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Article

Elemental Chalcogen (Se, S) in PEG-400 to the Synthesis of Seleno- and Thioflavones from 2-Chlorophenyl Ethynyl Ketone and Nucleophilic Species of Chalcogen

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An alternative green method was developed for the synthesis of thio- and selenoflavones by the ring closure of 2-chlorophenyl ethynyl ketone with NaHY (Y = S, Se). These nucleophilic chalcogen species were generated *in situ* using $NaBH_4$ to reduce the elemental chalcogen in the presence of polyethylene glycol-400 (PEG-400). The efficiency of this reaction is strongly dependent on the PEG-400 solvent, acting like a crown ether, complexing with the sodium atom of NaHY species, making the chalcogen nucleophile more active. The synthetic protocol proceeded efficiently at 100 °C under argon, using a range of 2-chlorophenyl ethynyl ketone containing alkyl, aryl, or vinyl groups and the sulfur and selenium chalcogen. By this efficient and simple approach, 18 chalcogenoflavones were obtained in good to excellent yields after 2 h.

Keywords: chromone, green chemistry, polyethyelene glycol-400, selenium, sulfur

Introduction

Interest in organochalcogen compounds has been continuously increasing due to their reputable synthetic and biologic applications.[1] In this field, the modification of heterocyclic compounds with sulfur, selenium, and tellurium atom is a good strategy to obtain more active species and increase the biological applicability.[2] Among the several heterocyclic cores, flavones and chromone derivatives constitute part of a large family of natural products with pharmaceutical applications. The flavone system (2-phenyl-4*H*-chromen-4-one, shown in Figure 1) is a key structural which play important roles in numerous biological processes.[3] Replacement of the oxygen atom in the pyran ring with selenium and sulfur results in selenoflavone and thioflavone, respectively (Figure 1). The chalcogenoflavones have received intensive attention from medicinal chemists due to their unique structure-activity relationship showing antioxidant, anti-inflammatory, anti-cancer, antimicrobial, and antifungal activities, among others.[4]

Regarding the synthesis of these bioactive compounds, they can be prepared by two main procedures: intramolecular cyclization of 2-alkylchalcogenolated alkynones;[5] and ring closure of 2-halophenyl ethynyl ketones with –SeH or –SH moiety.[6] Also, the thioflavone was prepared using non-conventional methodologies, such as multicomponent reactions,[7] intramolecular cyclization[8] and rearrangement,[9] decarbonylative cycloaddition,[10] condensation,[11] among others.[12] However, greener synthetic methods for the synthesis of both selenoflavones and thioflavones are still limited.

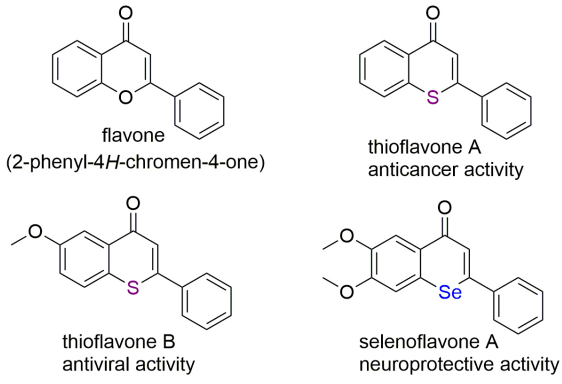

Figure 1. The flavone structure and its derivatives.

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In the context of green chemistry, several synthetic approaches have been progressed, producing a wide variety of compounds without or less environmental hazard.[13] A pivotal parameter to improve the sustainability of a reaction is the use of a suitable medium for environmentally friendly and safe chemical reactions.[14] Thus, polyethylene glycol-400 (PEG-400) might be a solvent with higher preference because of its versatile blessings as a green reaction media. PEG solvent is perceived to be cheap, easily accessible, non-volatile, biodegradable, biocompatible, with low flammability, recyclable, and thermally stable.[14,15]

Noticeable organic transformations involving PEG as a green reaction media were reported.[16] Specifically, this solvent has been described as the reaction medium for procedures involving organochalcogen compounds.[17] Our research group has recently described the *in situ* generation of chalcogenolate anions using the system RYYR/$NaBH_4$/PEG-400 (Y = S, Se, and Te) and their use in selective reactions.[18] So far, only two procedures were described using $NaBH_4$/PEG-400 system to reduce elemental chalcogen and their application to prepare bis(2-pyridyl) diselenide derivatives and divinyl selenides/tellurides.[19] We hypothesized that the nucleophilic chalcogen species generated *in situ* could be applied in other transformations. To test this conjecture and develop our continued interest in green chemistry, we herein disclose our latest work on the synthesis of selenoflavones **3** (Y = Se) and thioflavones **4** (Y = S) by ring closure of 2-chlorophenyl ethynyl ketone **2** under mild conditions (Scheme 1).

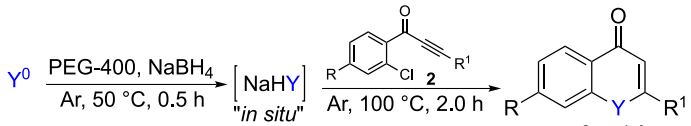
Experimental

General information

All reagents and solvents used were purchased from commercial sources (Sigma-Aldrich®, São Paulo, Brazil). The reactions were monitored by thin-layer chromatography (TLC) carried out on Merk silica gel (60 F_{254}) by using UV light as visualization agent and the mixture between 5% of vanillin in 10% of H_2SO_4 under heating conditions as developing agents. Merck silica gel (particle size 0.040-0.063 mm) was used to flash chromatography. Hydrogen nuclear magnetic resonance spectra (^{1}H NMR) were obtained on Bruker Avance III HD 400 MHz (Uster, Switzerland) employing a direct broadband probe 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 doublet), dt (doublet of triplet), t (triplet), q (quartet), quint (quintet) and m (multiplet). Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were obtained on Bruker Avance III HD 400 MHz (Uster, Switzerland) employing a direct broadband probe at 100 MHz. The chemical shifts are reported in ppm, referenced to the solvent peak of $CDCl_3$ (δ 77.0 ppm). Selenium-77 nuclear magnetic resonance spectra (^{77}Se NMR) were obtained on Bruker Avance III HD 400 MHz (Uster, Switzerland) employing a direct broadband probe at 76 MHz, measured without ^{1}H decoupling. The chemical shifts are reported in ppm, using as solvent the $CDCl_3$ and as an internal standard the diphenyl diselenide (δ 463.0 ppm). The high-resolution mass spectrometry (HRMS) quadrupole time-of-flight (QTOF) analyses were performed on a Bruker (Billerica, MA, USA) Daltonics micrOTOF-Q II instrument in 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, Compass 1.3 for micrOTOF-Q II software (Bruker Daltonics, USA) was used. The data were collected in the *m/z* range of 50-1200 at the speed of two scans *per* s. Low-resolution mass spectra were obtained with a Shimadzu (Kyoto, Japan) GC-MS-QP2010P mass spectrometer. Melting point (mp) values were measured in a Marte (São Paulo, Brazil) PFD III instrument with a 0.1 ºC precision.

General procedure for the synthesis of 2-chloroaryl ethynyl ketone **2**

Procedure adapted from the literature.[20] To a solution of corresponding acetylene (5.0 mmol, 1.0 equiv) in



Y^0 = Se **1a**
Y^0 = S **1b**
R = H, Cl; R^1 = aryl, alkyl, vinyl

Scheme 1. PEG-400 mediate synthesis of the chalcogenoflavones.

dry tetrahydrofuran (THF) (25 mL) was added ^{n}BuLi (2.5 mol L^{-1} in ^{n}hexane, 2.2 mL, 5.5 mmol, 1.1 equiv) dropwise at –78 ºC under nitrogen atmosphere. After the reaction mixture had been stirred at –78 °C for 1 h, 2-chlorobenzaldehyde (5.0 mmol, 1.0 equiv) was added dropwise at –78 °C. Upon stirring at same temperature for 1 h, the reaction solution was quenched with saturated solution of NH_4Cl and extracted with ethyl acetate (3 × 20 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude alcohol product. After, dichloromethane (15 mL) and MnO_2 (10 equiv) were added and the solution was stirred at room temperature till alcohol disappeared by TLC analysis. The reaction solution was filtered over celite, solvents were removed, and the crude product was purified by column chromatography on silica gel with hexane/EtOAc and concentrated to afford the corresponding 2-chlorophenyl ethynyl ketone **2**.

General procedure for synthesis of chalcogenoflavones **3** and **4**

In a 10.0 mL reaction vial containing Se or S (0.3 mmol) in PEG-400 (2.0 mL) under argon atmosphere was added $NaBH_4$ (0.7 mmol), and the mixture was slowly heated to 50 °C being stirred for 30 min. Then, compound **2** (0.25 mmol) was added, and the temperature was raised to 100 °C. The reaction mixture remained under magnetic stirring for 2 h. Then, water was added (25.0 mL) and the reaction was extracted with ethyl acetate (3 × 10.0 mL). The organic phase was separated, dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The product **3** or **4** was isolated by column chromatography using hexane/ethyl acetate (95/5) as eluent.

2-Phenyl-4*H*-selenochromen-4-one (**3a**)[6]

Yield: 0.070 g (98%); yellowish solid; mp 123-125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 1H, Ar-H), 7.35-7.46 (m, 5H, Ar-H), 7.50-7.54 (m, 2H, Ar-H), 7.57-7.59 (m, 1H, Ar-H), 8.50-8.53 (m, 1H, Ar-H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 125.5, 126.8, 127.8, 128.3, 129.2, 130.0, 130.6, 131.5, 131.6, 136.8, 138.0, 154.1, 182.7; distortionless enhancement by polarization transfer (DEPT)-135 NMR (100 MHz, $CDCl_3$) δ 125.5 (CH), 126.8 (2× CH), 127.8 (CH), 128.3 (CH), 129.2 (2× CH), 130.0 (CH), 130.6 (CH), 131.5 (CH); ^{77}Se NMR (76 MHz, $CDCl_3$) δ 391.4 (d, *J* 10.3 Hz); MS (relative intensity / %) *m/z*, 102 (20.3), 156 (56.7), 184 (100.0), 258 (29.9), 286 (85.8); HRMS (APCI-QTOF) *m/z*, calcd. for $C_{15}H_{11}OSe$ $[M + H]^+$: 286.9975, found: 286.9978.

2-(4-Tolyl)-4*H*-selenochromen-4-one (**3b**)[6]

Yield: 0.068 g (90%); yellowish solid; mp 136-138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H, Ar-CH_3), 7.25 (d, *J* 7.8 Hz, 2H, Ar-H), 7.34 (s, 1H, Ar-H), 7.46-7.53 (m, 4H, Ar-H), 7.62-7.67 (m, 1H, Ar-H), 8.57-8.61 (m, 1H, Ar-H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.2, 124.9, 126.6, 127.6, 128.2, 129.9, 131.4, 131.7, 135.1, 136.8, 141.1, 154.0, 182.7; DEPT-135 NMR (100 MHz, $CDCl_3$) δ 21.2 (CH_3), 124.9 (CH), 126.6 (2× CH), 127.6 (CH), 128.2 (CH), 129.9 (3× CH), 131.4 (CH); ^{77}Se NMR (76 MHz, $CDCl_3$) δ 388.3 (d, *J* 10.8 Hz); MS (relative intensity / %) *m/z*, 115 (54.9), 156 (48.1), 184 (100.0), 272 (13.5), 300 (58.8); HRMS (APCI-QTOF) *m/z*, calcd. for $C_{16}H_{13}OSe$ $[M + H]^+$: 301.0132, found: 301.0127.

2-(2-Tolyl)-4*H*-selenochromen-4-one (**3c**)

Yield: 0.074 g (98%); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H, Ar-CH_3), 7.05 (s, 1H, Ar-H), 7.24-7.35 (m, 4H, Ar-H), 7.49-7.56 (m, 2H, Ar-H), 7.64-7.66 (m, 1H, Ar-H), 8.62-8.67 (m, 1H, Ar-H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 19.9, 125.9, 127.7, 128.1, 128.3, 128.5, 129.5, 130.1, 130.8, 131.5, 131.7, 135.0, 137.5, 137.7, 154.5, 182.3; DEPT-135 NMR (100 MHz, $CDCl_3$) δ 19.9 (CH_3), 125.9 (CH), 127.7 (CH), 128.1 (CH), 128.3 (CH), 128.5 (CH), 129.5 (CH), 130.1 (CH), 130.8 (CH), 131.5 (CH); ^{77}Se NMR (76 MHz, $CDCl_3$) δ 414.5 (d, *J* 9.8 Hz); MS (relative intensity / %) *m/z*, 115 (41.9), 156 (47.3), 184 (100.0), 219 (73.3), 271 (7.6), 300 (90.8); HRMS (APCI-QTOF) *m/z*, calcd. for $C_{16}H_{13}OSe$ $[M + H]^+$: 301.0132, found: 301.0131.

2-(4-Chlorophenyl)-4*H*-selenochromen-4-one (**3d**)[6]

Yield: 0.049 g (61%); yellowish solid; mp 135-137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (s, 1H, Ar-H), 7.45 (d, *J* 8.6 Hz, 2H, Ar-H), 7.49-7.56 (m, 4H, Ar-H), 7.66-7.68 (m, 1H, Ar-H), 8.58-8.61 (m, 1H, Ar-H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 125.8, 127.9, 128.1, 128.2, 129.5, 130.1, 131.6, 131.7, 136.47, 136.49, 136.9, 152.3, 182.6; DEPT-135 NMR (100 MHz, $CDCl_3$) δ 125.8 (CH), 127.9 (CH), 128.1 (2× CH), 128.2 (CH), 129.5 (2× CH), 130.1 (CH), 131.7 (CH); ^{77}Se NMR (76 MHz, $CDCl_3$) δ 389.6 (d, *J* 11.2 Hz); MS (relative intensity / %) *m/z*, 136 (6.9), 156 (42.3), 184 (100.0), 292 (21.1), 320 (76.4); HRMS (APCI-QTOF) *m/z*, calcd. for $C_{15}H_{10}ClOSe$ $[M + H]^+$: 320.9585, found: 320.9579.

2-(2-Chlorophenyl)-4*H*-selenochromen-4-one (**3e**)

Yield: 0.061 g (76%); orange solid; mp 118-119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (s, 1H, Ar-H), 7.31-7.43 (m, 3H, Ar-H), 7.48-7.58 (m, 3H, Ar-H), 7.63-7.69 (m, 1H, Ar-H), 8.62-8.65 (m, 1H, Ar-H); ^{13}C{^{1}H} NMR (100 MHz,

$CDCl_3$) δ 127.0, 127.8, 128.1, 129.3, 130.1, 130.3, 130.4, 130.8, 131.57, 131.6, 132.0, 136.6, 137.5, 151.0, 182.3; DEPT-135 NMR (100 MHz, $CDCl_3$) δ 127.0 (CH), 127.8 (CH), 128.1 (CH), 129.3 (CH), 130.1 (CH), 130.3 (CH), 130.4 (CH), 130.8 (CH), 131.6 (CH); ^{77}Se NMR (76 MHz, $CDCl_3$) δ 419.2 (d, *J* 10.2 Hz); MS (relative intensity / %) *m/z*, 136 (5.2), 156 (41.3), 184 (100.0), 292 (15.3), 320 (76.9); HRMS (APCI-QTOF) *m/z*, calcd. for $C_{15}H_{10}ClOSe$ $[M + H]^+$: 320.9585, found: 320.9583.

2-(Naphthalen-2-yl)-4*H*-selenochromen-4-one (**3f**)

Yield: 0.082 g (98%); yellowish solid; mp 132-133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (s, 1H, Ar-H), 7.46-7.54 (m, 6H, Ar-H), 7.60-7.65 (m, 1H, Ar-H), 7.87-7.91 (m, 2H, Ar-H), 8.08-8.10 (m, 1H, Ar-H), 8.67-8.71 (m, 1H, Ar-H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 124.9, 125.0, 126.49, 126.5, 127.0, 127.8, 128.0, 128.4, 129.4, 130.05, 130.08, 130.1, 131.5, 131.8, 133.6, 135.4, 137.9, 153.1, 182.2; DEPT-135 NMR (100 MHz, $CDCl_3$) δ 124.9 (CH), 125.0 (CH), 126.49 (CH), 126.5 (CH), 127.0 (CH), 127.8 (CH), 128.0 (CH), 128.4 (CH), 129.4 (CH), 130.08 (CH), 130.11 (CH), 131.5 (CH); ^{77}Se NMR (76 MHz, $CDCl_3$) δ 427.3 (d, *J* 9.2 Hz); MS (relative intensity / %) *m/z*, 152 (96.0), 156 (30.7), 184 (34.8), 319 (100.0), 336 (35.5); HRMS (APCI-QTOF) *m/z*, calcd. for $C_{19}H_{13}OSe$ $[M + H]^+$: 337.0132, found: 337.0125.

(*E*)-2-Styryl-4*H*-selenochromen-4-one (**3g**)

Yield: 0.058 g (74%); yellowish solid; mp 133-135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, *J* 16.1 Hz, 1H, CH), 7.14-7.18 (m, 2H, Ar-H), 7.34-7.42 (m, 3H, Ar-H), 7.45-7.54 (m, 4H, Ar-H), 7.63-7.65 (m, 1H, Ar-H), 8.54 (dd, *J* 7.9 and 1.4 Hz, 1H, Ar-H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 127.0, 127.4, 127.6, 127.7, 128.3, 129.0, 129.6, 129.9, 131.7, 132.2, 135.1, 136.1, 149.6, 183.0; DEPT-135 NMR (100 MHz, $CDCl_3$) δ 127.0 (CH), 127.4 (2× CH), 127.6 (CH), 127.7 (CH), 128.3 (CH), 129.0 (2× CH), 129.6 (CH), 129.9 (CH), 131.7 (CH), 136.1 (CH); ^{77}Se NMR (76 MHz, $CDCl_3$) δ 360.2 (t, *J* 9.8 Hz); MS (relative intensity / %) *m/z*, 128 (60.6), 156 (39.5), 184 (100.0), 295 (9.3), 312 (37.0); HRMS (APCI-QTOF) *m/z*, calcd. for $C_{17}H_{13}OSe$ $[M + H]^+$: 313.0132, found: 313.0122.

2-Pentyl-4*H*-selenochromen-4-one (**3h**)[6]

Yield: 0.068 g (97%); yellowish solid; mp 38-39 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, *J* 7.4 Hz, 3H, CH_3), 1.31-1.41 (m, 4H, CH_2), 1.72 (quint, *J* 7.4 Hz, 2H, CH_2), 2.73 (t, *J* 7.4 Hz, 2H, CH_2), 7.01 (s, 1H, Ar-H), 7.44-7.51 (m, 2H, Ar-H), 7.58-7.63 (m, 1H, Ar-H), 8.55-8.57 (m, 1H, Ar-H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 13.8, 22.2, 29.7, 30.9, 38.9, 126.0, 127.4, 128.3, 129.9, 131.2, 131.8, 136.5, 158.2, 182.5; DEPT-135 NMR (100 MHz, $CDCl_3$) δ 13.8 (CH_3), 22.2 (CH_2), 29.7 (CH_2), 30.9 (CH_2), 38.9 (CH_2), 126.0 (CH), 127.4 (CH), 128.3 (CH), 129.9 (CH), 131.2 (CH); ^{77}Se NMR (76 MHz, $CDCl_3$) δ 400.5-401.0 (m); MS (relative intensity / %) *m/z*, 95 (5.0), 115 (43.9), 156 (35.2), 184 (100.0), 224 (79.0), 280 (34.0); HRMS (APCI-QTOF) *m/z*, calcd. for $C_{14}H_{17}OSe$ $[M + H]^+$: 281.0445, found: 281.0438.

7-Chloro-2-phenyl-4*H*-selenochromen-4-one (**3i**)

Yield: 0.058 g (72%); yellowish solid; mp 148-149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 1H, Ar-H), 7.44-7.51 (m, 4H, Ar-H), 7.59-7.61 (m, 2H, Ar-H), 7.67 (d, *J* 2.0 Hz, 1H, Ar-H), 8.51 (d, *J* 8.7 Hz, 1H, Ar-H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 125.6, 126.8, 127.6, 128.4, 129.3, 130.0, 130.9, 131.4, 137.7, 137.9, 138.3, 153.7, 181.8; DEPT-135 NMR (100 MHz, $CDCl_3$) δ 125.6 (CH), 126.8 (2× CH), 127.6 (CH), 128.4 (CH), 129.3 (2× CH), 130.9 (CH), 131.4 (CH); ^{77}Se NMR (76 MHz, $CDCl_3$) δ 396.5 (d, *J* 8.5 Hz); MS (relative intensity / %) *m/z*, 102 (14.4), 190 (32.6), 218 (100.0), 292 (29.1), 320 (84.5); HRMS (APCI-QTOF) *m/z*, calcd. for $C_{15}H_{10}ClOSe$ $[M + H]^+$: 320.9585, found: 320.9578.

2-Phenyl-4*H*-thiochromen-4-one (**4a**)[6]

Yield: 0.059 g (99%); yellowish solid; mp 95-96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 1H, Ar-H), 7.47-7.56 (m, 4H, Ar-H), 7.59-7.70 (m, 4H, Ar-H), 8.54 (d, *J* 7.8 Hz, 1H, Ar-H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 123.4, 126.4, 126.9, 127.7, 128.5, 129.2, 130.76, 130.8, 131.5, 136.5, 137.6, 153.0, 180.8; DEPT-135 NMR (100 MHz, $CDCl_3$) δ 123.4 (CH), 126.4 (CH), 126.9 (2× CH), 127.7 (CH), 128.5 (CH), 129.2 (2× CH), 130.76 (CH), 131.5 (CH); MS (relative intensity / %) *m/z*, 102 (6.4), 108 (53.9), 136 (57.5), 210 (94.5), 238 (100.0); HRMS (APCI-QTOF) *m/z*, calcd. for $C_{15}H_{11}OS$ $[M + H]^+$: 239.0531, found: 239.0523.

2-(4-Tolyl)-4*H*-thiochromen-4-one (**4b**)[6]

Yield: 0.047 g (75%); gray solid; mp 109-110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3H, Ar-CH_3), 7.23 (s, 1H, Ar-H), 7.30 (d, *J* 8.0 Hz, 2H, Ar-H), 7.52-7.66 (m, 5H, Ar-H), 8.54 (d, *J* 7.9 Hz, 1H, Ar-H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.3, 122.8, 126.4, 126.8, 127.6, 128.5, 129.9, 130.9, 131.5, 133.7, 137.7, 141.3, 153.1, 180.9; DEPT-135 NMR (100 MHz, $CDCl_3$) δ 21.3 (CH_3), 122.8 (CH), 126.4 (CH), 126.8 (2× CH), 127.6 (CH), 128.5 (CH), 129.9 (2× CH), 131.5 (CH); MS (relative intensity / %) *m/z*, 108 (51.7), 115 (30.8), 136 (65.5), 224 (91.8), 252 (100.0); HRMS (APCI-QTOF) *m/z*, calcd. for $C_{16}H_{13}OS$ $[M + H]^+$: 253.0687, found: 253.0677.

2-(2-Tolyl)-4*H*-thiochromen-4-one (**4c**)[6]

Yield: 0.051 g (81%); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H, Ar-CH_3), 6.92 (s, 1H, Ar-H), 7.25-7.38 (m, 4H, Ar-H), 7.53-7.57 (m, 1H, Ar-H), 7.59-7.64 (m, 2H, Ar-H), 8.58 (dt, *J* 8.0 and 1.0 Hz, 1H, Ar-H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 19.8, 126.0, 126.1, 126.2, 127.7, 128.6, 128.9, 129.7, 130.8, 130.84, 131.5, 135.6, 136.0, 138.3, 153.5, 180.4; DEPT-135 NMR (100 MHz, $CDCl_3$) δ 19.8 (CH_3), 126.0 (CH), 126.1 (CH), 126.2 (CH), 127.7 (CH), 128.6 (CH), 128.9 (CH), 129.7 (CH), 130.8 (CH), 131.5 (CH); MS (relative intensity / %) *m/z*, 108 (34.7), 115 (29.5), 136 (45.9), 223 (38.4), 252 (100.0); HRMS (APCI-QTOF) *m/z*, calcd. for $C_{16}H_{13}OS$ $[M + H]^+$: 253.0687, found: 253.0685.

2-(4-Chlorophenyl)-4*H*-thiochromen-4-one (**4d**)[6]

Yield: 0.042 g (62%); yellowish solid; mp 159-160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (s, 1H, Ar-H), 7.46 (d, *J* 8.5 Hz, 2H, Ar-H), 7.52-7.56 (m, 1H, Ar-H), 7.60-7.65 (m, 4H, Ar-H), 8.52 (d, *J* 7.7 Hz, 1H, Ar-H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 123.4, 126.4, 127.9, 128.1, 128.5, 129.5, 130.7, 131.7, 134.9, 137.0, 137.3, 151.5, 180.6; DEPT-135 NMR (100 MHz, $CDCl_3$) δ 123.4 (CH), 126.4 (CH), 127.9 (CH), 128.1 (2× CH), 128.5 (CH), 129.5 (2× CH), 131.7 (CH); MS (relative intensity / %) *m/z*, 108 (46.3), 136 (80.3), 244 (90.3), 272 (100.0); HRMS (APCI-QTOF) *m/z*, calcd. for $C_{15}H_{10}ClOS$ $[M + H]^+$: 273.0141, found: 273.0150.

2-(2-Chlorophenyl)-4*H*-thiochromen-4-one (**4e**)[6]

Yield: 0.057 g (83%); white solid; mp 126-127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (s, 1H, Ar-H), 7.36-7.46 (m, 3H, Ar-H), 7.51-7.59 (m, 2H, Ar-H), 7.62-7.67 (m, 2H, Ar-H), 8.58 (d, *J* 8.0 Hz, 1H, Ar-H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 126.3, 127.1, 127.2, 127.8, 128.7, 130.5, 130.7, 130.9, 131.1, 131.7, 132.6, 135.2, 138.1, 150.4, 180.4; DEPT-135 NMR (100 MHz, $CDCl_3$) δ 126.3 (CH), 127.1 (CH), 127.2 (CH), 127.8 (CH), 128.7 (CH), 130.5 (CH), 130.7 (CH), 131.1 (CH), 131.7 (CH); MS (relative intensity / %) *m/z*, 108 (41.9), 136 (73.0), 244 (71.4), 272 (100.0); HRMS (APCI-QTOF) *m/z*, calcd. for $C_{15}H_{10}ClOS$ $[M + H]^+$: 273.0141, found: 273.0133.

2-(Naphthalen-2-yl)-4*H*-thiochromen-4-one (**4f**)[21]

Yield: 0.068 g (94%); yellowish solid; mp 135-136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (s, 1H, Ar-H), 7.47-7.63 (m, 7H, Ar-H), 7.88-7.95 (m, 2H, Ar-H), 8.04-8.06 (m, 1H, Ar-H), 8.62 (d, *J* 7.7 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 124.8, 124.9, 126.1, 126.5, 127.06, 127.12, 127.2, 127.7, 128.4, 128.6, 130.3, 130.4, 131.0, 131.5, 133.6, 133.9, 138.5, 152.2, 180.2; DEPT-135 NMR (100 MHz, $CDCl_3$) δ 124.8 (CH), 124.9 (CH), 126.1 (CH), 126.5 (CH), 127.06 (CH), 127.12 (CH), 127.2 (CH), 127.7 (CH), 128.4 (CH), 128.6 (CH), 130.3 (CH), 131.5 (CH); MS (relative intensity / %) *m/z*, 108 (9.5), 136 (6.3), 152 (21.1), 271 (100.0), 288 (23.3); HRMS (APCI-QTOF) *m/z*, calcd. for $C_{19}H_{13}OS$ $[M + H]^+$: 289.0687, found: 289.0680.

(*E*)-2-Styryl-4*H*-thiochromen-4-one (**4g**)[6]

Yield: 0.040 g (61%); yellowish solid; mp 119-120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.0 (s, 1H, Ar-H), 7.04 (d, *J* 16.2 Hz, 1H, CH), 7.31 (d, *J* 16.2 Hz, 1H, CH), 7.35-7.44 (m, 3H, Ar-H), 7.49-7.64 (m, 5H, Ar-H), 8.48-8.50 (m, 1H, Ar-H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 124.6, 125.9, 126.4, 127.4, 127.5, 128.5, 129.0, 129.7, 131.3, 131.7, 135.1, 135.6, 136.6, 149.2, 181.1; DEPT-135 NMR (100 MHz, $CDCl_3$) δ 124.6 (CH), 125.9 (CH), 126.4 (CH), 127.4 (2× CH), 127.5 (CH), 128.5 (CH), 129.0 (2× CH), 129.7 (CH), 131.7 (CH), 135.6 (CH); MS (relative intensity / %) *m/z*, 108 (52.8), 128 (40.6), 136 (39.8), 247 (59.9), 263 (100.0), 264 (72.1); HRMS (APCI-QTOF) *m/z*, calcd. for $C_{17}H_{13}OS$ $[M + H]^+$: 265.0687, found: 265.0683.

2-Pentyl-4*H*-thiochromen-4-one (**4h**)[7]

Yield: 0.053 g (91%); yellowish solid; mp 36-37 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, *J* 7.3 Hz, 3H, CH_3), 1.35-1.39 (m, 4H, CH_2), 1.73 (quint, *J* 7.3 Hz, 2H, CH_2), 2.67 (t, *J* 7.3 Hz, 2H, CH_2), 6.86 (s, 1H, Ar-H), 7.47-7.52 (m, 1H, Ar-H), 7.55-7.59 (m, 2H, Ar-H), 8.50 (d, *J* 8.0 Hz, 1H, Ar-H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 13.8, 22.2, 29.4, 30.9, 37.3, 124.0, 126.1, 127.4, 128.4, 130.9, 131.2, 137.7, 156.5, 180.6; DEPT-135 NMR (100 MHz, $CDCl_3$) δ 13.8 (CH_3), 22.2 (CH_2), 29.4 (CH_2), 30.9 (CH_2), 37.3 (CH_2), 124.0 (CH), 126.1 (CH), 127.4 (CH), 128.4 (CH), 131.2 (CH); MS (relative intensity / %) *m/z*, 95 (1.8), 108 (21.3), 136 (67.2), 176 (100.0), 232 (28.0); HRMS (APCI-QTOF) *m/z*, calcd. for $C_{14}H_{17}OS$ $[M + H]^+$: 233.1000, found: 233.0996.

7-Chloro-2-phenyl-4*H*-thiochromen-4-one (**4i**)[7]

Yield: 0.056 g (83%); yellowish solid; mp 134-135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (s, 1H, Ar-H), 7.44-7.53 (m, 4H, Ar-H), 7.60 (d, *J* 1.8 Hz, 1H, Ar-H), 7.64 (dd, *J* 7.6 and 1.8 Hz, 2H, Ar-H), 8.44 (d, *J* 8.7 Hz, 1H, Ar-H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 123.4, 125.6, 126.8, 128.3, 129.2, 129.3, 130.1, 130.9, 136.0, 138.2, 138.9, 152.6, 179.8; DEPT-135 NMR (100 MHz, $CDCl_3$) δ 123.4 (CH), 125.6 (CH), 126.8 (2× CH), 128.3 (CH), 129.2 (2× CH), 130.1 (CH), 130.9 (CH); MS (relative intensity / %) *m/z*, 102 (6.9), 142 (20.1), 170 (39.5), 244 (92.1), 272 (100.0); HRMS (APCI-QTOF) *m/z*, calcd. for $C_{15}H_{10}ClOS$ $[M + H]^+$: 273.0141, found: 273.0141.

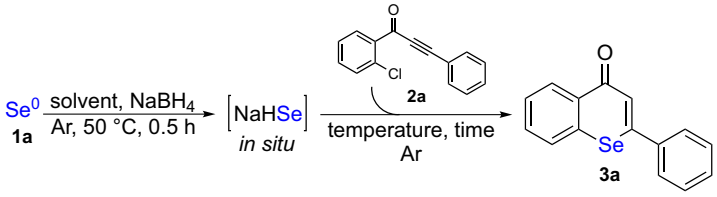
Procedure for identify the nucleophilic species formed through ^{77}Se NMR spectroscopy

In a 10.0 mL reaction vial containing Se (0.3 mmol) in PEG-400 (2.0 mL) under argon atmosphere was added $NaBH_4$ (0.7 mmol), and the mixture was slowly heated to 50 °C being stirred for 30 min. Then, 500 µL of this solution was transferred to a 5 mm NMR tube, purged with argon gas and a capillary tube with a solution of the diphenyl diselenide in $CDCl_3$ was used as the chemical shift reference (δ 463 ppm), after the NMR tube was capped with a rubber septum and analyzed by ^{77}Se NMR. The spectra were recorded at 298 K and with 845 scans.

Results and Discussion

Based on the results of our recent studies using elemental chalcogens,[19] we chose selenium powder **1a**, $NaBH_4$ and 1-(2-chlorophenyl)-3-phenylprop-2-yn-1-one **2a** as model substrates to identify the optimum conditions under argon (Ar) atmosphere and PEG-400 as the solvent (Table 1). For this test, a mixture of selenium (0.25 mmol) and $NaBH_4$ (2.3 equiv) in PEG-400 (2.0 mL) was stirred at 50 °C, for the *in situ* generation of the nucleophilic selenium species. This formation was monitored by the color change of the reaction medium, changing from grey to colorless after 0.5 h of stirring. After that, the 2-chlorophenyl ethynyl ketone **2a** (0.25 mmol) was added to the reaction vessel and the temperature was raised to 100 °C. In these conditions, the corresponding 2-phenyl-4*H*-selenochromen-4-one **3a** was obtained with 56% gas chromatography (GC) yield in a reaction time of 2 h (Table 1, entry 1). To our delight, increasing the amount of selenium powder to 0.3 mmol provides an improvement in the reaction performance, and the target compound **3a** could be achieved with 99% GC yield and an isolated yield of 98% (Table 1, entry 2). Reducing the reaction time to 1 h showed a negative effect to produce the desired Se-flavone **3a**, and only 69% GC yield was observed (Table 1, entry 3). We also investigated the effect of the temperature on the reaction yield. However, decreasing the temperature results in lower yields (Table 1, entries 4-6). Subsequently, other solvents were investigated under similar reaction conditions. Polar solvents such as EtOH, glycerol and water provided product **3a**, but in lower yields compared to the use of PEG-400, furthermore, several by-products were observed in gas chromatography mass spectrometry (GC-MS, Table 1, entries 7-9 *vs.* entry 2). Additionally, aprotic solvents were inefficient in our study and the use of dimethyl sulfoxide (DMSO) or MeCN failed to afford the desired product (Table 1, entries 10-11). Thus, we established the best reaction conditions as being a two steps onepot procedure, which starts with the reaction of selenium **1a** (0.3 mmol) and $NaBH_4$ (0.7 mmol) in PEG-400

Table 1. Optimization of the synthesis of Se-flavone **3a**[a]



entry	Se^0 / mmol	Solvent	Temperature / °C	time / h	Yield[b] / %
1	0.25	PEG-400	100	2	56
2	0.30	PEG-400	100	2	99 (98)[c]
3	0.30	PEG-400	100	1	69
4	0.30	PEG-400	80	2	82
5	0.30	PEG-400	50	2	76
6	0.30	PEG-400	25	2	57
7	0.30	EtOH	78	2	32
8	0.30	glycerol	100	2	12
9	0.30	H_2O	100	2	16
10	0.30	DMSO	100	2	NR
11	0.30	MeCN	82	2	NR

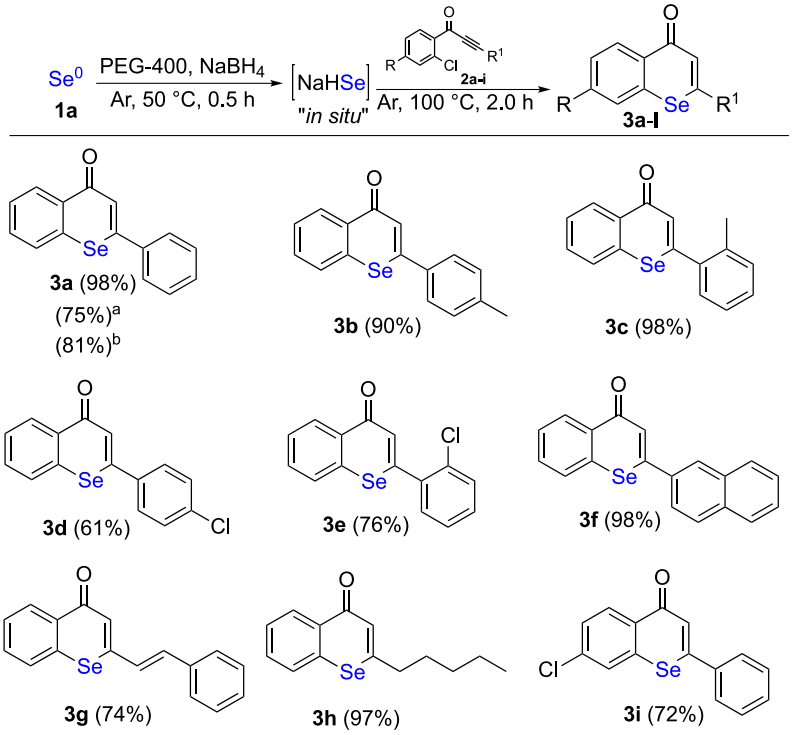
[a]Reactions were performed using Se^0 **1a**, $NaBH_4$ (2.33 equiv in relation to selenium powder) in 2.0 mL of the solvent at 50 °C under argon for 0.5 h. Then, 0.25 mmol of **2a** was added. [b]Yield determined by GC using *n*dodecane as an internal standard. [c]Yield for the isolated product. PEG-400: polyethylene glycol-400; DMSO: dimethyl sulfoxide; NR: no reaction.

(2.0 mL) at 50 °C under Ar for 0.5 h. Then, compound **2a** (0.25 mmol) is added into the reaction medium, and the resulting mixture is stirred for an additional 2 h at 100 °C (Table 1, entry 2).

With the optimal reaction conditions identified, various 2-chloroaryl ethynyl ketone **2** for this ring closure reaction were investigated and the results are summarized in Scheme 2. In the beginning, the electronic effects on the substituent R^1 of the compound **2** were investigated. Briefly, this method proved to be more efficient for electron-donating substituents when compared with electron-withdrawing substituents in the aromatic ring. When using electron-donating groups in the aromatic ring (2-CH_3 and 4-CH_3), the corresponding Se-flavones **3b** and **3c** were obtained in high yields. Since by using electron-withdrawing atoms in the aromatic ring (2-Cl and 4-Cl), the Se-flavones **3d** and **3e** were obtained 61 and 76%, respectively. To our delight, the substitution of the aryl group by naphthyl group did not affect the efficiency of this transformation, and the Se-flavone **3f** was obtained in an excellent yield of 98%. In the same manner, substrate possessing styryl moiety can also be effectively converted into Se-flavone functionalized with styryl derivative **3g** in 74% yield under well-established conditions. Despite employing a reduction system ($NaBH_4$/PEG-400), this method proved to be chemoselective, since no reaction in the carbon-carbon double bond of the styryl group was observed. We can also prepare an analogous compound with an aliphatic chain, through the reaction compound **2h**, leading to the formation of the product **3h** in an excellent yield of 97%. We also explored the R position of the 2-chloro ethynyl ketone **2**, substrate **2i** (R = Cl) reacted under well-established conditions, affording the desired product **3i** in 72% yield.

In addition, we explored the change of the chlorine atom by bromine atom in the substrate **2** under optimized conditions. After 2 h of reaction time, the Se-flavone **3a** was also obtained in a good yield, however lower than the chlorine one. This result is consistent because it clearly supports the point about halogen's atom role, in which electron-withdrawing groups improve the reactivity for the aromatic nucleophilic substitution reaction. Considering the straightforward method herein developed, it was successfully applied in the gram-scale synthesis of Se-flavone **3a** (4 mmol), leading to 81% yield of the corresponding product.

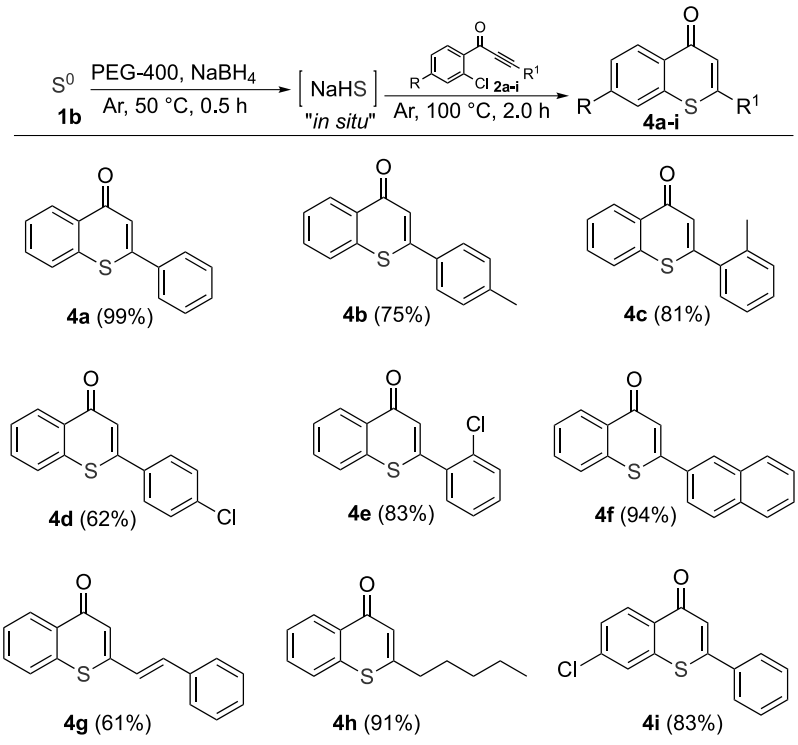
Encouraged by the Se-flavones results, we next studied the general applicability of the method for the synthesis of thioflavones **4** by the reaction of sulfur powder **1b** with a variety of 2-chloroaryl ethynyl ketones **2**, as shown in the Scheme 3. Thus, when using the compound **2a**, with a neutral group, the 2-phenyl-4*H*-thiochromen-4-one **4a**



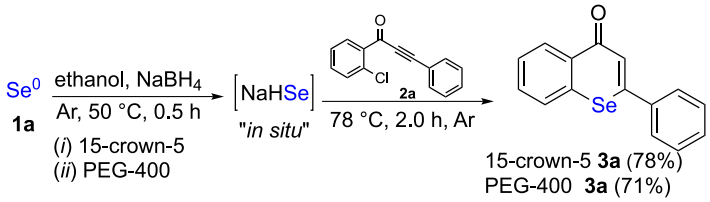
Scheme 2. Substrate scope to the synthesis of Se-flavones **3a**-**3i**. Reactions was performed using Se^0 **1a** (0.3 mmol), $NaBH_4$ (0.7 mmol, 2.33 equiv in relation to selenium powder) in 2.0 mL of the solvent at 50 °C under argon for 0.5 h. Then, 0.25 mmol of **2** was added. Yields for the isolated products. [a]Reaction was performed using 2-bromophenyl ethynyl ketone **2b** (0.25 mmol). [b]Performed on 4.0 mmol scale.

was afforded in 99% yield. Next, we explore the influence of the substituents on the 2-chlorophenyl ethynyl ketone **2** in the R^1 position, firstly, containing electron-donating groups (2-CH_3 and 4-CH_3), and subsequently with electron-withdrawing atoms (2-Cl and 4-Cl) in the aromatic ring. In both cases, substituents at the *ortho* position in the aromatic ring showed better results, when compared with the *para* position, affording the desired products **4c** and **4e** in 81 and 83% yield, respectively. According to the groups in the *para* position in the aromatic ring, the S-flavones **4b** and **4d** were obtained in 75 and 62% yield, respectively. Similar to the selenium reactivity, 2-naphthyl substituent did not influence the reaction performance, leading to product **4f** in an excellent yield of 94%. To our delight, when using the compound **2g**, possessing a styryl moiety, the respective S-flavone was obtained in 61% yield and no parallel reaction in the C–C double bond of the styrene group being observed. In addition, changing the substituent R^1 to an aliphatic chain was possible, and the desired product **4h** was obtained in 91% yield. We next evaluated the reaction of 2,4-dichlorophenyl ethynyl ketone **2i** containing a chlorine atom in the R position, under optimized conditions, and the S-flavone **4i** was obtained in a good yield. In counterpart, our attempts to synthesize the Te-flavones derivatives through the reaction between tellurium powder and compound **2a** under the optimized conditions have been proved fruitless. In all cases, only reduction by-products derived from substrate **2a** were observed by GC-MS analysis.[22]

In order to clarify the possible mechanism of the ring closure reaction, a set of control experiments were carried out (Scheme 4). Polyethylene glycols, open-chain analogs of crown ethers, are well documented to have the tendency to bind with alkali cations as crown ethers.[23] Our hypothesis is that the PEG-400 could be forming a crown-like structure in this reaction. For this purpose, the 2-chlorophenyl ethynyl ketone **2a** was reacted with selenium powder **1a**, $NaBH_4$ using ethanol as solvent (since among the tested solvents, it was able to form Se-flavone in a low yield; Table 1, entry 7) and 1.0 equiv of the 15-crown-5 was added in the reaction. In this condition, the desired product was obtained in 78% yield (Scheme 4, *i*). This result demonstrates that the presence of a crown-like species favors the formation of Se-flavone, once, in the absence of the crown ether, only 32% yield of the product was obtained (Table 1, entry 7). Similarly, compound **2a** was reacted with selenium powder **1a**, $NaBH_4$ using ethanol as solvent and 1.0 equiv of the PEG-400 was added in the reaction. Gratifyingly, the desired product was obtained in 71% yield. This result indicates a possible coordination of the PEG-400, such crown-like, to sodium atom and this complex cause the selenium anion to be more activated, favoring the formation of the Se-flavone **3a** (Scheme 4, *ii*).



Scheme 3. Substrate scope to the synthesis of S-flavones **4a**-**4i**. Reactions was performed using S^0 **1b** (0.3 mmol), $NaBH_4$ (0.7 mmol, 2.33 equiv in relation to sulfur powder) in 2.0 mL of the solvent at 50 °C under argon for 0.5 h. Then, 0.25 mmol of **2** was added. Yields for isolated products.



Scheme 4. Control experiments.

Our next endeavor was to identify the nucleophilic species formed by the reaction of the selenium powder with $NaBH_4$ in PEG-400 solvent, through ^{77}Se NMR spectroscopy. In 2016, Oliveira *et al.*[24] reported the identification of the nucleophilic selenium species from the reaction between Se^0 and $NaBH_4$ in ethanol solvent through a proton-coupled ^{77}Se NMR experiment. Thus, a similar procedure was performed, and a mixture of selenium powder **1a** (0.3 mmol) and $NaBH_4$ (0.7 mmol) was stirred at 50 °C in PEG-400 for 0.5 h and then a ^{77}Se NMR spectrum was immediately recorded. It was observed in the selenium spectrum a doublet resonance at –458.1 ppm with a coupling constant of 16.6 Hz, confirming the Se–H bonding (Figure 2). Oliveira *et al.*[24] reported a similar result (δ = –496 ppm), corroborating the characterization of this nucleophilic selenium species. It is noteworthy that as ^{15}N and ^{17}O NMR profile,[25,26] the deshielding of the ^{77}Se chemical shift in PEG-400 solvent indicates a solvent effect, producing a less effective solvation and, consequently, obtaining a more nucleophilic selenium species.[27]

On the basis of the above results and reported literature,[6] a plausible mechanism is proposed (Scheme 5). Firstly, the chalcogen **1** in its elemental form is reduced by $NaBH_4$, forming the corresponding sodium hydrochalcogenide (NaHSe or NaHS). In the presence of PEG-400, which behaves as a crown ether, the *in situ* formation of sodium complex is favored, making the chalcogen nucleophilic species species more active. Subsequently, the nucleophilic

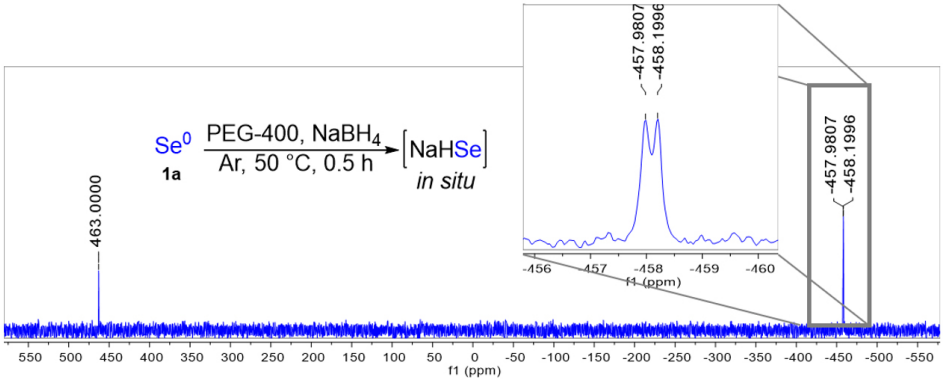
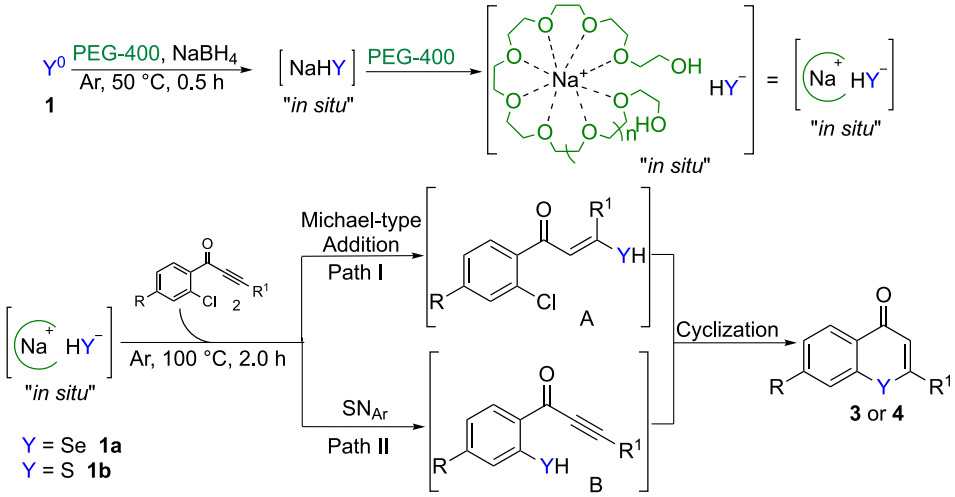


Figure 2. ^{77}Se NMR experiments to determination of the intermediate.



Scheme 5. Plausible mechanism.

species is added to the carbon-carbon triple bond of the 2-chlorophenyl ethynyl ketone **2** in a Michael-type addition, giving the intermediate **A**, that after an intramolecular cyclization result in the chalcogenoflavones **3** or **4** (Scheme 5, path I). The nucleophilic species can also attack the carbon atom attached to the chlorine atom of the compound **2** in an aromatic nucleophilic substitution reaction giving the intermediate **B**, that after the intramolecular cyclization results in the chalcogenoflavones **3** or **4** (Scheme 5, path II).

Conclusions

In summary, we have developed an efficient method for the synthesis of chalcogenoflavones by ring closure reaction of 2-chlorophenyl ethynyl ketones with nucleophilic chalcogen species. The nucleophiles were generated *in situ* using PEG-400 as solvent and $NaBH_4$ as reduction agent. This green and environmentally friendly strategy demonstrates great compatibility with selenium and sulfur derivatives, affording a series of chalcogenoflavones in good to excellent yields. Moreover, PEG-400 proved to be crucial in this method, acting as a green solvent and mainly forming crown-like complexes. In addition, the nucleophilic species was identified by proton-coupled ^{77}Se NMR experiments, contributing to the understanding about the reactivity of this nucleophilic chalcogen species in organic synthesis.

Supplementary Information

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

Acknowledgments

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Author Contributions

Patrick C. Nobre proposed the methodology adopted and conducted the experimental investigation; Thiago J. Peglow and Ricardo H. Bartz conducted the experimental investigation; Angelita M. Barcellos performed the formal analysis of data and visualization; Raquel G. Jacob, Márcio S. Silva, Thiago Barcellos and Gelson Perin conceptualized the experiment, funding acquisition, wrote the paper and supervision. Thiago Barcellos and Gelson Perin were responsible for project administration and coordinated the planning and execution of the study.

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