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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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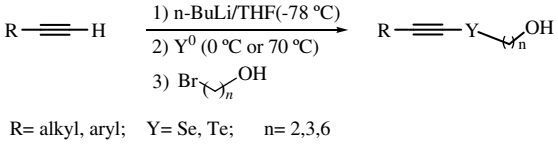


Scheme 1.

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]

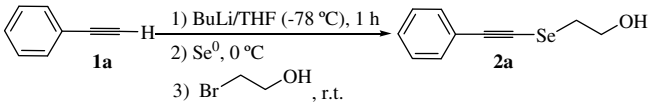
Alkynylchalcogen compounds are highly valuable intermediates in organic synthesis due to their potential for transformation into substituted olefins.[15] Consequently, a number of methodologies havef been developed for the synthesis of these compounds.[16] Most of the syntheses described involve the 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