European Journal of Medicinal Chemistry 109 (2016) 107–113

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Research paper

New approach towards the synthesis of selenosemicarbazones, useful compounds for Chagas' disease

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ARTICLE INFO

Article history:
Received 11 September 2015
Received in revised form
19 December 2015
Accepted 21 December 2015
Available online 23 December 2015

Keywords:
Chagas' disease
Selenosemicarbazone
Ishihara reagent
Iminochloride

ABSTRACT

Herein, we describe a new approach towards the synthesis of selenosemicarbazones. The reaction involves an *O–Se* exchange of semicarbazones using Ishihara reagent. Eleven selenosemicarbazones were prepared using this methodology, with low to moderate yields. Among the prepared compounds the *m*-bromo phenyl methyl derivative **1b** was selected to be evaluated *in vivo*, in a murine model of acute Chagas' disease. Compound **1b** 10 mg/kg bw/day reduced 50% of parasitaemia profile compared with the control group, but was less effective than Benznidazole (50 mg/kg bw/day reduced 90%) and toxic. These studies are important to guide future Chagas drug design.

1. Introduction

An important endemic neglected disease in South America is the American trypanosomiasis, known as Chagas' disease (CD). It is a lifelong infection caused by the protozoan *Trypanosoma cruzi*, found throughout the American continent in a variety of wild mammalian reservoirs and transmitted by the triatomine bug insect vector [1].

Symptomatic CD is a leading cause of morbidity and loss of productivity due to infectious disease in Latin America [2]. If not treated during the acute phase, Chagas' disease develops into a chronic condition that can be either symptomatic or asymptomatic, which is the most frequent clinical presentation. Symptomatic patients develop, usually decades after infection, either the cardiac form, characterized by progressive lesions in cardiac muscle, arrhythmias, and heart failure, in up to 30% of patients, or the digestive form, characterized by the enlargement of the esophagus and/or the colon. It is transmitted to humans by a blood-sucking triatomine bug through its infected faeces and breaks into the human skin during blood meal or through mucous membranes; occasionally, causing outbreaks with contaminated food. Transmission through blood transfusion, pregnancy and delivery are also possible, and less frequent through organ transplantation or laboratory accidents [3].

Since the 1970s Nifurtimox and Benznidazole are the only existing drugs effective in acute phase of the disease. Both nitroheterocyclic compounds cause severe side effects and their success at chronic phase is still debated [4–6]. Given the unsatisfactory performance of the currently available drugs, new approaches on more specific chemotherapy for Chagas have been advanced in the last three decades. Posaconazole and Ravuconazole were described as potential drugs by inhibiting the ergosterol biosynthesis [7,8], and recently phase-II clinical trials for its evaluation as antiparasitic drugs have been concluded. The studies revealed lower efficacy compared to the current standard Benznidazole treatment and highlighted the inadequacy of the existing pre-clinical testing paradigm for this disease [9,10]. A very limited number of controlled clinical trials for Chagas' disease have been conducted to date. The selection of these compounds for clinical evaluation relied on pre-clinical data obtained from in vitro screens and animal studies.

Abbreviations: bw/day, body weight/day; PBS, Phosphate-Buffered Saline.

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http://dx.doi.org/10.1016/j.ejmech.2015.12.040
0223-5234/

1.1. Selenosemicarbazones background

Recently, we reported a series of selenosemicarbazone (**1**) compounds, as Cruzipain inhibitors and anti *T. cruzi* agents against non-infective and infective forms of the parasite. *In vitro,* these compounds showed antichagasic activity at low μM concentrations [11]. Selenosemicarbazones were designed as the Se analogs of thiosemicarbazones, compounds also known as Cruzain inhibitors [12]. Recently, López et al. described a series of phenolic thiosemicarbazones and selenosemicarbazones, as potential multitarget drugs, showing a wide variety of biological properties [13].

In general, the synthesis of compounds **1** was achieved by condensing aldehydes or ketones with selenosemicarbazide **2** (see Fig. 1). Unfortunately, reagent **2** was discontinued from the market, limiting the preparation of new derivatives.

With the idea of preparing novel compounds, we aimed to develop an alternative methodology for the synthesis of N1-unsubstituted selenosemicarbazones. The described methodologies for the preparation of these compounds are: reaction of acyl isoselenocyanates with phenylhydrazine [14], or cyclohexanone with hydrazine and potassium selenocyanate followed by exchange with different aldehydes [15]. However, none of them were suitable for the preparation of N1 unsubstituted selenosemicarbazones, needed for structure activity relationship.

This fact prompted us to study alternative choices for the preparation of these compounds. Recently, we applied an *O–Se* exchange reaction for the preparation of selenazoles using the Ishihara reagent (LiAlHSeH) [16]. This reagent was developed in 2001 and its wide ranging utility was demonstrated for the preparation of diverse selenocarbonyl derivatives like selenoamides [17]. We reported a one-pot synthesis of selenazoles by in situ formation of propargyl selenoamides, using LiAlHSeH as a reagent for O–Se exchange, followed by the spontaneous 5-*exo* cyclization [16].

Based on these previous results, we studied the utility of LiAlHSeH as a selenating reagent for the preparation of selenosemicarbazones **1**, starting from the oxygenated compounds, the semicarbazones **3**.

2. Results and discussion

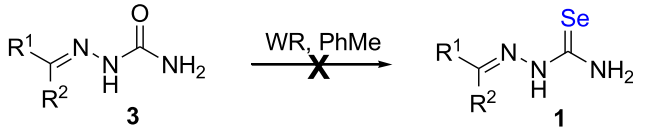
2.1. Chemistry

2.1.1. Optimization of the synthesis of selenosemicarbazones

Firstly, we worked through the optimization of selenosemicarbazone synthesis, via *O–Se* exchange with Woollins Reagent (WR) [18], using standard conditions, but all attempts were unsuccessful, see Table 1.

When Ishihara reagent (LiAlHSeH) was used in the conditions reported by Vishwanatha et al. [19], using PCl_5 (2 equiv), catalytic amount of DMF (0.3 equiv) in PhMe at 0 °C, following the addition of LiAlHSeH (1.5 equiv), led to the uncompleted conversion of **3a** (43%) and low yield (12%), see entry 1, Table 2. When CH_2Cl_2 was used as solvent at 0 °C, better conversion was obtained (85%), but in low yield (28%), see entry 2, Table 2. Increasing the amount of LiAlHSeH (2 equiv), afforded the complete conversion (100%) to selenosemicarbazone **1a**, but low recovery yield remained (19%), see entry 3, Table 2. Attempts to increase the yield at a lower temperature (−20 °C), did not conduct to the desired results, see entry 4, Table 2. Finally, the best conditions were achieved: PCl_5 (3 equiv), CH_2Cl_2, 0 °C, followed by the addition of LiAlHSeH (3.2 equiv), at 0 °C, see entry 5, Table 2. Then, selenosemicarbazone **1a** was prepared under these optimized conditions with a 100% conversion and 50% yield.

Table 1
Attempts for *O–Se* exchange reaction, using Woollins Reagent.



Entry	R^1	R^2	Conditions	Yield (%)
1	5-NO_2-furanyl	H	RW (1 equiv), 70 °C, 5 h	–
2	*m*-Br-Ph	H	RW (1 equiv), *p*-TsOH, reflux, 12 h	–

2.1.2. Preparation of selenosemicarbazones *1a–k*

Under optimized conditions, eleven selenosemicarbazones **1a–k** were prepared according to the two-step one-pot reaction showed in Scheme 1. The compounds were obtained starting from previous prepared semicarbazones **3** and PCl_5 (3 equiv), in CH_2Cl_2 at 0 °C, following the addition of freshly prepared LiAlHSeH (3.2 equiv) at 0 °C, according to Scheme 1.

The yields ranged from low to moderate (5–65%). Selenosemicarbazones derived from aldehydes (when R^1 = H; compounds **1h–k**) were obtained with lower yields than the ketone derivatives (when R^1 = alkyl, aryl; compounds **1a–c**, and **1e–g**). Also, the highest yields were obtained when using unsubstituted or *meta* substituted aromatic derivatives with electron withdrawing groups (EWG) (compounds **1a–b**, and **1e–f**).

Compound **1f** was obtained as an inseparable mixture of *Z:E* isomers, at the C=N group. Attempts to isolate both isomers failed due to their re-equilibration, as previously reported [11].

When R^1 and R^2 were alkyl groups, selenosemicarbazone **1d** was obtained in low yield (7%), see Scheme 1.

We also tried to apply this methodology to prepare selenosemicabazide **2** via oxygen selenium exchange of semicarbazide, using LiAlHSeH reagent, but was unsuccessful, probably due to solubility problems. We also tried a different procedure described in literature using thiourea, Se^0 and $NaBH_4$ [20], in different conditions, but the conversion was never achieved. Even the afforded yields using our methodology are moderated, it is a new approach towards the synthesis of N1-unsubstituted selenosemicarbazones, using commercially available reagents (Se^0, PCl_5, $LiAlH_4$) otherwise

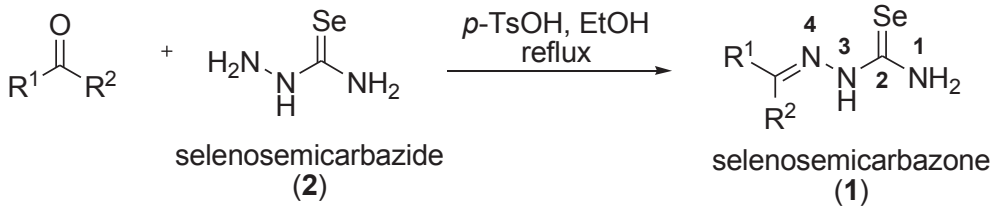


Fig. 1. Synthesis of selenosemicarbazones