred

overnight (16 h) at room temperature. Acetonitrile was removed by a rotary evaporator and the residue was extracted with methylene chloride (2 × 20 mL). The organic phase was dried over $CaCl_2$, the solvent was removed by a rotary evaporator and the residue was dried in, vacuum giving a compound **3** (586 mg, quantitative yield) as a grey oil.

$^1$H NMR (400 MHz, $CDCl_3$): 1.98–2.03 (m, 2H, $CH_2$), 2.14–2.18 (m, 2H, $CH_2$), 2.36–2.40 (m, 2H, $CH_2$), 2.71–2.76 (m, 2H, $CH_2$), 3.01–3.06 (m, 2H, SeCH), 4.32–4.37 (m, 2H, NCH.

$^{13}$C NMR (100 MHz, $CDCl_3$): 28.5 ($CH_2$), 28.6 ($CH_2$), 29.3 (SeCH), 63.6 (NCH).

Anal. calcd for $C_8H_{12}N_6Se$ (271.18): C 35.43, H 4.46, N 30.99, Se 29.12%. Found: C 35.16, H 4.27, N 31.29, Se 28.86.

### *3.3. Synthesis of Compounds* **5a–f**

*2,6-Bis(4-propyl-1H-1,2,3-triazol-1-yl)-9-selenabicyclo[3.3.1]nonane* (**5a**). A solution of sodium ascorbate (56 mg, 0.28 mmol) in water (2 mL) was added to $Cu(OAc)_2.H_2O$ (28 mg, 0.14 mmol) and the mixture was stirred for 5 min. A solution of compound **3** (189 mg, 0.7 mmol) and 1-pentyne (136 mg, 2 mmol) in methanol (3 mL) were added dropwise for 5 min. The reaction mixture was stirred overnight (16 h) at room temperature. The reaction mixture was diluted with $H_2O$ (8 mL) and extracted with methylene chloride (3 × 10 mL). The organic phase was dried over $Na_2SO_4$, the solvent and an excess of 1-pentyne was removed by a rotary evaporator and the residue was dried in vacuum giving the product (279 mg, 98% yield) as a light-yellow oil.

$^1$H NMR (400 MHz, $CDCl_3$): 0.99 (t, 6H, $CH_3$, $J$ = 7.5Hz), 1.68–1.77 (m, 4H, $CH_2$), 2.25–2.31 (m, 2H, C$\underline{H_2}$CHSe), 2.39–2.55 (m, 4H, C$\underline{H_2}$CHN, C$\underline{H_2}$CHSe), 2.73 (t, 4H, $CH_2$, $J$ = 7.7 Hz), 3.01–3.13 (m, 2H, C$\underline{H_2}$CHN), 3.32–3.35 (m, 2H, CHSe), 5.42–5.46 (m, 2H, $CH_2$C$\underline{H}$N), 7.43 (s, 2H, NCC$\underline{H}$N).

$^{13}$C NMR (100 MHz,$CDCl_3$): 13.9 ($CH_3$), 22.8 ($CH_2$), 25.3 ($CH_2$), 27.4 ($\underline{C}H_2$CHSe), 27.7 ($CH_2$), 29.3 ($\underline{C}H_2$CHN), 30.4 (CHSe, $^1J_{Se–C}$ = 54.7 Hz), 63.1 ($CH_2\underline{C}$HN), 119.8 (NC$\underline{C}$HN), 147.9 (N$\underline{C}$CHN).

Anal. calcd for $C_{18}H_{28}N_6Se$ (407.41): C 53.07, H 6.93, N 20.63, Se 19.38%. Found: C 53.01, H 6.97, N 20.59, Se 19.46

*2,6-Bis(4-butyl-1H-1,2,3-triazol-1-yl)-9-selenabicyclo[3.3.1]nonane* (**5b**) (296 mg, 97% yield) was obtained under the same conditions as compound **5a**.

$^1$H NMR (400 MHz, $CDCl_3$): 0.87 (t, 6H, $CH_3$, $J$ = 7.3 Hz), 1.28–1.37 (m, 4H, $CH_2$), 1.56–1.64 (m, 4H, $CH_2$), 2.17–2.24 (m, 2H, C$\underline{H_2}$CHSe), 2.31–2.47 (m, 4H, C$\underline{H_2}$CHN, C$\underline{H_2}$CHSe), 2.66 (t, 4H, $CH_2$, $J$ = 7.7 Hz), 2.95–3.07 (m, 2H, C$\underline{H_2}$CHN), 3.25–3.28 (m, 2H, CHSe), 5.34–5.40 (m, 2H, $CH_2$C$\underline{H}$N), 7.38 (s, 2H, NCC$\underline{H}$N).

$^{13}$C NMR (100 MHz,$CDCl_3$): 13.8 ($CH_3$), 22.3 ($CH_2$), 25.3 ($CH_2$), 27.2 ($\underline{C}H_2$CHSe), 29.1 ($\underline{C}H_2$CHN), 30.3 (CHSe, $^1J_{Se–C}$ = 54.5 Hz), 31.5 ($CH_2$), 62.7 ($CH_2\underline{C}$HN), 119.4 (NC$\underline{C}$HN), 148.0 (N$\underline{C}$CHN).

Anal. calcd for $C_{20}H_{32}N_6Se$ (435.47): C 55.16, H 7.41, N 19.30, Se 18.13%. Found: C 55.02, H 7.48, N 19.22, Se 18.34%.

*2,6-Bis(4-pentyl-1H-1,2,3-triazol-1-yl)-9-selenabicyclo[3.3.1]nonane* (**5c**) (308 mg, 95% yield) was obtained under the same conditions as compound **5a**.

$^1$H NMR (400 MHz, $CDCl_3$): 0.89 (t, 6H, $CH_3$, $J$ = 6.9 Hz), 1.32–1.38 (m, 8H, $CH_2$), 1.66–1.71 (m, 4H, $CH_2$), 2.23–2.32 (m, 2H, C$\underline{H_2}$CHSe), 2.38–2.52 (m, 4H, C$\underline{H_2}$CHN, C$\underline{H_2}$CHSe), 2.72 (t, 4H, $CH_2$CN), 3.00–3.12 (m, 2H, C$\underline{H_2}$CHN), 3.30–3.34 (m, 2H, CHSe), 5.39–5.45 (m, 2H, $CH_2$C$\underline{H}$N), 7.40 (s, 2H, NCC$\underline{H}$N).

$^{13}$C NMR (100 MHz, $CDCl_3$): 14.1 ($CH_3$), 22.5 ($CH_2$), 25.8 ($CH_2$), 27.4 ($CH_2$), 29.2 ($CH_2$), 29.3 ($CH_2$), 30.4 (CHSe, $1J_{Se–C}$ = 53.9 Hz), 31.6 ($CH_2$), 63.0 (CHN), 119.5 (C=$\underline{C}$H), 148.7 ($\underline{C}$=CH).

Anal. calcd for $C_{22}H_{36}N_6Se$ (463.52): C 57.01, H 7.83, N 18.13, Se 17.13%. Found: C 56.89, H 7.78, N 18.18, Se 17.22%

*2,6-Bis(4-hexyl-1H-1,2,3-triazol-1-yl)-9-selenabicyclo[3.3.1]nonane* (**5d**) (327 mg, 95% yield) was obtained under the same conditions as compound **5a**.

$^1$H NMR (400 MHz, $CDCl_3$): 0.85 (t, 6H, $CH_3$, *J* = 6.7 Hz), 1.26–1.36 (m, 12H, $CH_2$), 1.61–1.69 (m, 4H, $CH_2$), 2.21–2.29 (m, 2H, C$\underline{H}_2$CHSe), 2.35–2.51 (m, 4H, C$\underline{H}_2$CHN, C$\underline{H}_2$CHSe), 2.70 (t, 4H, $CH_2$, *J* = 7.7 Hz), 2.99–3.10 (m, 2H, C$\underline{H}_2$CHN), 3.28–3.32 (m, 2H, CHSe), 5.37–5.43 (m, 2H, $CH_2$C$\underline{H}$N), 7.38 (s, 2H, NCC$\underline{H}$N).

$^{13}$C NMR (100 MHz,$CDCl_3$): 14.1 ($CH_3$), 22.6 ($CH_2$), 25.8 ($CH_2$), 27.3 ($\underline{C}H_2$CHSe), 29.0 ($CH_2$), 29.2 ($\underline{C}H_2$CHN), 29.4 ($CH_2$), 30.4 (CHSe, $^1J_{Se–C}$ = 52.0 Hz), 31.6 ($CH_2$), 62.9 ($CH_2\underline{C}$HN), 119.5 (NC$\underline{C}$HN), 148.1 (N$\underline{C}$CHN).

Anal. calcd for $C_{24}H_{40}N_6Se$ (491.57): C 58.64, H 8.02, N 17.10, Se 16.06%. Found: C 58.54, H 7.96, N 16.94, Se 16.31%.

*2,6-Bis(4-phenyl-1H-1,2,3-triazol-1-yl)-9-selenabicyclo[3.3.1]nonane* (**5e**) (320 mg, 96% yield) was obtained under the same conditions as compound **5a**.

$^1$H NMR (400 MHz, $CDCl_3$): 0.85 (t, 6H, $CH_3$, *J* = 6.7 Hz), 1.26–1.36 (m, 12H, $CH_2$), 1.61–1.69 (m, 4H, $CH_2$), 2.21–2.29 (m, 2H, C$\underline{H}_2$CHSe), 2.35–2.51 (m, 4H, C$\underline{H}_2$CHN, C$\underline{H}_2$CHSe), 2.70 (t, 4H, $CH_2$, *J* = 7.7 Hz), 2.99–3.10 (m, 2H, C$\underline{H}_2$CHN), 3.28–3.32 (m, 2H, CHSe), 5.37–5.43 (m, 2H, $CH_2$C$\underline{H}$N), 7.38 (s, 2H, NCC$\underline{H}$N).

$^{13}$C NMR (100 MHz, $CDCl_3$): 14.1 ($CH_3$), 22.6 ($CH_2$), 25.8 ($CH_2$), 27.3 ($\underline{C}H_2$CHSe), 29.0 ($CH_2$), 29.2 ($\underline{C}H_2$CHN), 29.4 ($CH_2$), 30.4 (CHSe, $^1J_{Se–C}$ = 52.0 Hz), 31.6 ($CH_2$), 62.9 ($CH_2\underline{C}$HN), 119.5 (NC$\underline{C}$HN), 148.1 (N$\underline{C}$CHN).

Anal. calcd for $C_{24}H_{24}N_6Se$ (475.45): C 60.63, H 5.09, N 17.68, Se 16.61%. Found: C 60.91, H 4.93, N 17.94, Se 16.90%.

*2,6-Bis(4-trimethylsilyl-1H-1,2,3-triazol-1-yl)-9-selenabicyclo[3.3.1]nonane* (**5f**) (304 mg, 93% yield, white flakes, mp 190–191 °C) was obtained under the same conditions as compound **5a**.

$^1$H NMR (400 MHz, $CDCl_3$): 0.32 (s, 18H, $CH_3$), 2.24–2.31 (m, 2H, C$\underline{H}_2$CHSe), 2.39–2.55 (m, 4H, C$\underline{H}_2$CHN, C$\underline{H}_2$CHSe), 3.05–3.17 (m, 2H, C$\underline{H}_2$CHN), 3.33–3.37 (m, 2H, CHSe), 5.47–5.53 (m, 2H, $CH_2$C$\underline{H}$N), 7.63 (s, 2H, NCC$\underline{H}$N).

$^{13}$C NMR (100 MHz,$CDCl_3$): 1.0 ($CH_3$), 27.7 ($\underline{C}H_2$CHSe), 29.4 ($\underline{C}H_2$CHN), 30.4 (CHSe, $^1J_{Se–C}$ = 54.5 Hz), 62.8 ($CH_2\underline{C}$HN), 127.7 (NC$\underline{C}$HN), 146.2 (N$\underline{C}$CHN).

Anal. calcd for $C_{18}H_{32}N_6Si_2Se$ (467.62): C 46.23, H 6.90, N 17.97, Si 12.01, Se 16.89%. Found: C 46.35, H 7.01, N 18.04, Si 11.89, Se 16.92%.

### *3.4. Synthesis of Compounds* **5g**−**j**

*2,6-Bis[4-(1-hydroxy-1-methylethyl)-1H-1,2,3-triazol-1-yl]-9-selenabicyclo[3.3.1]nonane* (**5g**). A solution of sodium ascorbate (84 mg, 0.42 mmol) in water (3 mL) was added to $Cu(OAc)_2.H_2O$ (42 mg, 0.21 mmol) and the mixture was stirred for 5 min. A solution of compound **3** (189 mg, 0.7 mmol) and dimethylethynylcarbinol (136 mg, 2 mmol) in methanol (3 mL) was added dropwise for 10 min. The reaction mixture was stirred for 24 h at room temperature. Methanol was distilled off by a rotary evaporator. The residue was extracted with methylene chloride (3 × 15 mL). The organic phase was dried over $Na_2SO_4$, the solvent and an excess of dimethylethynylcarbinol was removed by a rotary evaporator and by drying in a vacuum. The product (295 mg, 96% yield) was obtained as a white powder, mp 180–182 °C.

$^1$H NMR (400 MHz, DMSO-$d_6$): 1.49 (s, 12H, $CH_3$), 2.11–2.18 (m, 2H, C$\underline{H}_2$CHSe), 2.21–2.33 (m, 4H, C$\underline{H}_2$CHN, C$\underline{H}_2$CHSe), 3.00–3.14 (m, 2H, C$\underline{H}_2$CHN), 3.27–3.32 (m, 2H, CHSe), 5.11 (s, 2H, OH), 5.40–5.46 (m, 2H, $CH_2$C$\underline{H}$N), 8.15 (s, 2H, NCC$\underline{H}$N).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): 26.1 ($\underline{C}H_2$CHSe), 28.6 ($\underline{C}H_2$CHN), 29.9 (CHSe), 30.7 ($CH_3$), 30.7 ($CH_3$), 62.2 ($CH_2\underline{C}$HN), 67.0 (COH), 119.5 (NC$\underline{C}$HN), 155.4 (N$\underline{C}$CHN).

Anal. calcd for $C_{18}H_{28}N_6O_2Se$ (439.41): C 49.20, H 6.52, N 19.13, Se 17.97%. Found: C 48.92, H 6.38, N 18.96, Se 18.15%.

*2,6-Bis(4-phenyloxymethyl-1H-1,2,3-triazol-1-yl)-9-selenabicyclo[3.3.1]nonane* (**5h**). A solution of sodium ascorbate (56 mg, 0.28 mmol) in water (2 mL) was added to $Cu(OAc)_2.H_2O$ (28 mg, 0.14 mmol), and the mixture was stirred for 5 min. A solution of compound **3** (189 mg, 0.7 mmol) and phenylpropargyl ether (185 mg, 1.4 mmol) in methanol (3 mL) was added dropwise for 5 min. The reaction mixture was for 28 h at room temperature. The reaction

mixture was diluted with $H_2O$ (8 mL) and extracted with methylene chloride (3 × 10 mL). The organic phase was dried over $Na_2SO_4$, the solvent and an excess of 1-pentyne was removed by a rotary evaporator and the residue was dried in a vacuum, giving the product (356 mg, 95% yield) as a white powder, mp 165–167 °C.

$^1$H NMR (400 MHz, DMSO-$d_6$): 2.17–2.24 (m, 2H, C$\underline{H}_2$CHSe), 2.26–2.38 (m, 4H, C$\underline{H}_2$CHN, C$\underline{H}_2$CHSe), 3.04–3.15 (m, 2H, C$\underline{H}_2$CHN), 3.34–3.38 (m, 2H, CHSe), 5.16 (s, 4H, $CH_2O$), 5.47–5.53 (m, 2H, $CH_2C\underline{H}N$), 6.95 (m, 2H, $CH_{Ar}$), 7.06–7.07 (m, 4H, $CH_{Ar}$), 7.31 (m, 2H, $CH_{Ar}$), 8.47 (s, 2H, NCC$\underline{H}$N).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): 26.2 ($\underline{C}H_2$CHSe), 28.7 ($\underline{C}H_2$CHN), 29.8 (CHSe, $^1J_{Se–C}$ = 53.0 Hz), 61.1 ($CH_2O$), 62.4 ($CH_2\underline{C}$HN), 114.7($CH_{Ar}$), 120.8 ($CH_{Ar}$), 123.7 (NC$\underline{C}$HN), 129.5 ($CH_{Ar}$), 142.4 (N$\underline{C}$CHN), 158.1 ($OC_{Ar}$).

Anal. Calcd for $C_{26}H_{28}N_6O_2Se$ (535.50): C 58.32, H 5.27, N 15.69, O 5.98, Se 14.75%. Found: C 59.44, H 5.31, N 15.61, Se 14.89%.

*2,6-Bis(4-methoxycarbonyl)-1H-1,2,3-triazol-1-yl)-9-selenabicyclo[3.3.1]nonane* (**5i**) (301 mg, 98% yield), was obtained under the same conditions as compound **5a**, but the reaction time was 9 h.

$^1$H NMR (400 MHz, $CDCl_3$): 2.31–2.39 (m, 2H, C$\underline{H}_2$CHSe), 2.48–2.53 (m, 4H, C$\underline{H}_2$CHN, C$\underline{H}_2$CHSe), 3.02–3.12 (m, 2H, C$\underline{H}_2$CHN), 3.39–3.41 (m, 2H, CHSe), 3.96 (s, 6H, $CH_3$), 5.53–5.58 (m, 2H, $CH_2C\underline{H}N$), 8.25 (s, 2H, NCC$\underline{H}$N).

$^{13}$C NMR (100 MHz,$CDCl_3$): 25.5 ($\underline{C}H_2$CHSe), 28.0 ($\underline{C}H_2$CHN), 29.2 (CHSe, $^1J_{Se–C}$ = 53.0 Hz), 51.3 ($CH_3O$), 62.6 ($CH_2\underline{C}$HN), 126.9 (NC$\underline{C}$HN), 138.4 (N$\underline{C}$CHN), 160.4 (COO).

Anal. Calcd for $C_{16}H_{20}N_6O_4Se$ (439.33): C 43.74, H 4.59, N 19.13, O 14.57, Se 17.97%. Found: C 43.65, H 4.56, N 19.08, Se 18.11%.

*2,6-Bis(4-ethoxycarbonyl)-1H-1,2,3-triazol-1-yl)-9-selenabicyclo[3.3.1]nonane* (**5j**) (320 mg, 97% yield) was obtained under the same conditions as compound **5a**, but the reaction time was 9 h.

$^1$H NMR (400 MHz, $CDCl_3$): 1.42 (t, 6H, $CH_3$, $J$ = 7.1 Hz), 2.31–2.38 (m, 2H, C$\underline{H}_2$CHSe), 2.48–2.54 (m, 4H, C$\underline{H}_2$CHN, C$\underline{H}_2$CHSe), 3.02–3.14 (m, 2H, C$\underline{H}_2$CHN), 3.39–3.42 (m, 2H, CHSe), 4.44 (q, 4H, C$\underline{H}_2$CH$_3$, $J$ = 7.1 Hz), 5.53–5.58 (m, 2H, $CH_2C\underline{H}N$), 8.23 (s, 2H, NCC$\underline{H}$N).

$^{13}$C NMR (100 MHz,$CDCl_3$): 14.5 ($CH_3$), 27.3 ($\underline{C}H_2$CHSe), 28.9 ($\underline{C}H_2$CHN), 30.0 (CHSe, $^1J_{Se–C}$ = 55.2 Hz), 61.6 ($CH_2\underline{C}$HN), 63.6 ($CH_2O$), 126.4 (NC$\underline{C}$HN), 140.1 (N$\underline{C}$CHN), 160.8 (COO).

Anal. calcd for $C_{18}H_{24}N_6O_4Se$ (467.38): C 46.26, H 5.18, N 17.98, O 13.69, Se 16.89%. Found: C 46.28, H 5.16, N 18.03, Se 16.86%.

### *3.5. Synthesis of Compounds* **7a**,**b** *by the Thermal Reaction*

*2,6-Bis[4,5-bis(methoxycarbonyl)-1H-1,2,3-triazol-1-yl]-9-selenabicyclo[3.3.1]nonane* (**7a**). A solution of compound **3** (189 mg, 0.7 mmol) and dimethyl acetylenedicarboxylate 199 mg, 1.4 mmol) in toluene (3 mL) was refluxed for 8 h. The solvent was removed by a rotary evaporator and the residue was subjected to column chromatography (eluent: hexane -> hexane/chloroform 7:1), giving the product (359 mg, 92% yield) as a white powder, mp 165–167 °C.

$^1$H NMR (400 MHz, $CDCl_3$): 2.13–2.21 (m, 2H, C$\underline{H}_2$CHSe), 2.34–2.43 (m, 2H, C$\underline{H}_2$CHN), 2.56–2.64 (m, 2H, C$\underline{H}_2$CHSe), 3.21–3.23 (m, 2H, CHSe), 3.48–3.60 (m, 2H, C$\underline{H}_2$CHN), 3.92 (s, 6H, $CH_3$), 3.97 (s, 6H, $CH_3$), 5.69–5.74 (m, 2H, $CH_2C\underline{H}N$).

$^{13}$C NMR (100 MHz,$CDCl_3$): 26.9 ($\underline{C}H_2$CHSe), 29.5 ($\underline{C}H_2$CHN), 29.7 (CHSe, $^1J_{Se–C}$ = 55.5 Hz), 52.7($CH_3$), 53.7($CH_3$), 63.5 ($CH_2\underline{C}$HN), 130.1 ($\underline{C}NCH_2$), 139.7 (CN=N), 159.3 (COO), 160.6 (COO). Anal. calcd for $C_{20}H_{24}N_6O_8Se$ (555.40): C 43.25, H 4.36, N 15.13, O 23.05, Se 14.22%. Found: C 43.38, H 4.24, N 15.11, Se 14.32%.

*2,6-Bis[4,5-bis(ethoxycarbonyl)-1H-1,2,3-triazol-1-yl]-9-selenabicyclo[3.3.1]nonane* (**7b**) (387 mg, 90% yield) was obtained under the same conditions as compound **7a**.

$^1$H NMR (400 MHz, $CDCl_3$): 1.31–1.37 (m, 12H, $CH_3$), 2.11–2.18 (m, 2H, C$\underline{H}_2$CHSe), 2.31–2.41 (m, 2H, C$\underline{H}_2$CHN), 2.54–2.61 (m, 2H, C$\underline{H}_2$CHSe), 3.19–3.21 (m, 2H, CHSe), 3.48–3.57 (m, 2H, C$\underline{H}_2$CHN), 4.33–4.42 (m, 8H, C$\underline{H}_2$CH$_3$), 5.67–5.71 (m, 2H, $CH_2C\underline{H}N$).

$^{13}$C NMR (100 MHz,$CDCl_3$): 13.9 ($CH_3$), 14.1 ($CH_3$), 26.8 ($\underline{C}H_2CHSe$), 29.5 ($\underline{C}H_2CHN$), 29.7 (CHSe, $^1J_{Se-C}$ = 54.1 Hz), 61.8 ($CH_2O$), 63.1 ($CH_2O$), 63.3 ($CH_2\underline{C}HN$), 130.0 ($\underline{C}NCH_2$), 139.7 (CN=N), 158.7 (COO), 160.2 (COO).

Anal. calcd for $C_{24}H_{32}N_6O_8Se$ (611.51): C 47.14, H 5.27, N 13.74, O 20.93, Se 12.91%. Found: C 47.03, H 5.26, N 13.70, Se 13.12%.

## 4. Conclusions

First representatives of selenium heterocycles, combined with two 1,2,3-triazole moieties, were obtained in high yields by the 1,3-dipolar cycloaddition reaction of 2,6-diazido-9-selenabicyclo[3.3.1]nonane with a variety of terminal acetylenes: 1-pentyne, 1-hexyne, 1-heptyne, 1-octyne, phenylacetylene, trimethylethynylsilane, dimethylethynylcarbinol, phenylpropargyl ether, methyl and ethyl propiolates,. The process was catalyzed by the copper acetate/sodium ascorbate system. It is worthy to note that all reaction with terminal acetylenes proceeded in a regioselective manner with the formation of only one regioisomer: 1,4-substituted 1,2,3-triazole. The most reactive to acetylenes were methyl and ethyl propiolates: a 9 h duration was sufficient for the reaction to be completed at room temperature. The reactions with 1-pentyne, 1-hexyne, 1-heptyne, 1-octyne, phenylacetylene and trimethylethynylsilane also proceeded very smoothly and in a regioselective fashion giving the corresponding products in high yields.

The reaction of 2,6-diazido-9-selenabicyclo[3.3.1]nonane with dimethyl and diethyl acetylenedicarboxylates was carried out as thermal 1,3-dipolar Huisgen cycloaddition, giving the corresponding 4,5-disubstituted 1,2,3-triazole derivatives of 9-selenabicyclo[3.3.1]nonane in high yields. 2,6-Diazido-9-selenabicyclo[3.3.1]nonane was obtained in quantitative yield by the reaction of sodium azide with 2,6-dibromo-9-selenabicyclo[3.3.1]nonane at room temperature (this is the second step of this approach of the selenium dihalides triple-click chemistry, i.e., the second efficient "click"). The dibromo derivative was synthesized by stereoselective transannular addition of selenium dibromide to cis, cis-1,5-cyclooctadiene (the first step of this approach of the selenium dihalides triple-click chemistry).

**Supplementary Materials:** The following supporting information is available: https://www.mdpi.com/article/10.3390/catal12091032/s1, $^1$H and $^{13}$C NMR spectra of the products.

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