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Article

Oxone®-Promoted One-Pot Synthesis of 1-Aryl-4-(organylselanyl)-1*H*-pyrazoles

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We describe herein an efficient protocol for the one-pot synthesis of 4-organylselanylpyrazoles by direct cyclocondensation and C–H bond selenylation reactions starting from hydrazines, 1,3-diketones and diorganyl diselenides promoted by Oxone®. The products were obtained through a metal catalyst free methodology, under mild conditions, in short reaction times and moderate to excellent yields.

Keywords: Oxone®, organoselenium compounds, pyrazoles

Introduction

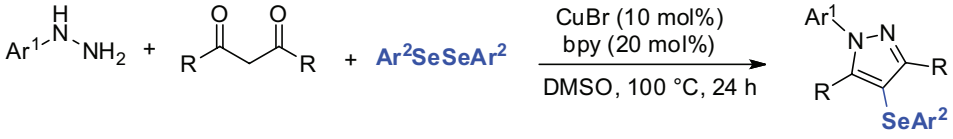
Pyrazoles have synthetic interest due to its numerous biological activities[1-5] such as, anti-inflammatory properties (celecoxib),[6,7] insecticidal effects (fipronil),[8] analgesic effects (metamizole),[9] treatment of erectile dysfunction (sildenafil)[10] and sedative-hypnotic agents (zaleplon).[11] Regarding the available methods for the synthesis of pyrazoles, these structures are usually synthesized by the 1,3-dipolar cycloaddition reaction using alkenes or alkynes,[12,13] reacting unsaturated ketones or aldehydes with hydrazines[14-16] and the condensation reaction of 1,3-dicarbonyl compounds with hydrazines.[17-19]

In addition, organoselenium compounds are attractive synthetic targets due to their applicability in organic synthesis in selective reactions,[20-23] chiral catalysts,[24,25] photophysical properties[26-28] and pharmacological activities.[29-37] Thus, the presence of selenium in the pyrazole ring could result in compounds with new pharmacological and medicinal activities.

In recent years, several methods to synthesize 4-(arylselanyl)pyrazoles were reported.[38-42] However, these protocols usually require pre-functionalization of substrates,[38-40] use of transition metals as catalysts,[41] multi-step synthesis and long reaction times. In 2015, our research group[41] reported the direct synthesis of 4-(organylselanyl)pyrazoles by copper-catalyzed one-pot cyclocondensation and C–H bond selenylation reactions starting from hydrazines, 1,3-diketones and diorganoyl diselenides (Scheme 1).

Recently, Zora *et al.*[42] reported the one-pot preparation of 4-phenylselanyl-1*H*-pyrazoles through electrophilic cyclization of α,β-alkynil hydrazones with phenylselanyl chloride (Scheme 2).

The potassium peroxymonosulfate exists as a stable triple salt ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$), it is a white crystallin solid known as trademark Oxone®. In recently years, the use of Oxone® has shown an efficient alternative to traditional oxidants in organic synthesis. As oxidizing agent it has many advantages, such as water solubility, stability under several conditions, simplicity in handling, cheap, not toxic acid, easy-to-handle and environmentally safe (generates nonpolluting by-products).[43] Recently, the Oxone® has been used in the preparation of important heterocycles, for



Scheme 1. Synthesis of 4-arylselanylpyrazoles by copper-catalyzed one-pot cyclization.[41]

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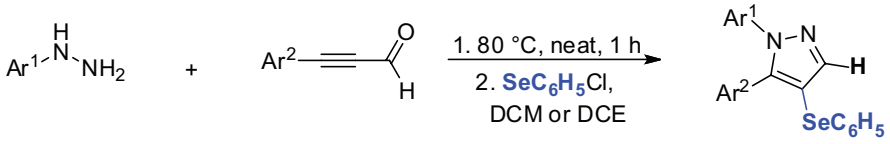


Scheme 2. Synthesis of 4-(phenylselanyl)pyrazole via electrophilic cyclization.[42]

example in the synthesis of pyrazoles,[44] benzoxazoles and benzimidazoles.[45,46] Other examples are included, such as synthesis of isoxazolines and isoxazoles,[47] chromene and carbazole,[48] and pyridines and pyrimidines derivatives.[49]

Our research group recently reported the use of Oxone® to generate electrophilic species of selenium evidencing its application in selenylation reactions.[50-54] As an example, we reported an alternative metal-free methodology for the synthesis of diorganyl selenides and tellurides mediated by Oxone®.[51] Other examples include the selenomethoxylation of inactivated alkenes,[52] the synthesis of 2-organoselanyl-naphthalenes under ultrasonic irradiation,[53] the selective synthesis of 5-arylselanyl-imidazo[2,1-*b*]thiazoles, 3-arylselanyl-imidazo[1,2-*a*]pyridines and 4-arylselanyl-1*H*-pyrazoles derivatives via direct selenylation C–Se coupling reaction mediated by Oxone®.[54]

Thus, based on literature,[38-42] our recent report using Oxone® in selenylation reactions[50-54] and due to our continuous interest in the preparation of nitrogen-functionalized organoselenium compounds,[55-59] we describe herein our results on the synthesis of a range of 4-(organylselanyl)-1*H*-pyrazoles **4** by Oxone®-mediated oxidative multicomponent reaction of hydrazines **1**, 1,3-diketones **2** and diorganyl diselenides **3** (Scheme 3).

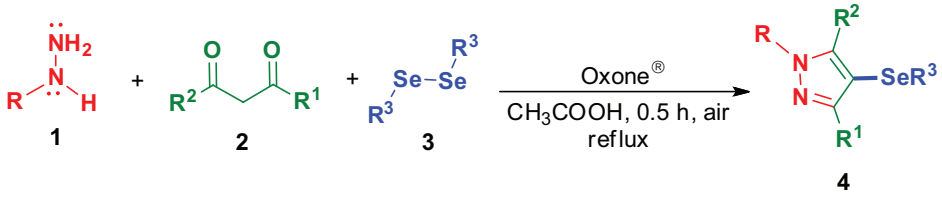
Results and Discussion

Based in our previous results,[41] the reaction was peformed using phenylhydrazine **1a** (0.250 mmol), 2,4-pentanedione **2a** (0.250 mmol) and diphenyl diselenide **3a** (0.125 mmol) in CH_3CN (1.0 mL). After that we added Oxone® (0.500 mmol) keeping the reaction mixture under stirring at 50 °C for 24.0 h and air atmosphere. The desired product 3,5-dimethyl-1-phenyl-1*H*-pyrazole **4a** was obtained in 50% yield (Table 1, entry 1).

Aiming to improve the yield of the **4a**, we examined the influence of different solvents, temperature, reaction time, amount of **3a** and Oxone®, as depicted in Table 1, entries 2 to 10. Thus, when the reaction was performed with 0.188 and 0.250 mmol of the **3a** an increase in the yield of the product **4a** was observed with reduction of the reaction time (Table 1, entries 2 and 3). However, a decrease in the yield of product **4a** was observed when the amount of the Oxone® was reduced to 0.250 mmol (Table 1, entry 4). This result is probably due to the incomplete oxidation of diphenyl diselenide **3a** in the presence of Oxone®. Next, the reaction was performed at 25 °C and reflux temperature and a decrease in the yield of product **4a** was observed (Table 1, entries 5 and 6).

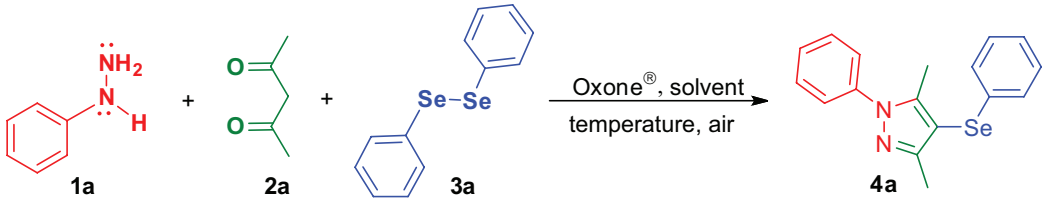
Next, the reaction was performed using different solvents (Table 1, entries 7 to 10). When acetic acid was used as a solvent the yield was increased to 98% and the reaction time was reduced to only 0.5 h (Table 1, entry 7). However, when it was used other solvents including EtOH, H_2O or PEG-400, lower yields of **4a** (Table 1, entries 8, 9 and 10 *vs.* 7) was obtained.

In order to verify the scope and limitations of this protocol, the generality of our method was explored by extending the optimized reaction conditions (Table 1, entry 7) to other substituted reagents, and the results are shown in Table 2. Firstly, 1,3-diketones **2a-c** were reacted with phenylhydrazine **1a** and diphenyl diselenide **3a** (Table 2, entries 1 to 3). Thus, when the reactions were performed with 3,5-heptanedione **2b** the desired product **4b** was obtained in 90% yield (Table 2, entry 2). When unsymmetrical 1-phenyl-1,3-butanedione **2c** was used, two regioisomers were obtained providing the corresponding 4-selanylpyrazoles **4c** and **4c'** in the ratio (96:4) determined by gas chromatography mass spectrometry (GC-MS) analysis in 89% yield (Table 2, entry 3). We believe that steric hinderance of **2c** associated to the conjugative effect of aromatic ring can contribute to stabilize the enol tautomer increasing the regioselectivity of this cyclization towards the formation of product **4c** as major isomer.



Scheme 3. General scheme for synthesis of 1-aryl-4-(organylselanyl)-1*H*-pyrazoles.

Table 1. Reaction conditions optimization[a]



1a 2a 3a 4a

entry	**3a** / mmol	Oxone® / mmol	Temperature / °C	time / h	Solvent	Yield[b] **4a** / %
1	0.125	0.500	50	24.0	CH_3CN	50
2	0.188	0.500	50	24.0	CH_3CN	85
3[c]	0.250	0.500	50	1.0	CH_3CN	97
4	0.250	0.250	50	1.0	CH_3CN	54
5	0.250	0.500	25	2.0	CH_3CN	68
6	0.250	0.500	reflux	0.5	CH_3CN	85
7[c]	0.250	0.500	50	0.5	CH_3COOH	98
8	0.250	0.500	50	1.0	EtOH	83
9	0.250	0.500	50	24.0	H_2O	40
10	0.250	0.500	50	2.0	PEG-400	71

[a]Reactions were performed with substrates **1a** (0.250 mmol), **2a** (0.250 mmol), **3a** and Oxone® in 1.0 mL of solvent in the open atmosphere; [b]yields are given for isolated products; [c]the excess of **3a** was recovered by column chromatography.

Subsequently, the reactions were performed with arylhydrazines **1b** and **1c** containing electron-donating group (EDG) and electron-withdrawing groups (EWG), to give the corresponding 4-arylselanylpyrazoles **4d** and **4e** in 69 and 44% yields, respectively (Table 2, entries 4 and 5). These results reveal that the reactions are sensitive to the electronic effect of the aromatic ring in the arylhydrazine. On the other hand, when hydrazine hydrochloride **1d** was used as a starting substrate, the desired product **4f** was obtained in 75% yield (Table 2, entry 6).

Furthermore, varying substituted diaryl diselenides **3** was evaluated to determine the influence of electron-donating (−Me, −OMe) and electron-withdrawing groups (−Cl, −F) in this reaction. The corresponding 4-selanylpyrazoles **4g-j** were obtained in good yields (Table 2, entries 7-10). The reaction of substituted diaryl diselenides is well tolerated and the results reveal that yields are not sensitive to the electronic effects in the diaryl diselenides containing EDG (**3b** and **3c**) and EWG (**3d** and **3e**).

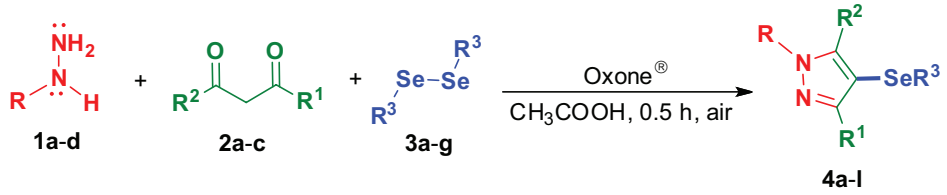
The reaction also worked well with dibutyl diselenide **3f**, and the corresponding 4-butylselanyl-3,5-dimethyl-1-phenyl-1*H*-pyrazole **4k** was obtained in good yield (Table 2, entry 11). Moreover, 2,2'-dipyridyl diselenide **3g** also gives the desired 2-[(3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-yl)selanyl]pyridine **4l** in a moderate yield of 58% (Table 2, entry 12). In this case the respective pyrazole containig a selanyl-pyridine group showed a decrease in yield probably due to the decrease of the electrophilic character of the selenium species, reducing their reactivity, caused by the conjugation of the electrons of the pyridine ring.

To extend the reaction scope, the multicomponent reaction (MCR) was evaluated in presence of (*E*)-chalcone **5** using optimized reaction conditions. Under this reaction condition the desired 1,3,5-triaryl-4-(phenylselanyl)-1*H*-pyrazoles **4m** was obtained in only 15% yield. Based on this result, a mixture of phenylhydrazine **2a** and chalcone **5** in acetic acid was stirred at reflux temperature for 2.0 h to afford *in situ* the pyrazolyl nucleus **A**. After this, diphenyl diselenide **3a** and Oxone® were added at 50 °C for 0.5 h and the desired product 1,3,5-triphenyl-4-(phenylselanyl)-1*H*-pyrazoles **4m** was obtained in 81% yield (Scheme 4).

Conclusions

In summary, we developed an efficient method for the synthesis of 4-organylselanylpyrazoles through the multicomponent reaction of 1,3-diketones, hydrazine and diaryl selenides. The reaction was Oxone®-promoted in acetic acid at 50 °C under air atmosphere and in short reaction times, a range of substituted 4-organylselanylpyrazoles was obtained in good to excellent yields.

Table 2. Reaction scope for the synthesis of 4-organylselanylpyrazoles **4a-l**[a]



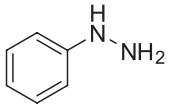
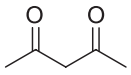
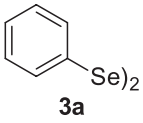
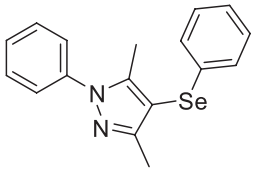
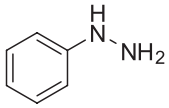
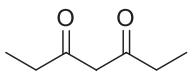
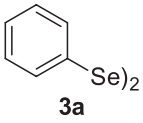
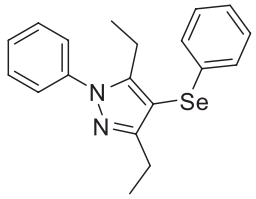
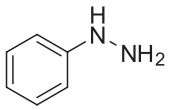
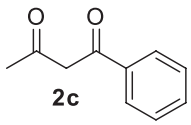
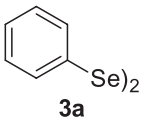
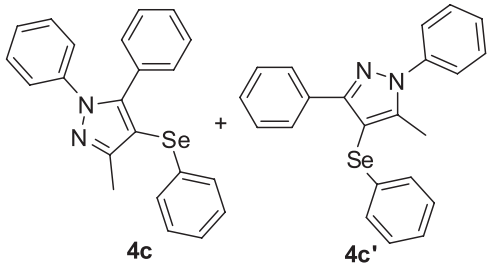
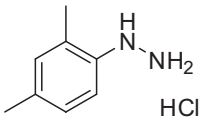
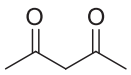
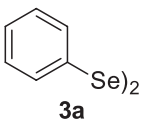
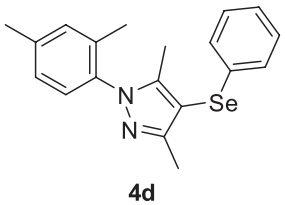
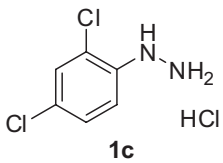
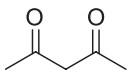
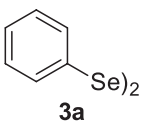
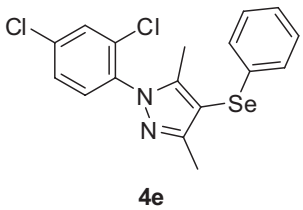
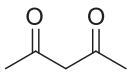
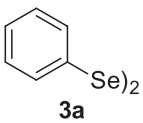
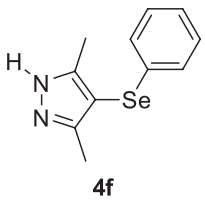
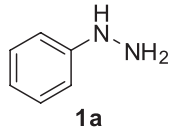
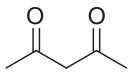
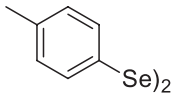
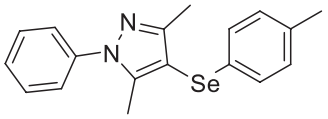
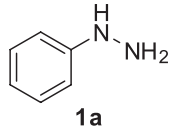
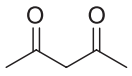
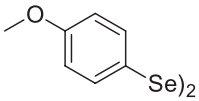
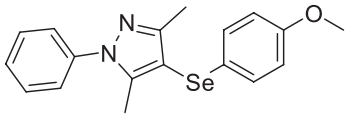
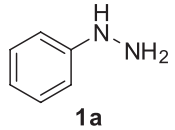
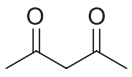
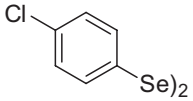
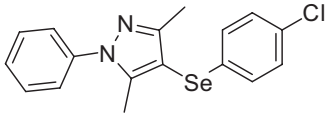
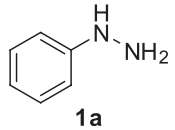
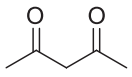
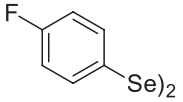
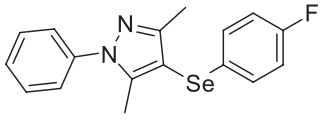
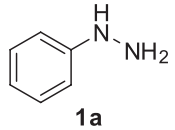
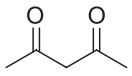
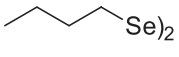
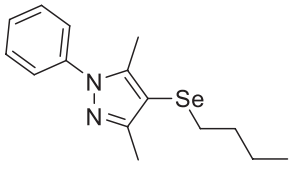
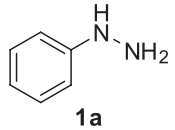
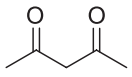
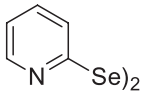
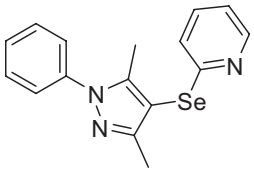
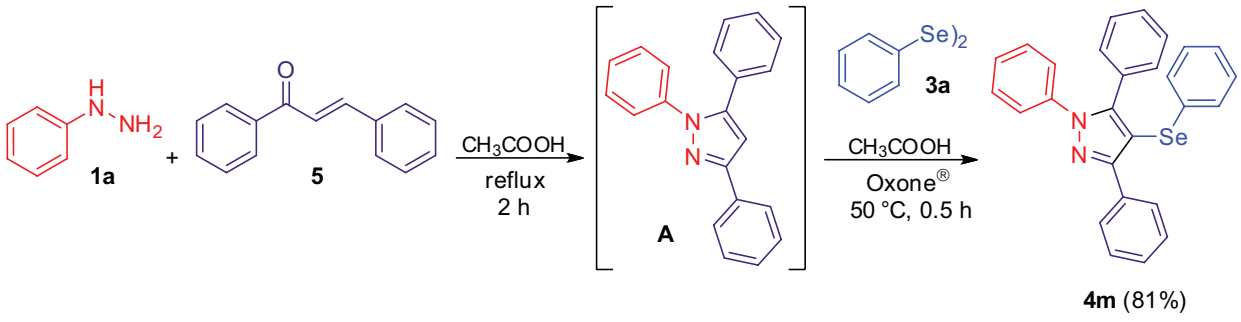
entry	Hydrazine **1**	1,3-Diketone **2**	Diselenide **3**	Product **4**	Yield[b] / %
1	 **1a**	 **2a**	 **3a**	 **4a**	98
2	 **1a**	 **2b**	 **3a**	 **4b**	90
3	 **1a**	 **2c**	 **3a**	 **4c** **4c'**	89[c]
4	 **1b**	 **2a**	 **3a**	 **4d**	69[d]
5	 **1c**	 **2a**	 **3a**	 **4e**	44[d]
6	$NH_2NH_2.HCl$ **1d**	 **2a**	 **3a**	 **4f**	75[d]

Table 2. Reaction scope for the synthesis of 4-organylselanylpyrazoles **4a-l**[a] (cont.)

entry	Hydrazine **1**	1,3-Diketone **2**	Diselenide **3**	Product **4**	Yield[b] / %
7	 **1a**	 **2a**	 **3b**	 **4g**	77
8	 **1a**	 **2a**	 **3c**	 **4h**	84
9	 **1a**	 **2a**	 **3d**	 **4i**	81
10	 **1a**	 **2a**	 **3e**	 **4j**	90
11	 **1a**	 **2a**	 **3f**	 **4k**	90
12	 **1a**	 **2a**	 **3g**	 **4l**	58

[a]Reactions were performed with substrates **1a-d** (0.250 mmol), **2a-c** (0.250 mmol), **3a-g** (0.250 mmol), Oxone® (0.500 mmol) in acetic acid (1.0 mL) as solvent at 50 °C in air atmosphere for 0.5 h; [b]yields are given for isolated products; [c]the mixture of regioisomers **4c/4c'** (96:4) was obtained and determined by GC-MS analysis; [d]the reaction was carried for 1.0 h.



Scheme 4. General scheme for synthesis of 1,3,5-triphenyl-4-(phenylselanyl)-1*H*-pyrazole, **4m**.

Experimental

General information

The reactions were monitored by thin layer chromatography (TLC) carried out on Merck silica gel (60 F_{254}) by using UV light as visualization agent and the mixture between of vanillin 5% and of H_2SO_4 10% under heating conditions as developing agents. Merck silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. Hydrogen nuclear magnetic resonance spectra (^{1}H NMR) were obtained on Bruker Ascend 400 spectrometer at 400 MHz. The spectra were recorded in $CDCl_3$ solutions. The chemical shifts are reported in ppm, referenced to tetramethylsilane (TMS) as the internal 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 doublets), ddd (doublet of doublet of doublets), dt (doublet of triplets), t (triplet), q (quartet), quint (quintet), sext (sextet), and m (multiplet). Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were obtained on Bruker Ascend 400 spectrometer at 100 MHz. The chemical shifts are reported in ppm, referenced to the solvent peak of $CDCl_3$. Low-resolution mass spectra were obtained with a Shimadzu GC-MS-QP2010 mass spectrometer. The high-resolution electrospray ionization mass spectrometry (QTOF) analysis were performed on a Bruker Daltonics micrOTOF-Q II instrument in operating positive mode. The samples were solubilized in high-performance liquid chromatography (HPLC)-grade acetonitrile and injected into the atmospheric pressure chemical ionization (APCI) source by means of a syringe pump at a flow rate of 5.0 μL min^{-1}. The follow instrument parameters were applied: capillary and cone voltages were set to +3500 and −500 V, respectively, with a desolvation temperature of 180 ºC. For data acquisition and processing and isotopes simulations, Compass 1.3 for micrOTOF-Q II software (Bruker Daltonics) was used. Melting point (mp) values were measured in a Marte PFD III instrument with a 0.1 ºC precision.

Synthesis

General procedure for synthesis of 4-arylselanyl-1*H*-pyrazoles (**4a**-**l**)

In a reaction tube of 10.0 mL it was added a mixture of the respectives hydrazines **1a**-**d** (0.25 mmol), 1,3-diketones **2a**-**c** (0.25 mmol), diselenides **3a**-**g** (0.25 mmol) and Oxone® 0.5 mmol in CH_3COOH (1.0 mL). The mixture was stirred at 50 °C for the time indicated in Table 2. The aqueous sodium bicarbonate solution 5% (10.0 mL) and ethyl acetate (15.0 mL) were added. The organic phase was washed with water (2 × 10.0 mL), separated, dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The product was isolated by column chromatography using hexane/ethyl acetate (98/2% v/v) as eluent.

3,5-Dimethyl-1-phenyl-4-(phenylselanyl)-1*H*-pyrazole (**4a**)[40,41]

Yield: 0.080 g (98%); orange solid; mp 82-84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 7.11-7.16 (m, 1H, Ar-H), 7.19-7.20 (m, 4H, Ar-H), 7.34-7.40 (m, 1H, Ar-H), 7.44-7.48 (m, 4H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 12.9, 102.5, 124.6, 125.7, 127.7, 128.2, 129.0, 129.1, 132.9, 139.7, 144.0, 153.2; MS (relative intensity / %) *m/z*: 77 (96.2), 118 (55.0), 157 (3.8), 171 (5.2), 248 (100.0), 328 (75.4).

3,5-Diethyl-1-phenyl-4-(phenylselanyl)-1*H*-pyrazole (**4b**)[40,41]

Yield: 0.080 g (90%); orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, 3H, *J* 7.6 Hz, CH_3), 1.23 (t, 3H, *J* 7.6 Hz, CH_3), 2.72 (q, 2H, *J* 7.6 Hz, CH_2), 2.78 (q, 2H, *J* 7.6 Hz, CH_2), 7.10-7.15 (m, 1H, Ar-H), 7.19-7.20 (m, 4H, Ar-H), 7.37-7.42 (m, 1H, Ar-H), 7.47-4.48 (m, 4H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 13.9, 19.1, 20.8, 100.3, 125.3, 125.6, 128.0, 129.0, 129.1, 133.6, 140.0, 149.7, 158.3; MS (relative intensity / %) *m/z*: 77 (48.4), 132 (17.0), 157 (2.1), 199 (3.2), 275 (100.0), 356 (36.8).

3-Methyl-1,5-diphenyl-4-(phenylselanyl)-1*H*-pyrazole (**4c**)[40,41]

Yield: 0.087 g (89%); beige solid; mp 68-69 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H, CH_3), 7.11-7.22 (m, 7H, Ar-H), 7.23-7.32 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.0, 103.5, 124.8, 125.8, 127.2, 128.2, 128.5, 128.7, 128.8, 129.1, 129.9, 130.1, 133.3, 139.9, 147.0, 154.0; MS (relative intensity / %) *m/z*: 77 (71.6), 157 (0.9), 180 (18.8), 233 (5.3), 310 (100.0), 390 (69.5).

1-(2,4-Dimethylphenyl)-3,5-dimethyl-4-phenylselanyl-1*H*-pyrazole (**4d**)

Yield: 0.061 g (69%); yellowish solid; mp 84-86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03 (s, 3H, Ar-CH_3), 2.11 (s, 3H, Ar-CH_3), 2.31 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 7.07-7.22 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.3, 12.9, 17.1, 21.1, 100.4, 125.6, 127.2, 127.4, 128.0, 129.1, 131.5, 133.3, 135.5, 136.2, 139.2, 145.2, 152.7; MS (relative intensity / %) *m/z*: 77 (45.0), 105 (28.4), 118 (4.5), 157 (12.9), 199 (11.0), 275 (66.4), 356 (100.0). HRMS (APCI-QTOF) *m/z*, calcd. for $C_{19}H_{20}N_2Se$ $[M + H]^+$: 357.0870, found: 357.0865.

1-(2,4-Dichlorophenyl)-3,5-dimethyl-4-phenylselanyl-1*H*-pyrazole (**4e**)

Yield: 0.044 g (44%); orange solid; mp 80-82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 7.12-7.23 (m, 5H, Ar-H), 7.39 (d, 2H, *J* 1.2 Hz, Ar-H), 7.56 (t, 1H, *J* 1.2 Hz, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.3, 13.0, 101.7, 125.7, 128.0, 128.1, 129.2, 130.1, 130.4, 132.8, 133.3, 135.9, 136.1, 146.2, 154.0; MS (relative intensity / %) *m/z*: 77 (24.7), 118 (4.4), 144 (57.8), 157 (5.7), 239 (5.7), 361 (100.0), 396 (75.4); HRMS (APCI-QTOF) *m/z*, calcd. for $C_{17}H_{14}Cl_2N_2Se$ $[M + H]^+$: 396.9778, found: 396.9767.

3,5-Dimethyl-4-(phenylselanyl)-1*H*-pyrazole (**4f**)[41]

Yield: 0.047 g (75%); white solid; mp 104-105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 6H, $2CH_3$), 7.03-7.12 (m, 5H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 100.1, 125.6, 128.2, 129.1, 133.1, 149.0; MS (relative intensity / %) *m/z*: 77 (16.3), 95 (13.2), 118 (1.6), 157 (10.6), 172 (100.0), 252 (58.9).

3,5-Dimethyl-1-phenyl-4-(4-tolylselanyl)-1*H*-pyrazole (**4g**)[40,41]

Yield: 0.066 g (77%); slightly orange solid; mp 96-97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3H, Ar-CH_3), 2.33 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 7.01-7.03 (m, 2H, Ar-H), 7.10-7.13 (m, 2H, Ar-H), 7.34-7.40 (m, 1H, Ar-H), 7.44-7.47 (m, 4H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 12.9, 20.9, 103.0, 124.7, 127.6, 128.7, 128.97, 129.04, 129.9, 135.6, 139.9, 143.8, 153.1; MS (relative intensity / %) *m/z*: 77 (55.1), 118 (32.1), 170 (3.9), 171 (5.7), 262 (100.0), 342 (46.7).

4-[(4-Methoxyphenyl)selanyl]-3,5-dimethyl-1-phenyl-1*H*-pyrazole (**4h**)[40,41]

Yield: 0.075 g (84%); red oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 6.76-6.80 (m, 2H, Ar-H), 7.19-7.22 (m, 2H, Ar-H), 7.34-7.38 (m, 1H, Ar-H), 7.43-7.48 (m, 4H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 12.9, 55.2, 103.9, 114.9, 122.6, 124.7, 127.6, 129.0, 131.1, 139.9, 143.6, 152.9, 158.5; MS (relative intensity / %) *m/z*: 77 (39.7), 118 (22.1), 171 (2.0), 187 (1.5), 278 (100.0), 358 (32.2).

4-[(4-Chlorophenyl)selanyl]-3,5-dimethyl-1-phenyl-1*H*-pyrazole (**4i**)[40,41]

Yield: 0.073 g (81%); yellowish solid; mp 124-125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 7.10-7.13 (m, 2H, Ar-H), 7.15-7.18 (m, 2H, Ar-H), 7.35-7.42 (m, 1H, Ar-H), 7.45-7.50 (m, 4H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 12.8, 102.3, 124.7, 127.8, 129.1, 129.2, 129.6, 131.2, 131.8, 139.7, 144.0, 153.1; MS (relative intensity / %) *m/z*: 77 (100.0), 118 (59.5), 171 (3.9), 191 (2.3), 282 (83.9), 362 (66.3).

4-[(4-Fluorophenyl)selanyl]-3,5-dimethyl-1-phenyl-1*H*-pyrazole (**4j**)

Yield: 0.078 g (90%); orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 6.89-6.95 (m, 2H, Ar-H), 7.16-7.21 (m, 2H, Ar-H), 7.36-7.40 (m, 1H, Ar-H), 7.44-7.50 (m, 4H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 12.9, 103.1, 116.2 (d, *J* 21.7 Hz), 124.7, 127.2 (d, *J* 3.4 Hz), 127.8, 129.1, 130.5 (d, *J* 7.4 Hz), 139.8, 143.9, 153.0, 161.6 (d, *J* 243.6 Hz); MS (relative intensity / %) *m/z*: 77 (94.1), 118 (55.3), 171 (4.7), 175 (3.6), 266 (100.0), 346 (74.7); HRMS (APCI-QTOF) *m/z*, calcd. for $C_{17}H_{15}FN_2Se$ $[M + H]^+$: 347.0463, found: 347.0459.

4-(Butylselanyl)-3,5-dimethyl-1-phenyl-1*H*-pyrazole (**4k**)[41]

Yield: 0.069 g (90%); yellowish oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, 3H, *J* 7.5 Hz, CH_3), 1.41 (sext, 2H, *J* 7.5 Hz, CH_2), 1.58 (quint, 2H, *J* 7.5 Hz, CH_2), 2.39 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.58 (t, 2H, *J* 7.5 Hz, CH_2), 7.33-7.37 (m, 1H, Ar-H), 7.41-7.47 (m, 4H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5, 13.0, 13.5, 22.7, 28.3, 32.3, 103.2, 124.6, 127.4, 129.0, 140.0, 143.2, 152.8; MS (relative intensity / %) *m/z*: 57 (6.1), 77 (72.3), 118 (75.4), 171 (100.0), 251 (24.3), 308 (43.9).

2-[(3,5-Dimethyl-1-phenyl-1*H*-pyrazol-4-yl)selanyl]pyridine (**4l**)

Yield: 0.048 g (58%); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 6.88 (dt, 1H, *J* 8.0, 0.9 Hz, Ar-H), 7.02 (ddd, 1H, *J* 7.4, 4.8, 0.9 Hz, Ar-H), 7.37-7.44 (m, 2H, Ar-H), 7.48-7.50 (m, 4H, Ar-H), 8.43 (ddd, 1H, *J* 4.8, 1.9, 0.9 Hz, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 12.9, 102.2, 120.0, 121.9, 124.7, 127.8, 129.1, 136.6, 139.8, 144.3, 149.9, 153.2, 158.7; MS (relative intensity / %) *m/z*: 77 (53.5), 118 (31.9), 156 (11.0), 171 (100.0), 248 (54.9), 329 (31.5); HRMS (APCI-QTOF) *m/z* calcd. for $C_{16}H_{15}N_3Se$ $[M + H]^+$: 330.0509, found: 330.0520.

General procedure for synthesis of 1,3,5-triphenyl-4-(phenylselanyl)-1*H*-pyrazole (**4m**)

In a reaction flask of 25.0 mL has added a mixture of the chalcone **5** (0.25 mmol) and phenylhydrazine **1a** (0.25 mmol) in CH_3COOH (1.0 mL). The mixture was stirred for 2 h under reflux, then the temperature was lowered to 50 °C and the diphenyl diselenide **3a**

(0.25 mmol) and Oxone® (0.5 mmol) were added. The mixture was stirred for 0.5 h. The aqueous sodium bicarbonate solution 5% (10.0 mL) and ethyl acetate (15.0 mL) were added. The organic phase was washed with water (2 × 10.0 mL), separated, dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The product was isolated by column chromatography using hexane/ethyl acetate (98/2% v/v) as eluent.

1,3,5-Triphenyl-4-(phenylselanyl)-1*H*-pyrazole (**4m**)

Yield: 0.092 g (81%); yellowish solid; mp 127-129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09-7.22 (m, 7H, Ar-H), 7.23-7.39 (m, 11H, Ar-H), 7.96-7.99 (m, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 101.7, 124.9, 125.8, 127.4, 128.1, 128.2, 128.3, 128.4, 128.6, 128.78, 128.82, 129.1, 129.9, 130.3, 132.8, 134.1, 139.9, 148.4, 155.0; MS (relative intensity / %) *m/z*: 157 (0.9), 180 (49.7), 372 (100.0), 452 (60.2).

Supplementary Information

Supplementary information is available free of charge at http://jbcs.sbq.org.br as PDF file.

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