Synthesis of 4-Arylselanyl-1H-1,2,3-triazoles from Selenium-Containing Carbinols

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Abstract: In this work, we present a simple way to achieve 4-arylselanyl-1H-1,2,3-triazoles from selenium-containing carbinols in a one-pot strategy. The selenium-containing carbinols were used as starting materials to produce a range of selanyl-triazoles in moderate to good yields, including a quinoline and Zidovudine derivatives. One-pot protocols are crucial to the current concerns about waste production and solvent consumption, avoiding the isolation and purification steps of the reactive terminal selanylalkynes. We could also isolate an interesting and unprecedented by-product with one alkynylselenium moiety connected to the triazole.

Keywords: selenium; 1,2,3-triazoles; click chemistry; cycloaddition; carbinols; heterocycles

1. Introduction

Triazoles are a significant class of heterocycles which have received considerable attention because of their application in materials science, medicinal chemistry and organic synthesis [1–3]. Particularly, 1,2,3-triazoles derivatives exhibit a broad spectrum of biological properties, such as anti-inflammatory, antifungal, antibacterial, anticancer, antivirus and antituberculosis [4–13]. 1,2,3-Triazoles derivatives are an important connecting group, linking a broad range of substituted substrates in a simple fashion, being used as peptide mimetics [14,15]. Inspired in the Huisgen [3 + 2] cycloaddition reaction of an organic azide and a terminal alkyne [16], a number of catalytic strategies employing transition metals have been used to address the reactivity and selectivity issues inherent to the seminal strategy [17–26]. In addition, recent studies have been directed toward the development of metal-free methodologies for triazole synthesis. Organocatalytic approaches involving [3 + 2] cycloaddition have been reported for the synthesis of functionalized 1,2,3-triazoles [27–34].

Despite the significant advances toward the synthesis of highly substituted 1,2,3-triazoles, the need of a deep study on the combinations of substrates for the synthesis of highly functionalized and complex structures is still an open issue. In this sense, organoselanyl-triazoles constitute an interesting class of molecules, which combine the importance of a triazole nucleus [1–3] with an organoselenium moiety [35–38]. Selenium is an essential nutrient for mammals, playing important roles in metabolic pathways [39,40], and the interest in selenium pharmacology [41–46] and chemistry [47–49] has increased in this century.

Several methodologies have been reported for the selective synthesis of a range of 1,2,3-triazole scaffolds containing an organoselenium moiety [50–52]. However, only a few procedures to directly prepare 5-arylselanyl- and 4-arylselanyl-1H-1,2,3-triazoles have been...
described (Figure 1). For example, Cui et al. developed a simple and efficient method for the preparation of 5-arylselanyl-1H-1,2,3-triazoles from propiolic acids, diselenides and azides, in which a selanylalkyne was firstly formed via decarboxylative reactions, followed by the intermolecular copper-catalyzed azide-alkyne cycloaddition reaction (CuAAC) to afford the desired products [53]. Wang et al. described the use of PhSO_2SePh as an electrophile in the copper (I)-catalyzed interrupted click reaction of phenylacetylene with benzylazide, giving 5-arylselanyl-1H-1,2,3-triazole in 71% yield [54]. Manarin et al. developed a general method for the synthesis of 4-arylselanyl-1H-1,2,3-triazoles via a CuAAC reaction between organic azides and a terminal selanylalkyne, generated by the in situ deprotection of the silyl group [55]. The synthesis of 1-benzyl-4-(phenylselanyl)-1H-1,2,3-triazole was described by Saraiva et al., in which ethynyl(phenyl)selenide underwent CuAAC with benzylazide to give the product in 84% yield [56]. However, for the synthesis of ethynyl(phenyl)selenide, the protocol available at the time to achieve such starting material was described by Braga et al., dating from 1994 [57]. Recently, we have developed an alternative way to prepare these terminal alkynes containing selenium and sulfur, starting from chalcogen-containing alkynyl carbinols [58]. In this study, during the preparation of the terminal selanylalkynes, it was observed that in air without solvent, these compounds showed signals of decomposition. Furthermore, we observed that in a hexane solution, the terminal selanylalkynes were stable in the presence of air. With these observations in mind, we wondered if selanylalkynylcarbinols could serve as starting materials for the synthesis of a range of 4-arylselanyl-1H-1,2,3-triazoles in a one-pot procedure.

**Cui et al.**

\[
\text{ArSeSeAr} + \text{RN}_3 + \text{R}^1\equiv\text{COOH} \xrightarrow{\text{Cu(OAc)}_2\cdot\text{H}_2\text{O} (10 \text{ mol\%}), \text{K}_2\text{CO}_3 (1 \text{ equiv}), \text{toluene}, 120 \degree\text{C}} \text{N}_\text{N} \text{N} \text{R}^1 \text{SeAr}
\]

53-86%

**Wang et al.**

\[
\text{PhSO}_2\text{SePh} + \text{BnN}_3 + \text{Ph} \equiv \text{H} \xrightarrow{\text{LiO}^+\text{Bu} (2.0 \text{ equiv}), 4\text{ÅMS}, \text{THF}, 40 \degree\text{C}} \text{N}_\text{N} \text{N} \text{Bn}
\]

71%

**Stefani et al.**

\[
\text{R}^1\equiv\text{Se} \xrightarrow{\text{TBAF (1.2 equiv)}, \text{THF, 50} \degree\text{C}} \text{N}_\text{N} \text{N} \text{R}^1 \text{Se}
\]

42-80%

**Saraiva et al.**

\[
\text{PhSe} \equiv \text{H} + \text{BnN}_3 \xrightarrow{\text{Cu(OAc)}_2\cdot\text{H}_2\text{O} (3 \text{ mol\%}), \text{THF/}H_2\text{O} (1:1), \text{r.t., air}} \text{N}_\text{N} \text{N} \text{Bn}
\]

84%

**Figure 1.** Previous protocols to prepare 5-arylselanyl- and 4-arylselanyl-1H-1,2,3-triazoles.

In view of the above, and in continuation to our research endeavors in the development of efficient and selective methods to access functionalized selanyl-1,2,3-triazoles, we report herein a one-pot strategy to prepare 4-arylselanyl-1H-1,2,3-triazoles, starting from easily available and bench-stable selanylalkynylcarbinols and organic azides (Scheme 1).
2. Results and Discussion

Initial experiments to optimize the reaction conditions were carried out using 2-methyl-4-(phenylselanyl)but-3-yn-2-ol 1a and 1-azido-4-chlorobenzene 3a as standard reaction substrates (Table 1). The key step of the protocol involved the deprotection of the hydroxypropargyl selenide 1a (1 mmol) to give the terminal selanylalkyne intermediate 2a according to a retro-Favorskii reaction mechanism. For this reaction, we used our previously optimized conditions (KOH/hexanes, 50 °C) [58], and after 1 h, the propargyl alcohol 1a (monitored by TLC) was completely consumed. Then, the crude reaction mixture was allowed to reach room temperature, and a 1:1 mixture of THF/H2O (1.0 mL) was added, followed by 1-azido-4-chlorobenzene 3a (0.5 mmol), sodium ascorbate (10 mol%) and Cu(OAc)2·H2O (5 mol%). The resulting mixture was then stirred at 50 °C until all the azide 3a was not observable anymore by TLC, 8.0 h. Under these conditions, the expected 4-phenylselanyl-1H-1,2,3-triazole 4a was obtained in 85% yield.

From this promising result, some additional experiments were conducted, aiming to increase the yield of 4a while reducing the reaction time (Table 1). Firstly, different copper species (CuI, CuOnps and CuCl2) were tested under the same conditions, but in all the cases we observed lower yields than that obtained using Cu(OAc)2·H2O (Table 1, entry 1 vs. entries 2–5). For instance, the use of CuI gave 4a in 60% yield under the conditions of entry

![Scheme 1. Synthesis of 4-arylselanyl-1H-1,2,3-triazoles from selenium-containing carbinols.](image-url)
1, and only 32% using Et$_3$N in the place of sodium ascorbate and in DMSO as the solvent (entries 2 and 3). Only traces of 4a were observed using CuO$_{nps}$, while CuCl$_2$ afforded the expected product in 75% yield (Table 1, entries 4 and 5). The presence of water in the reaction medium was essential for the success of the reaction once no product was observed using dry THF (Table 1, entry 6). The use of lower amounts of both, sodium ascorbate (6 mol%) and Cu(OAc)$_2$·H$_2$O (3 mol%), or an argon atmosphere, negatively influenced the reaction, affording 4a in 40% and 65% yield, respectively (Table 1, entries 7 and 8). The influence of the temperature and the stoichiometry of the reagents was evaluated. At room temperature, the pre-formed terminal selanylacetylene 1a reacted with azide 3a to give 4a in 40% yield (Table 1, entry 9). A moderate result was also observed when equivalent amounts of 2a and 3a were reacted, affording 4a in 50% yield (Table 1, entry 10).

After analyzing these results, we determined that the best reaction conditions were those reported in Table 1, entry 1: after stirring a mixture of the propargyl alcohol 1a and KOH in hexanes, the resulting in situ formed terminal alkyne 2a mixed with the azide 3a (0.5 equiv.) were stirred in the presence of sodium ascorbate (10 mol%) and Cu(OAc)$_2$·H$_2$O (5 mol%) in a 1:1 mixture of THF and H$_2$O as the solvent.

The scope of the proposed methodology was then extended to differently substituted alkynyl selenides 1b–f, in the reaction with 1-azido-4-chlorobenzene 3a, aiming to investigate the generality and limitations of the method (Scheme 2). Interestingly, there is a little influence of the electronic effect in the reaction, and the presence of electron-donating groups in the para-position of the pendant phenyl increase the reactivity. For instance, electron-rich 4-((4-methoxyphenyl)selanyl)-1b (Ar = 4-MeOC$_6$H$_4$) and 2-methyl-4-((p-tolyiselenyl)but-3-yn-2-ol 1c (Ar = 4-MeC$_6$H$_4$) afforded the respective 4-arylselanyl-1H-1,2,3-triazoles 4b and 4c in 75% and 66% yield, while the electron-poor one 2-methyl-4-((4-fluoroselanyl)but-3-yn-2-ol 1e (Ar = 4-FC$_6$H$_4$) afforded the triazole 4e in 55% yield. A remarkable result was obtained in the reaction of 2-methyl-4-((4-bromoselanyl)but-3-yn-2-ol 1d (Ar = 4-BrC$_6$H$_4$), which afforded the bromo-functionalized triazole 4d (59% yield), which can be subject to further transformation via Sonogashira cross-coupling reaction. A decrease in yield was observed, however, when the strong electron withdrawing CF$_3$ group was present in the meta-position. Thus, 2-methyl-4-((3-(trifluoromethyl)phenyl)selanyl)but-3-yn-2-ol 1e reacted with 3a under the optimal conditions to afford the expected triazole 4f in 45% yield (Scheme 2).

![Scheme 2](image-url)
Subsequently, we investigated the reactivity of a variety of organic azides 3 with 2-methyl-4-(phenylselanyl)but-3-yn-2-ol 1a under the best reaction conditions (Scheme 3). As for the alkynyl selenide counterpart, electronic effect does not seem to influence the reactivity of the para-substituted aryl azides 3. For instance, the electron-rich 1-azido-4-methoxybenzene 3b (R = 4-MeOC$_6$H$_4$) and the electron-deficient 1-azido-4-fluorobenzene 3c (R = 4-FC$_6$H$_4$) afforded the respective triazoles 4g and 4h in 82% and 79% yield after reaction with 2a. A similarly good result was observed from the 4-iodo-substituted azide 3d, affording the iodo-containing triazole 4i in 77% yield, which could be subject to further modifications, as mentioned for 4d. The presence of a fluoro atom at the ortho-position, like in 3e (R = 2-FC$_6$H$_4$), slightly affected the reactivity, and the respective product 4j was isolated in 56% yield. Interestingly, the strong electron-withdrawing nitro group positively affected the reaction, and 1-azido-3-nitrobenzene 3f (R = 3-NO$_2$C$_6$H$_4$) gave 4k in 75% yield. (Azidomethyl)benzene 3g was a suitable substrate in the reaction with 2a (generated in situ from 1a), affording 1-benzyl-4-(phenylselanyl)-1H-1,2,3-triazole 4l in 72% yield. Molecular hybridization is a valuable strategy in medicinal chemistry, allowing access to potent multitarget drugs [59,60]. In view of the recognized bioactivity of both, organoselenium and triazole units, we decided to explore the functionalization of two known nuclei, 7-chloroquinoline and Zidovudine, which could present interesting pharmacological properties to be explored. Thus, 4-azido-7-chloroquinoline 3h reacted with 2a to give the 7-chloroquinoline-derivative 4m in 80% yield, while the azido-derivative of Zidovudine 3i was converted to the respective triazole 4n in 48% yield.

While performing these CuAAC reactions, the formation of a by-product was observed, with a retention factor (RF) in thin layer chromatography remarkably similar to product 4. This by-product was isolated and characterized as the triazole derived from the reaction of the organyl azide 3 with two equiv. of alkynyl selenide 2a. Unfortunately, the purification of this by-product is extremely difficult because of the similarity of RF with the main product 4. Fortunately, the by-products 5a and 5b could be isolated, even if in low yields, and were fully characterized (Scheme 4). A possible explanation for the formation of
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Scheme 4. By-products 5a and 5b from the reaction of 3a or 3c with 2a generated in situ.

3. Materials and Methods

Reactions were carried out in a two-necked round-bottomed flask with a Teflon-coated magnetic stirring bar. Solvents and reagents were used as received unless otherwise noted. The reactions were monitored by TLC performed by using Merck silica gel (60 F254), 0.25 mm thickness. For visualization, TLC plates were either placed under UV light, or stained with iodine vapor or 5% vanillin in 10% H2SO4 under heating. Column chromatography was performed by using Merck silica gel (230–400 mesh). Carbon-13 nuclear magnetic resonance spectra (13C NMR) were obtained at 75 MHz on a Bruker DPX 300 spectrometer and at 100 MHz on a Bruker Avance III HD 400 spectrometer. Spectra were recorded in CDCl3 solutions. Chemical shifts are reported in ppm, referenced to tetramethylsilane (TMS) as the external reference (1H NMR) or to the solvent peak of CDCl3 (13C NMR). Coupling constants (J) are reported in Hertz. Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), t (triplet), dd (double doublet), q (quartet) and m (multiplet). High resolution mass spectra (HRMS) were recorded on a Bruker Micro TOF-QII spectrometer 10416. Reagents 2-methyl-3-butyn-2-ol and selenium powder were purchased from Sigma-Aldrich. The starting materials selanylalkynylcarbinols were synthesized according to previous literature [58]. 1H and 13C NMR spectra of all compounds are available in Supplementary Materials.

General Procedure for the Synthesis of 4-Arylselanyl-1H-1,2,3-triazoles 4

Arylselanyl carbinol 1 (1.0 mmol), KOH (1.1 mmol, 0.062 g) and hexanes (3.0 mL) were added to a 25 mL two-necked round-bottomed flask equipped with a reflux condenser. The system was then immersed in a preheated oil bath at 50 °C and stirred at this temperature for 1 to 5 h (the consumption of carbinol 1 was followed by TLC) [58]. Then, 0.5 mmol of the appropriate azide 3, Cu(OAc)2·H2O (0.025 mmol), sodium ascorbate (0.5 mmol), THF (0.5 mL) and H2O (0.5 mL) were added to the reaction flask. The resulting solution was stirred at 50 °C for 8 h. Then, a saturated solution of NH4Cl (10 mL) was added, followed by the addition of EtOAc (10 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL), dried over MgSO4, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel with a mixture of hexane/ethyl acetate (9:1) as eluent. Spectral data for the prepared products are listed below.

1-(4-Chlorophenyl)-4-(phenylselanyl)-1H-1,2,3-triazole (4a): Pale yellow solid, mp: 105–107 °C. Yield: 0.142 g (85%). 1H NMR (300 MHz, CDCl3) δ: 8.05 (s, 1H), 7.67 (d, J = 8.9 Hz, 2H), 7.54–7.47 (m, 4H), 7.26–7.24 (m, 3H). 13C NMR (75 MHz, CDCl3) δ: 135.0, 134.8, 133.7, 131.9, 129.9, 129.4, 127.6, 126.3, 124.4, 121.6. HRMS Calcd. for C14H10Cl1Se [M + H]+: 335.9799. Found: 335.9802.

1-(4-Chlorophenyl)-4-(4-methoxyphenylselanyl)-1H-1,2,3-triazole (4b): Yellow solid, mp: 86–88 °C. Yield: 0.137 g (75%). 1H NMR (400 MHz, CDCl3) δ: 7.92 (s, 1H), 7.64 (d,
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\[ J = 8.9 \text{ Hz}, 2H), 7.57 \text{ (d, } J = 8.8 \text{ Hz, 2H), 7.47 \text{ (d, } J = 8.9 \text{ Hz, 1H), 6.82 \text{ (d, } J = 8.8 \text{ Hz, 2H), 3.78} \text{ (s, } 3H) \]. 13C NMR (100 MHz, CDCl3) δ: 159.8, 135.4, 135.2, 134.7, 129.9, 125.1, 124.3, 121.6, 119.3, 115.1, 55.3. HRMS Calcd. for C15H12ClN2OSe [M+N2+H]⁺: 337.9843. Found: 337.9843.

1-(4-Chlorophenyl)-4-(p-tolylselanyl)-1H-1,2,3-triazole (4c): Yellow solid, mp: 78–80 °C. Yield: 0.126 g (79%). 1H NMR (300 MHz, CDCl3) δ: 8.02 (s, 1H), 7.83 (d, \( J = 8.7 \) Hz, 2H), 7.26–7.24 (m, 3H), 7.22–7.19 (m, 2H). 13C NMR (75 MHz, CDCl3) δ: 162.5 (d, \( J_{CF} = 249.6 \text{ Hz} \)), 133.4, 132.8 (d, \( J_{CF} = 3.4 \text{ Hz} \)), 131.9, 130.0, 129.4, 127.5, 126.6, 122.5 (d, \( J_{CF} = 8.7 \text{ Hz} \)), 116.7 (d, \( J_{CF} = 23.2 \text{ Hz} \)). HRMS Calcd. for C14H10FN3Se [M+N2+H]⁺: 320.0097. Found: 320.0099.

1-(4-Lodo-phenyl)-3-(phenylselanyl)-1H-1,2,3-triazole (4c): Yellow solid, mp: 78–80 °C. Yield: 0.126 g (79%). 1H NMR (300 MHz, CDCl3) δ: 8.02 (s, 1H), 7.72–7.68 (m, 2H), 7.54–7.51 (m, 2H), 7.26–7.24 (m, 3H), 7.22–7.19 (m, 2H). 13C NMR (75 MHz, CDCl3) δ: 162.5 (d, \( J_{CF} = 249.6 \text{ Hz} \)), 133.4, 132.8 (d, \( J_{CF} = 3.4 \text{ Hz} \)), 131.9, 130.0, 129.4, 127.5, 126.6, 122.5 (d, \( J_{CF} = 8.7 \text{ Hz} \)), 116.7 (d, \( J_{CF} = 23.2 \text{ Hz} \)). HRMS Calcd. for C14H10FN3Se [M+N2+H]⁺: 320.0097. Found: 320.0099.

1-(3-Nitrophenyl)-1H-1,2,3-triazole (4k): Yellow solid, mp: 109–111 °C. Yield: 0.130 g (75%). 1H NMR (400 MHz, CDCl3) δ: 8.50 (s, 1H), 8.24 (d, \( J = 7.1 \text{ Hz, 1H} \), 8.11–8.08
(m, 2H), 7.68 (d, J = 8.1 Hz, 1H), 7.50–7.49 (m, 2H), 7.21–7.19 (m, 3H). 13C NMR (100 MHz, CDCl3): δ: 148.9, 137.3, 134.9, 132.4, 131.1, 129.5, 127.9, 126.0 (2C), 125.9, 123.4, 115.2. HRMS Calcd. for C14H10N2O2Se [M-N2 + H]+: 318.9891. Found: 318.9897.

1-Benzyl-4-(phenylselanyl)-1H-1,2,3-triazole (5a): White solid, mp: 54–56 °C. Yield: 0.113 g (72%). 1H NMR (400 MHz, CDCl3): δ: 7.48 (s, 1H), 7.35–7.33 (m, 2H), 7.29–7.25 (m, 3H), 7.18–7.17 (m, 2H), 7.13–7.10 (m, 3H), 5.45 (s, 2H). 13C NMR (100 MHz, CDCl3): δ: 134.1, 132.5, 131.3, 130.6, 129.0, 129.1, 128.9, 128.4, 128.1, 127.2, 54.3.

7-Chloro-4-(4-(phenylselanyl)-1H-1,2,3-triazol-1-yl)quinoline (5b): White solid, mp: 74–76 °C. Yield: 0.154 g (80%). 1H NMR (400 MHz, CDCl3): δ: 8.93 (d, J = 4.6 Hz, 1H), 8.12 (d, J = 2.1 Hz, 1H), 8.01 (s, 1H), 7.84 (d, J = 9.1 Hz, 1H), 7.52–7.47 (m, 3H), 7.37 (d, J = 4.6 Hz, 1H), 7.21–7.18 (m, 3H). 13C NMR (100 MHz, CDCl3): δ: 151.3, 150.1, 140.4, 136.9, 134.1, 132.4, 129.5 (2C), 129.4, 129.1, 128.9, 127.9, 124.3, 120.3, 115.9. HRMS Calcd. For C17H12ClN4Se [M + H]+: 386.9916. Found: 386.9921.

4. Conclusions

In summary, we have described a one-pot strategy to prepare 4-arylselanyl-1H-1,2,3-triazoles starting from easily prepared and bench-stable selanylalkynylcarbinols. The protocol avoids the isolation and purification steps of the reactive terminal selanylalkynes. The protocol involves the generation of the terminal selanyl alkynes in situ and afforded the expected selenium-containing triazoles in a selective and efficient way. The use of a one-pot protocol avoids the isolation and purification steps of the reactive terminal selanylalkynes. The strategy was successfully employed in the synthesis of selanyltriazole-functionalized chloroquine and Zidovudine. Further studies are ongoing to better characterize the pharmacological potential of these new compounds.

Supplementary Materials: The following are available online, 1H and 13C NMR spectra of all compounds.

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Sample Availability: Samples of the compounds 4a-n are available from the authors.

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