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Oxone®-mediated direct arylselenylation of imidazo[2,1-*b*]thiazoles, imidazo[1,2-*a*]pyridines and 1*H*-pyrazoles

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ABSTRACT

Oxone mediated reaction of imidazo[2,1-*b*]thiazole, imidazo[1,2-*a*]pyridine and 1*H*-pyrazole derivatives with diaryl diselenides is presented here. The methodology represents an efficient and simple protocol for carrying out the selective synthesis of 5-arylselanyl-imidazo[2,1-*b*]thiazoles, 3-arylselanyl-imidazo [1,2-*a*]pyridines and 4-arylselanyl-1*H*-pyrazoles in high yields using a stable, nontoxic and cheap oxidant. The reactions were conducted at 60 °C in air using acetonitrile as solvent. Alternatively, the use of ultrasound irradiation is presented as a tool for fast and efficient energy transfer that significantly reduced the reaction time.

1. Introduction

Selenium-containing compounds have been frequently found in several new synthetic and biological active molecules [1]. In a synthetic approach, organoselenium compounds are valuable intermediates in selective reactions, acting as organocatalysts and as selective ligands for soft metals to design complexes [2]. Still, organoselenium scaffolds are easily oxidized and capable to capture unpaired electrons, scavenging free radicals in biological media and acting as mimetic to glutathione peroxidase enzyme [3]. More recently, many of these molecules have been associated to other important biological activities such as antimicrobial [4], anti-inflammatory [5], and inhibitor of acetylcholinesterase enzyme [6].

On the other hand, imidazo[2,1-*b*]thiazoles, imidazo[1,2-*a*]pyridines and pyrazoles are important nitrogen containing heterocycles widely used as chemical building blocks in synthetic organic chemistry and as pharmacophore in new drug discovery [7]. For example, many of these derivatives are bioactive compounds exhibiting potent antitumor activity and antiproliferative effect against human cancer cells [8].

In this way, due to the chemical and biological importance, the synthesis of selenium-containing *N*-heterocycles, mainly those electron rich by direct selenylation, is a useful method to incorporate differently substituted organylselanyl units to these molecules [7–10]. Over the last years some methodologies have been reported employing iodine-catalyzed reactions [9], transition metal-catalyzed reactions [10], use of phenylselenium bromide [11], and photo-induced reaction [12]. Despite the number of reported methodologies, some of their synthesis suffer from use of difficult to handle, toxic and corrosive materials, high temperature, and a very limited scope. In view of this, the search for a versatile, general and safe methodology under mild conditions is desired.

In this context, potassium peroxymonosulfate, known as trademark oxone, is a stable triple salt that have been used for more than fifty years for many reactions including epoxidation, halogenation, oxidation of amines to hydroxylamines, oxidation of alcohols, between others [13]. Oxone is a white solid, easy to handle, nontoxic and cheap. In this context, Prasad and coworkers explored a metal-free sulfenylation of 1*H*-indole and demonstrated that

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oxone could be an option to generate electrophilic sulfur species [14]. However, the expected 3-phenylthio-1*H*-indole was obtained in lower yield when compared to ammonium persulfate. Thus, based on this recent report and our interest to develop new synthetic methodologies to prepare selenium-containing compounds [10b,10c], we hypothesize that oxone could be an ideal mild oxidant to promote the direct selenylation of rich *N*-heterocycles.

2. Results and discussion

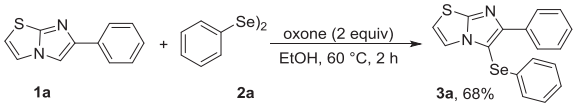
Then, to test our hypothesis, we performed a preliminary experiment selecting 6-phenylimidazo[2,1-*b*]thiazole **1a** and diphenyl diselenide **2a** as model substrates in the presence of oxone and ethanol in air. This reaction was carried out at 60 °C and monitored by TLC. After 2 h the complete disappearance of the substrate **1a** was observed and the reaction was quenched. After purification by column chromatography the expected 6-phenyl-5-phenylselanyl-imidazo[2,1-*b*]thiazole **3a** was obtained in 68% yield (Scheme 1).

With this result in hand we turn our attention to establish the best reaction condition, and the conducted experiments are presented in Table 1. Initially a set of experiments were performed to examine the ideal temperature, amount of diphenyl diselenide **2a** and oxone and the nature of the solvent.

Thus, our first attempt was focused on choosing the best solvent to conduct the reaction. Protic and aprotic solvents such as ethanol, methanol, water, polyethyleneglycol-400, ethyl acetate and acetonitrile were tested (Table 1, entries 1–8). After a careful analysis of these results, we observed that acetonitrile was the most suitable solvent to conduct the reaction, which furnished the expected product in 80% yield (Table 1, entry 8). Gratifyingly, an excellent result was obtained when anhydrous acetonitrile was used, giving **3a** in 95% yield (Table 1, entry 9). Further, decreasing the amount of oxone from 0.3 mmol to 0.2 mmol led to an incomplete consumption of starting materials, and the product was isolated in 84% yield (Table 1, entry 10). When the reaction was conducted under a slight excess of diphenyl diselenide, the reaction yield decreased dramatically to 56% (Table 1, entry 11). To investigate the appropriate temperature, the same reaction was performed at 30 °C; however, the reaction did not proceed until completion even after 24 h (Table 1, entry 12).

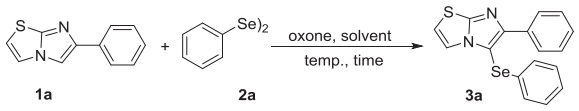
With this best experimental condition to oxone mediated synthesis of **3a** (Table 1, entry 9), we envisioned to extend the methodology to a variety of diaryl diselenides **2**, as well as, differently substituted imidazo[2,1-*b*]thiazoles **1**. Under the optimized conditions the respective 5-arylselanyl-imidazo[2,1-*b*]thiazoles **3a-p** could be obtained efficiently in good to excellent yields and the results are presented in Table 2.

Regarding to diaryl diselenides **2a-j**, various functional groups directly attached to the benzene ring at *ortho*-, *meta*- or *para*-position were tolerated. However, it is important to point out that electronic effects of the substituents gave a somewhat influence in the reaction yield of the corresponding 5-arylselanyl-imidazo[2,1-*b*]thiazole **3**. For example, the products obtained for non-substituted diaryl diselenide **3a** or having electron donating substituents such as methyl **3b** or methoxyl **3c** had better yields if compared to their analogous containing electron withdrawing



Scheme 1. Preliminary conducted reaction.

Table 1
Optimization of the reaction conditions.[a]



Entry	Solvent	Yield (%)	Entry	Solvent	Yield (%)
1	EtOH	68	7	AcOEt	traces
2	EtOH/H_2O	64	8	MeCN	80
3	MeOH	75	9	MeCN[b]	95
4	H_2O	44	10[c]	MeCN[b]	84
5	PEG-400	20	11[d]	MeCN[b]	56
6	Glycerol	35	12[e]	MeCN[b]	57

[a] Reactions were conducted using **1a** (0.15 mmol), **2a** (0.15 mmol) and oxone (0.30 mmol) in solvent (2.0 mL) at 60 °C in air for 2 h.
[b] Anhydrous MeCN was used.
[c] The oxone amount was reduced to 0.2 mmol.
[d] The diphenyl diselenide amount was reduced to 0.10 mmol.
[e] Reaction conducted at 30 °C for 24 h.

groups such as chloro **3d** and fluoro **3e** (Table 2, entries 1–5). When the diaryl diselenide having a trifluoromethane group at *meta*-position was used, the electronic influence of the substituent becomes still more evident, which furnished the 5-(3-(trifluoromethyl)phenylselanyl)imidazo[2,1-*b*]thiazole **3f** in 66% yield (Table 2, entry 6). In this way, the use of bis(4-nitrophenyl)diselenide **2g** gave only 15% yield (Table 2, entry 7). On the other hand, when we turn to analyze steric effects of the substituents at benzene ring of diaryl diselenide, no significant influence was noted. It was evidenced when dimesityl diselenide **2h** was employed and gave the corresponding product **3h** in 81% yield (Table 2, entry 8). The mild reaction condition also gave access to thiophene and pyridine substituted selenides **3i** and **3j** in 75% and 72% yield, respectively (Table 2, entries 9 and 10). Still, we explored the possibility to extend the methodology to different imidazo[2,1-*b*]thiazoles **1b-g**. It was found that the reaction worked well, affording the arylselanyl imidazothiazoles **3k-p** in good yields under the same reaction conditions (Table 2, entries 11–16).

Moreover, analysis of the results described in entries 12, 13, 15 and 16 demonstrated that for these cases the reaction was not sensitive to electronic effects of the substituents at imidazothiazole. The imidazothiazoles **1c** and **1f** bearing a methoxy group gave the products **3l** and **3o** in comparable yields to imidazothiazoles **3m** and **3p** containing chloro as substituent.

In the same way, due to the importance of imidazo[1,2-*a*]pyridines as valuable chemicals and worldwide consumed drugs such as Sumatriptan, Zolimidine, and Zolpiden [15], we decided to explore the selenylation reaction in this class of compounds under the same optimized conditions (Scheme 2). Thus, diphenyl diselenide **2a** (0.15 mmol) reacted with 2-arylimidazo[1,2-*a*]pyridine **4a-c** (0.15 mmol) to afford 2-aryl-3-(phenylselanyl)imidazo[1,2-*a*]pyridines **5a-c** in 76–83% yield.

In addition, we also explored commercially available 1*H*-pyrazoles to produce 4-selanyl-1*H*-pyrazoles **7** via direct selenylation mediated by oxone. In this case the substrates 1*H*-pyrazole **6a** and 3,5-dimethyl-1*H*-pyrazole **6b** were allowed to react with different diaryl diselenides **2** to produce the corresponding 4-selanyl-pyrazoles **7a-f** in good to excellent yields after 4 h at 50 °C. In these cases the amount of oxone was reduced from 2 equiv to 1 equiv without yield loss (Scheme 3).

It is important to mention that all conducted experiments furnished the products selectively with no detectable regioisomers. Besides the structural elucidation described in support information material, the chemical structure of 5-(mesitylselanyl)-6-