Palladium-Catalyzed Suzuki Cross-Coupling of 2-Haloselenophenes: Synthesis of 2-Arylselenophenes, 2,5-diarylselenophenes and 2-Arylselenophenyl Ketones

Patrícia Prediger,^a Angélica Venturini Moro,^a Cristina W Nogueira,^a Lucielli Savegnago,^a Paulo Henrique Menezes,^b João B T Rocha^a and Gilson Zeni^{a,}*

^aLaboratório de Síntese, Reatividade, Avaliação Farmacológica e Toxicológica de Organocalcogênicos, CCNE, UFSM, Santa Maria - Rio Grande do Sul – Brazil - 97105-900

^bDepartamento de Química Fundamental – UFPE – Recife - PE – Brazil - 50670-901

gzeni@quimica.ufsm.br

SUPPORTING INFORMATION

CONTENTS

Materials and Methods	S2
General Procedure for the Preparation of the Arylselenophenes from 2-iodoselenophene	S2
General Procedure for the Preparation of the Arylselenophenes from 2-bromoselenophene	S2
General Procedure for the Preparation of the Biarylselenophene from 2,5-diiodoselenophene	S4
General Procedure for the Synthesis of Diaryl Ketones from 2-iodoselenophene	S5
Selected Spectra	S7

Materials and Methods

Proton nuclear magnetic resonance spectra (^1H NMR) were obtained at 400 MHz. Spectra were recorded in CDCl_3 solutions. Chemical shifts are reported in ppm, referenced to the solvent peak of CDCl_3 or tetramethylsilane (TMS) as the external reference. Data are reported as follows: chemical shift (δ), multiplicity, coupling constant (J) in Hertz and integrated intensity. Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 100 MHz. Spectra were recorded in CDCl_3 solutions. Chemical shifts are reported in ppm, referenced to the solvent peak of CDCl_3 . Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). High resolution mass spectra were recorded on a double focusing magnetic sector mass spectrometer using EI at 70 eV. Column chromatography was performed using silica gel (230-400 mesh) following the methods described by Still.¹ Thin layer chromatography (TLC) was performed using silica gel GF₂₅₄, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light, or stained with iodine vapor, or acidic vanillin. The following solvents were dried and purified by distillation from the reagents indicated: tetrahydrofuran from sodium with a benzophenone ketyl indicator. All other solvents were ACS or HPLC grade unless otherwise noted. Air- and moisture-sensitive reactions were conducted in flame-dried or oven dried glassware equipped with tightly fitted rubber septa and under a positive atmosphere of dry nitrogen or argon. Reagents and solvents were handled using standard syringe techniques. Temperatures above room temperature were maintained by use of a mineral oil bath with an electrically heated coil connected to a controller.

General Procedure for the Preparation of the Arylselenophenes from 2-iodoselenophene: The solution of 2-iodoselenophene (0.128 g, 0.5 mmol) in DME (5 mL) was added to $\text{Pd}(\text{OAc})_2$ (0.003 g, 3 mol %) and boronic acid (0.7 mmol), under argon. The resulting solution was stirred for 15 min at room temperature. After this time, a solution of K_2CO_3 (2.4 mmol, 0.309 g) in H_2O (1.2 mL) was added. The mixture was then heated at reflux for the time indicated in Table 3, cooled to room temperature, diluted with dichloromethane (20 mL) and washed with brine (2x20 mL). The organic phase was separated, dried over MgSO_4 and concentrated under vacuum. The residue was purified by flash chromatography and eluted with hexane/ethyl acetate (95:5) or hexane.

General Procedure for the Preparation of the Arylselenophenes from 2-bromoselenophene: The solution of 2-bromoselenophene (0.105 g, 0.5 mmol) in Toluene (3.5 mL) was added to a mixture of $\text{Pd}(\text{PPh}_3)_4$ (0.017 g, 3 mol%) and boronic acid (0.75 mmol), under argon. After, was added the solution of Na_2CO_3 (1.1 mL of a solution 2 M in H_2O , 2.17 mmol). The mixture was then heated at reflux for the time indicated in table 4, cooled to room temperature, diluted with dichloromethane (20 mL) and washed with brine (2x20 mL). The organic phase was separated, dried over MgSO_4 and concentrated under vacuum. The residue was purified by flash chromatography and eluted with hexane/ethyl acetate (95:5) or hexane.

2-phenylselenophene: Yield: I = 0.079 g (77 %); Br = 0.070 g (69 %). ^1H NMR: CDCl_3 , 400 MHz, δ (ppm): 7.89 (d, J = 5.55 Hz, 1H), 7.53 (d, J = 7.75 Hz, 2H), 7.42 (d, J = 4.10

¹ Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, 43, 2923-2925.

Hz, 1H), 7.34-7.30 (m, 3H), 7.27-7.24 (m, 1H). ^{13}C NMR: CDCl_3 , 100 MHz, $\delta(\text{ppm})$: 150.8, 136.4, 130.5, 129.9, 128.8, 127.5, 126.3, 125.2. MS (EI, 70 eV) m/z (relative intensity): 210 (25), 208 (99), 128 (100), 115 (38), 102 (35). HRMS Calcd. For $\text{C}_{10}\text{H}_8\text{Se}$: 207.9791. Found: 207.9796.

2-p-tolylselenophene: Yield: I = 0.104 g (95 %); Br = 0.093 g (85 %). ^1H NMR: CDCl_3 , 400 MHz, $\delta(\text{ppm})$: 7.87 (d, $J = 5.55$ Hz, 1H), 7.44 (d, $J = 8.04$ Hz, 2H), 7.39 (d, $J = 3.51$ Hz, 1H), 7.29-7.26 (m, 1H), 7.14 (d, $J = 8.04$ Hz, 2H), 2.34 (s, 3H). ^{13}C NMR: CDCl_3 , 100 MHz, $\delta(\text{ppm})$: 150.9, 137.4, 133.7, 130.5, 129.5, 129.3, 126.3, 124.7, 21.1. MS (EI, 70 eV) m/z (relative intensity): 224 (22), 222 (96), 182 (56), 167 (31), 141 (100), 115 (68). HRMS Calcd. For $\text{C}_{11}\text{H}_{10}\text{Se}$: 221.9948. Found: 221.9953.

2-(4-methoxyphenyl)selenophene: Yield: I = 0.098 g (83 %); Br = 0.095 g (81 %). ^1H NMR: CDCl_3 , 400 MHz, $\delta(\text{ppm})$: 7.84 (d, $J = 5.55$ Hz, 1H), 7.47 (d, $J = 8.77$ Hz, 2H), 7.32 (d, $J = 3.65$ Hz, 1H), 7.28-7.26 (m, 1H), 6.88 (d, $J = 8.77$ Hz, 2H), 3.81 (s, 3H). ^{13}C NMR: CDCl_3 , 100 MHz, $\delta(\text{ppm})$: 159.3, 150.7, 130.5, 129.3, 128.7, 127.6, 124.1, 114.3, 55.3. MS (EI, 70 eV) m/z (relative intensity): 240 (17), 238 (100), 223 (90), 195 (4), 115 (88). HRMS Calcd. For $\text{C}_{11}\text{H}_{10}\text{OSe}$: 237.9897. Found: 237.9903.

2-(selenophen-2-yl)thiophene: Yield: I = 0.085 g (80 %). ^1H NMR: CDCl_3 , 400 MHz, $\delta(\text{ppm})$: 7.85 (d, $J = 5.55$ Hz, 1H), 7.31 (d, $J = 3.65$ Hz, 1H), 7.25-7.19 (m, 2H), 7.12 (d, $J = 3.65$ Hz, 1H), 7.00-6.98 (m, 1H). ^{13}C NMR: CDCl_3 , 100 MHz, $\delta(\text{ppm})$: 130.2, 129.7, 129.5, 127.8, 126.7, 125.9, 124.5, 124.4. MS (EI, 70 eV) m/z (relative intensity): 214 (85), 134 (100), 121 (10), 108 (20), 89 (23). HRMS Calcd. For $\text{C}_8\text{H}_6\text{SSe}$: 213.9355. Found: 213.9361.

2-o-tolylselenophene: Yield: I = 0.060 g (55 %); Br = 0.021 g (20 %). ^1H NMR: CDCl_3 , 400 MHz, $\delta(\text{ppm})$: 8.02 (d, $J = 5.55$ Hz, 1H), 7.39-7.37 (m, 1H), 7.33-7.31 (m, 1H), 7.26-7.18 (m, 4H), 2.41 (s, 3H). ^{13}C NMR: CDCl_3 , 100 MHz, $\delta(\text{ppm})$: 149.4, 136.3, 135.7, 130.7, 130.6, 130.5, 129.6, 128.6, 127.7, 125.8, 29.7. HRMS Calcd. For $\text{C}_{11}\text{H}_{10}\text{Se}$: 221.9948. Found: 221.9955.

2-mesitylselenophene: Yield: I = 0.039 g (32 %); Br = 0.013 g (11 %). ^1H NMR: CDCl_3 , 400 MHz, $\delta(\text{ppm})$: 8.04 (d, $J = 5.55$ Hz, 1H), 7.31-7.29 (m, 1H), 6.93-6.92 (m, 3H), 2.31 (s, 3H), 2.14 (s, 6H). ^{13}C NMR: CDCl_3 , 100 MHz, $\delta(\text{ppm})$: 148.1, 137.6, 133.1, 130.9, 130.2, 129.5, 128.6, 128.1, 21.0, 20.8. MS (EI, 70 eV) m/z (relative intensity): 252 (14), 250 (74), 235 (32), 169 (100), 155 (41), 128 (29), 115 (26). HRMS Calcd. For $\text{C}_{13}\text{H}_{14}\text{Se}$: 250.0261. Found: 250.0266.

2-(3-(trifluoromethyl)phenyl)selenophene: Yield: I = 0.099 g (72 %); Br = 0.094 g (69 %). ^1H NMR: CDCl_3 , 400 MHz, $\delta(\text{ppm})$: 7.98 (d, $J = 5.55$ Hz, 1H), 7.78 (s, 1H), 7.69 (d, $J = 7.75$ Hz, 1H), 7.58-7.43 (m, 2H), 7.45 (t, $J = 7.75$ Hz, 1H), 7.33-7.31 (m, 1H). ^{13}C NMR: CDCl_3 , 100 MHz, $\delta(\text{ppm})$: 148.9, 137.2, 131.5 (q, $J = 32.53$ Hz), 131.2, 130.7, 129.6, 129.4, 126.4, 124.0 (q, $J = 3.53$ Hz), 123.9 (q, $J = 272.68$ Hz), 122.9 (q, $J = 3.53$ Hz). MS

(EI, 70 eV) m/z (relative intensity): 276 (100), 196 (48), 175 (13), 146 (23), 126 (10), 115 (11). HRMS Calcd. For $C_{11}H_7F_3Se$: 275.9665. Found: 275.9671.

2-(3-nitrophenyl)selenophene: Yield: I = 0.081 g (65 %); Br = 0.079 g (64 %). 1H NMR: $CDCl_3$, 400 MHz, δ (ppm): 8.38 (s, 1H), 8.10 (d, J = 7.89 Hz, 1H), 8.04 (d, J = 5.55 Hz, 1H), 7.83 (d, J = 7.60 Hz, 1H), 7.57 (d, J = 3.51 Hz, 1H), 7.52 (t, J = 8.04 Hz, 1H), 7.37-7.34 (m, 1H). ^{13}C NMR: $CDCl_3$, 100 MHz, δ (ppm): 167.7, 147.6, 138.1, 132.3, 131.9, 130.8, 129.8, 127.1, 121.9, 120.7. MS (EI, 70 eV) m/z (relative intensity): 253 (9), 207 (7), 127 (14), 115 (100). HRMS Calcd. For $C_{10}H_7NO_2Se$: 252.9642. Found: 252.9648.

1-(4-(selenophen-2-yl)phenyl)ethanone: Yield: I = 0.094 g (76 %); Br = 0.097 g (79 %). 1H NMR: $CDCl_3$, 400 MHz, δ (ppm): 8.02 (d, J = 5.55 Hz, 1H), 7.93 (d, J = 8.33 Hz, 2H), 7.62 (d, J = 8.33 Hz, 2H), 7.58 (d, J = 3.51 Hz, 1H), 7.35-7.33 (m, 1H), 2.59 (s, 3H). ^{13}C NMR: $CDCl_3$, 100 MHz, δ (ppm): 197.2, 149.2, 140.7, 135.8, 131.8, 130.8, 129.1, 126.8, 126.1, 26.5. MS (EI, 70 eV) m/z (relative intensity): 250 (9), 235 (100), 207 (5), 126 (25), 115 (99). HRMS Calcd. For $C_{12}H_{10}OSe$: 249.9897. Found: 249.9905.

2-(4-chlorophenyl)selenophene: Yield: I = 0.113 g (94 %); Br = 0.084 g (70 %). 1H NMR: $CDCl_3$, 400 MHz, δ (ppm): 7.91 (d, J = 5.55 Hz, 1H), 7.44 (d, J = 8.33 Hz, 2H), 7.42-7.38 (m, 1H), 7.30-7.27 (m, 3H). ^{13}C NMR: $CDCl_3$, 100 MHz, δ (ppm): 149.3, 134.9, 130.6, 130.4, 128.9, 128.1, 127.5, 125.6. MS (EI, 70 eV) m/z (relative intensity): 244 (6), 242 (100), 162 (69), 126 (26), 115 (27). HRMS Calcd. For $C_{10}H_7ClSe$: 241.9401. Found: 241.9407.

General Procedure for the Preparation of the Bis-arylselenophene from 2,5-diiodoselenophene: The solution of 2,5-diiodoselenophene (0.096 g, 0.25 mmol) in DME (5 mL) was added, under argon, to a mixture of $Pd(OAc)_2$ (0.003 g, 6 mol %) and boronic acid (0.7 mmol). The resulting solution was stirred for 15 min at room temperature. After this time, was added to the solution of K_2CO_3 (2.4 mmol, 0.309 g) in H_2O (1.2 mL). The mixture was then heated at reflux for the time indicated in Scheme 3, cooled to room temperature, diluted with dichloromethane (20 mL) and washed with brine (2x20 mL). The organic phase was separated, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography and eluted with hexane/ethyl acetate (95:5) or hexane.

2,5-bis-*p*-tolylselenophene: Yield: 0.148 g (95 %). 1H NMR: $CDCl_3$, 400 MHz, δ (ppm): 7.44 (d, J = 7.65 Hz, 4H), 7.36 (s, 2H), 7.14 (d, J = 7.61 Hz, 4H), 2.34 (s, 6H). ^{13}C NMR: $CDCl_3$, 100 MHz, δ (ppm): 149.4, 137.4, 133.7, 129.6, 125.9, 125.6, 21.1. MS (EI, 70 eV) m/z (relative intensity): 312 (100), 309 (26), 215 (26), 154 (20), 115 (27), 101 (10), 89 (7). HRMS Calcd. For $C_{18}H_{16}Se$: 312.0417. Found: 312.0424.

2,5-bis-(3-(trifluoromethyl)phenyl)selenophene: Yield: 0.151 g (72 %). 1H NMR: $CDCl_3$, 400 MHz, δ (ppm): 7.80 (s, 2H), 7.71 (d, J = 7.64 Hz, 2H), 7.57-7.49 (m, 6H). ^{13}C NMR: $CDCl_3$, 100 MHz, δ (ppm): 149.0, 136.8, 131.5 (q, J = 32.53 Hz), 129.5, 129.3, 127.4, 124.3 (q, J = 3.53 Hz), 123.9 (q, J = 272.68 Hz), 122.6 (q, J = 3.53 Hz). MS (EI, 70 eV) m/z (relative intensity): 420 (100), 418 (48), 340 (13), 270 (16), 210 (16). HRMS Calcd. For $C_{18}H_{10}F_6Se$: 419.9852. Found: 419.9858.

2,5-bis-phenylselenophene: Yield: 0.078 g (55 %). ^1H NMR: CDCl_3 , 400 MHz, $\delta(\text{ppm})$: 7.56 (d, $J = 7.60$ Hz, 4H), 7.44 (s, 2H), 7.38-7.23 (m, 6H). ^{13}C NMR: CDCl_3 , 100 MHz, $\delta(\text{ppm})$: 149.9, 136.4, 128.9, 127.6, 126.2, 126.1. MS (EI, 70 eV) m/z (relative intensity): 284 (100), 280 (22), 203 (53), 142 (14), 101 (30). HRMS Calcd. For $\text{C}_{16}\text{H}_{12}\text{Se}$: 284.0104. Found: 284.0110.

General Procedure for the Synthesis of Diaryl Ketones from 2-iodoselenophene: A dried Schlenk flask containing $\text{Pd}(\text{PPh}_3)_4$ (0.017 g, 3 mol %) and boronic acid (0.75 mmol) was evacuated and connected to an atmosphere of argon. The 2-iodoselenophene (0.128 g, 0.5 mmol), toluene (3 mL) and aqueous Na_2CO_3 (1.1 mL of solution 2 M in H_2O , 2.17 mmol) were added. After removal of argon atmosphere, the system was purged with CO three times using a balloon. The mixture was stirred at 110 $^\circ\text{C}$ under carbon monoxide atmosphere (balloon) for 12 hours. The resulting mixture was quenched by addition of NH_4Cl solution (10 mL), and then extracted with EtOAc (3x10 mL). The combined organic extracts were dried with MgSO_4 , filtered and evaporated under reduced pressure. The crude products were purified by flash column chromatography (EtOAc:hexane, 20:80).

selenophen-2-yl(*p*-tolyl)methanone: Yield: 0.101 g (81 %). ^1H NMR: CDCl_3 , 400 MHz, $\delta(\text{ppm})$: 8.40 (d, $J = 5.55$ Hz, 1H), 7.83 (d, $J = 3.95$ Hz, 1H), 7.76 (d, $J = 8.04$ Hz, 2H), 7.42-7.39 (m, 1H), 7.28 (d, $J = 8.04$ Hz, 2H), 2.43 (s, 3H). ^{13}C NMR: CDCl_3 , 100 MHz, $\delta(\text{ppm})$: 189.0, 150.7, 139.9, 136.8, 130.5, 130.1, 129.3, 129.0, 128.8, 21.5. MS (EI, 70 eV) m/z (relative intensity): 252 (13), 250 (69), 159 (74), 119 (100), 91 (75). HRMS Calcd. For $\text{C}_{12}\text{H}_{10}\text{OSe}$: 249.9897. Found: 249.9904.

(4-methoxyphenyl)(selenophen-2-yl)methanone: Yield: 0.107 g (80 %). ^1H NMR: CDCl_3 , 400 MHz, $\delta(\text{ppm})$: 8.38 (d, $J = 5.55$ Hz, 1H), 7.87 (d, $J = 8.77$ Hz, 2H), 7.82 (d, $J = 3.65$ Hz, 1H), 7.41-7.39 (m, 1H), 6.96 (d, $J = 8.77$ Hz, 2H), 3.86 (s, 3H). ^{13}C NMR: CDCl_3 , 100 MHz, $\delta(\text{ppm})$: 187.9, 162.9, 150.7, 139.4, 136.2, 132.0, 131.4, 130.4, 130.2, 55.3. MS (EI, 70 eV) m/z (relative intensity): 266 (53), 264 (29), 251 (13), 159 (38), 135 (100), 77 (40). HRMS Calcd. For $\text{C}_{12}\text{H}_{10}\text{O}_2\text{Se}$: 265.9846. Found: 265.9852.

(4-chlorophenyl)(selenophen-2-yl)methanone: Yield: 0.093 g (69 %). ^1H NMR: CDCl_3 , 400 MHz, $\delta(\text{ppm})$: 8.45 (d, $J = 5.55$ Hz, 1H), 7.81-7.77 (m, 3H), 7.45 (d, $J = 8.48$ Hz, 2H), 7.43-7.40 (m, 1H). ^{13}C NMR: CDCl_3 , 100 MHz, $\delta(\text{ppm})$: 188.0, 149.9, 140.7, 138.4, 137.1, 135.9, 130.7, 130.5, 128.6. MS (EI, 70 eV) m/z (relative intensity): 270 (52), 159 (100), 139 (40), 111 (42), 75 (38). HRMS Calcd. For $\text{C}_{11}\text{H}_7\text{ClOSe}$: 269.9351. Found: 269.9357.

mesityl(selenophen-2-yl)methanone: Yield: 0.074 g (53 %). ^1H NMR: CDCl_3 , 400 MHz, $\delta(\text{ppm})$: 8.42 (d, $J = 5.55$ Hz, 1H), 7.49 (d, $J = 3.97$ Hz, 1H), 7.33-7.29 (m, 1H), 6.88 (s, 2H), 2.31 (s, 3H), 2.17 (s, 6H). ^{13}C NMR: CDCl_3 , 100 MHz, $\delta(\text{ppm})$: 193.9, 151.4, 141.2, 138.5, 137.4, 134.0, 130.9, 128.2, 128.1, 21.0, 19.2. MS (EI, 70 eV) m/z (relative intensity): 280 (18), 278 (89), 197 (100), 169 (33), 147 (26), 119 (25), 91 (40). HRMS Calcd. For $\text{C}_{14}\text{H}_{14}\text{OSe}$: 278.0210. Found: 278.0216.

phenyl(selenophen-2-yl)methanone: Yield: 0.049 g (42 %). ^1H NMR: CDCl_3 , 400 MHz, $\delta(\text{ppm})$: 8.42 (d, $J = 5.55$ Hz, 1H), 7.84-7.79 (m, 3H), 7.59-7.41 (m, 1H), 7.49-7.41 (m,

3H). ^{13}C NMR: CDCl_3 , 100 MHz, $\delta(\text{ppm})$: 189.3, 150.4, 140.3, 137.3, 132.0, 130.6, 129.9, 129.0, 128.3. MS (EI, 70 eV) m/z (relative intensity): 238 (12), 236 (64), 159 (100), 105 (53), 77 (10), 51 (5). HRMS Calcd. For $\text{C}_{11}\text{H}_8\text{OSe}$: 235.9740. Found: 235.9744.

Selected Spectra