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Organoselenium Compounds

Ultrasound-Promoted Radical Synthesis of 5-Methylselanyl-4,5-dihydroisoxazoles

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Abstract: The ultrasound-promoted synthesis of 5-methylselanyl-4,5-dihydroisoxazoles through the radical cyclization of unsaturated oximes with diaryl diselenides using Oxone® as an oxidant and ethanol as the solvent is described. The key step of the reaction is the ultrasound-initiated homolytic cleavage of $KHSO_5$, leading to the formation of sulfate and hydroxyl radicals. The reactions proceed efficiently using several oximes and diselenides containing both electron-withdrawing and electron-donating groups in the aromatic ring. The positive effect of the sonication resulted in high selectivity, short reaction times (15 to 40 min) and moderate to excellent yields of the expected products (60–93 %).

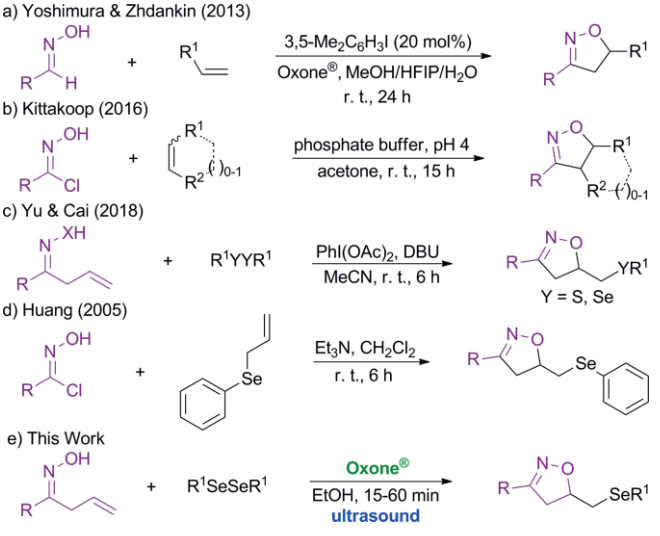
Introduction

The search for new methods for the synthesis of heterocyclic compounds has been increasing, once these molecules have a significant importance in the pharmaceutical field.[1] More specifically, isoxazoles are outstanding due to their biological activities, such as antifungal,[2] antiparasitic[3] and anticancer.[4] Besides, this scaffold is used in the synthesis of more complex molecules.[5] Another important class of compounds are the organoselenium ones, which are used both as intermediate in organic synthesis and in drug discovery.[6] There are several methods to introduce selenium into organic molecules, which include the use of nucleophilic,[7] electrophilic[8] and radical Se-centered reagents.[9]

Among the methodologies described to prepare isoxazole derivatives, the 1,3-dipolar cycloaddition of alkenes and oximes (Scheme 1a)[10] or oxime chlorides (Scheme 1b) are the most atom-efficient.[11] However, the preparation of selenium-containing isoxazole derivatives has been scarcely described. For example, Se-containing 4,5-dihydroisoxazoles or isoxazolines were obtained through the selenofunctionalization of β,γ-unsaturated oximes (Scheme 1c; only two examples)[12] and by the reaction between hydroximoyl chlorides and allyl-phenylselenide (Scheme 1d).[13]

A way to make organic synthesis more environmentally benign is by using efficient energy sources, such as ultrasonic irradiation.[14] In recent years, the use of ultrasound in organic synthesis, the so-called sonochemistry, has emerged in key steps of the synthesis of several compounds, including 3-(5,6-dihydropyrazinyliden)-1*H*-indol-2-ones[15] dihydropyranone, dihydropyrano[2,3-*d*][1,3]dioxinedione derivatives,[16] and linked bis-heterocycle peptidomimetics.[17] Sonochemistry can accelerate and modify the course of reactions and even generate intermediates that would not be feasible in conventional synthesis.[18] Recently, our research group has described the efficient synthesis of 3-selanylindoles[19] and selenium-containing chrysin derivatives[20] using ultrasonic irradiation.

In parallel, Oxone® is an environmentally friendly oxidant used in the transformation of a wide range of organic compounds. This oxidant is commercially available as a blend of three inorganic salts ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$), being potassium peroxymonosulfate ($KHSO_5$) the active species.[21] Interestingly,



Scheme 1. Previous strategies vs. present work.

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Oxone® decomposition leads to the formation of free radicals by homolytic cleavage of $KHSO_5$. This decomposition can be accelerated by homogeneous catalysis in the presence of transition metals (e.g., Co^{2+}, Mn^{2+}, Fe^{2+}), or by ultraviolet light irradiation.[22] The use of Oxone® combined with ultrasound irradiation (US) was explored in environmental chemistry, in the degradation of the cationic dye cresol red.[23] It was observed an acceleration in the degradation rate due to the formation in situ of hydroxyl radical and sulfate radical anion ($HO^{\bullet}$ + $SO_4^{\bullet-}$), which are powerful oxidant species. In the recent years, Oxone® has been used as a mild and green oxidant in the synthesis of valuable selenium-containing molecules.[24]

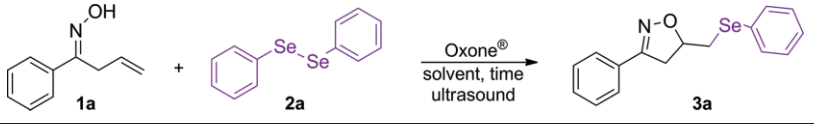
Considering the synergistic effect of Oxone® under sonication, and the importance of organoselenium compounds and isoxazoline derivatives, we have designed an ultrasound-based protocol to prepare Se-containing isoxazolines. This new strategy involves the Oxone®/ultrasound-promoted intermolecular radical cyclization of β,γ-unsaturated oximes with diorganyl diselenides, affording the respective 5-methylselanyl-4,5-dihydroisoxazoles (Scheme 1e).

Results and Discussion

Combining the environmental and economic advantages of using Oxone® under ultrasonic irradiation, a feasibility study was carried out to obtain 5-methylselanyl-4,5-dihydroisoxazoles **3**. Initially, a test was performed using 0.250 mmol of oxime **1a**, 0.125 mmol of diselenide **2a**, 0.250 mmol of Oxone® and ethanol (2.0 mL) as solvent under ultrasonic irradiation at an amplitude of 60 % and a frequency of 20 kHz (Table 1, entry 1). After 20 min of sonication, the total consumption of the starting materials was observed (monitored by TLC), and the expected 5-methylselanyl-4,5-dihydroisoxazole **3a** was obtained in 85 % yield. Other conditions to prepare **3a** were investigated, including the use of different amounts of the starting material **2a** and of Oxone®, as well as, the nature of the solvent (Table 1, entries 2–11). Firstly, we studied the effect of the Oxone® amount in the reaction. By using a lower amount of Oxone® (0.125 mmol), there was no total consumption of the starting materials after 40 min of sonication, and the desired product **3a** was obtained in only 42 % yield (Table 1, entry 2). When an excess of Oxone® was used (0.300 mmol), the starting materials were consumed in 20 min and the product was isolated in 85 % yield (Table 1, entry 3). No product was observed in the absence of Oxone®, evidencing that this reagent is crucial to trigger the radical cyclization step in the reaction (Table 1, entry 4 and see a plausible mechanism below). The use of an excess of diphenyl diselenide **2a** (0.250 mmol) was not effective in increasing the reaction yield, giving the product **3a** in 80 % yield (Table 1, entry 5). Subsequently, the reaction was tested in methanol, polyethylene glycol-400 (PEG-400), glycerol, water, acetonitrile and dimethylformamide (Table 1, entries 6–11). When MeOH, MeCN and DMF were used, good yields were obtained; however, considering that EtOH is a more environmentally benign solvent because it can be obtained from biomass, it was chosen in this synthesis. Based on the results depicted in Table 1, and taking into consideration the toxicity of the tested solvents, the best reaction condition was defined as the sonication of a mixture of 0.250 mmol of oxime **1a**, 0.125 mmol of diphenyl diselenide **2a** and 0.250 mmol of Oxone® in ethanol as the solvent (2.0 mL) (Table 1, entry 1).

In order to evaluate the role of the ultrasound irradiation in the synthesis of 5-methylselanyl-4,5-dihydroisoxazoles, additional studies were carried out using other energy sources, like thermal heating (oil bath), focused microwaves (MW) and the use of an ultrasonic cleaner bath (Table 2). As mentioned before, the product was obtained in 85 % yield in only 20 min using the ultrasound probe type equipment (Table 2, entry 1). When a cleaner ultrasound bath was used however, a longer reaction time was necessary to obtain a similar yield of **3a** (2 h, 82 %) (Table 2, entry 2). When a conventional heating system (oil bath) was used at 65 °C, product **3a** was obtained in 72 % yield after stirring for 18 h (Table 2, entry 3). Finally, the same reaction was performed using MW irradiation at two different

Table 1. Optimization of the reaction conditions.[a]



Entry	**2a** [mmol]	Oxone® [mmol]	Solvent	Time [min]	Yield [%][b]
1	0.125	0.250	EtOH	20	85
2	0.125	0.125	EtOH	40	42
3	0.125	0.30	EtOH	20	85
4	0.125	–	EtOH	60	NR
5	0.250	0.250	EtOH	20	80
6	0.125	0.250	MeOH	20	86
7	0.125	0.250	PEG-400	20	60
8	0.125	0.250	Glycerol	15	20
9	0.125	0.250	H_2O	10	20
10	0.125	0.250	MeCN	30	90
11	0.125	0.250	DMF	30	85

[a] A mixture of **1a** (0.250 mmol), **2a**, Oxone® and the solvent (2.0 mL) in a glass tube was sonicated (60 % of amplitude) for the time indicated in the Table. [b] Isolated yields after column chromatography. NR: no reaction.

temperatures: 65 °C and 80 °C, and the expected product **3a** was obtained in 80 % yield after 2.5 h and 2 h, respectively (Table 2, entries 4 and 5). These results clearly indicate the advantage of using the ultrasound probe to promote this reaction.

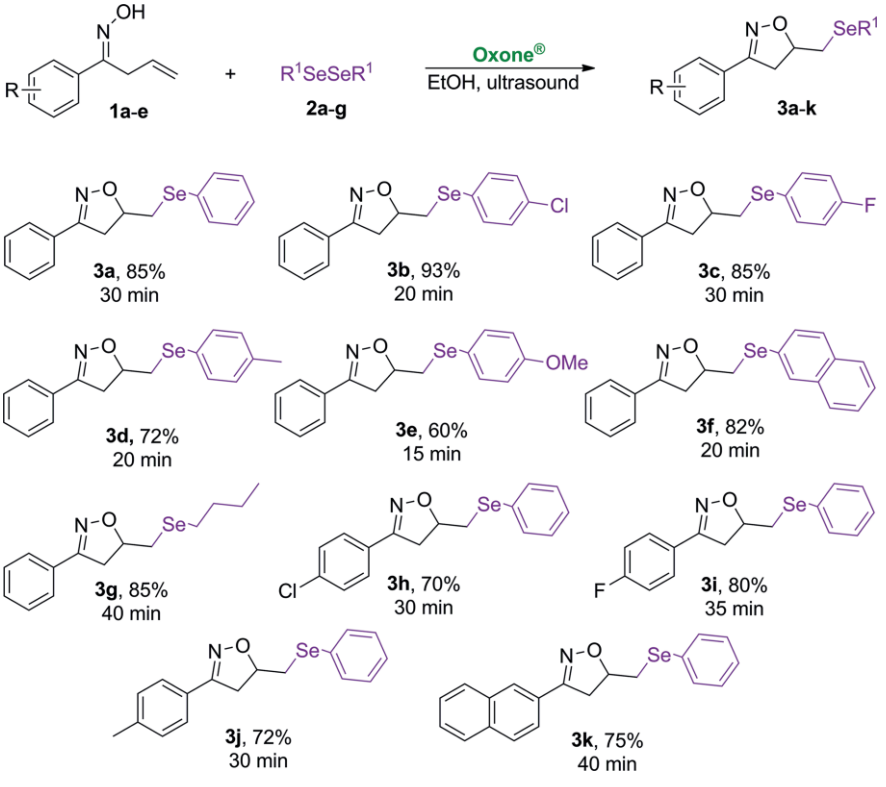
Table 2. Different energy sources in the synthesis of 3-phenyl-5-[(phenylselanyl)methyl]-4,5-dihydroisoxazole **3a**.[a]

Entry	Energy source	Time	Yield of **3a** [%][b]
1	ultrasound probe	20 min	85
2	ultrasound cleaner bath	2 h	82
3	oil bath[c]	18 h	72
4	microwave[c]	2.5 h	80
5	microwave[d]	2 h	80

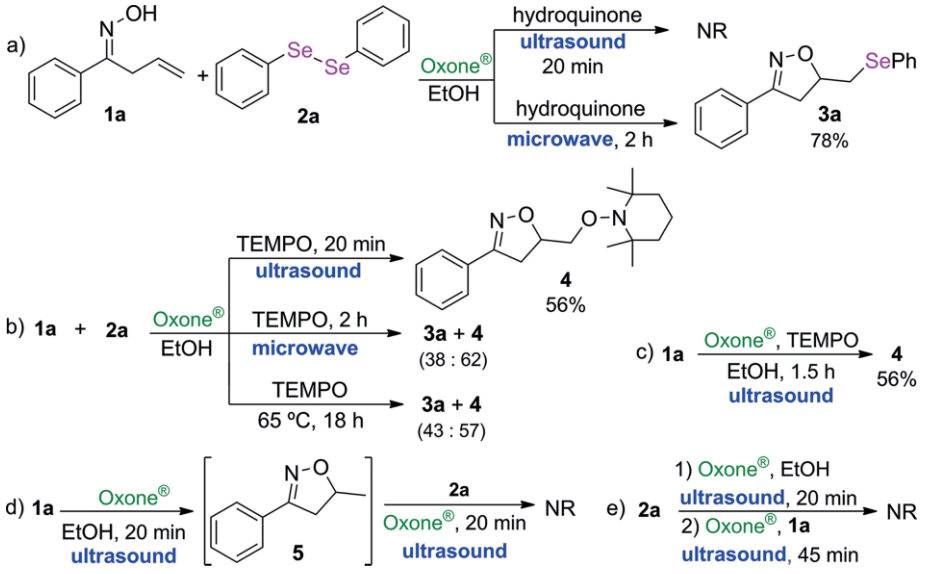
[a] The reaction was carried out using **1a** (0.250 mmol), **2a** (0.125 mmol), Oxone® (0.250 mmol) in EtOH (2.0 mL) in a glass vial. [b] Isolated yields after column chromatography. [c] The reaction was carried out at 65 °C. [d] The reaction was carried out at 80 °C.

Once the best conditions were determined, the methodology was extended to different substrates, in order to evaluate its generality and robustness in the synthesis of different organoselanyl-4,5-dihydroisoxazoles **3** (Scheme 2). Firstly, the effect of electron-withdrawing groups (EWG) and electron-donor ones (EDG) attached to the aromatic ring of the diselenide **2** was evaluated in the reaction with 1-phenylbut-3-en-1-one oxime **1a** (Scheme 2). In general, electron-deficient diaryl diselenides were more reactive substrates than the electron-rich ones, affording higher yields of the respective products. For instance, *para*-substituted diaryl diselenides **2b** (R^1 = 4-ClC_6H_4) and **2c** (R^1 = 4-FC_6H_4) reacted with **1a** to afford the respective Se-containing 4,5-dihydroisoxazoles **3b** and **3c** in 93 % and 85 % yields after 20 min and 30 min, respectively (Scheme 2). In contrast, electron-rich *p*-tolyl diselenide **2d** (R^1 = 4-$CH_3C_6H_4$) and *p*-anisyl diselenide **2e** (R^1 = 4-$CH_3OC_6H_4$) afforded the respective products **3d** and **3e** in 72 % and 60 % yields (Scheme 2). The moderate yields of products **3d** and **3e** can be also attributed to their low stability under the purification conditions compared to the other derivatives, once it was observed decomposition in this step. The optimal conditions were successfully applied in the reaction of 2-naphthyl diselenide **2f** with **1a**, and the expected product **3f** was obtained in 82 % yield after 20 min of sonication (Scheme 2). The alkyl-substituted dibutyl diselenide **2g** was a good substrate for the reaction, and the desired product **3g** was obtained in 85 % yield after 40 min (R^1 = C_4H_9, Scheme 2).

Also, we examined the reaction between oxime **1a** and diphenyl telluride and diphenyl disulfide. Unfortunately, in both cases the desired products were not obtained, even after 2 h of sonication, and the formation of products of oxidation of the dichalcogenides was observed. The possibility of performing these reactions with another oximes **1b**–**e** was also investigated. Oximes containing EDG and EWG at the aromatic ring efficiently reacted with diphenyl diselenide **2a**, affording the respective products **3h**, **3i** and **3j** in 70 %, 80 % and 72 % yields after 30–35 min of reaction (Scheme 2). Differently to the observed for the diaryl diselenide counterpart **2**, it was not possible to infer any electronic effect due to the substituents in the aromatic ring of oximes **1b**–**d**. 2-Naphthyl oxime **1e** was also a suitable substrate for the reaction with **2a**, and the ex-



Scheme 2. Synthesis of 5-methylselanyl-4,5-dihydroisoxazoles **3a**–**k**.



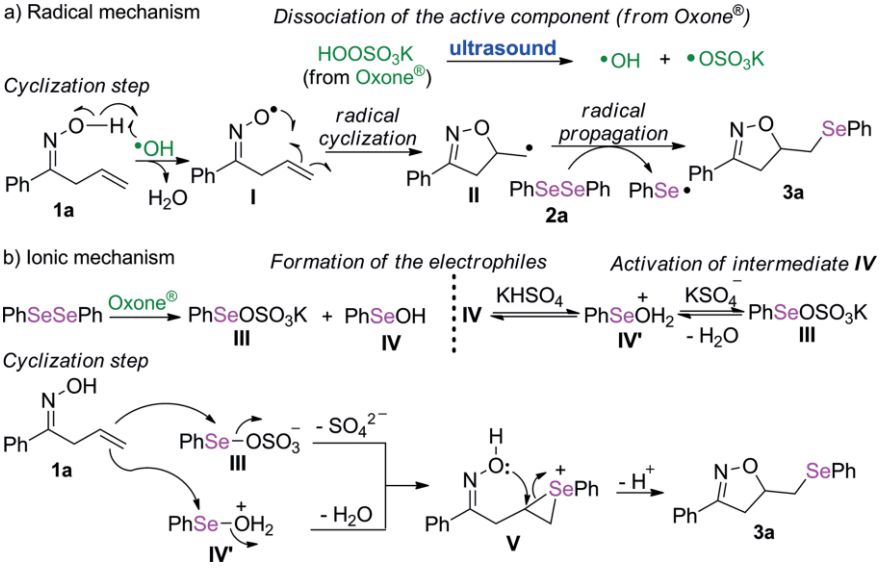
Scheme 3. Control experiments and mechanistic studies.

pected product **3k** was obtained in 75 % yield after 40 min (Scheme 2).

Aiming to gain a better understanding of this ultrasound-promoted process, some control experiments and mechanistic studies were conducted in the reaction of **1a** with **2a** (Scheme 3). As observed before, Oxone® is essential to the formation of the desired compound **3a** under ultrasound. Thus, to verify the involvement of radical intermediates in the reaction, the radical scavenger hydroquinone (3.0 equiv.) was added to the standard reaction. After 20 min of sonication, no product **3a** was observed, indicating that a radical pathway is involved. In order to verify the influence of the energy source, the same reaction was performed using microwave irradiation at 65 °C, and after 2 h, product **3a** was isolated in 78 % yield (Scheme 3a). This observation indicates that by switching from ultrasound to microwave, the reaction pathway changes from predominantly radical to ionic. When 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO, 3.0 equiv.) was used as a radical scavenger under the standard conditions, the adduct **4** was obtained in 56 % yield under sonication. This outcome is like the observed by Yu and Cai,[12] and it corroborates the involvement of a radical pathway under ultrasound. On the other hand, under microwave and conventional heating (oil bath, 65 °C) the concomitant formation of products **3a** and **4** occurred (determined by GC/MS), indicating that ionic and radical mechanisms co-exist (Scheme 3b). In order to verify if diphenyl diselenide **2a** participates in the initial stage of the reaction, a mixture of oxime **1a**, TEMPO and Oxone® was sonicated for 1.5 h, and the adduct **4** was formed in 56 % yield (Scheme 3c), showing that diphenyl diselenide **2a** does not participate in the first step of the mechanism. A two step, one-pot reaction starting from the reaction of oxime **1a** with Oxone®, to form the isoxazoline intermediate **5**, followed by the addition of diselenide **2a** and more Oxone®, did not give the expected product **3a**, and only the intermediate **5** and the starting materials were observed by GC/MS analysis (Scheme 3d).

Following, the addition sequence was reversed, i.e., firstly diselenide **2a** and Oxone® reacted for 20 min under ultrasound; then, oxime **1a** and more Oxone® were added in the reaction vial. The resulting mixture was sonicated for additional 45 min, however only the starting materials were present at the end of the process (Scheme 3e). Taken together, the outcomes of the control experiments clearly indicate that the energy source influences the reaction mechanism, with the ultrasound irradiation promoting the formation of the product **3a** via a radical pathway, while under microwave or conventional heating the reaction occurs mainly by an ionic pathway.

Based on the literature[12,24] and in our own results, two plausible mechanisms for the formation of 5-methylselanyl-4,5-dihydroisoxazoles **3** were proposed, as illustrated in Scheme 4. In the radical pathway, the first step is the formation of HO$^{\bullet}$ and $SO_4^{\bullet-}$ from the ultrasound-promoted dissociation of Oxone®. Following, the hydroxyl radical reacts with oxime **1a** to form water and the oxygen-centered radical intermediate **I**, which undergoes a radical cyclization leading to the 5-methyl-4,5-dihydroisoxazole radical **II**. Then, intermediate **II** reacts with diphenyl diselenide **2a** to form the desired product **3a** and a radical PhSe$^{\bullet}$ (Scheme 4a). When the ionic mechanism is operating, the first step is the formation of the electrophilic species of selenium **III** and **IV**, from the reaction of diselenide **2a** with Oxone®. The species **IV** reacts in the acidic reaction medium to form the more active electrophile **IV′**. Then, oxime **1a** reacts with **III** and/or **IV′** to form the seleniranium intermediate **V**, which undergoes an intramolecular attack from the oxygen, followed by deprotonation and formation of the desired product **3a** (Scheme 4b).



Scheme 4. Proposed mechanism.

Conclusions

In this work we have shown for the first time the ultrasound-promoted synthesis of selenium-containing 4,5-dihydroisoxazoles starting from β,γ-unsaturated oximes and diselenides in the presence of Oxone® and ethanol as the solvent. The key role of the ultrasound was demonstrated in the mechanistic studies, directing the reaction via a radical pathway, while the use of microwaves or conventional heating favors an ionic mechanism. The method enabled the use of various diorganoyl diselenides, as well as, different oximes as starting materials, allowing a diversity of products in yields ranging from good to excellent and in only 15–40 min of sonication.

Experimental Section

General Remarks: The reactions were monitored by TLC carried out on Merck silica gel (60 F254) by using UV light as visualizing agent and 5 % vanillin in 10 % H_2SO_4 and heat as developing agents. Baker silica gel (particle size of 0.040–0.063 mm) was used for flash column chromatography. Hydrogen nuclear magnetic resonance (^{1}H NMR) spectra were obtained at 400 MHz. Spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in ppm, referenced to tetramethylsilane (TMS) as the external reference. Coupling constants (*J*) are reported in Hertz. Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), dd (doublet of doublet), sex (sextet), t (triplet) and m (multiplet). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were obtained at 100 MHz. Chemical shifts are reported in ppm, referenced to the solvent peak of $CDCl_3$. Selenium-77 nuclear magnetic resonance (^{77}Se NMR) spectra were obtained at 76 MHz, using $(PhSe)_2$ as an internal standard. Low-resolution mass spectra (MS) were obtained with a Shimadzu GC-MS-QP2010 mass spectrometer. High-resolution mass spectra (HRMS) were obtained for all compounds on a LTQ Orbitrap Discovery mass spectrometer (Thermo Fisher Scientific). This hybrid system meets the LTQ XL linear ion trap mass spectrometer and an Orbitrap mass analyzer. The experiments were performed via direct infusion of sample (flow: 10 μL/min) in the positive-ion mode using electrospray ionization. Elemental composition calculations for comparison were executed using the specific tool included in the Qual Browser module of Xcalibur (Thermo Fisher Scientific, release 2.0.7) software. The IR spectra were obtained with a Shimadzu – IRAffinity-1. The ultrasound-promoted reactions were performed using a Cole Parmer-ultrasonic processor Model CPX 130, with a maxim power of 130 W, operating at amplitude of 60 % and a frequency of 20 kHz. The temperature of the reactions under ultrasound was monitored using an Incoterm digital infrared thermometer model Infraterm (Brazil). Melting point (m.p.) values were measured in a Marte PFD III instrument with a 0.1 °C precision. Oxone® was purchased from Sigma Aldrich.

General Procedure for the Synthesis of 5-Methylselanyl-4,5-dihydroisoxazoles 3: To a 10 mL round-bottomed glass vial, the appropriate oxime **1a**–**f** (0.250 mmol), diselenide **1a**–**g** (0.125 mmol), Oxone® (0.077 g; 0.250 mmol) and ethanol (2.0 mL) were added. The ultrasound probe was placed in the reaction vial, and the mixture was sonicated (20 kHz, 60 % of sonic amplitude) for the time indicated in Scheme 2. The reaction progress was monitored by TLC in order to evaluate the starting materials consumption. After that, the product was extracted with ethyl acetate (3× 15.0 mL), the organic phase was separated, dried with $MgSO_4$ and the solvent evaporated under reduced pressure. The product was purified by washing the crude with hexane (2.0 mL) followed by removal of solvent with a pipette. This addition and removal process was carried out until the solvent used in the extraction became colorless (around 5 times). The pure product was dried under reduced pressure. All the compounds were properly characterized by MS, FTIR, ^{1}H, ^{13}C and ^{77}Se NMR and HRMS (for the new ones).

3-Phenyl-5-[(phenylselanyl)methyl]-4,5-dihydroisoxazole (3a):[17] Yield: 0.067 g (85 %). White solid; m.p. 55–56 °C. Lit.:[17] 54–56 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ [ppm] = 7.56–7.54 (m, 2H); 7.50–7.47 (m, 2H); 7.35–7.29 (m, 3H); 7.21–7.18 (m, 3H); 4.87–4.79 (m, 1H); 3.36 (dd, *J* = 16.8, 10.2 Hz, 1H); 3.23 (dd, *J* = 12.7, 4.6 Hz, 1H); 3.12 (dd, *J* = 16.8, 6.9 Hz, 1H); 2.92 (dd, *J* = 12.7, 9.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ [ppm] = 156.1, 133.2, 130.1, 129.4, 129.3, 128.7, 127.5, 126.8, 126.7, 80.3, 40.0, 31.4. ^{77}Se NMR (76 MHz, $CDCl_3$) δ [ppm] = 261.28. IR (KBr) $\tilde{\nu}$ [cm^{-1}] = 1683.86 (C-O), 1595.13 (C=N). MS (rel. int., %) *m/z*: 317 (16.2), 171 (50.7), 146 (100.0), 118 (47.4), 103 (10.2), 77 (92.3).

5-{[(4-Chlorophenyl)selanyl]methyl}-3-phenyl-4,5-dihydroisoxazole (3b): Yield: 0.082 g (93 %). Yellowish solid; m.p. 61–63 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ [ppm] = 7.58–7.54 (m, 2H); 7.43–7.40 (m, 2H); 7.34–7.31 (m, 3H); 7.20–7.16 (m, 2H); 4.86–4.78 (m, 1H); 3.37 (dd, *J* = 16.7, 10.3 Hz, 1H); 3.20 (dd, *J* = 12.7, 4.8 Hz, 1H); 3.11 (dd, *J* = 16.7, 6.8 Hz, 1H); 2.93 (dd, *J* = 12.7, 8.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ [ppm] = 156.2, 134.6, 133.8, 130.2, 129.4, 129.3, 128.7, 126.9, 126.7, 80.1, 40.1, 31.8. ^{77}Se NMR (76 MHz, $CDCl_3$) δ [ppm] = 260.95. IR (KBr) $\tilde{\nu}$ [cm^{-1}] = 1643.24 (C-O), 1568.13 (C=N). MS (rel. int., %) *m/z*: 350 (11.1), 205 (25.0), 190 (8.7), 146 (100.0), 160 (2.4), 111 (1.7), 77 (57.3). HRMS (APCI-QTOF) calculated mass for $C_{16}H_{14}ClNOSe$ $[M]^+$: 350.9929, found 350.9922.

5-{[(4-Fluorophenyl)selanyl]methyl}-3-phenyl-4,5-dihydroisoxazole (3c): Yield: 0.071 g (85 %). Yellowish solid; m.p. 70–72 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ [ppm] = 7.64–7.62 (m, 2H); 7.57–7.53 (m, 2H); 7.41–7.38 (m, 3H); 7.01–6.95 (m, 2H); 4.91–4.83 (m, 1H); 3.43 (dd, *J* = 16.8, 10.3 Hz, 1H); 3.23 (dd, *J* = 12.6, 4.7 Hz, 1H); 3.17 (dd, *J* = 16.8, 6.9 Hz, 1H); 2.97 (dd, *J* = 12.6, 8.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ [ppm] = 162.2 (d, *J* = 246.4 Hz), 156.1, 135.9 (d, *J* = 8.0 Hz), 130.1, 129.3, 128.7, 126.6, 123.1 (d, *J* = 3.3 Hz), 116.4 (d, *J* = 21.4 Hz), 80.2, 40.0, 32.3. ^{77}Se NMR (76 MHz, $CDCl_3$) δ [ppm] = 259.23. IR (KBr) $\tilde{\nu}$ [cm^{-1}] = 1637.56 (C-O), 1583.56 (C=N). MS (rel. int., %) *m/z*: 335 (4.9), 206 (19.5), 189 (15.6), 146 (54.6), 77 (41.2), 40 (100.0). HRMS (APCI-QTOF) calculated mass for $C_{16}H_{14}FNOSe$ $[M]^+$: 335.0225, found 335.0219.

3-Phenyl-5-[(*p*-tolylselanyl)methyl]-4,5-dihydroisoxazole (3d): Yield: 0.060 g (72 %). Orange oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ [ppm] = 7.64–7.62 (m, 2H); 7.47–7.44 (m, 2H); 7.40–7.38 (m, 3H); 7.10–7.08 (m, 2H); 4.91–4.83 (m, 1H); 3.42 (dd, *J* = 16.8, 10.3 Hz, 1H); 3.26 (dd, *J* = 12.5, 4.5 Hz, 1H); 3.19 (dd, *J* = 16.8, 6.8 Hz, 1H); 2.93 (dd, *J* = 12.5, 9.2 Hz, 1H); 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ [ppm] = 156.1, 140.4, 133.2, 129.4, 129.3, 128.7, 127.5, 126.6, 126.5, 80.2, 40.2, 31.4, 21.4. ^{77}Se NMR (76 MHz, $CDCl_3$) δ [ppm] = 255.02. IR (KBr) $\tilde{\nu}$ [cm^{-1}] = 1610.38 (C-O), 1572.82 (C=N). MS (rel. int., %) *m/z*: 331 (12.0), 207 (12.4), 171 (12.6), 146 (68.6), 91 (100.0), 77 (51.0). HRMS (APCI-QTOF) calculated mass for $C_{17}H_{17}NOSe$ $[M]^+$: 331.0475, found 331.0470.

5-{[(4-Methoxyphenyl)selanyl]methyl}-3-phenyl-4,5-dihydroisoxazole (3e): Yield: 0.052 g (60 %). Yellowish solid; m.p. 61–63 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ [ppm] = 7.57–7.55 (m, 2H); 7.44 (d, *J* = 8.8 Hz, 2H); 7.34–7.30 (m, 3H); 6.75 (d, *J* = 8.8 Hz, 2H); 4.82–4.74 (m, 1H); 3.72 (s, 3H); 3.35 (dd, *J* = 16.8, 10.3 Hz, 1H); 3.15–3.08 (m, 2H); 2.82 (dd, *J* = 12.5, 9.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ [ppm] = 159.7, 156.1, 138.2, 136.1, 130.1, 128.7, 126.7, 118.4, 115.0, 80.5, 55.3, 40.0, 32.3. ^{77}Se NMR (76 MHz, $CDCl_3$) δ [ppm] = 252.33. IR (KBr) $\tilde{\nu}$ [cm^{-1}] = 1615.07 (C-O), 1591.61 (C=N). MS (rel. int., %) *m/z*: 347 (48.6), 187 (46.8), 146 (98.8), 121 (100.0), 77 (90.5), 41 (41.6). HRMS (APCI-QTOF) calculated mass for $C_{17}H_{17}NO_2Se$ $[M]^+$: 347.0425, found 347.0419.

5-[(Naphthalen-2-ylselanyl)methyl]-3-phenyl-4,5-dihydroisoxazole (3f): Yield: 0.075 g (82 %). Yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ [ppm] = 8.34 (d, *J* = 8.8, 1H); 7.82–7.35 (m, 3H); 7.54–7.43 (m, 4H); 7.33–7.29 (m, 4H); 4.79–4.71 (m, 1H); 3.33 (dd, *J* = 16.8, 10.3 Hz, 1H); 3.25 (dd, *J* = 12.4, 4.6 Hz, 1H); 3.11 (dd, *J* = 16.8, 10.3, 1H); 2.95 (dd, *J* = 12.4, 8.9, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ [ppm] = 156.1, 134.4, 134.1, 133.5, 130.1, 129.4, 129.1, 128.8, 128.7, 127.8, 127.6, 127.0, 126.7, 126.4, 125.8, 80.4, 40.1, 31.6. ^{77}Se NMR (76 MHz, $CDCl_3$) δ [ppm] = 262.37. IR (KBr) $\tilde{\nu}$ [cm^{-1}] = 1643.93 (C-O), 1591.27 (C=N). MS (rel. int., %) *m/z*: 367 (20.6), 222 (26.1), 206 (34.4), 146 (43.0), 141 (56.3), 77 (51.6). HRMS (APCI-QTOF) calculated mass for $C_{20}H_{17}NOSe$ $[M]^+$: 367.0475, found 367.0470.

5-[(Butylselanyl)methyl]-3-phenyl-4,5-dihydroisoxazole (3g): Yield: 0.063 g (85 %). Yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ [ppm] = 7.68–7.66 (m, 2H); 7.41–7.38 (m, 3H); 4.99–4.91 (m, 1H); 3.47 (dd, *J* = 16.7, 10.2 Hz, 1H); 3.21 (dd, *J* = 16.7, 7.2 Hz, 1H); 2.91 (dd, *J* = 12.6, 4.7 Hz, 1H); 2.74 (dd, *J* = 12.6, 8.3 Hz, 1H); 2.68 (t, *J* = 7.5 Hz, 2H); 1.66 (quint, *J* = 7.5 Hz, 2H); 1.40 (sext, *J* = 7.5 Hz, 2H); 0.92 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ [ppm] = 156.1, 130.0, 129.5, 128.6, 126.6, 81.0, 40.2, 32.6, 27.4, 24.5, 22.8, 13.5. ^{77}Se NMR (76 MHz, $CDCl_3$) δ [ppm] = 128.97. IR (KBr) $\tilde{\nu}$ [cm^{-1}] = 1616.35 (C-O), 1568.13 (C=N). MS (rel. int., %) *m/z*: 297 (3.9), 152 (30.1), 146 (100.0), 118 (25.1), 91 (13.8), 77 (34.3). HRMS (APCI-QTOF) calculated mass for $C_{14}H_{19}NOSe$ $[M]^+$: 297.0632, found 297.0626.

3-(4-Chlorophenyl)-5-[(phenylselanyl)methyl]-4,5-dihydroisoxazole (3h):[17] Yield: 0.061 g (70 %). Yellowish solid; m.p. 72–73 °C. Lit.:[17] 70–71 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ [ppm] = 7.50–7.47 (m, 4H); 7.31–7.28 (m, 2H); 7.23–7.20 (m, 3H); 4.88–4.80 (m, 1H); 3.33 (dd, *J* = 16.8, 10.3 Hz, 1H); 3.23 (dd, *J* = 12.6, 4.5 Hz, 1H); 3.09 (dd, *J* = 16.8, 6.9 Hz, 1H); 2.92 (dd, *J* = 12.6, 9.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ [ppm] = 155.3, 136.1, 133.3, 129.3, 129.0, 128.6, 127.9, 127.8, 127.6, 80.7, 39.9, 31.3. ^{77}Se NMR (76 MHz, $CDCl_3$) δ [ppm] = 262.53. IR (KBr) $\tilde{\nu}$ [cm^{-1}] = 1683.86 (C-O), 1595.13 (C=N). MS (rel. int., %) *m/z*: 350 (22.0), 281 (24.7), 207 (63.6), 157 (21.0), 91 (100.0), 77 (51.1), 41 (57.7).

3-(4-Fluorophenyl)-5-[(phenylselanyl)methyl]-4,5-dihydroisoxazole (3i):[17] Yield: 0.067 g (80 %). White solid; m.p. 81–82 °C. Lit.:[17] 83–84 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ [ppm] = 7.63–7.60 (m, 2H); 7.57–7.54 (m, 2H); 7.30–7.26 (m, 3H); 7.08 (t, *J* = 8.7 Hz, 2H); 4.94–4.87 (m, 1H); 3.41 (dd, *J* = 16.8, 10.3 Hz, 1H); 3.30 (dd, *J* = 12.6, 4.5 Hz, 1H); 3.17 (dd, *J* = 16.8, 6.9 Hz, 1H), 2.99 (dd, *J* = 12.6, 9.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ [ppm] = 163.7 (d, *J* = 249.2 Hz), 155.2, 133.2, 129.3, 128.6 (d, *J* = 8.4 Hz), 127.6, 125.7 (d, *J* = 3.4 Hz), 115.8 (d, *J* = 21.8 Hz), 80.5, 40.1, 31.3. ^{77}Se NMR (76 MHz, $CDCl_3$) δ [ppm] = 262.32. IR (KBr) $\tilde{\nu}$ [cm^{-1}] = 1643.24 (C-O), 1516.49 (C=N). MS (rel. int., %) *m/z*: 335 (17.4), 172 (64.7), 164 (100.0), 136 (39.1), 109 (26.7), 95 (44.3), 77 (32.1).

3-(4-Tolyl)-5-[(phenylselanyl)methyl]-4,5-dihydroisoxazole (3j):[17] Yield: 0.060 g (72 %). White solid; m.p. 60–61 °C. Lit.:[17] 59–60 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ [ppm] = 7.57–7.51 (m, 4H); 7.29–7.26 (m, 3H); 7.21–7.18 (m, 2H); 4.92–4.84 (m, 1H); 3.42 (dd, *J* = 16.8, 10.2 Hz, 1H); 3.30 (dd, *J* = 12.6, 4.5 Hz, 1H); 3.18 (dd, *J* = 16.8, 6.8 Hz, 1H); 2.98 (dd, *J* = 12.6, 9.0 Hz, 1H); 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ [ppm] = 156.1, 137.7, 133.7, 130.1, 129.4, 128.6, 126.6, 124.7, 80.4, 40.0, 31.6, 21.1. ^{77}Se NMR (76 MHz, $CDCl_3$) δ [ppm] = 262.29. IR (KBr) $\tilde{\nu}$ [cm^{-1}] = 1637.56 (C-O), 1597.96 (C=N). MS (rel. int., %) *m/z*: 331 (19.9), 174 (12.2), 160 (100.0), 132 (39.9), 105 (19.1), 91 (80.6), 65 (26.8).

3-(Naphthalen-2-yl)-5-[(phenylselanyl)methyl]-4,5-dihydroisoxazole (3k): Yield: 0.069 g (75 %). Yellowish solid; m.p. 72–73 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ [ppm] = 7.94–7.91 (m, 1H); 7.82–7.79 (m, 4H); 7.57–7.54 (m, 2H); 7.50–7.48 (m, 2H); 7.27–7.26 (m, 3H); 4.97–4.89 (m, 1H); 3.50 (dd, *J* = 16.7, 10.2 Hz, 1H); 3.34–3.25 (m, 2H); 3.0 (dd, *J* = 12.6, 9.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ [ppm] = 156.3, 133.9, 133.1, 132.9, 129.2, 128.7, 128.4, 128.3, 127.7, 127.5, 127.1, 126.9, 126.6, 123.4, 80.5, 39.9, 31.3. ^{77}Se NMR (76 MHz, $CDCl_3$) δ [ppm] = 262.70. IR (KBr) $\tilde{\nu}$ [cm^{-1}] = 1657.32 (C-O), 1582.21 (C=N). MS (rel. int., %) *m/z*: 367 (20.0), 196 (100.0), 172 (41.5), 127 (68.3), 115 (12.7), 95 (44.3), 77 (30.), 41 (47.8). HRMS (APCI-QTOF) calculated mass for $C_{20}H_{17}NOSe$ $[M]^+$: 367.0475, found 367.0470.

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Ultrasound-Promoted Radical Synthesis of 5-Methylselanyl-4,5-dihydroisoxazoles

An ultrasound-promoted method to synthesize 5-methylselanyl-4,5-dihydroisoxazoles through the radical cyclization of unsaturated oximes with diaryl diselenides using Oxone® as an oxidant and ethanol as the solvent is described.

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