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# Synthesis of ω-hydroxy-α-alkyl/aryl-γ-organo-selenium and γ-organo-tellurium: a new class of organochalcogen compounds with antinociceptive activity

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**Abstract**

We present here the results on the synthesis of alkynylselenoalcohols and alkynyltelluroalcohols using the reaction of lithium-alkynylchalcogenolates, generated via the reaction of alkynyllithium with elemental Se or Te, with bromo-alcohols. The reaction proceeded cleanly under mild reaction conditions, and alkynylchalcogenoalcohols were formed in good to excellent yields. The obtained compounds **2o** and **2v** were screened for antinociceptive activity using the acetic acid-induced writhing reaction in mice. Compound **2o** administered by oral route at 5–50 mg/kg produced a significant inhibition of the acetic acid-induced abdominal constriction in mice.


*Keywords:* Selenium; Tellurium; Pharmacological activity

## 1. Pharmacology

Organoselenium compounds such as selenocystine and a variety of diorganoyl diselenides can react with thiols such as cysteine, dithiothreitol, and reduced glutathione to produce selenocysteine, selenols, and disulfides.[1] In line with these findings, Günther[2] showed that dithiothreitol, a compound with extremely low redox potential, reduced a variety of diorganoyl diselenides, forming selenols and *trans*-4,5-dihydroxy-1,2-dithiane, the oxidation product of dithiothreitol. Some decades ago, the reduction of diorganoyl diselenides to selenol derivatives by reaction with thiols was considered to be of physiological significance.[3] Indeed, Walter and co-workers hypothesized that selenoamino acids, particularly methylselenocysteine, could act as reversible catalytically effective biological antioxidants.[1] After that a variety of organoselenium compounds with potential pharmacological activity including ebselen analogues, benzoselenazolinones, diaryl diselenides, selenamide, and related derivatives have been reported.[4]

## 2. Chemistry

Organoselenium chemistry is a very broad and exciting field, with many opportunities for research and development of applications. Organoselenium compounds have become attractive synthetic targets because of their chemo-, regio-, and stereo-selective reactions, and their useful biological activities.[5] Furthermore, organoselenium compounds can usually be used in a wide variety of functional groups, thus avoiding protection group chemistry.[6] Most organoselenium methodologies proceed stereo- and regio-selectively in excellent yields. Although, the first

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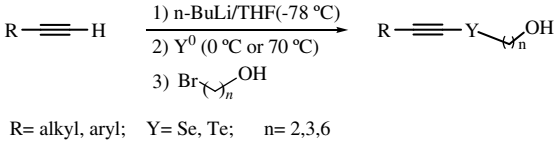



Scheme 1.

organoselenium compound has been prepared by Wöhler in 1847,[7] only in the early 1970s did the chemistry of organoselenium become a versatile tool in organic chemistry.[8] The organoselenium chemistry developed rapidly, mainly in the area of selenocarbohydrates, selenoaminoacids, and selenopeptides. The selenium group can be introduced in an organic substrate via both nucleophilic and electrophilic reagents. After being introduced in an organic substrate, the organoselenium group can easily be removed by selenoxide *syn* elimination,[9] and [2,3] sigmatropic rearrangement.[10] In addition, carbon–selenium bond can also be replaced by a carbon–hydrogen,[11] carbon–halogen,[12] carbon–lithium,[13] or carbon–carbon bonds.[14]

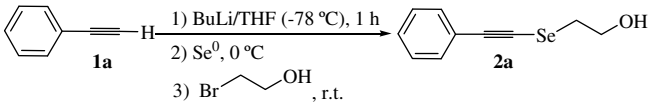
Alkynylchalcogen compounds are highly valuable intermediates in organic synthesis due to their potential for transformation into substituted olefins.[15] Consequently, a number of methodologies havef been developed for the synthesis of these compounds.[16] Most of the syntheses described involve the use of diorganoyl diselenides as starting materials, which are volatile, unstable, and have an unpleasant odor. Additionally, to the best of our knowledge the preparation of alkynylchalcogenoalcohols, having a free hydroxyl group in the chemical structure, has been scarcely reported.[17] In view of these limitations, there is still a need for the development of clean procedures for the synthesis of these useful organochalcogen compounds. In this Letter, we present our contribution to the field by developing a mild protocol for the alkynylchalcogenoalcohols synthesis via the reaction of lithium-alkynylchalcogenolates with bromo-alcohols, avoiding the previous preparation of diorganoyl diselenides or selenols (Scheme 1).

## 3. Results and discussion

Since our initial studies have focused on the development of an optimum set of reaction conditions, we have initially chosen phenylacetylene and 2-bromoethanol as standard substrate. In this way, *n*-butyllithium (2 mmol) was added at −78 °C to a solution of phenylacetylene (2 mmol) and THF (6 mL), after 1 h, elemental selenium was added at 0 °C, and subsequent addition of 2-bromo ethanol (1 mmol) gave the alkynylselenoalcohol corresponding in 82% yield.

Regarding the influence of the solvent, better results were achieved using THF, which furnished the desired product **2a** in 82% yield (Table 1, entry 3). We observed that hexane and diethyl ether were less effective since product **2a** was obtained in poor yields (Table 1, entries 1 and 2). It is relevant to note that when the amount of *n*-BuLi is reduced from 2 to 1 equiv, a notable decrease in the yields was observed (Table 1, entries 4 and 5). The use of 2.5 equiv of *n*-BuLi did not improve the yield (Table 1, entry 6).

Table 1
Reaction conditions optimization[a]




| No. | Solvent | *n*-BuLi (equiv) | Yield (%) |
|---|---|---|---|
| 1 | Hexane | 2 | 22 |
| 2 | Diethyl ether | 2 | 35 |
| 3 | THF | 2 | 82 |
| 4 | THF | 1 | 39 |
| 5 | THF | 1.5 | 61 |
| 6 | THF | 2.5 | 81 |

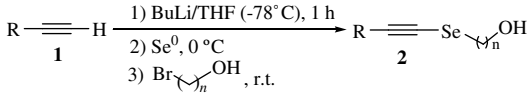
[a] Reactions performed in the presence of **1a** (2 mmol), $Se^0$ (2 mmol), and 2-bromoethanol (1 mmol).

Thus, the careful analysis of the optimized reaction revealed that the optimum condition for this protocol was the addition of *n*-butyllithium (2 mmol) to a solution of phenylacetylene (2 mmol) and THF (6 mL), at −78 °C. The resulting solution was stirred for 30 min at this temperature. After this the reaction was warmed to 0 °C and elemental selenium was added. The reaction was allowed to stir at room temperature until all $Se^0$ has been consumed (yellow solution), and then bromoalcohol (1 mmol) was added. To demonstrate the efficiency of this reaction, we explored the generality of our method, extending the conditions to other alkynes and different bromoalcohols and the results are summarized in Table 2.[18]

Inspection of Table 2 shows that the reaction worked well for a variety of bromoalcohols and alkynes. Both hindered and non-hindered alkyl and aryl alkynes gave the desired alkynylselenoalcohols. A closer inspection of the results revealed that the reaction is not sensitive to the distance of hydroxyl group from bromine in the bromoalcohol.

In an attempt to broaden the scope of our methodology, the possibility of performing the reaction with tellurium instead of selenium was also investigated. Thus, the standard reaction condition applied to prepare the alkynylselenoalcohols was also tested for the alkynyltelluroalcohol derivatives. Unfortunately, this condition was not effective and products were obtained in poor yields. Thus, a variety of conditions were investigated, including temperature, solvent, stoichiometry, and time. It was gratifying to discover that simply changing the temperature from 0 °C to reflux, just after the tellurium addition, gave the alkynyltelluroalcohols generally in reasonable to good yields (68–94%) but in some cases (Table 3, entries 1, 4, 5 and 7) low yields (40%, 12%, 30%, and 23%) occurred. Thus, the careful analysis of the optimized reaction conditions revealed that the general synthetic procedure for the reaction is as follows: *n*-butyllithium (2 mmol) is added

Table 2
Synthesis of alkynylselenoalcohols



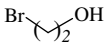
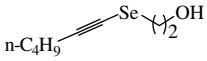
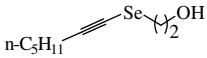
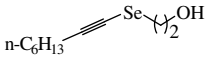
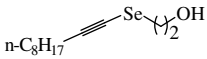
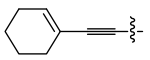
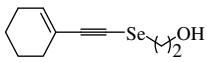
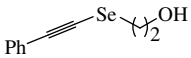
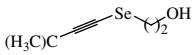
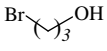
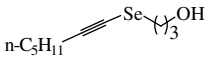
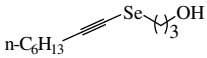
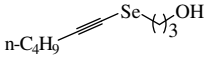
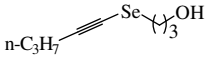
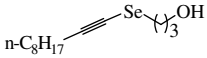
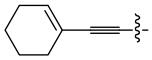
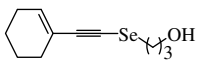
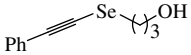
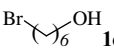
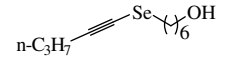
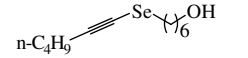
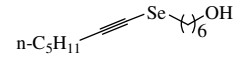
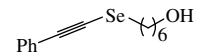

| No. | Bromo-alcohol | R | Product[a] (yield/%) |
|---|---|---|---|
| 1 |  **1c** | $n$-$C_3H_7$ |  **2b** (50) |
| 2 | **1c** | $n$-$C_4H_9$ |  **2c** (54) |
| 3 | **1c** | $n$-$C_5H_{11}$ |  **2d** (71) |
| 4 | **1c** | $n$-$C_6H_{13}$ |  **2e** (81) |
| 5 | **1c** | $n$-$C_8H_{17}$ |  **2f** (76) |
| 6 | **1c** |  |  **2g** (19) |
| 7 | **1c** | Ph |  **2a** (82) |
| 8 | **1c** | $(CH_3)_3C$ |  **2h** (75) |
| 9 |  **1d** | $n$-$C_5H_{11}$ |  **2i** (89) |
| 10 | **1d** | $n$-$C_6H_{13}$ |  **2j** (87) |
| 11 | **1d** | $n$-$C_4H_9$ |  **2k** (97) |
| 12 | **1d** | $n$-$C_3H_7$ |  **2l** (67) |
| 13 | **1d** | $n$-$C_8H_{17}$ |  **2m** (86) |
| 14 | **1d** |  |  **2n** (50) |
| 15 | **1d** | Ph |  **2o** (80) |

Table 2 (*continued*)

| No. | Bromo-alcohol | R | Product[a] (yield/%) |
|---|---|---|---|
| 16 | **1d** | $(CH_3)_3C$ |  **2p** (96) |
| 17 |  **1e** **1e** | $n$-$C_3H_7$ |  **2q** (70) |
| 18 | **1e** | $n$-$C_4H_9$ |  **2r** (67) |
| 19 | **1e** | $n$-$C_5H_{11}$ |  **2s** (94) |
| 20 | **1e** | $n$-$C_6H_{13}$ |  **2t** (76) |
| 21 | **1e** | $n$-$C_8H_{17}$ |  **2u** (72) |
| 22 | **1e** | Ph |  **2v** (70) |
| 23 | **1e** | $(H_3C)_3C$ |  **2w** (60) |

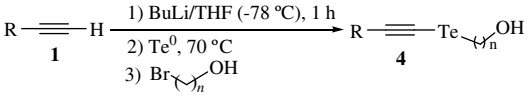
[a] Yields of **2a–w** are given for isolated products.

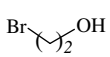
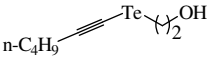
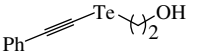
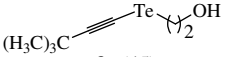
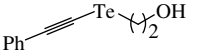
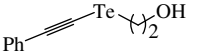
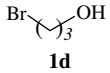
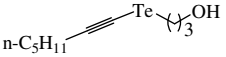
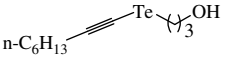
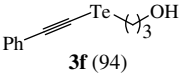
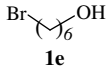
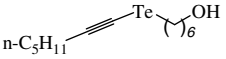
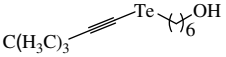
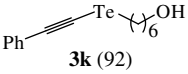
to a solution of alkyne (2 mmol) and THF (6 mL), at −78 °C. The resulting solution is stirred for 30 min at this temperature. The temperature was warmed to room temperature and tellurium powdered was added. This mixture was then heated at reflux for 5 h and bromoalcohol (1 mmol) was added at room temperature. Next, we extended our studies on the scope of this reaction to different alkynes and bromoalcohols and the results are summarized in Table 3.[19] Our investigations focused on the influence of alkyl and aryl groups at terminal alkynes. Satisfactorily, all alkynes were found to be effective, although lesser yields were observed to alkylalkynes. Our experiments also showed that performing *n*-BuLi and tellurium addition at 0 °C and room temperature, respectively, gave the product in an unsatisfactory yield.

## 4. Pharmacology

Based on the previous screening for antioxidant activity of alkynylselenoalcohol compounds, **2o** and **2v** were chosen for evaluating antinociceptive activity of this class of organochalcogens. The obtained compounds **2o** and **2v** were screened for antinociceptive activity using the acetic acid-induced writhing reaction in mice. The acetic acid-induced writhing reaction in mice is described as a model for visceral pain. This methodology has long been used

Table 3
Synthesis of alkynyltelluroalcohols[a]




| No. | Bromo-alcohol | R | Product[a] (yield/%) |
|---|---|---|---|
| 1 |  **1c** | $n$-$C_4H_9$ |  **3a** (40) |
| 2 | **1c** | Ph |  **3b** (68) |
| 3 | **1c** | $(CH_3)_3C$ |  **3c** (45) |
| 4[b] | **1c** | Ph |  **3b** (12) |
| 5[c] | **1c** | Ph |  **3b** (NR) |
| 6 |  **1d** | $n$-$C_5H_{11}$ |  **3d** (30) |
| 7 | **1d** | $n$-$C_6H_{13}$ |  **3e** (23) |
| 8 | **1d** | Ph |  **3f** (94) |
| 9 |  **1e** | $n$-$C_5H_{11}$ |  **3g** (34) |
| 10 | **1e** | $(CH_3)_3C$ |  **3j** (67) |
| 11 | **1e** | Ph |  **3k** (92) |

[a] Yields of **3a–i** are given for isolated products.
[b] $n$-BuLi was added at room temperature.
[c] $Te^0$ was added at room temperature.

as a screening tool for the assessment of antinociceptive property of new agents.[20] The results of antinociceptive effect induced by compounds **2o** and **2v** on acetic acid-induced abdominal constriction response in mice are presented in Figure 1. The best result was obtained using compound **2o**. In fact, compound **2o** administered by oral route at 5–50 mg/kg produced a significant inhibition of the acetic acid-induced abdominal constriction in mice when compared to the control group ($p < 0.05$ by Newman–Keuls' test). Conversely, compound **2v** (1–50 mg/kg) did not cause significant inhibition of the nociceptive response induced by acetic acid. All alkynylchacogenoalcohols are currently under study on acetic acid-induced abdominal constriction and will be reported in due course.

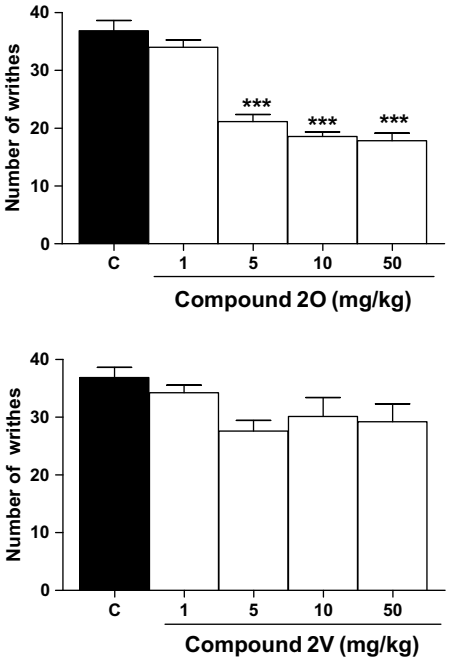



Fig. 1. Effect of compounds **2o** and **2v** administered orally against acetic acid-induced writhing movements in mice. Each column represents the mean with SEM. for 6–12 mice in each group. Control (C) indicates the animal injected with canola oil. Asterisks denote the significance levels, when compared to the control group (one-way ANOVA followed by Duncan's test) $^{***}P < 0.001$.[22]

In summary, the procedure described herein provides an interesting protocol for the synthesis of alkynylchalcogenoalcohols. We have shown that the anion lithium-alkynylchalcogenolate readily reacts with bromoalcohols in THF to give the corresponding alkynylchalcogenoalcohols in good yields. Additionally, by our method the preparation of diorganoyl diselenides or selenol is avoided. The synthesized compounds have promising antinociceptive activity and should be pharmacologically interesting. We expect that these findings would be useful in choosing a method for the synthesis of ω-hydroxy-γ-organo-selenium and γ-organo-tellurium alkynes. This reaction associated with the nickel-catalyzed cross-coupling of selenides[14] or palladium cross-coupling of tellurides[21] can contribute to an interesting alternative route to the preparation of more functionalized alkynes. Analysis of the $^1H$ and $^{13}C$ NMR spectra showed that all the obtained products presented data in full agreement with their assigned structures.

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18. *General procedure for the alkynylselenoalcohols synthesis*: To a two-neck round-bottomed flask, under argon, containing a solution of appropriated alkyne (2 mmol) in THF (6 mL) at −78 °C was added to *n*-BuLi (0.8 mL of a 2.5 M solution in hexane; 2 mmol). The reaction mixture was stirred for 30 min. After this the reaction was warmed to 0 °C and elemental selenium (0.158 g; 2 mmol) was added. The reaction was allowed to stir at room temperature until all $Se^0$ has been consumed (yellow solution), and then the appropriated bromoalcohol (1 mmol) was added. The reaction mixture was allowed to stir at room temperature for 12 h. After this time, the mixture was diluted with ethyl acetate (20 mL) and washed with aqueous $NH_4Cl$ (20 mL) and water ($3 \times 20$ mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel using ethyl acetate/hexane as the eluent. Selected spectral for **2a**. Yield: 0.185 g (82%). $^1$H NMR: (400 MHz, $CDCl_3$): $\delta$ 7.42–7.38 (m, 2H), 7.30–7.27 (m, 3H), 4.02–3.99 (t, 2H, $J = 5.8$ Hz), 3.01 (t, 2H, $J = 5.8$ Hz), 2.55 (sl, 1H). $^{13}$C NMR: (100 MHz, $CDCl_3$): $\delta$ 131.45, 128.21, 128.19, 123.08, 99.42, 68.91, 61.14, 32.26.
19. *General procedure for the alkynyltelluroalcohols synthesis*: To a two-neck round-bottomed flask, under argon, containing a solution of appropriated alkyne (2 mmol) in THF (6 mL) at −78 °C was added to *n*-BuLi (0.8 mL of a 2.5 M solution in hexane; 2 mmol). The reaction mixture was stirred for 30 min. After this the reaction was warmed to 0 °C and elemental tellurium (0.256 g; 2 mmol) was added. The reaction was allowed to stir at reflux for 5 h. After this time, the reaction was cooled to room temperature and then the appropriated bromoalcohol (1 mmol) was added. The reaction mixture was allowed to stir at room temperature for additional 12 h. After this time, the mixture was diluted with ethyl acetate (20 mL) and washed with saturated aqueous $NH_4Cl$ (20 mL) and water ($3 \times 20$ mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel using ethyl acetate/hexane as the eluent. Selected spectral for **(3c)**. Yield: 0.114 g (45%). $^1$H NMR: (400 MHz, $CDCl_3$): $\delta$ 4.03 (t, 2H, $J = 6.3$ Hz), 2.98 (t, 2H, $J = 6.3$ Hz), 2.60 (sl, 1H), 1.24 (s, 9H). $^{13}$C NMR: (100 MHz, $CDCl_3$): $\delta$ 121.19, 62.93, 31.06, 29.43, 28.79, 13.08.
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22. *Bioassay*: The abdominal constriction was induced according to procedures described previously by Côrrea[23] and modified by Nogueira[24] and resulted in the contraction of the abdominal muscle together with a stretching of the hind limbs in response to an intraperitoneal injection of acetic acid (1.6%) at the time of the test. Mice were pre-treated with compounds **2o** and **2v** (1–50 mg/kg) by oral route, 30 min before the irritant injection. Control animals received a similar volume of vehicle (10 ml/kg, canola oil). After the challenge, mice were individually placed in separate boxes and the abdominal constrictions were counted cumulatively over a period of 20 min. Antinociceptive activity was expressed as the reduction in the number of abdominal constrictions, that is, the difference between control animals (mice pre-treated with vehicle) and animals pre-treated with the drug.
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