One-Pot Synthesis of Alkyl Aryl Selenides with Hydroxy-, Amino-, and Carboxy-Functionality from Aryl Halides

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Various alkyl aryl selenides are incorporated into many biological compounds and commercial reagents in organic chemistry.[1,2] Grand efforts have been directed towards the synthesis of stable selenium-containing compounds on demand in pharmaceutical and chemical industry.[3] Despite the advantages and increasing applicability of organoselenium compounds, current synthetic methods have been limited in use by lengthy synthetic steps, harsh reaction conditions, unstable intermediates and a limited diversity of functional groups of starting materials. An efficient synthetic route for selenides is thus needed, accessing to more functionalized organoselenium compounds.

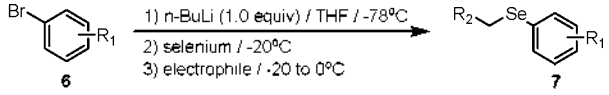
During the course of our synthetic studies for bioactive compounds, we developed a facile one-pot synthetic method for the formation of functionalized alkyl aryl selenides from aryl bromides through extention of our previous work.[4] Although the preparation of diorganoselenides from metal alkyl or aryl selenolates is a classical technique,[5] there has been no report of the synthesis of various alkyl aryl selenides via lithium aryl selenolates that are prepared from aryl bromides and BuLi in the presence of selenium. In this work, we report that easily prepared lithium selenolates couple directly with a variety of alkyl halides to give aryl alkyl selenides containing various functional groups, especially such as hydroxy, amino, and carboxylic acid.

The preparation of alkyl aryl selenides **7** was summarized from various substituted aryl bromides **6** in Table 1. Alkyl aryl selenides **7** were produced in sequence by direct lithiation of aryl bromides **6** with *n*-BuLi at -78 °C for 15 min, followed by addition of selenium powder, and then quenching the resulted selenolates with alkyl bromides. Addition of selenium power at -20 °C was very critical in the success of the reaction. At 0 °C and room temperature, lithiated selenolates found to be decomposed.

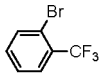
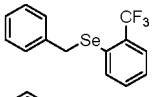
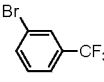
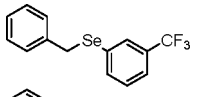
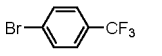
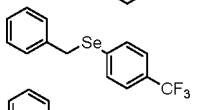
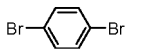
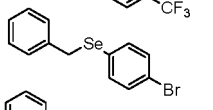
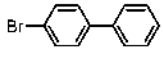
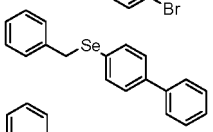
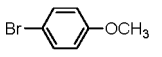
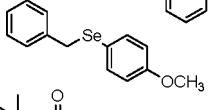
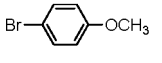
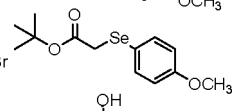
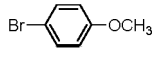
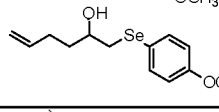
In the reactivity of *ortho*-, *meta*-, and *para*-substituted aryl bromides, yields of the target selenides increased according to the order of *para* > *ortho* > *meta* under the same conditions, suggesting that the *para*-substituted isomer form the most stable lithium selenolate (Table 1, entries 1-3). In the reaction of 1, 4-dibromobenzene as an aryl bromide (Table 1, entry 4), only monoalkyl-substituted aryl selenide was obtained in 84% yield in spite of 2 equivalents of reaction reagents being used. The presence of an electron-donating or -withdrawing group on aryl bromides (Table 1, entries 3-6) did not affect yields of products (84-91%). Bromoacetate and epoxide as electrophiles gave the respective product in 85% and 75% yields (Table 1, entries 7 and 8).

We have also developed a simple and good yielding one-pot synthesis of alkyl aryl selenides **9** containing a functional group such as -OH, -NH_2, and -COOH (Table 2). The procedure is the following: 1) in situ protection of the functional group by

Table 1. Simple One-Pot Synthesis of Alkyl Aryl Selenides **7**



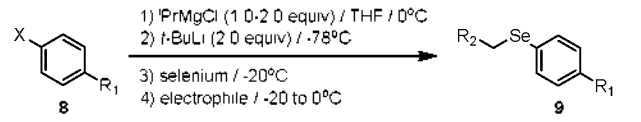
6 **7**

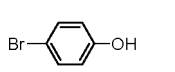
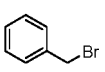
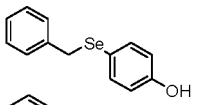
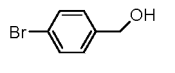
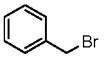
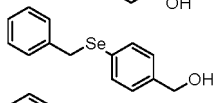
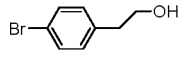
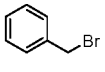
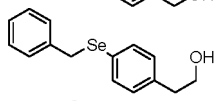
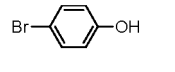
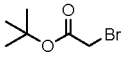
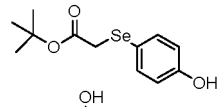
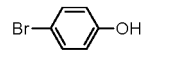
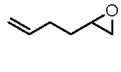
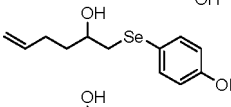
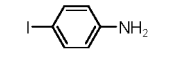
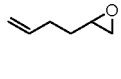
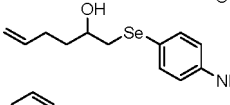
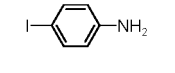
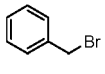
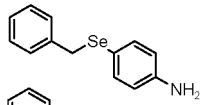
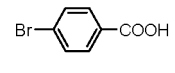
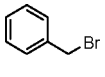
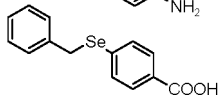
entry	6	electrophile	product (7)	yield[a] %
1				74
2				68
3				91
4				84
5				87
6				87
7				85
8[b]				75

[a]Yields were given for the isolated products. [b]Epoxide as an electrophile was used is a racemic mixture.

[†]These authors contributed equally to this work.

Table 2. One-Pot Synthesis of Alkyl Aryl Selenides **9** *via in situ* Protection of Various Functional Groups



entry	8	electrophile	product (9)	yield[a] %
1				86
2				81
3				84
4				81
5[b]				78
6[b]				76
7				83
8				82

[a]Yields were given for the isolated products. [b]Epoxide as an electrophile was used is a racemic mixture.

reacting with isopropylmagnesium chloride, 2) halogen-lithium exchange, 3) selenium powder insertion, and 4) a substitution reaction with an electrophile **8**.

We successfully performed the coupling of hydroxylated aryl bromides (4-bromophenol, 4-bromophenyl methanol, and 4-bromophenyl ethanol) with benzyl bromides, bromoacetate and epoxide. The reactions afforded desired products in good yields (Table 2, entries 1-5). 4-Iodoaniline (Table 2, entries 6 and 7) that needed 2 equivalents of Grignard reagent for the in situ protection of amine group gave the desired selenides in 76% and 83% yields, respectively. Also, bromobenzoic acid (Table 2, entry 8) readily reacted with benzyl bromide and then gave the corresponding product in 82% yield.

In summary, we have successfully developed a facile one-pot synthetic method to form functionalized alkyl aryl selenides from various aryl halides. This method is very quick (less than 1 hour) and catalyst-free, and could be used for the preparation of bioactive pharmaceuticals and their intermediates containing alkyl aryl selenide moieties.

Experimental Section

General Procedure for the Formation of Alkyl Aryl Selenides 7 from Aryl Bromides 6 (Table 1). To a solution of aryl bromide **6** (0.5 mmol) in anhydrous THF (5 mL) was added slowly a solution of *n*-BuLi (1.6 M in hexane, 0.5 mmol) at -78 °C, and the solution was stirred for 15 min under N_2 atmosphere. When the reaction temperature reached -20 °C, selenium powder (0.5 mmol) was added all at once. The selenium was completely dissolved, and then electrophile (0.5 mmol) was added to the reaction mixture at -10 °C. The reaction mixture was stirred for an additional 20 min at 0 °C and then quenched with aqueous NH_4Cl (5 mL). The aqueous layer was extracted with EtOAc (2×5 mL) and the combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The desired product **7** was isolated by flash column chromatography on silica gel.

Benzyl 2-Trifluoromethylphenyl Selenide (entry 1): (117 mg, 74%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 (d, 1H, J = 7.7 Hz), 7.51 (d, 1H, J = 7.6 Hz), 7.35-7.29 (m, 2H), 7.26-7.18 (m, 5H), 4.15 (s, 2H); HRMS (FAB) *m/z* calcd for $C_{14}H_{11}F_3Se$ $[M+H]^+$ 315.9978, found 315.9979.

Benzyl 3-Trifluoromethylphenyl Selenide (entry 2): (107 mg, 68%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.56 (d, 1H, J = 7.8 Hz), 7.46 (d, 1H, J = 7.8 Hz), 7.29 (t, 1H, J = 7.8 Hz), 7.24-7.16 (m, 5H), 4.11 (s, 2H); HRMS (FAB) *m/z* calcd for $C_{14}H_{11}F_3Se$ $[M+H]^+$ 315.9978, found 315.9990.

Benzyl 4-Trifluoromethylphenyl Selenide (entry 3): (143 mg, 91%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 (d, 2H, J = 8.1 Hz), 7.46 (d, 2H, J = 8.1 Hz), 7.28-7.21 (m, 5H), 4.17 (s, 2H); HRMS (FAB) *m/z* calcd for $C_{14}H_{11}F_3Se$ $[M+H]^+$ 315.9978, found 315.9993.

Benzyl 4-Bromophenyl Selenide (entry 4): (137 mg, 84%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (d, 2H, J = 8.4 Hz), 7.26 (d, 2H, J = 8.4 Hz), 7.24-7.17 (m, 5H), 4.07 (s, 2H); HRMS (FAB) *m/z* calcd for $C_{13}H_{11}BrSe$ $[M+H]^+$ 325.9209, found 325.9193.

Benzyl 4-Biphenyl Selenide (entry 5): (140 mg, 87%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57-7.19 (m, 14H), 4.14 (s, 2H); HRMS (FAB) *m/z* calcd for $C_{19}H_{16}Se$ $[M+H]^+$ 324.0417, found 324.0415.

Benzyl 4-Methoxyphenyl Selenide (entry 6): (121 mg, 87%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (d, 2H, J = 8.5 Hz), 7.25-7.18 (m, 3H), 7.12 (d, 2H, J = 7.3 Hz), 6.77 (d, 2H, J = 8.6 Hz), 4.00 (s, 2H), 3.78 (s, 3H); HRMS (FAB) *m/z* calcd for $C_{14}H_{14}OSe$ $[M+H]^+$ 278.0210, found 278.0244.

***tert*-Butyl 2-(4-Methoxyphenylselanyl)acetate (entry 7):** (128 mg, 85%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, 2H, J = 10.5 Hz), 6.81 (d, 2H, J = 10.5 Hz), 3.76 (s, 3H), 3.31 (s, 2H), 1.38 (s, 9H); MS (ESI) *m/z* 302.90 ($[M+H]^+$).

1-(4-Methoxyphenylselanyl)hex-5-en-2-ol (entry 8): (107 mg, 75%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (d, 2H, J = 8.6 Hz), 6.80 (d, 2H, J = 8.6 Hz), 5.77 (m, 1H), 4.96 (m, 2H), 3.77 (s, 3H), 3.64 (m, 1H), 3.01 (dd, 1H, J = 12.7, 3.6 Hz), 2.79 (dd, 1H, J = 12.6, 8.7 Hz), 2.64 (brs, 1H), 2.19 (td, 1H, J = 14.5, 7.1 Hz), 2.09 (td, 1H, J = 14.7, 7.3 Hz), 1.59 (q, 2H, J = 7.2 Hz); HRMS (FAB) *m/z* calcd for $C_{13}H_{18}O_2Se$ $[M+H]^+$ 286.0472, found 286.0444.

General Procedure for the Formation of Alkyl Aryl Selenides 9 from Aryl Halides 8 (Table 2). To a solution of aryl halides **8** (0.5 mmol) in anhydrous THF (5 mL) was added a solution of ^{i}PrMgCl (2.0 M solution in Et_2O, 0.5 mmol; entries 6 and 7, 1.0 mmol used) at 0 °C under N_2 atmosphere.

The reaction mixture was cooled to -78 °C and then a solution of *t*-BuLi (1.7 M solution in pentane, 2.0 mmol) was slowly added for 15 min. After 30 min, selenium powder (0.5 mmol) was added at -20 °C. The selenium was completely dissolved, and then electrophile (0.5 mmol) was added at -10 °C. The reaction mixture was stirred for an additional 20 min at 0 °C and then quenched with aqueous NH_4Cl (10 mL). The aqueous layer was extracted with EtOAc (3×10 mL) and the combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The desired product **9** was isolated by flash column chromatography on silica gel.

4-(Benzylselanyl)phenol (entry 1): (117 mg, 86%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 (d, 2H, J = 8.5 Hz), 7.25-7.16 (m, 3H), 7.11 (d, 2H, J = 7.2 Hz), 6.69 (d, 2H, J = 8.5 Hz), 4.88 (s, 1H), 3.99 (s, 2H); HRMS (FAB) *m/z* calcd for $C_{13}H_{12}OSe$ $[M+H]^+$ 264.0053, found 264.0042.

(4-(Benzylselanyl)phenyl)methanol (entry 2): (112 mg, 81%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (d, 2H, J = 8.0 Hz), 7.25-7.17 (m, 7H), 4.62 (s, 2H), 4.08 (s, 2H), 2.00 (brs, 1H); HRMS (FAB) *m/z* calcd for $C_{14}H_{14}OSe$ $[M+H]^+$ 278.0210, found 278.0222.

2-(4-(Benzylselanyl)phenyl)ethanol (entry 3): (123 mg, 84%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (d, 2H, J = 8.0 Hz), 7.24-7.17 (m, 5H), 7.09 (d, 2H, J = 7.9 Hz), 4.06 (s, 2H), 3.80 (t, 2H, J = 6.6 Hz), 2.81 (t, 2H, J = 6.6 Hz), 1.68 (brs, 1H); HRMS (FAB) *m/z* calcd for $C_{15}H_{16}OSe$ $[M+H]^+$ 292.0366, found 292.0370.

***tert*-Butyl 2-(4-Hydroxyphenylselanyl)acetate (entry 4):** (116 mg, 81%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 (d, 2H, J = 8.5 Hz), 6.67 (d, 2H, J = 8.5 Hz), 3.31 (s, 2H), 1.42 (s, 9H); HRMS (FAB) *m/z* calcd for $C_{12}H_{16}O_3Se$ $[M+H]^+$ 288.0265, found 288.0294.

4-(2-Hydroxyhex-5-enylselanyl)phenol (entry 5): (106 mg, 78%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (d, 2H, J = 8.5 Hz), 6.72 (d, 2H, J = 8.5 Hz), 5.76 (m, 1H), 4.96 (m, 2H), 3.67 (m, 1H), 3.05 (dd, 1H, J = 12.8, 3.6 Hz), 2.80 (dd, 1H, J = 12.8, 8.7 Hz), 2.67 (brs, 1H), 2.13 (m, 2H), 1.82 (brs, 1H), 1.62 (m, 2H); HRMS (FAB) *m/z* calcd for $C_{12}H_{16}O_2Se$ $[M+H]^+$ 272.0316, found 272.0358.

1-(4-Aminophenylselanyl)hex-5-en-2-ol (entry 6): (102 mg, 76%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (d, 2H, J = 8.4 Hz), 6.57 (d, 2H, J = 8.4 Hz), 5.77 (m, 1H), 4.96 (m, 2H), 3.61 (m, 1H), 2.98 (dd, 1H, J = 12.6, 3.5 Hz), 2.73 (dd, 1H, J = 12.6, 8.8 Hz), 2.13 (m, 2H), 1.59 (m, 2H); HRMS (FAB) *m/z* calcd for $C_{12}H_{17}NOSe$ $[M+H]^-$ 271.0475, found 271.0465.

4-(Benzylselanyl)aniline (entry 7): (109 mg, 83%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 (d, 2H, J = 8.7 Hz), 7.25-7.16 (m, 3H), 7.12 (d, 2H, J = 7.2 Hz), 6.47 (d, 2H, J = 8.7 Hz), 3.95 (s, 2H); HRMS (FAB) *m/z* calcd for $C_{13}H_{13}NSe$ $[M+H]^+$ 263.0213, found 263.0261.

4-(Benzylselanyl)benzoic Acid (entry 8): (119 mg, 82%); ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.86 (s, 1H), 7.81 (d, 2H, J = 8.0 Hz), 7.55 (d, 2H, J = 7.9 Hz), 7.35 (d, 2H, J = 7.4 Hz), 7.28 (t, 2H, J = 7.5 Hz), 7.21 (t, 1H, J = 7.3 Hz), 4.34 (s, 2H); HRMS (FAB) *m/z* calcd for $C_{14}H_{12}O_2Se$ $[M+H]^-$ 292.0003, found 291.9997.

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