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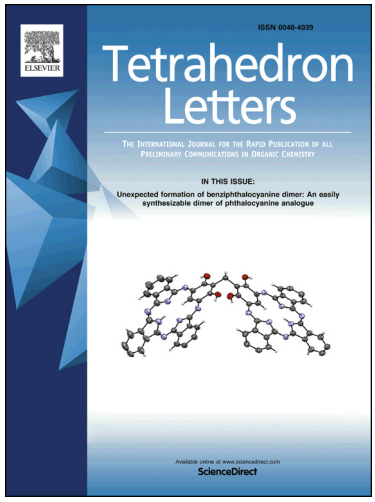

Preparation of Bis(2-pyridyl) diselenide Derivatives: Synthesis of Selenazolo[5,4-*b*]pyridines and Unsymmetrical Diorganyl Selenides, and Evaluation of Antioxidant and Anticholinesterasic Activities

Thiago J. Peglow, Ricardo F. Schumacher, Roberta Cargnelutti, Angélica S. Reis, Cristiane Luchese, Ethel A. Wilhelm, Gelson Perin

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Graphical Abstract

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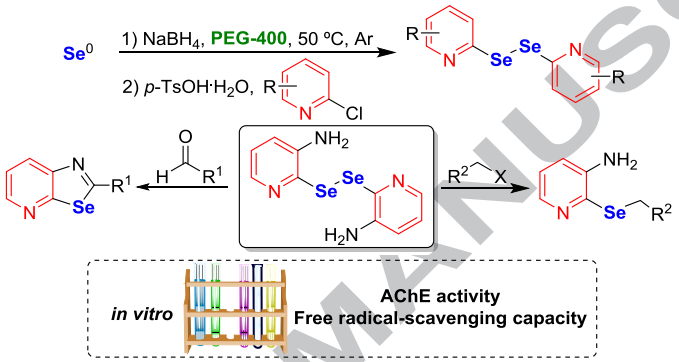

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Preparation of Bis(2-pyridyl) diselenide Derivatives: Synthesis of Selenazolo[5,4-*b*]pyridines and Unsymmetrical Diorganyl Selenides, and Evaluation of Antioxidant and Anticholinesterasic Activities

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ABSTRACT

We describe here an alternative method to prepare bis(2-pyridyl) diselenide derivatives using reduced selenium species, generated *in situ*, and different 2-chloropyridines promoted by *p*-TSOH in PEG-400 as solvent. This is a straightforward protocol to prepare bis(3-amino-2-pyridyl) diselenides unprecedented to date. Still, this article describe the employment of synthesized bis(3-amino-2-pyridyl) diselenide and a diverse array of aryl aldehydes to afford the corresponding 2-aryl-selenazolo[5,4-*b*]pyridines in satisfactory yields and, in a short reaction time under basic condition. Furthermore, when the bis(3-amino-2-pyridyl) diselenide reacted with aliphatic halides, in the presence of $NaBH_4$, a wide range of unsymmetrical diorganyl selenides was obtained. To complete this investigation the bis(3-amino-2-pyridyl) diselenide was evaluated for its inhibitory effect on the acetylcholinesterase (AChE) activity and free radical-scavenging capacity. Results demonstrated that this compound was antioxidant and inhibitor of the AChE activity, being a promising therapeutic agent for the treatment of Alzheimer's disease and other neurodegenerative disorders.

1. Introduction

In the last years the chemistry of the organoselenium compounds has emerged as an interesting field of research due their versatility in a diverse array of organic transformations.[1] Furthermore, selenium is a trace element essential that participates in major metabolic functions and has potent antioxidant properties.[2] In this context, many organoselenium compounds has received attention as promising drugs candidates presenting important pharmacological properties such as anti-inflammatory, antiviral, antifungal, antinociceptive, anti HIV, antitumor and, so on.[2,3]

As previously reported, the interest in this compound class is strongly correlated to the high potential therapeutic application of drugs that can finely modulate a catalytic redox equilibrium involved in several different pathologies.[2a-b] Indeed, the development of new and efficient strategies to afford selenides and diselenides represents an interesting opportunity for the potential use of these compounds as antioxidant but also as new green bio-mimetic catalysts.[2c]

Due their chemical and biological importance, the development of synthetic methodologies to prepare new selenium-containing molecules has grown from the 80's, when the results for the synthetic Ebselen revealed its promising antioxidant properties.[4] In this way, the synthesis and applications of bis(2-pyridyl) diselenides and its derivatives has been focus of many studies including development of synthetic methodologies and evaluation of their biological properties.[5] In this sense, as the most recent publication, Potapov and co-workers described in 2016 the use of 2-pyridinylselanyl derivatives in the synthesis of vinyl and propargyl selenides.[6] On the other hand, Prabhu and co-workers examined 2,2'-diselanediyldinicotinamide for its glutathione peroxidase (GPx)-like catalytic activity.[7] Singh and co-workers also described their results describing a 6,6'-dibromo-2,2'-dipyridyl diselenide derivative as mimics of the GPx.[8] Sancineto and co-workers

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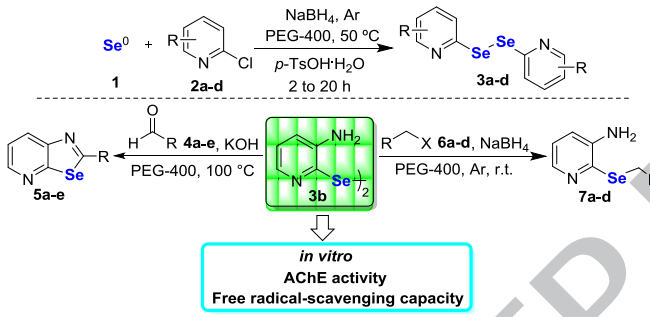
examined a series of 2,2′-diselenobisbenzamides as novel HIV retroviral nucleocapsid protein 7 (NCp7) inhibitors, including a nicotinic derivative that presented good antiviral activity although with certain toxicity.[9] Cargnelutti and collaborators described the use of dipyridyl diselenide and bis(pyridin-2-ylselanyl)alkanes as ligands for coordination chemistry and copper-catalyzed C-S bond formation.[10]

Although some dipyridyl diselenide derivatives are well known, there are however, only one report of Sakakibara and co-workers that describes the synthesis and synthetic use of bis(3-amino-2-pyridyl) diselenide.[5d] In this sense, envisioning an direct and easy method to obtain this compound, we describe an alternative method to prepare bis(2-pyridyl) diselenides **3** using 2-chloropyridines **2** and reduced selenium species in the presence of *p*-toluenesulfonic acid monohydrate in PEG-400 as solvent. Still, due our interest in the synthesis and biological evaluation of new organoselenium compounds, the bis(3-amino-2-pyridyl) diselenide **3b** was used to synthesize new 2-aryl-[1,3]selenazolo[5,4-*b*]pyridines **5** and (3-amine-2-pyridyl) alkyl selenides **6**. To complete our investigation, the bis(3-amino-2-pyridyl) diselenide compound **3b** was also evaluated for their *in vitro* inhibitory effect on the acetylcholinesterase (AChE) activity and free radical-scavenging capacity (Scheme 1).



Scheme 1: General scheme of the present work.

2. Results and Discussion

2.1 Chemistry

Initially, we chose elemental selenium **1**, 2-chloropiridine **2a** and $NaBH_4$ as the standard starting materials to establish the best reaction conditions under argon atmosphere (Table 1). We examined temperature, Brønsted acid, amount of Se^0, amount of $NaBH_4$, and the nature of the solvent.

In our preliminary experiment, a mixture of 0.5 mmol of selenium powder **1** and 1.1 mmol of $NaBH_4$ in PEG-400 (3.0 mL) was stirred at 50 ºC for 0.5 h to afford *in situ* the nucleophilic selenium specie. The reduction was accompanied by the change in the solution color, from black to whitish. After this, the reaction mixture was cooled to r.t., then a solution of 2-chloropiridine **2a** (0.5 mmol) and *p*-toluenesulfonic acid monohydrate (1.0 mmol) in PEG-400 (1.0 mL) was added in the reaction vessel and the reaction remained at r.t. for an additional 17 h. Under these reaction conditions the desired bis(2-pyridyl) diselenide **3a** was obtained in 60% yield (Table 1, entry 1). Due the incomplete consumption of **3a** in entry 1, we then used an excess of elemental selenium (0.6 mmol) and the product **3a** could be obtained in 78% yield (Table 1, entry 2). To our satisfaction, when the reaction was conducted with gently heating (50 ºC) the product **3a** was isolated in 78% yield after only 2 hours (Table 1, entry 3). In contrast, when a higher excess of Se^0 (Table 1, entries 4 and 5), an increment of the reducing agent (Table 1, entry 6), and temperature of 80 ºC (Table 1, entry 7) were applied, comparable results were observed. On the other hand, when the reaction was performed without the Brønsted acid, the desired product **3a** was not formed (Table 1, entry 8).

Table 1. Optimization of reaction conditions.[a]

Entry	Se^0 **1** (mmol)	Brønsted Acid	Temp (°C)	Time (h)	Yield (%)[b]
1	0.5	*p*-TsOH·H_2O	20	17	60
2	0.6	*p*-TsOH·H_2O	20	17	78
3	**0.6**	***p*-TsOH·H_2O**	**50**	**2**	**78**
4	0.7	*p*-TsOH·H_2O	50	2	77
5	1.0	*p*-TsOH·H_2O	50	2	75
6[c]	0.6	*p*-TsOH·H_2O	50	2	73
7	0.6	*p*-TsOH·H_2O	80	2	72
8	0.6	-	50	2	N.R.
9[d]	0.6	H_3PO_2 (50% w/v)	50	2	11
10[d]	0.6	HCl (36% w/v)	50	2	58
11[d]	0.6	H_3PO_4 (85% w/v)	50	2	8
12[d]	0.6	CH_3COOH	50	2	53
13[e]	0.6	*p*-TsOH·H_2O	50	2	15
14[f]	0.6	*p*-TsOH·H_2O	50	2	19

[a] The mixture of Se^0 and $NaBH_4$ (1.1 mmol) in PEG-400 (3.0 mL) under argon was heated to 50 °C and stirred for approximately 0.5 h. After that, a mixture of compound **2a** (0.5 mmol), *p*-TsOH·H_2O (1.0 mmol) and PEG-400 (1.0 mL) was added. [b] Yield are given for isolated product **3a**. [c] 1.3 mmol of $NaBH_4$ was used. [d] 0.3 mL of the respective acid was added. [e] Ethanol (4.0 mL) was used as solvent. [f] 1:1 mixture of ethanol/THF (4.0 mL) was used as solvent.

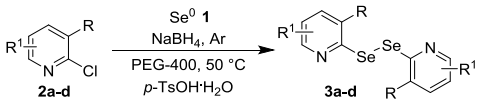
Subsequently, various organic or inorganic Brønsted acids such as hypophosphorous acid (50 wt. % in H_2O), hydrochloric acid (36 wt. % in H_2O), phosphoric acid (85 wt. % in H_2O) and glacial acetic acid were used, however, lower yields were obtained when compared with *p*-toluenesulfonic acid monohydrate (Table 1, entry 3 *vs* entries 9-12). Regarding the influence of the solvent, we explored the use of ethanol and a 1:1 mixture of ethanol/THF (Table 1, entries 13 and 14). However, analysis of these results revealed that PEG-400 was much superior in terms of product yield.

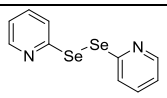
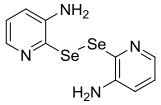
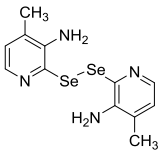
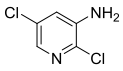
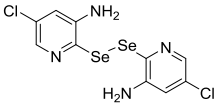
From the results displayed in Table 1, it is possible to concluded that the best reaction condition to obtain the bis(2-pyridyl) diselenide **3a** is using 0.6 mmol of selenium powder **1** and 1.1 mmol of $NaBH_4$ in 3.0 mL of PEG-400 at 50 ºC for 0.5 h under argon, followed by addition of a mixture of 0.5 mmol of 2-chloropyridine **2a** and 1.0 mmol of *p*-TsOH.H_2O in 1.0 mL of PEG-400 and stirring for more 2 h (Table 1, entry 3).

In the next series of experiments, we studied the applicability of this reaction condition to different 2-chloropiridines **2a-d**, and these results are shown in Table 2.

The results shown in Table 2 revealed that the present protocol is suitable to the use of unprecedent 2-chloropyridines to prepare new bis(3-amino-2-pyridyl) diselenides **3b-d**. A close inspection of table 2 revealed, however, that the introduction of a strong electron-donating amine group hamper the nucleophilic attack of selenium species to the chloropyridine and lower yields were obtained after 20 hours when compared to **3a** (Table 2, entries 1 *vs* 2-4). In this sense, the formation of products **3b-d** was achieved from 48% to 66% yield.

Table 2. Synthesis of bis(2-pyridyl) diselenides **3a-d**.[a]



Entry	Pyridine **2**	Time (h)	Product **3**	Yield (%)[b]
1	 **2a**	2	 **3a**	78
2	 **2b**	20	 **3b**	48
3	 **2c**	20	 **3c**	51
4	 **2d**	20	 **3d**	66

[a] A mixture of Se^0 (0.6 mmol) and $NaBH_4$ (1.1 mmol) in PEG-400 (3.0 mL) under argon was stirred at 50 ºC for 0.5 h, followed by the addition of a solution of compound **2** (0.5 mmol), *p*-TsOH·H_2O (1.0 mmol) in 1.0 mL of PEG-400 and stirred for the indicated time at 50 °C. [b] Yields are given for isolated products.

To confirm the chemical structure of the synthesized bis(3-amino-2-pyridyl) diselenides, the product **3b** was crystallized and analyzed by single-crystal X-ray diffraction.[10] The molecular structure is demonstrated in Figure 1.

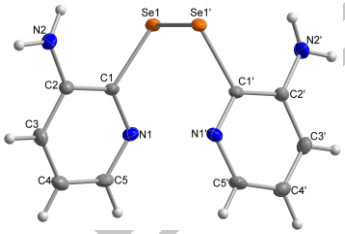
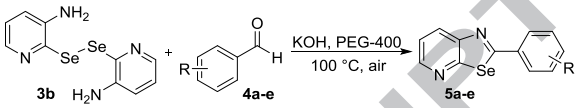


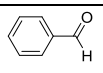
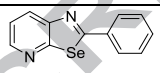
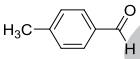
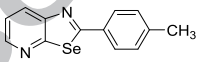
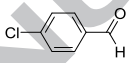
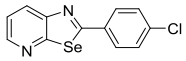
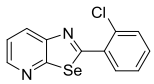
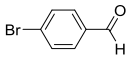
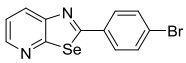
Figure 1: Molecular structure of compound **3b**.[12] Symmetry operation used: (′) = 1-x+1, -y+, z.

After that, bis(3-amine-2-pyridyl) diselenide **3b** (0.25 mmol) and benzaldehyde **4a** (0.5 mmol) were elected expecting to react through an intermolecular condensation reaction to generate an imine intermediate, which subsequently undergoes an intramolecular cyclization to produce 2-phenyl-[1,3]selenazolo[5,4-*b*]pyridine **5a**. Initially, we performed a methodology described by Radatz and collaborators[13] which use sodium metabisulfite ($Na_2S_2O_5$) as reducing agent in DMSO at 120 °C, but only traces of the expected product **5a** were obtained with a complete decomposition of the diselenide **3b**. On the other hand, Ma and co-workers described a procedure based on KOH-promoting cleavage of Se-Se bond.[14] In this way, after carried out a modified procedure by using KOH (2.0 equiv), bis(3-amine-2-pyridyl) diselenide **3b** (0.25 mmol) and freshly distilled benzaldehyde **4a** (0.5 mmol) in PEG-400 at 100 °C for 24 h under argon atmosphere, the product **5a** could be obtained in 23% yield. With this result in hand we subsequently increased the KOH amount to 4.0 equivalents and, all the starting materials were consumed in only 5 h in air to produce **5a** in 53% yield. It was also verified the influence of other solvents such as acetonitrile, DMF and glycerol, or the use of an excess of benzaldehyde (1 mmol and 1.5 mmol), but unsatisfactory yields were obtained.

Considering the novelty of this study, we next extended the method to other aryl aldehydes **4b-e**, and these results are show in Table 3.

Table 3. Synthesis of 2-aryl[1,3]selenazolo[5,4-*b*]pyridines **5a-e**.[a]



Entry	Aldehyde **4**	Product **5**	Yield (%)[b]
1	 **4a**	 **5a**	53
2	 **4b**	 **5b**	45
3	 **4c**	 **5c**	25
4	 **4d**	 **5d**	40
5	 **4e**	 **5e**	33

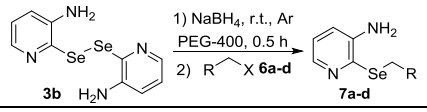
[a] Reactions were carried out using **3b** (0.25 mmol), aryl aldehyde **4** (0.5 mmol), and KOH (1 mmol) in PEG-400 (3.0 mL) at 100 °C in air. [b] Yields are given for isolated products.

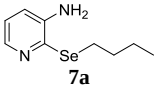
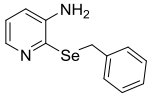
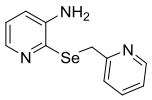
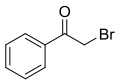
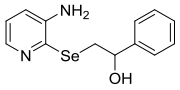
By using aromatic aldehydes containing electron-donating and electron-withdrawing groups at the *ortho*- and *para*-position the reaction was successfully performed, affording satisfactory yields for the respective 2-aryl[1,3]selenazolo[5,4-*b*]pyridines **5b-e** (Table 3, entries 2-5).

Still, regarding the reactivity of bis(3-amino-2-pyridyl) diselenide **3b** and the possibility to produce new organoselenium derivatives, we also performed the reaction of 3-aminopyridine 2-selenolate, generated *in situ*, with alkyl halides **6** (Table 4).

These reactions were carried out using a simple and efficient methodology with bis(3-amino-2-pyridyl) diselenide **3b** (0.25 mmol), PEG-400 as solvent and $NaBH_4$ (0.75 mmol) as reducing agent, stirred at room temperature for 0.5 h under argon atmosphere. Then, the desired alkyl halide **6** (0.5 mmol) was added, and the stirring was maintained for additional 0.5 hour. The products **7a-d** were obtained in excellent yields (Table 4). It should be mentioned that when 2-bromoacetophenone **6d** was used as substrate, after 15 minutes the alcohol **7d** was obtained due the excess of $NaBH_4$ (Table 4, entry 4).

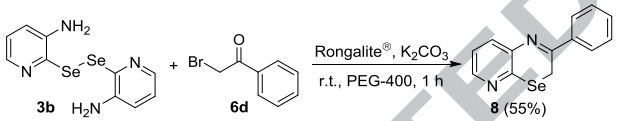
Table 4. Synthesis of 2-(alkylselanyl)pyridin-3-amine **7a-d**.[a]



Entry	Alkyl halide **6**	Product **7**	Yield (%)[b]
1	 **6a**	 **7a**	85
2	 **6b**	 **7b**	97
3	 **6c**	 **7c**	85
4	 **6d**	 **7d**	98

[a] Reactions were carried out using **3b** (0.25 mmol) and $NaBH_4$ (0.75 mmol) in PEG-400 at r.t. under Ar for 0.5 h, followed by the addition of desired alkyl halide **6** (0.5 mmol) and stirring for additional 0.5 h or 0.25 h (entry 4). [b] Yields are given for isolated products.

Envisioning to complete our synthetic investigation, we performed a reaction by using Rongalite® (0.75 mmol) as a mild reducing agent for Se-Se bond cleavage and K_2CO_3 (0.25 mmol) in PEG-400 (2.0 mL).[15] In this procedure we employed the diselenide **3b** (0.25 mmol) and 2-bromoacetophenone (1.0 mmol). After stirred the reaction at room temperature for 1 h the 2-phenyl-3*H*-pirido[2,3-*b*][1,4]selenazine **8** was obtained as the main product in 55% yield (Scheme 2).



Scheme 2. Synthesis of pyridoselenazine **8**.

2.2 In vitro assays

2.2.1 AChE activity assay

Alzheimer's disease, the most common type of dementia, is a progressive neurodegenerative disorder that results in memory impairment and cognitive dysfunction.[16] One of the critical elements in producing dementia in Alzheimer's disease patients appears to be the immoderate reduction of acetylcholine (ACh) hydrolyzed by acetylcholinesterase (AChE). In this sense, the approach is to inactivate AChE activity, a key enzyme that cleaves ACh in the synaptic cleft and terminates neuronal signaling.[17] Since the clinical application of the first cholinesterase inhibitor, most clinicians and probably most patients were considered the cholinergic drugs, donepezil, galantamine and rivastigmine, as the first-line pharmacotherapy for moderate Alzheimer's disease.[18]

Importantly, our results revealed the potential of compound **3b** as inhibitor of the AChE activity. Figure 2 shows the effect of compound **3b** on AChE activity in cerebral cortex of mice. Compound **3b** significantly inhibited the AChE activity in the cerebral cortex at concentrations equal to or greater than 100 µM and the Imax was 79.3 % (ANOVA: $F(4,10) = 41.24$, $p < 0.0001$).

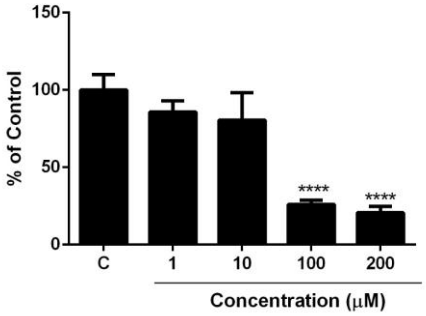


Figure 2. Effect of compound **3b** on the AChE activity in the cerebral cortex of mice. Data are reported as mean ± S.D. of 3 independent experiments. AChE activity was expressed as µmol acetylthiocholine/h/mg protein. **** $p < 0.0001$ as compared with the control (C) group (one-way ANOVA/Newman-Keuls).

2.2.2 Free radical-scavenging capacity

Excessive production of reactive species by cellular respiration and other metabolic activities can cause damage to all cellular structures, including DNA, lipids and proteins from biological membranes.[19] Oxidative stress is critical to the etiology of many chronic and degenerative diseases such as cancer, cardiovascular diseases, diabetes, obesity, epilepsy and Alzheimer's disease.[20] Therefore, the synthesis of compounds with antioxidant potential has received attention from researchers.[21]

The determination of 2,2'-diphenyl-1-picrylhydrazyl (DPPH) and 2,2'-azino bis-3-ethylbenzothiazoline-6 sulfonic acid (ABTS) radicals scavenging activities are among the most common spectrophotometric methods used for the evaluation of antioxidant capacity.[22] As verified in Figure 3, the compound **3b** presented scavenger activity of ABTS radicals at concentrations equal to or greater than 1 µM and the Imax was 99.4 % (ANOVA: $F(4,10) = 301.9$, $p < 0.0001$), suggesting that it is the mechanism by which this compound could display antioxidant action. However, as demonstrated in Figure 4, compound **3b** at all concentrations tested did not have DPPH radical scavenging activity (ANOVA: $F(4,10) = 0.3175$, $p > 0.05$).

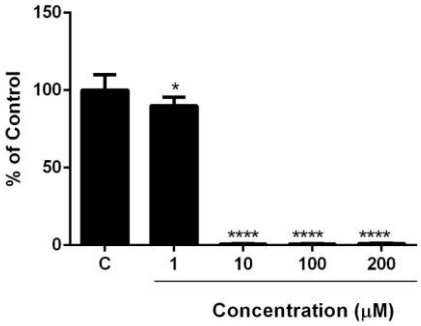


Figure 3. Scavenging effect of compound **3b** on ABTS radicals. Data are reported as mean ± S.D. of 3 independent experiments. The values are expressed in percentage of control (C) (100 %). * $p < 0.05$ denotes when compared to the control, **** $p < 0.0001$ denotes when compared to the control (C) (one-way ANOVA followed by the Newman– Keuls' test).

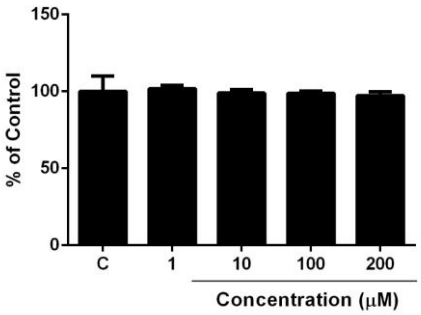


Figure 4. Scavenging effect of compound **3b** on DPPH radicals. Data are reported as mean ± S.D. of 3 independent experiments. The values are expressed in percentage of control (C) (100 %) (one-way ANOVA followed by the Newman– Keuls' test).

In the DPPH assay, antioxidants could reduce the stable radical DPPH by donating hydrogen to a free radical to remove the extra electron (which is responsible for the activity of free radicals). Moreover, protonated radical ABTS is used for evaluating the scavenger activity of proton radicals.[23] Our results revealed that the compound **3b** was an effective scavenger against the ABTS radical species, but there was no scavenging activity for DPPH radical. In this regard, we believed that the antioxidant effect of compound **3b** is related to protonated radical-scavenger activity. The different effect of compound **3b** in DPPH and ABTS assays can be due to the different chemical structure of these two radicals. Moreover, it could be rationalized that nitrogen atom into pyridine ring is important to scavenger activity of proton radicals. As evidenced by Luchese and collaborators (2012),[24] bis(2-pyridyl) diselenide has excellent antioxidant potential and it is a better antioxidant that other disubstituted diaryl diselenides due the presence of pyridine ring. However, in line with our results, it is important to highlight that ABTS radicals scavenging activity of compound **3b** is better than bis(2-pyridyl) diselenide.

3. Conclusion

In summary, we have developed a simple and efficient method for the synthesis of bis(2-pyridyl) diselenides using 2-chloropyridynes in acid medium. This method allowed to prepare the bis(3-amino-2-pyridyl) diselenide, which reactivity was tested to synthesize a new class of 2-aryl[1,3]selenazolo[5,4-*b*]pyridines, 2-(alkylselanyl)pyridin-3-amino and 2-phenyl-3*H*-pirido[2,3-*b*][1,4]selenazine. These compounds were obtained by simple and environmentally benign protocols in good to excellent yields. On the other hand, results obtained after preliminary biological assays shown that the compound **3b** has an important potential to act against the oxidative stress and as inhibitor of AChE activity. In addition, other compounds of this class are being studied and additional pharmacological aspects are being elucidated.

Acknowledgments

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11. Crystal data for **3b**: Orthorhombic, space group Fdd2, T = 100(2) K, a = 12.5638(4) Å, b = 23.6753(9) Å, c = 7.6802(4) Å, α = 90°, β = 90°, γ = 90°, V = 2284.49(16) Å^3, Z = 8, Bruker APEX-II CCD, Mo Kα radiation (λ = 0.71073 Å), μ = 6.450 mm^{-1}, absorption correction: multi-scan, Tmin = 0.5002, Tmax = 0.7461. Structure solution and refinement: SHELXL-2014, [G. M. Sheldrick, SHELXS-2014, Program for Crystal Structure Solution, University of Göttingen, 2014]. R^1 = 0.0159, wR^2 = 0.0335, GooF = 1.053, CCDC deposit number: 1555010.
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Supplementary Material

CCDC 1555010 contain the supplementary crystallographic data obtained for compound **3b**. These data can be obtained free of charge via http://www.ccdc.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk.

Preparation of Bis(2-pyridyl) diselenide Derivatives: Synthesis of Selenazolo[5,4-b]pyridines and Unsymmetrical Diorganyl Selenides, and Evaluation of Antioxidant and Anticholinesterasic Activities

Thiago J. Peglow , Ricardo F. Schumacher , Roberta Cargnelutti , Angélica S. Reis , Cristiane Luchese , Ethel A. Wilhelm and Gelson Perin

Highlights

Synthesis and applications of bis(2-pyridyl) diselenide derivatives are described.

Synthesis of new 2-aryl-selenazolo[5,4-*b*]pyridines is presented.

Unsymmetrical diorganyl selenides are prepared in excelente yields.

Synthesis of a new 2-phenyl-3*H*-pirido[2,3-*b*][1,4]selenazine.

The inhibitory effect on the AChE activity and free radical-scavenging capacity.