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Sonochemistry: an efficient alternative to the synthesis of 3-selanylindoles using CuI as catalyst.

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Abstract: Ultrasonic (US) irradiation was successfully used as an alternative energy source to prepare 3-selanylindoles through the direct selanylation of indoles with diorganoyl diselenides using CuI (20 mol%) as catalyst and DMSO as the solvent. By using this US-promoted reaction, eleven 3-organylselanylindoles were prepared selectively and in good yields. A comparative study between the reactions under conventional heating, microwave and ultrasound irradiations was performed, and it was observed advantage in using US over the other heating systems.

Keywords: sonochemistry; 3-arylselanylindoles; organoselenium; copper-catalysis; green chemistry.

1. Introduction

The structural unit heterocyclic indole is widely distributed as basic frame both in naturally occurring bioactive molecules and in synthetic ones. Uses of compounds containing the indole scaffold include drugs, agrochemicals, dyes and pigments (indigo and analogs), dietary supplements, nutraceuticals, flavor enhancers and perfumes [1-3]. 3-Arylthioindoles (Figure 1) are an emergent class of synthetic indoles, which have been shown to possess important pharmacological properties, including selective inhibition of the COX-2 enzyme similar to etoricoxib and analogs (compounds **I** and **II**) [4], anti HIV-1 [5] and anti-asmathic [6]. The imidazole-functionalyzed 3-arylthioindole **III** and the 3-arylsulfonyl indole **IV** are potent anti-cancer, acting by inhibiting the polymerization of tubulin [7]. Compounds **III** and **IV** proved to be even more active than combretastatin-A-4, which is a natural compound with excellent antineoplastic properties (Fig.1).

In vitro and *in vivo* models studies have been demonstrated the pharmacological properties of organoselenium compounds [8-10], which include antinociceptive [11,12], hepatoprotective [13,14], anti-cancer [15-18], antidepressant [18,19], memory enhancer [19] and GPx-like activities [20-22].

The so-called “synthetic multivalent molecules”, which combine two or more bioactive moieties, have been used as an effective stratagem for designing new drugs [23]. In this line, 3-arylselanylindoles could be an interesting target to prospect novel drugs candidates and the first bioassays involving this class of compounds appeared only this year [24]. 3-Arylselanylindole **V** and the selenoxide **VI** (Fig. 1) were superior to combretastatin-A-4 in inhibiting the tubulin polymerization and disrupt tubulin microtubule dynamics. The selenide **V** was obtained by the reaction of 1,2-*bis*-(3,4,5-trimethoxyphenyl)diselenide with 5-methoxy-1,2-dimethyl-1*H*-indole in the presence of $I_2/FeCl_3$, and under microwave irradiation for 30 min. at 80 ^oC [24].

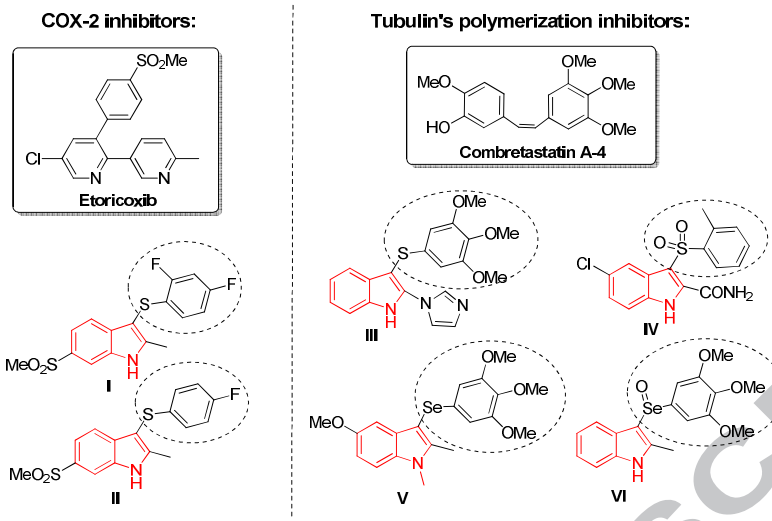


Figure 1. Chalcogenoindoles with analog activities to etoricoxib and combretastatin A-4.

The synthesis and pharmacological studies of 3-arylthioindoles are well documented [1-6]. However, in spite of a large number of pharmacological activities reported for both, the indole scaffold and organoselenium compounds, the synthesis and potential bioactivity of 3-arylselenoindoles have not been extensively explored [25-27]. These compounds can be obtained by two main routes: (A) the electrophilic cyclization of 2-alkynylanilines [28-30]; and (B) the direct selanylation of the indole by electrophilic selenium species [31-34]. Because it involves the use of easily available indole as starting material, approach B is the more attractive. This protocol, however, suffers of the inconvenience of having to previously prepare the (in most cases) unstable electrophilic species of selenium. This drawback was circumvented by Silveira and co-workers [32], which used the PhSeSePh/TCCA/MgO system to generate PhSeCl *in situ*. In addition, these reactions are not atom economic, once only a portion of the atoms involved (the arylselenium moiety of the electrophile) is incorporated in the final product [35,36]. More recently, the microwave-promoted synthesis of 3-arylthio and 3-arylselenoindoles starting from ArYYAr (Y= S, Se) in the presence of I_2/DMSO [37], using $(NH_4)_2S_2O_8$ in refluxing MeOH [38] or I_2/EtOH (only two examples with selenium) [39] were described. These approaches enable to incorporate two ArSe of ArSeSeAr, improving the atomic efficiency of the reaction.

Cu-catalytic coupling processes are an interesting alternative to C_{Ar}-Se bond formation, being a versatile method, which use generally mild reaction conditions. [40-42] Furthermore, the use of non-noble metals, such as copper in

catalytic amount, is important to the development of eco-friendly organic synthesis [40]. The use of Cu-catalysis to prepare 3-arylchalcogenylindoles was described by Zhou and co-workers. [43,44] They performed the chalcogenoamination of 2-alkynylanilines with dichalcogenides in the presence of CuI (10 mol%), DMSO and $CsCO_3$ at 80 °C for 4 h [43] or the reaction of indole with diaryl dichalcogenides in presence of CuI and DMSO at 110 °C for 10-18 h [44]. As the authors were interested in the synthesis of 3-arylthioindoles, only diphenyl diselenide was used in these reactions.

On the other hand, ultrasonic irradiation (US) have gained popularity in the past decades as a versatile tool in a large variety of industrial and academic applications [45-50] The role of ultrasound waves as a green tool in promoting organic synthesis (the so-called sonochemistry) is well documented [49,50]. This non-conventional energy source is able to accelerate reactions or even to change completely their course and selectivity, through the formation of new reactive intermediates and compounds that are not usually observed under classical thermal conditions [49]. In addition, reactions under US are considered environmentally friendly processes, being less energy consumer and generating fewer side products [45-50].

Despite the large interest in organoselenium compounds, the number of papers describing the use of sonochemistry to prepare these species is limited [51-56] and, to the best of our knowledge, the Cu-catalyzed C-Se bond formation on the synthesis of 3-arylselanylindoles by direct selanylation of indoles has not yet been extensively studied [44]. Besides, in view of the important biological activities recently discovered of 3-arylselanylindoles, the development of general, selective and greener methods to prepare this class of compounds is desirable.

Due our continued interest in the development of green procedures to access organoselenium compounds with potential pharmacological activities [12,31,57-61], we present here the results on the study of the sonochemical synthesis of 3-arylselanylindoles, through the direct selenylation of indoles using diorganyl diselenides under Cu-catalysis. Moreover, we have developed a comparative study of this new reaction under conventional thermal heating, microwave and ultrasonic irradiation, aiming to show the role of the ultrasound in this synthesis.

2. Experimental

2.1. General procedure for the synthesis of 3-organylselanylindoles 3:

Indole **1** (0.5 mmol), diorganyl diselenide **2** (0.3 mmol), CuI (0.0114g, 20 mol %), and DMSO (0.5 mL) were added in a glass tube. The reaction was performed using three different methods: **Method A** (Ultrasound): The US probe was placed in a glass vial containing the reaction mixture. The amplitude of the US waves was fixed in 60%. The temperature was monitored and after 1 min was around 60-61 ^{o}C, which maintains until the end of the reaction. **Method B** (Microwave): The glass tube was sealed and placed in a CEM Discover microwave apparatus. A maximum irradiation power of 100 W and a temperature of 60 °C were applied for 2 hours. **Method C** (Oil Bath): The glass tube was placed in a pre-heated oil bath at 60 °C and the mixture was vigorously stirred. The progress of the reaction was monitored by TLC and the resulting solution was stirred for the time indicated in Table 2. After that, the reaction mixture was received in water (10.0 mL), extracted with ethyl acetate (3 x 5.0 mL), dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by preparative chromatographic plate using ethyl acetate/hexane as the eluent.

*3-(Phenylselanyl)-1H-indole (**3a**)*

White solid; mp 130-131 °C. Lit. [33]: 135.4–137.0 °C. Yield, **Method A**: 0.1010g (74%); **Method B**: 0.0273g (20%); **Method C**: 0.0614g (45%); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.34 (br s, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.40-7.37 (m, 2H), 7.24-7.08 (m, 7H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 150.43, 137.06, 134.55, 129.69, 128.92, 125.74, 113.60, 113.10, 40.24. MS *m/z* (rel. int.): 273 (18.4), 193 (100.0), 116 (6.4), 77 (7.0).

*5-Bromo-3-(phenylselanyl)-1H-indole (**3b**)*

White solid; mp 102-104 °C. Lit. [33]: 108.1–109.4 °C. Yield: **Method A**: 0.1684g (96%); **Method B**: 0.0122g (7%); **Method C**: 0.1667g (95%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.47 (br s, 1H), 7.76 (d, *J* = 1.4 Hz, 1H), 7.41 (d, *J* = 2.5 Hz, 1H), 7.31 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.26-7.07 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 135.0, 133.3, 132.4, 131.8, 129.0, 128.6, 125.9, 125.8, 122.8, 114.3, 112.9, 97.7. MS *m/z* (rel. int.): 351 (36.5), 271 (100.0), 192 (36.9), 115 (12.1), 77 (12.6).

*1-Methyl-3-(phenylselanyl)-1H-indole (**3c**)*

White solid; mp 63-65 °C. Lit. [34]: 67 °C. Yield: **Method A**: 0.1334g (93%); **Method B**: 0.0287g (20%); **Method C**: 0.1148g (80%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.62 (d, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.28-7.18 (m, 4H), 7.15 (t, *J* = 7.9 Hz, 1H), 7.11-7.03 (m, 3H), 3.70 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 137.4, 135.6, 134.2, 130.6, 128.8, 128.5, 125.4, 122.4, 120.4, 120.3, 109.5, 95.9, 33.0. MS *m/z* (rel. int.): 287 (21.8), 207 (100.0), 130 (15.5), 77 (6.7).

*3-[(4-Methoxyphenyl)selanyl]-1H-indole (**3d**):*

White solid; mp 77-79 °C. Yield: **Method A**: 0.0348g (23%); **Method B**: 0.0257g (17%); **Method C**: 0.0560g (35%); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.24 (br, s, 1H),), 7.63 (d, *J* = 7.7 Hz, 1H), 7.31-7.29 (m, 2H), 7.23-7.11 (m, 5H), 6.69-6.64 (m, 2H), 3.65 (s, 3H).^{13}C NMR ($CDCl_3$, 75 MHz): δ = 158.2, 136.2, 131.1, 130.6, 129.7, 123.3, 122.7, 120.6, 120.2, 114.7, 111.3, 99.1, 55.2. MS *m/z* (rel. int.): 303 (13.5), 223 (100.0), 180 (24.8), 77 (12.2). HRMS calcd. for $C_{15}H_{13}NOSe$: $[M + H]^+$ 304.0241. Found: 304.0229.

*3-(o-Tolylselanyl)-1H-indole (**3e**)*

Yellow solid; mp 104-106 °C. Yield: **Method A**: 0.0846 g (59%); **Method B**: 0.0358g (25%); **Method C**: 0.0617g; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.30 (br s, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.40-7.36 (m, 2H), 7.24 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.19-7.09 (m, 2H), 7.04-6.96 (m, 1H), 6.86-6.79 (m, 2H), 2.46 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 136.4, 136.0, 134.5, 131.5, 129.8, 127.8, 126.4, 125.3, 122.9, 120.8, 120.3, 111.4, 97.0, 21.2. MS *m/z* (rel. int.): 287 (43.6), 206 (80.9), 117 (100.0), 77 (8.4). HRMS calcd. for $C_{15}H_{13}NSe$: $[M + H]^+$ 288.0291. Found: 288.0280.

*3-(4-Chlorophenylselanyl)-1H-indole (**3f**)*

White solid; mp 132-133 °C. Lit. [37]: 134–135.0 °C. Yield: **Method A**: 0.0859 g (56%); **Method B**:0.0260g (17%); **Method C**: 0.0322g (21%); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.40 (br s, 1H) 7.59 (d, *J* = 7.9 Hz, 1H), 7.43-7.39 (m, 2H), 7.26 (td, *J* = 8.0, 1.1 Hz, 1H), 7.22-7.05 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 136.3, 132.0, 131.5, 131.2, 129.9, 129.6, 128.9, 123.0, 120.9, 120.1, 111.4, 97.7. MS *m/z* (rel. int.): 307 (19.3), 227 (100.0), 116 (5.8), 77 (4.1).

*3-[(4-Fluorophenyl)selanyl]-1H-indole (**3g**)*

White solid; mp 117-118 °C. Yield: **Method A**: 0.0582g (40%); **Method B**: 0.0436g; **Method C**:0.0887g; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.28 (br s, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.38-7.35 (m, 2H), 7.26-7.14 (m, 4H), 6.80 (t, *J* = 8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 161.4 (d, $^{1}J_{C-F}$ = 244.7 Hz), 136.3, 131.0, 130.6 (d, $^{3}J_{C-F}$ = 7.6 Hz), 129.6, 127.8 (d, $^{4}J_{C-F}$ = 3.2 Hz), 123.0, 120.9, 120.1, 116.0 (d, $^{2}J_{C-F}$ = 21.6 Hz), 111.4, 98.4. MS *m/z* (rel. int.): 291 (12.9), 211 (100.0), 183 (15.4), 77 (3.8). HRMS calcd. for $C_{14}H_{10}FNSe$: $[M + H]^+$ 292.0041. Found: 292.0030.

*3-{[3-(Trifluoromethyl)phenyl]selanyl}-1H-indole (**3h**)*

Yellow solid; mp 70-71 °C. Lit. [37]: 75.8–77.0 °C. Yield: **Method A**: 0,1244g (73%); **Method B**: 0.0170g (10%); **Method C**: 0.1142g (67%); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.43 (br s, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.53 (s, 1H), 7.46 (d, *J* = 2.5 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.33-7.24 (m, 3H), 7.22-7.14 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 136.4, 135.2, 131.7, 131.6, 131.5, 131.0 (q, $^{2}J_{C-F}$ = 32.1 Hz), 129.6, 129.2, 125.0 (q, $^{3}J_{C-F}$ = 3.9 Hz), 123.8 (q, $^{1}J_{C-F}$ = 272.8 Hz), 122.3 (q, $^{3}J_{C-F}$ = 3.8 Hz), 121.1, 120.0, 111.5, 97.1. MS *m/z* (rel. int.): 341 (17.4), 261 (100.0), 116 (8.4), 77 (4.2).

*5-Bromo-3-(4-chlorophenylselanyl)-1H-indole (**3i**)*

White solid; mp 136-138 °C Lit. [32]: 118-121°C. Yield: **Method A**: 0.1347 g (70%); **Method B**: 0.0327g; **Method C**: 0.1636g (85%); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.4 (br s, 1H), 7.73-7-72 (m, 1H), 7.45 (d, *J* = 2.5 Hz, 1H), 7.33 (dd, *J* = 8.6, 1.8 Hz, 2H), 7.27 (d, *J* = 8.6 Hz, 1H), 7.13-7.06 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 135.0, 132.4, 131.7, 131.5, 129.9, 129.8, 129.1, 126.0, 122.7, 114.4, 112.9, 97.5. MS *m/z* (rel. int.): 385 (4.7), 306 (100.0), 190 (22.1), 114 (15.3), 75 (14.9).

*3-(4-Chlorophenylselanyl)-1-methyl-1H-indole (**3j**)*

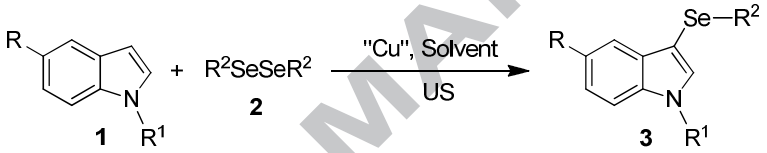
White solid; mp 116-119 °C. Lit. [32]: 110-114 °C. Yield: **Method A**: 0.0979 g (61%); **Method B**: 0.0272g (17%); **Method C**: 0.1316g (82%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.57 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.30-7.25 (m, 2H), 7.20-7.03 (m, 5H), 3.78 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 137.4, 135.6, 132.4, 131.4, 130.3, 129.7, 128.9, 122.5, 120.5, 120.2, 109.6, 95.5, 30.0. MS *m/z* (rel. int.): 321 (13.1), 240 (100.0), 130.0 (29.0), 77 (13.9).

*3-(Butylselanyl)-1H-indole (**3k**)*

Brown oil. Yield: **Method A**: 0.1113g (88%); **Method B**: no reaction; **Method C**: 0.0670g; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.13 (br s, 1H), 7.75-7.72 (m, 1H), 7.31-7.27 (m, 1H), 7.24-7.15 (m, 3H), 2.65 (t, *J* = 7.3 Hz, 2H), 1.61-1.51 (m, 2H), 1.47-1.29 (m, 2H), 0.83 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 136.1, 130.2, 130.0, 122.4, 120.2, 120.0, 111.2, 98.6, 32.6, 28.5, 22.6, 13.5. MS *m/z* (rel. int.): 253 (14.3), 196 (15.5), 117 (100.0), 77 (5.4). HRMS calcd. for $C_{12}H_{15}NSe$: $[M + H]^+$ 254.0448. Found: 254.0436.

3. Results and Discussion

Based on our previous works on the C-H bond cleavage to form new C_{Ar}-Se bond using Cu-catalysis [31,57,58,60,61], here is reported the synthesis of 3-organylselanylindoles **3**, containing a number of substituents both in the indole and in the organoselenium moieties, according the procedure depicted on Scheme 1.



Scheme 1. Synthesis of 3-arylselanylindoles using ultrasonic irradiation (US).

We start from indole (**1a**, 0.5 mmol) and diphenyl diselenide (**2a**, 0.3 mmol) to establish the best conditions for the direct arylselanylation reaction under ultrasonic irradiation using different copper species. When a mixture of **1a** and **2a** was sonicated in the presence of CuO_{NPs} (10 mol%) and DMSO (0.5 mL) as the solvent during 1h (60% of frequency) no product was observed by TLC or GC-MS (Table 1, entry 1). Whereas, the use of CuBr and CuCl afforded the desired 3-(phenylselanyl)-1*H*-indole **3a** in low yields (18% and 34% respectively, entries 2 and 3). When CuI was used as catalyst (10 mol%), the conversion to product **3a** increased to 82% (Table 1, entry 4) and increasing the catalyst amount to 20% produced slightly better yields (97%, entry 6). The use of stoichiometric amounts of indole **1a** and diphenyl diselenide **2a** decreased the conversion to 81% (Table 1, entry 7), indicating that a little excess of diselenide is necessary. We also tested other solvents, such as water, glycerol, DMF, toluene and THF; but in all the cases the yields resulted to be not satisfactory, and no reaction was observed using toluene and THF (Table 1, entries 8-12). The use of $FeCl_3$ and $NiCl_2$ as catalyst

(20 mol5) was also tested; however, low yields of 3-(phenylselanyl)-1*H*-indole **3a** were obtained after sonication for 1 or 2 h (Table 1, entries 13-14).

Insert Table 1 here

With the optimized conditions in hands, a detailed study was performed with substituted indoles **1a**-**e** and diorganyl diselenides **2a**-**g**, to verify the scope of the methodology, as well as the electronic effect of substituents (Table 2, Method A). It was observed that the presence of the bromo group in the position 5 of the indole ring in **1b** (1.0 h of reaction, 96% yield of **3b**) facilitates the reaction compared to unsubstituted indol **1a**, which afforded **3a** in 74% yield after 1.5 h (Table 2, entry 2 *versus* entry 1). Similar behavior was observed when *N*-methyl-1*H*-indole **1c** was used, with the *N*-methyl- substituted selanylindole **3c** being obtained in 93% yield after ultrasonic irradiation for 2 h (Table 2, entry 3, Method A).

The study proceeded fixing the indole **1a** to evaluate the effect of electron-donor and electron-withdrawing groups in the aromatic ring on the organoselenium reagent **2**. When the reaction was carried out using diaryl diselenide **2b**, containing a methoxyl group at the *para* position of the aromatic ring, the corresponding 3-arylselanylindole **3c** was obtained in 23% yield, even after 20 h of ultrasonic irradiation. Better results were achieved using the *ortho*-methyl substituted diaryl diselenide **2c**, which afforded the desired product **3e** in 59% yield after 4 h of reaction (Table 2, entry 5). Diaryl diselenides substituted with electron-withdrawing groups, such as *p*-chloro (**2d**), *p*-fluoro (**2e**) and *m*-trifluoromethyl (**2f**), gave good yields of the respective desired products **3f-h** in 56, 40 and 73% yield, respectively; even if larger reaction times (4-5 h) are required in comparison to that with diphenyl diselenide **2a** (Table 2, entries 6-8, Method A).

The accelerating effect produced by 5-bromo and *N*-methyl substituents in the indole was verified in the reaction with the *p*-chloro substituted diaryl diselenide **2d** (Table 2, entry 2). Thus, 5-bromo-indole **1b** reacted with diselenide **2d** to afford the respective arylselanylindole **3i** in 70% yield in 1.5 h under sonication, while **3j** was obtained in 61% yield after 6 h from *N*-methyl-1*H*-indole **1c** and **2d** under the same conditions (Table 2, entries 9-10).

To our delight, our new Cu-catalyzed ultrasonic-promoted protocol worked well also with the reaction of dibutyl diselenide **2g**, affording the 3-butylselanylindole **3k** in 88% yield after 5 h (Table 2, entry 11, Method A). This is

the first well succeeded preparation of this compound ever described. Unfortunately, no reaction was observed with protected indoles *N*-tosyl (**1d**) and *N*-Boc (**1e**), even after 24 h of ultrasonic irradiation (Table 2, entries 12-13).

With the aim to compare the effect of different energy sources in the Cu-catalyzed reaction, the direct selenylation of indoles at 60 ^{o}C in DMSO was also performed under microwave irradiation (Method B) and thermal heating (Method C) with an oil bath. The obtained results are depicted in Table 2 and Figures 1 and 2.

In a general way, the microwave irradiation gave low yields of product, while thermal heating afforded the desired products at similar yields but in larger reaction times compared to the ultrasonic-promoted reactions. Thus, the reaction of indole **1a** with diphenyl diselenide **2a** afforded **3a** in 20% and 45% yields after 2 h and 5 h using the Methods B and C respectively (Table 2, entry 1), while only 7% of **3b** was obtained after 2 h under MW irradiation (Method B, entry 2). In this case, thermal heating allowed preparing **3b** in 95% yield after 2.5 h (entry 2, Method C). Noteworthy, no reaction was observed between dibutyl diselenide **2g** and indole **1a** using the Method B (MW irradiation), while only 53% of desired butylselanylindole **3k** was isolated after 20 h of reaction (Table 2, entry 11, Method B *versus* Method C).

Insert Table 2 here

From the analysis of the results reported in Table 2 and graphically summarized in Figure 2, it can be seen that the use of microwave is not appropriated in our reaction, affording the products in modest yields or even failing completely in some cases. The positive effect of ultrasonic irradiation in the reaction is highlighted on Figure 3. Despite similar yields were obtained in most of tested examples, the reaction time is drastically reduced when ultrasound was used compared to conventional heating. The acceleration of the reaction under ultrasound is due the cavitation, which leads to turbulent flow of the liquid phase and enhanced mass transfer in the system [62].

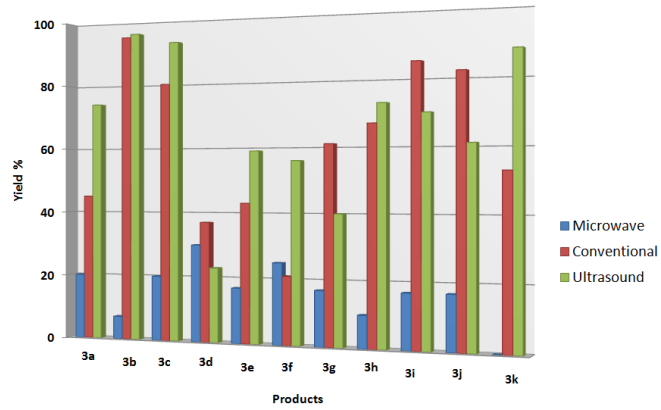


Figure 2

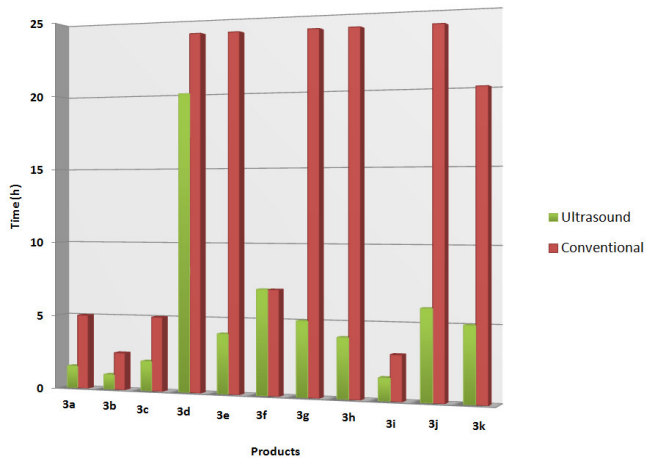
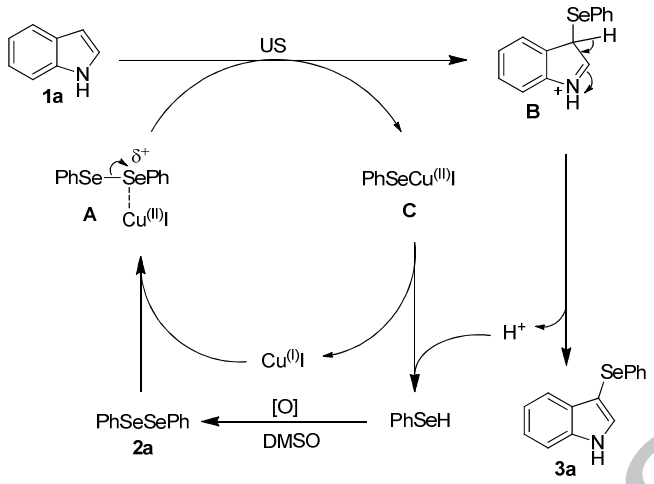


Figure 3.

Based on the recent literature [42,43,60], a plausible mechanism is depicted in Scheme 2 for the reaction between indole **1a** and diphenyl diselenide **2a**. At first, we believe that CuI reacts with diphenyl diselenide forming the intermediate **A**, which suffers the attack by the indole to afford **B** and **C**; Then, intermediate **B** releases a proton to **C**, to form the product **3a** and phenylselenol and regenerating CuI. PhSeH, in the presence of DMSO and air, is oxidized to PhSeSePh and a new cycle is initiated. To speculate if the reaction could be catalyzed by iodine from the copper(I)iodide, similarly to the I_2/DMSO- catalyzed, MW- promoted reaction described by Silveira and Braga [37], the same reaction was tested using KI instead CuI and no product was detected after 2 h under sonication. Thus, the presence of copper is crucial for the reaction, reinforcing the proposed mechanism.



Scheme 2: A plausible mechanism for the reaction.

3. Conclusion

In this study, we provide a new, copper-catalyzed ultrasonic-promoted method to make 3-selanylindoles through the direct selenylation of indole derivatives. The method is atom-economic and selective, allowing the transfer of the two RSe groups from the diorganyl diselenide to the indole. A comparative study between ultrasonic, microwave and conventional thermal heating, showed that ultrasonic irradiation is advantageous, affording the products selectively in higher yields and shorter reaction times.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ultsonch.xxxxx.

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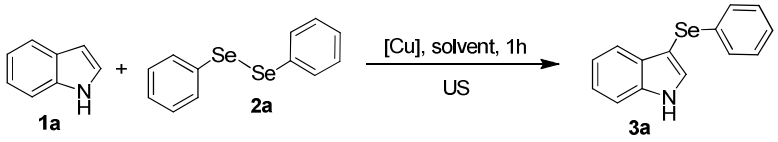
Figure captions

Figure 1. Reaction yields according the energy source.

Figure 2. Reaction times using US (green, Method A) and conventional heating (red, Method C).

Tables

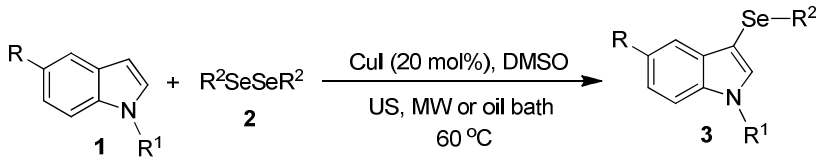
Table 1. Optimization studies for preparation of 3-(phenylselanyl)-1*H*-indole **3a**[a]



Entry	Catalyst (mol%)	Solvent	**3a** Conv. (%)[b]
1	CuO_{NPs} (10)	DMSO	-
2	CuBr (10)	DMSO	18
3	CuCl (10)	DMSO	34
4	CuI (10)	DMSO	82
5	CuI (15)	DMSO	75
6	CuI (20)	DMSO	97 (69)[c]
7	CuI (20)	DMSO	81[d]
8	CuI (20)	H_2O	1.5
9	CuI (20)	glycerol	1
10	CuI (20)	DMF	30
11	CuI (20)	toluene	nr
12	CuI (20)	THF	nr
13	$FeCl_3$ (20)	DMSO	20
14	$NiCl_2.6H_2O$	DMSO	6

[a] The reaction was performed using indole (**1a**, 0.5 mmol) and diphenyl diselenide (**2a**, 0.3 mmol) in 0.5 mL of solvent under ultrasound irradiation in 60% of frequency. The final temperature measured in the reaction flask using DMSO was 60 °C. [b] Conversion calculated by gas chromatography coupled to a mass spectrometer after 1 h of reaction; [c] Isolated yield. [d] An equimolar amount of reagents was used.

Table 2. Synthesis of 3-organylselanylindoles.[a]



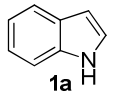
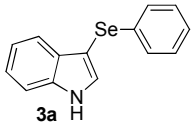
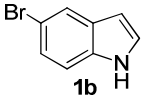
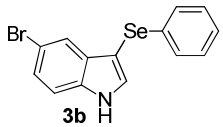
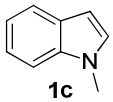
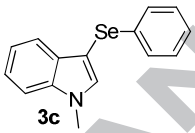
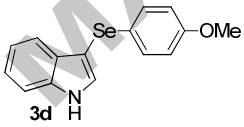
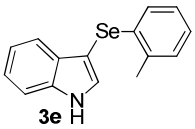
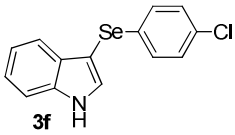
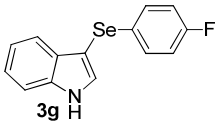
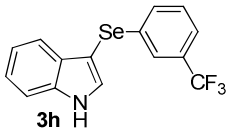
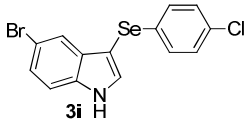
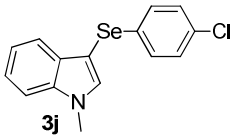
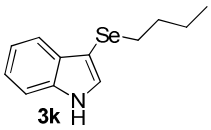
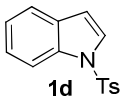
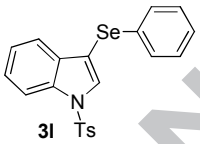
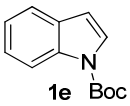
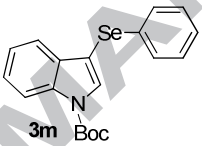
Entry	Indole **1a-c**	R^2 **2a-g**	Product **3a-m**	Method[b]	Time (h)	Yield (%)[c]
1	 **1a**	C_6H_5 **2a**	 **3a**	**A**	1.5	74
				B	2	20
				C	5	45
2	 **1b**	**2a**	 **3b**	**A**	1	96
				B	2	7
				C	2.5	95
3	 **1c**	**2a**	 **3c**	**A**	2	93
				B	2	20
				C	5	80
4	**1a**	4-$CH_3OC_6H_4$ **2b**	 **3d**	**A**	20	23
				B	2	17
				C	24	37
5	**1a**	2-$CH_3C_6H_4$ **2c**	 **3e**	**A**	4	59
				B	2	25
				C	24	43
6	**1a**	4-ClC_6H_4 **2d**	 **3f**	**A**	7	56
				B	2	17
				C	7	21
7	**1a**	4-FC_6H_4 **2e**	 **3g**	**A**	5	40
				B	2	30
				C	24	61
8	**1a**	3-$CF_3C_6H_4$ **2f**	 **3h**	**A**	4	73
				B	2	10
				C	24	67

Table 2, Continuation[a]

Entry	Indole **1a-c**	R^2 **2a-g**	Product **3a–i**	Method[b]	Time (h)	Yield (%)[c]
9	**1b**	**2d**	 **3i**	**A** **B** **C**	1.5 2 3	70 17 85
10	**1c**	**2d**	 **3j**	**A** **B** **C**	6 2 24	61 17 82
11	**1a**	C_4H_9 **2g**	 **3k**	**A** **B** **C**	5 2 20	88 nr 53
12	 **1d**	**2a**	 **3l**	**A** **B** **C**	24 2 24	nr nr nr
13	 **1e**	**2a**	 **3m**	**A** **B** **C**	24 2 24	nr nr nr

[a] The reaction was performed using indole (**1**, 0.5 mmol), diorganyl diselenide (**2**, 0.3 mmol), CuI (20 mol%) in DMSO (0.5 mL) at 60 °C. [b] **Method A**: an ultrasound probe was used; **Method B**: a scientific microwave apparatus was used; **Method C**: conventional heating with an oil bath was used. [c] Yields of purified products using preparative chromatographic plates.

Highlights:

Ultrasonic irradiation accelerates the direct selenylation of indoles.

US is more effective than MW irradiation to prepare 3-organylselanylindoles.

CuI in DMSO is effective to prepare 3-organylselanylindoles from RSeSeR and indole.