

Synthesis of new selenides-1,2,3-triazoles with potential activity against *Trypanossoma cruzi* †

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Abstract: Chagas disease, considered by the World Health Organization as a neglected tropical disease, is responsible for the deaths of more than 10,000 people annually. The main drugs used to overcome the disease, Benzonidazole and Nifurtimox, besides being old, have limitations regarding the adverse effects related to the treatment time and consequently their toxicity. Therefore, the need for a new drug to be used against this disease becomes evident. The classes of organoselenium and aromatic heterocycles 1,2,3-triazoles are promising for this issue, profile of both classes for further evaluation against *Trypanossoma cruzi*, the since both have their known chemistry and antiparasitic activity already described. In this work, the molecular hybridization technique was used in order to combine the individual bioactive protozoan that causes Chagas disease. The methodology used was based on works described in the literature. Initially, benzene azides were synthesized from commercial anilines, while ethynyl(phenyl)selane came from different aromatic diselenides. With these intermediates, a 1,3-dipolar cyclo-addition was performed to obtain the new target molecules 1-phenyl-4-(phenylselenanyl)-1H-1,2,3-triazoles with moderate to good yields ranged from 52 to 75%. The characterization of the final molecules is in process and when finished they will be send for evaluation of biological activity. It's possible to conclude that the method used is simple and easy to access, an important factor for potential drugs against neglect diseases. After the assessment of bioactivity, it will be possible to identify the efficiency of these substances, as well as, if necessary, the optimization of their structure.

Keywords: Chagas disease, organoselenium; triazol;

1. Introduction

Chagas disease, caused by the protozoan *Trypanossoma cruzi* (*T. cruzi*), is considered by the World Health Organization to be a neglected tropical disease. Despite this, it's estimated that this disease affects between 6 and 8 million people worldwide and it is responsible for the deaths of 10,600 to 12,500 people annually^[1]. The drugs currently used for its treatment are Benzonidazole (1) and Nifurtimox (2), two derivatives of nitrogenous heterocycles (Figure 1).

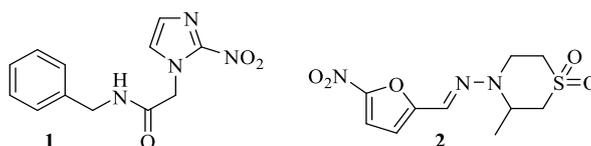


Figure 1. Chemical structures of Benzonidazole (1) and Nifurtimox (2).

However, they have been used for more than 40 years as the only viable treatment options. Furthermore, their maximum efficiency are found only in the acute phase of the infection and the long treatment time results in high toxicity.^[2] In this context, motivated by the neglect of the Chagas disease even with a significant number of deaths caused by it, also the few options of drugs for its treatment and mainly because it still has no cure, some research groups have been dedicated to developing new alternatives to fight this disease that affects the most vulnerable population around the world. Some of these studies include organoselenium compounds and nitrogenous heterocycles.

Selenium was discovered in the 19th century, however, due to its strong odor and supposed toxicity, this element did not attract attention in that time. Nevertheless, in 1950s, it was discovered that selenium is an essential element in the animal diet^[3]. Today it is known that selenium has an antioxidant function, being part of the active site of the Glutathione Peroxidase (GPx), an important enzyme that works in the reduction of reactive oxygen species (ROS)^[4]. In this context, organoselenium compounds have already been described as antioxidants, apoptosis inducers, chemopreventors of cancers in various organs (brain, liver, skin, prostate, for example), antimicrobial, antihypertensive, anti-HIV and anti-protozoan^[5]. As an example of interest for this work, in 2017, Chao and collaborators developed a series of selenocyanates with inhibitory activity of an important enzyme in the growth of *T. Cruzi*, being extremely selective substances and strong candidates for antiparasitic agents^[6].

On the other hand, nitrogen-containing aromatic heterocycles, especially 1,2,3-triazoles, have been widely described in the literature because of their several pharmacological activities, such as antiplatelet^[7], antimicrobial^[8], antiviral^[9], anti-inflammatory^[10], anti-allergic, among others. Their extensive pharmacological activity together with the fact that they don't have major adverse effects, make their importance undoubted in the medical field.

Therefore, in view of the need for new drugs for the treatment of Chagas disease, which are more active and selective, the objective of this work is the synthesis of new selenium containing 1,2,3-triazoles (Figure 2) for the evaluation against *Trypanosoma cruzi*.

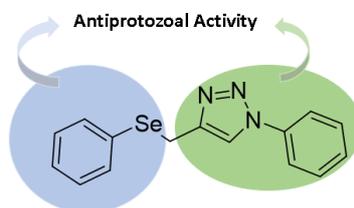


Figure 2. General structure of selenium containing 1,2,3-triazoles.

2. Materials and Methods

The structural determination of the synthesized substances was performed using instrumental methods of hydrogen nuclear magnetic resonance spectroscopy (¹H NMR) and by infrared (IR) spectroscopy. The NMR spectra were obtained in a Varian VNMRS 500 MHz or Varian VNMRS 300 MHz device and the chemical shifts were determined using TMS as an internal reference. The spectra in the infrared region were obtained using a Perkin-Elmer spectrophotometer, model 1420 with double beam in a beam over KCl windows. The absorption values were expressed as a wave number, using the reciprocal centimeter (cm⁻¹) as the unit.

The reaction monitoring process was carried out using thin layer chromatography (TLC) with silica gel plates 60-F-254, 0.2 mm thick (ref. Merck 5554). For the purification of the substances by column chromatography, 230-400 Mesh ASTM flash silica gel 60 (0.035-0.070 mm, ref. Acros Organics) was used.

2.1. Synthesis of azides

The synthesis of azidobenzene compounds, 4a, 4b, 4c and 4d, started from commercial anilines using the same methodology already described in the literature^[11]. Aniline was dissolved in

hydrochloric acid (6M HCl) in an ice bath, with the temperature controlled between 0-5 ° C. Sodium nitrite (NaNO₂) dissolved in water was added dropwise. The the reaction mixture was kept under stirring for 30 min.. Then, sodium azide (NaN₃), dissolved in water, was added dropwise. After the addition, the system was stirred for two hours at room temperature and extracted with ethyl acetate (3 x 15 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was used without purification.

2.2. Synthesis of the alkynes

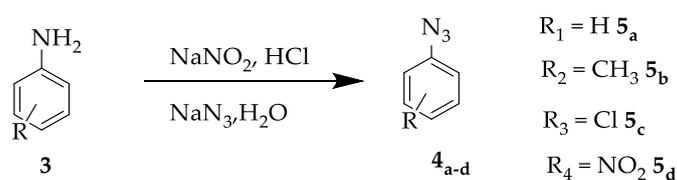
The ethynyl (phenyl) selane compounds, 6a, 6b, 6c and 6d were synthesized from the corresponding diselenides, previously synthesized. Based on a methodology described in the literature^[12], a solution containing the diphenyl diselenide in THF under a nitrogen atmosphere was added dropwise in a ethanolic suspension of sodium boron hydride (NaBH₄). The reaction mixture was kept under stirring at 0 ° C and propargyl bromide, in THF, was added. After 25 minutes the reaction was poured into water and the organic phase was extracted using diethyl ether. The combined organic phases were dried over anhydrous sodium sulfate and concentrated under vacuum. The reaction was purified using flash chromatography using hexane as the eluent.

2.3. Synthesis of triazoles containing selenium

From a methodology of cycloaddition of azides and alkynes already described in the literature^[13] the 1-phenyl-4- (phenylselanyl) -1H-1,2,3-triazoles, 7a, 7b and 7c were synthesized. Azide and alkali were added in a suspension of water and dichloromethane. To the system, under stirring, copper sulfate and sodium ascorbate were added. The mixture was kept under stirring and at room temperature. The progress of the reactions was monitored by TLC. After the end of the reaction, extraction was done using dichloromethane. The organic phases were washed with brine, saturated sodium bicarbonate solution and dried with anhydrous sodium sulfate. The product was concentrated using vacuum and purified by recrystallization.

3. Results and Discussion

Initially, using a methodology already described in the literature^[11], the synthesis of azides was carried out from commercial anilines. Through a reaction of diazonium salt formation, followed by substitution by the azide group the **4a-d** products were obtained with quantitative yields (Scheme 1).



Scheme 1. Synthesis of azides **5a-d**.

The obtained products, oily compounds, were characterized by infrared (IR) spectroscopy, and to exemplify the IR spectrum of compound **4b** illustrated in Figure 3. The inclusion of donor and withdrawer groups was carried out for further evaluation of the influence on biological activity.

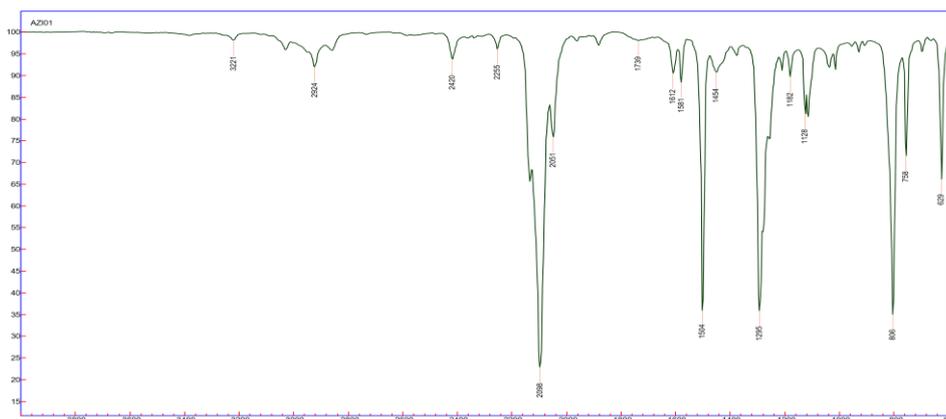
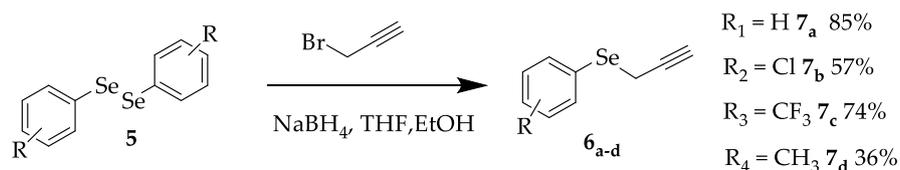


Figure 3. Infrared spectroscopy for substituted methyl azide – 4b.

From the IR it's possible to see the band in 2098 cm^{-1} characteristic of the azide group (N_3)^[11], which proves, therefore, the formation of the desired product.

The molecules containing selenium were synthesized starting from different previously obtained diphenyl diselenides, which underwent cleavage by the reducing agent, giving rise to the nucleophile responsible for replacing the bromine atom in the propargyl bromide (Scheme 2)^[12].



Scheme 2. Synthesis of alkyne functionalized with selenium 6a-d.

The 4 structures were obtained as orange solids and had yields that varied between 36 and 85%. The best result, with 85% yield, was shown in compound 7a. The presence of a donor group decreases the yield, but the synthesis of compounds with donor groups and electron withdrawers will be important for the evaluation of biological activity. The selenofunctionalized alkynes were characterized by ¹H NMR, as shown in Figure 4.

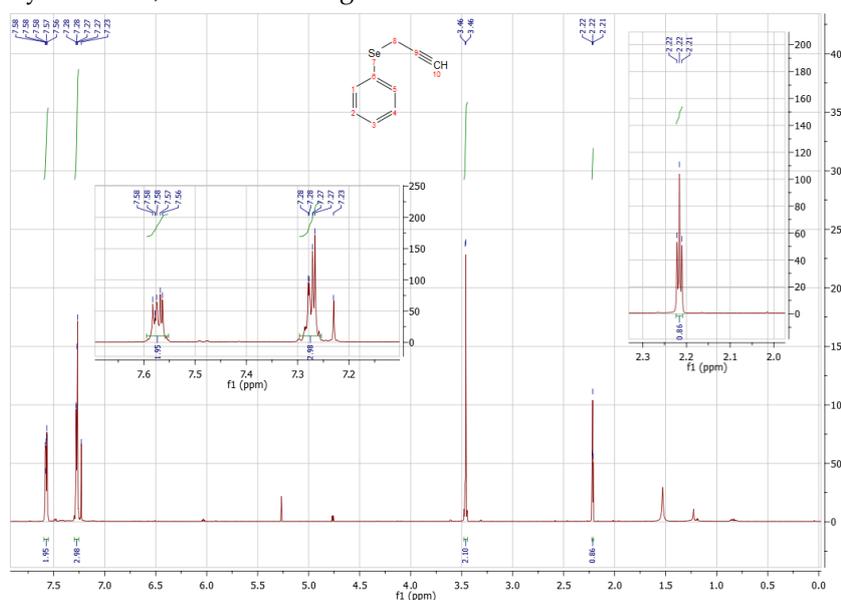
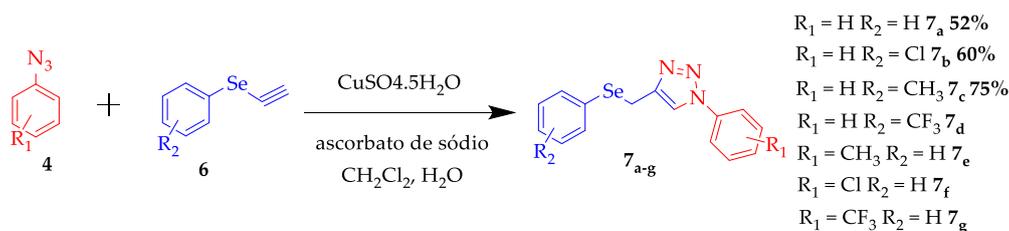


Figure 4. ¹H-NMR spectrum of compound 6a (300 MHz, CD_3Cl , 25° C).

In this spectrum, we can see that according to the integrals of each signal, there is a total of 8 hydrogens that correspond to the 8 hydrogens that are expected in the molecule in question. There are two multiplets at 7.58 and 7.27 ppm, with integrations of 2 and 3 hydrogens respectively, totaling the aromatic H of the molecule. Then there is a doublet at 3.46 ppm integrating 2 hydrogens, referring to the 2 H of CH₂ of the substance. Finally the triplet in 2.22 ppm, integrating 1 H, characteristic of the H of the CH of the triple bond^[12].

The last step to synthesize the target is the stage of formation of triazole from the previously synthesized anilines and selenoalkynes. The seven 1,3-dipolar addition cycle reactions were performed to obtain the final products **7_{a-g}** (Scheme 2).



Scheme 2. Synthesis of triazoles containing selenium.

Only 3 compounds have their yields, which vary from 52 to 75% where it is possible to observe an increase in income with an electron donor group. The reactions to obtaining **7_{d-g}** were accompanied by thin layer chromatography (TLC), were purified by chromatographic column and, unfortunately, due to the pandemic of the COVID-19, the authors couldn't performed the characterization for further verification of their structure, thus it was not possible to calculate yields. Until now, compounds **7_a**, **7_b** and **7_c** were analyzed by ¹H NMR spectroscopy, taking as an example the **8_c** spectrum represented in Figure 5.

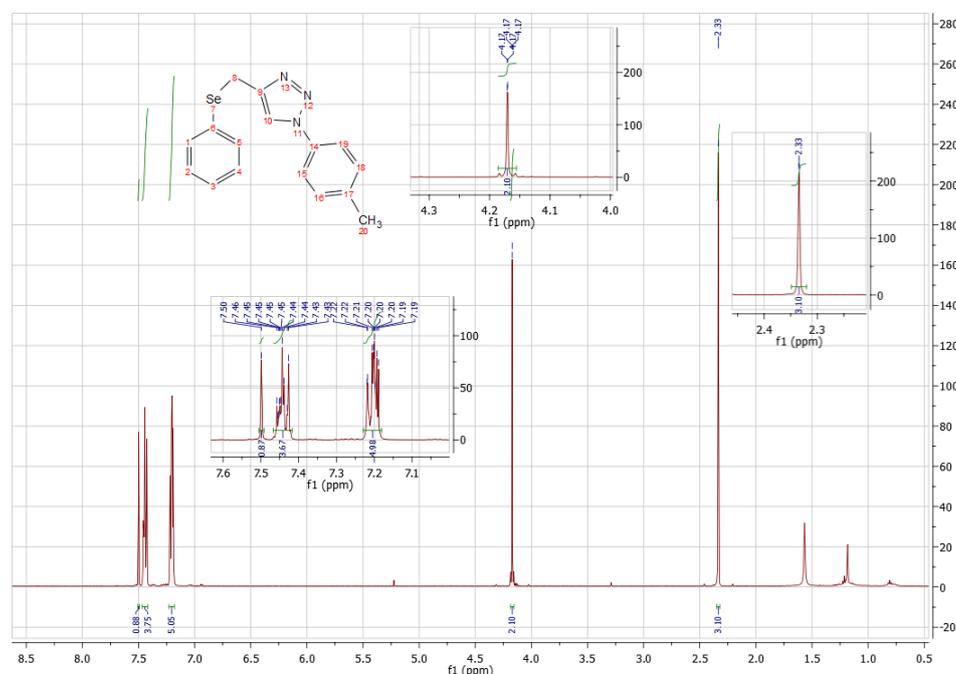


Figure 5. H-NMR spectrum of compound **8_c** (300 MHz, CD₃Cl, 25°C).

It is possible to determine by the integrations of this spectrum the presence of 15 hydrogens, this value being compatible with the 15 hydrogens existing in the molecule. Initially, there is a simplet at 7.50 ppm, integrating 1 H, which is relative to the H of the triazolic ring. Then, there are two

multiplets centered at 7.45 and 7.20 ppm, integrating 4 and 5 H respectively, these being related to the aromatic hydrogens of the substance. sequentially, a doublet is seen at 4.17 ppm, comprising 2 hydrogens, which refer to the 2 H of the compound's CH₂. Finally, a singlet at 2.33 ppm, integrating 3 H, characteristic of the compound's methyl hydrogens.

4. Conclusion and Perspectives

The present work showed an efficient methodology to obtaining the new selenium containing 1,2,3-triazoles, which was able to unite two important nuclei in the same structure. When the activities that were interrupted due to COVID-19 come back, purification and characterization of the **7d-g** products will be carried out, followed by the sending of all examples for pharmacological tests, in partner laboratories, against *T. cruzi*, the protozoan that causes Chagas disease.

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Conflicts of Interest: The authors declare no conflict of interest.

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