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One-Pot Synthesis of Aryl Selenonic Acids and Some Unexpected Byproducts

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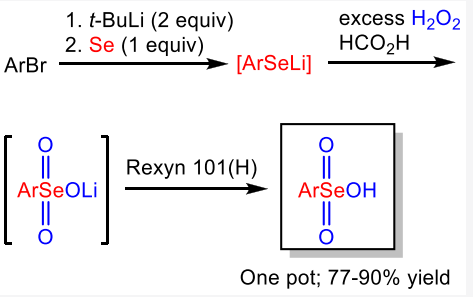
ABSTRACT: The synthesis of aryl selenonic acids was achieved from diverse aryl bromides via a one-pot method involving metalation, selenation, and oxidation with hydrogen peroxide followed by ion exchange to afford the pure products in 77−90% yield. An *o*-hydroxymethyl derivative was found to dehydrate readily, affording the first example of a cyclic selenonic ester, while two minor byproducts were isolated and shown by X-ray crystallography to be mixed salts of aryl selenonic acids with either the corresponding aryl seleninic or selenious acid.



INTRODUCTION

Benzeneseleninic acid (**1a**) and its anhydride **2a**, as well as various analogues, have been widely studied and used in a diverse range of synthetically useful oxidations.[1] Some of these processes employ catalytic amounts of the selenium compound in the presence of inexpensive and environmentally friendly stoichiometric co-oxidants such as hydrogen peroxide.[2] Examples include the conversion of alcohols to aldehydes or ketones,[3] phenols to quinones,[4] dehydrogenation of steroidal ketones,[5] lactones,[6] and lactams[3b] to α,β-unsaturated compounds, epoxidations[7] and dihydroxylations[8] of alkenes, and Baeyer−Villiger oxidations.[9] In the latter three cases, the corresponding peroxyseleninic acid **3a** was proposed as the active oxidant.

In contrast, although the corresponding selenonic acids **4** were first reported more than a century ago, they have been studied less frequently and have found little application as synthetic reagents. This is in large measure due to difficulties in their preparation and characterization, which led to errors and uncertainties in their structure identification in earlier work. For example, in 1909, Doughty[10] reported the preparation of **4a** by heating selenic acid (H_2SeO_4) in benzene in a sealed tube for 100 h at 110 °C. Subsequently, a more efficient variation of this process employed selenium trioxide and benzene in liquid sulfur dioxide to obtain the same product.[11] However, in 1964, Paetzold and Lienig[12] repeated the earlier work of Doughty and demonstrated the presence of both Se(IV) and Se(VI) in the product by means of a Bunsen test. On this basis, they suggested that the product was actually the selenonium selenonate salt **5a**, produced by protonation of **1a** by **4a**. Several other early reports of selenonic acids were based on the oxidation of diselenides or seleninic acids with oxidants like nitric acid or potassium permanganate. The products were typically either isolated as their metal salts or were obtained from the latter by treatment with strong acids such as perchloric acid.[13−15] Purification and characterization were often minimal with the methods available at the time. In more recent examples, Abdo and Knapp[16] prepared sodium and triethylammonium salts of selenonic acid derivatives of carbohydrates, while Singh et al.[17] obtained the selenonic acid analogue of selenocysteine and confirmed its structure by X-ray diffraction. Perfluoro analogues[18] and *p*-chlorobenzeneselenonic acid[19] have also been reported. In general, the preparation of selenonic acids is hampered by their strong acidity and water solubility, the difficulty in separating the free acids from byproduct metal salts, their high polarity that generally precludes chromatographic purification on common adsorbents like silica gel, and their hygroscopic nature. Moreover, diselenide and seleninic acid precursors of selenonic acids are not always readily available, resulting in the need for alternative procedures based on more common starting materials.

Very recently, we reported that, contrary to previous reports,[7] the epoxidation of cyclooctene with benzeneseleninic acid (**1a**) and hydrogen peroxide proceeds chiefly via stepwise formation of selenonium selenonate salt **5a**, followed by **4a** and finally the proposed peroxyselenonic acid **6a**, as shown in Scheme 1. Epoxidation with **6a** generated in this manner proved significantly faster than with the peroxyseleninic acid

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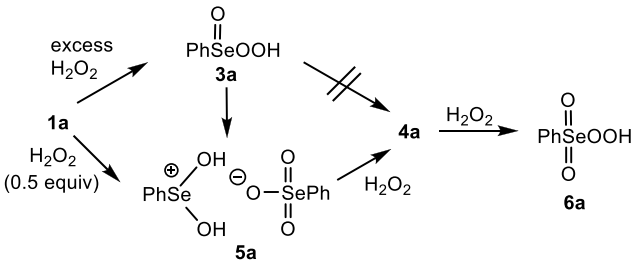
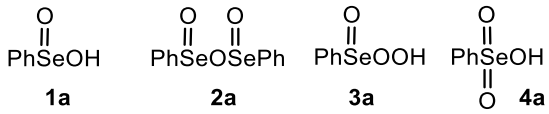
Scheme 1. Oxidation Pathways for the Reaction of Benzeneseleninic Acid (1a) with Hydrogen Peroxide



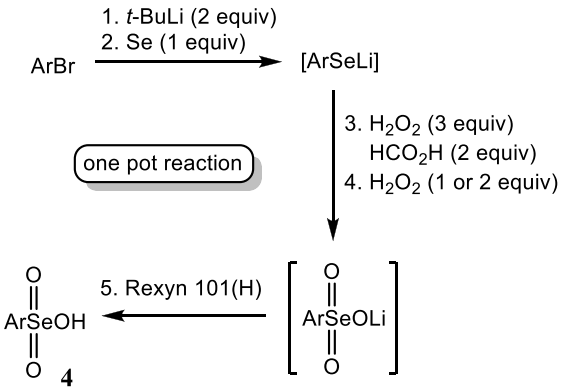
3a.[20] Furthermore, Syper and Młochowski[21] isolated peroxyseleninic acid **3a** and indicated that it isomerized to selenonic acid **4a** upon heating in acetonitrile. However, we found that this reaction, which proceeded even at room temperature in solution and was accompanied by oxygen evolution, actually produced the salt **5a** and not **4a**, as confirmed by an X-ray structure of the product.[20] This also confirmed the earlier structure proposed by Paetzold and Lienig on the basis of their Bunsen test of the product obtained by the method of Doughty. Since **4a** alone failed to effect epoxidation, its further conversion to the postulated peroxyselenonic acid **6a** with hydrogen peroxide is a requirement for epoxidation. Thus, **6a** appears to be the most active oxidant species in this redox manifold, but proved too unstable to isolate. Given the difficulties in the preparation of selenonic acids and their incomplete characterization in much of the earlier work, along with the newly discovered and unexpected role that **4a** and **6a** play in the epoxidation of a typical alkene, we now report a new protocol for the preparation of a series of diverse selenonic acids.



RESULTS AND DISCUSSION

The synthesis of arylselenonic acids **4a**–**4l** (Scheme 2 and Figure 1) was achieved in one pot from a series of aryl bromides by metalation with *tert*-butyllithium in THF solution at −78 °C, addition of powdered selenium, and oxidation of the resulting selenolates (ArSeLi) with hydrogen peroxide at

Scheme 2. Preparation of Aryl Selenonic Acids 4 from Aryl Bromides



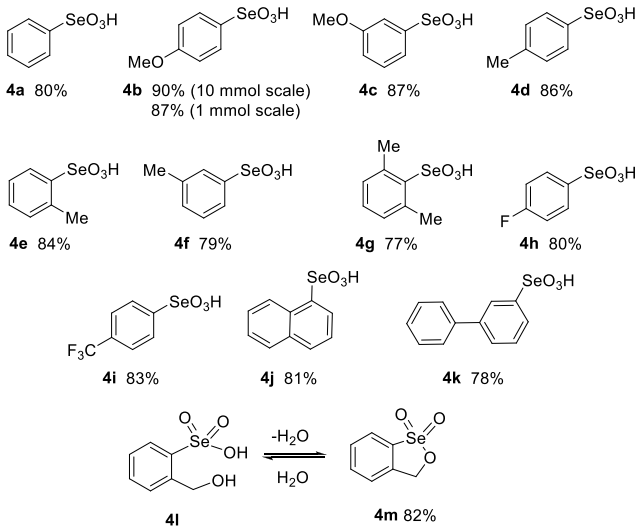


Figure 1. Structures and yields of aryl selenonic acids.

room temperature in the presence of formic acid. The lithium selenonates were then extracted into water and passed through a short column of Rexyn 101(H) ion-exchange resin to generate the free selenonic acids **4**. The aqueous solutions of **4** were freeze-dried under vacuum to afford the final products in a high state of purity. Although some selenonic acids have been prepared by the further oxidation of seleninic acids or diselenides,[13] usually with harsh oxidants, the advantage of the present method is that it starts with more widely available aryl bromides for products where the corresponding diselenides and seleninic acids are not readily available.

During optimization studies of the preparation of **4b**, we observed that *tert*-butyllithium was more effective than *n*-butyllithium in the metalation–selenation sequence, as the latter resulted in the formation of significant amounts of the corresponding aryl *n*-butyl selenides. Low temperatures also proved necessary to avoid decomposition of the products (vide infra) as well as to avoid reaction of *tert*-butyllithium with the solvent THF. Although the overall stoichiometry of the process requires only 3 equiv of hydrogen peroxide to convert the lithium selenolates (ArSeLi) to selenonic acids **4**, a total of 4 or 5 equiv of hydrogen peroxide was typically added in two portions to achieve complete oxidation. Attempts were made to catalyze the formation of the selenonic acids with several acids. Acetic acid had little effect and proved difficult to remove from the product, while trifluoroacetic acid resulted in considerable decomposition. However, formic acid enhanced the rate ca. 3-fold, afforded products of high purity, and was easily removed from the product. While the precise reason for the beneficial effects of formic acid is unclear, one possibility is that it protonates an intermediate seleninic acid, thereby activating it toward further attack by hydrogen peroxide.[22,23] Alternatively, it is conceivable that formation of the corresponding peroxyformic acid (HC(=O)OOH) in situ[24] enhances the oxidation of the selenium species in Scheme 2 en route to products **4**. Since the selenonic acids are hygroscopic, removal of water from their aqueous solutions by rotary evaporation required elevated temperatures that led to extensive decomposition. This was easily avoided by freeze-drying the solutions under high vacuum. All of the products were then characterized by ^{1}H, ^{13}C, and ^{77}Se NMR spectroscopy as well as by high-resolution mass spectrometry.

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The results shown in Figure 1 indicate that good to high (77−90%) yields of diverse aryl selenonic acids can be produced, including products containing electron-donating (**4b**, **4c**, **4d**, **4e**, **4f**, and **4g**) and -withdrawing substituents (**4h**, **4i**), located at either the *ortho*-, *meta*-, or *para*-positions. The naphthalene (**4j**) and biphenyl (**4k**) derivatives were also obtained without difficulty. The attempted preparation of 2-(hydroxymethyl)benzeneselenonic acid (**4l**) by the usual method resulted instead in the formation of the cyclic selenonate ester **4m** through dehydration of **4l**. The ^{77}Se NMR spectrum of **4m** in $CDCl_3$ revealed a signal at 1116.5 ppm, which is considerably further downfield than the resonances of selenonic acids **4a**−**4k** (1020−1031 ppm in D_2O). Crystallization of **4m** by slow evaporation from water produced crystals suitable for X-ray crystallography, which confirmed its structure unequivocally (Figure 2). When **4m**

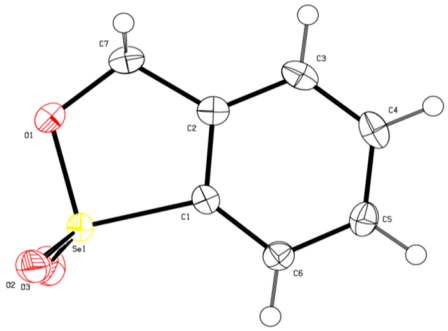

Figure 2. ORTEP diagram of cyclic selenonate ester **4m**. For details, see the Supporting Information, Figure S54 and Table S1.

was dissolved in D_2O, the NMR spectra were quite different from those in $CDCl_3$, including a ^{77}Se signal at 1021.9 ppm, consistent with the selenonic acid structure **4l** and indicating that the dehydration is reversible. While cyclic seleninate esters containing Se(IV) are well known,[25] to our knowledge, cyclic selenonate esters have not been previously reported.

The above selenonic acids proved stable at or below room temperature and could be stored for at least several weeks when refrigerated. However, during optimization studies, several unexpected byproducts were also discovered. Attempted recrystallization of a sample of crude **4b** from dichloromethane delivered a small amount of the salt **7b** instead of **4b**. Its ^{77}Se NMR spectrum revealed signals at 1299.7[26] and 1024.5 ppm, typical of selenious and selenonic acid species, respectively, and an X-ray crystal structure (Figure 3) confirmed that it was the salt derived from protonation of

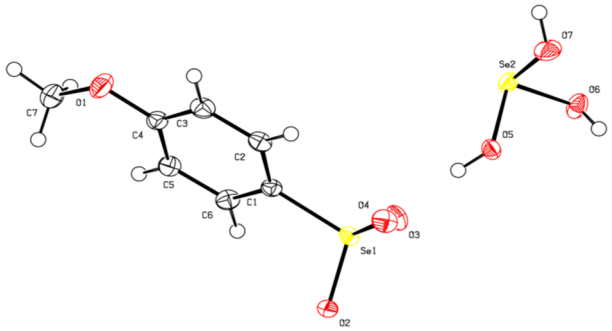

Figure 3. ORTEP diagram of salt **7b**. For details, see the Supporting Information, Figure S55 and Table S2.

selenious acid (H_2SeO_3) by the more strongly acidic selenonic acid **4b**.[27] The formation of **7b** in this instance was attributed to a small amount of excess unreacted elemental selenium that remained after the selenation step and was subsequently converted to selenious acid by oxidation with hydrogen peroxide, followed by protonation by the principal product, the selenonic acid **4b**. Alternatively, it is conceivable that selenious acid was produced by oxidative C−Se bond cleavage of an arylseleno intermediate during the process. While the compounds prepared by the typical procedure in the Experimental Section and listed in Figure 1 were free of selenious acid, on the basis of the ^{77}Se NMR and HRMS spectra of the final products, this result indicates that care must be taken to ensure that the selenation step is allowed to go to completion and that the use of excess selenium is avoided in the preparation of the products **4**.

When a sample of 2,6-dimethylbenzeneselenonic acid (**4g**) was heated in dioxane at 70 °C, followed by cooling to room temperature, a small amount of the salt **8g** crystallized and its structure was determined by X-ray crystallography (see Figure 4). Interestingly, the structure consists of a dimeric hydrogen-

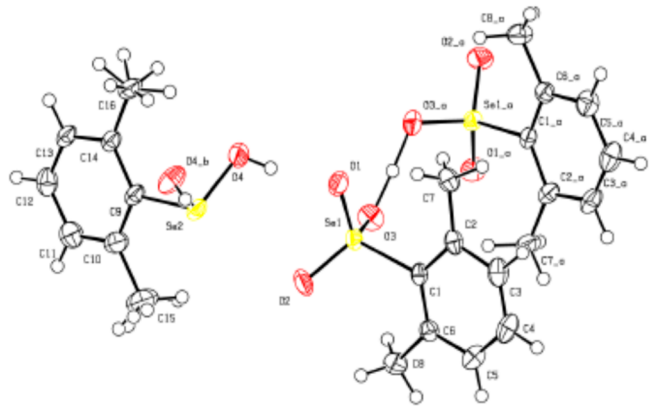

Figure 4. ORTEP diagram of salt **8g**. For details, see the Supporting Information, Figure S56 and Table S3.

bridged selenonate anion and a protonated seleninic acid cation. While this resembles the 1:1 salt **5a** in Scheme 1, the 2:1 stoichiometry in **8g** was unexpected. However, evaporation of the mother liquor and examination of the residue by NMR spectroscopy in $CDCl_3$ revealed the presence of the corresponding 1:1 salt **5g** as the main product. This experiment thus demonstrates that heating selenonic acids **4** can result in the facile loss of oxygen to generate the corresponding seleninic acid **1** followed by its protonation by **4** to afford the more stable mixed Se(IV)−Se(VI) salts such as **8g** and **5g** (Scheme 3).

Attempts to extend the procedure shown in Scheme 2 to the preparation of free alkyl selenonic acids proved more difficult because of their decomposition upon treatment with Rexyn 101(H), which was required to liberate the free acids from their lithium salts. However, crude lithium methane- and *n*-butaneselenonates (**9** and **10**, respectively) could be prepared by a modification of the general procedure (see the Experimental Section). Similarly, *endo*-3-camphorselenonic acid (**11**) was obtained in solution from the hydrogen peroxide oxidation of the corresponding diselenide[28] in the presence of HCl−diethyl ether but decomposed upon attempted isolation.

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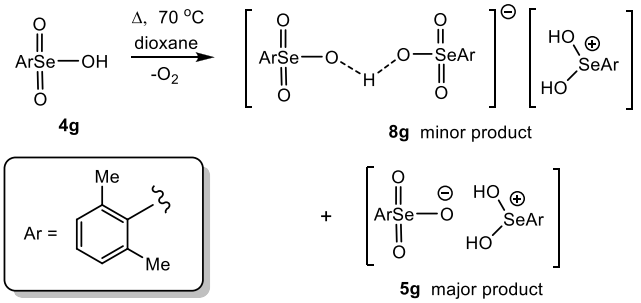
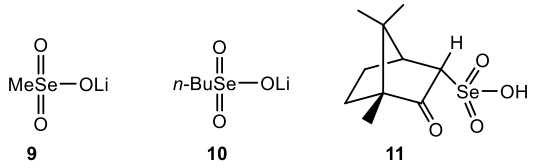
Scheme 3. Thermal Decomposition of Selenonic Acid 4g to Produce Mixed Se(IV)−Se(VI) Salts





In summary, the process described here provides a one-pot method for the preparation and characterization of diverse aryl selenonic acids from the corresponding readily available aryl bromides. The cyclic selenonic ester **4m** appears to be the first example of its class. Several unexpected salts **7b**, **4g**, and **5g** were formed by protonation of Se(IV) oxyacids by the stronger Se(VI) acids **4** during initial attempts to prepare selenonic acids **4b** and **4g**.

EXPERIMENTAL SECTION

General Experimental. All reactions were performed using oven-dried glassware under a nitrogen atmosphere. Tetrahydrofuran was dried over $LiAlH_4$ and was freshly distilled before use. Hydrogen peroxide was titrated before use[29] and had a concentration of 50 ± 1%. Yields reported are isolated yields. Rexyn 101(H) ion-exchange resin was washed with water, methanol, and water before use. ^1H, ^{13}C, ^{19}F, and ^{77}Se NMR spectra were recorded in D_2O or $CDCl_3$ at 400, 101, 377, and 76 MHz, respectively. External references of C_6F_6 in C_6D_6 (δ −164.9 ppm relative to $CFCl_3$)[30] or PhSeSePh (δ 463 relative to Me_2Se),[26] respectively, were used. ^{13}C and ^{19}F NMR spectra were recorded with broadband proton decoupling. ^{77}Se NMR were recorded using the UDEFT pulse program.[31] Multiplicities are reported as s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet. Exact mass determinations were performed with a Q-TOF LC/MS instrument, using electrospray ionization (ESI) in either positive or negative mode, as indicated.

CAUTION! While no explosive behavior was observed during the preparation of any of the selenonic acids in Figure 1 by the following procedure, peroxyseleninic and peroxyselenonic acids are potentially explosive materials that should be handled with appropriate precautions. On a few occasions during the optimization of the process, we did note that the reaction mixture foamed and effervesced from the sudden release of oxygen, presumably from the decomposition of peroxy species formed during the reaction. Furthermore, elevated temperatures should be avoided to prevent decomposition of the selenonic acid products.

Typical Procedure: Preparation of Benzeneselenonic Acid (4a). 4-Bromobenzene (0.11 mL, 164 mg, 1.0 mmol) was diluted with 10 mL of dry THF and cooled to −78 °C. *tert*-Butyllithium (1.6 M, 1.25 mL, 2.0 mmol)[32] was added dropwise, and the reaction mixture was stirred for 10 min. Selenium (79 mg, 1.0 mmol) was added, and stirring was continued at −78 °C for 15 min. The cold bath was removed, and the reaction mixture was stirred at room temperature for an additional 15 min. Hydrogen peroxide (50%, 0.17 mL, 3.0 mmol) was added, followed immediately by formic acid (75 μL, 2.0 mmol), and the mixture was stirred at room temperature for 30 min. An additional portion of hydrogen peroxide (50%, 60 μL, 1.0 mmol) was added, and stirring at room temperature was continued for 3 h. The reaction mixture was then diluted with water (5 mL), and the aqueous layer was collected. The organic layer was extracted with H_2O (1 mL), and the combined aqueous layers were washed with diethyl ether (5 mL). The aqueous layer was then passed through a short column of Rexyn 101(H) ion-exchange resin (2.0 g/mmol), and the resin was washed with an additional 2 mL of H_2O. Removal of the water by freezing the solution in an acetone−dry ice bath and sublimation under high vacuum afforded 163 mg (80%) of residual product **4a** as an off-white solid. Mp: 57−59 °C (lit. mp 64 °C,[12] 63−64 °C;[11b] 58−60 °C;[20] the mp of 142 °C[10] or 144 °C[21] reported in the older literature was incorrectly assigned to **4a** and is due to the salt **5a**).[12,20] ^1H NMR (400 MHz, D_2O): δ 7.77−7.75 (m, 2 H), 7.61 (crude tt, J = 7.4, 1.7 Hz, 1 H), 7.54 (crude tt, J = 7.4, 1.5 Hz, 2 H). $^{13}C\{^1H\}$ NMR (101 MHz, D_2O): δ 143.0, 134.0, 130.3, 125.7. $^{77}Se\{^1H\}$ NMR (76 MHz, D_2O): δ 1024.3. HRMS (ESI) m/z calcd for $C_6H_5O_3{}^{80}Se$ $[M - H]^-$: 204.9409; found: 204.9405.

Preparation of 4-Methoxybenzeneselenonic Acid (4b).[15a] The product was isolated (205 mg, 87%) as a waxy off-white solid. Mp: dec from 86 °C. ^1H NMR (400 MHz, D_2O): δ 7.70 (d, J = 7.9 Hz, 2 H), 7.11 (d, J = 8.0 Hz, 2 H), 3.74 (s, 3 H). $^{13}C\{^1H\}$ (101 MHz, D_2O): δ 163.2, 134.6, 127.8, 115.5, 55.8. $^{77}Se\{^1H\}$ (76 MHz, D_2O): δ 1024.4. HRMS (ESI) m/z calcd for $C_7H_7O_4{}^{80}Se$ $[M - H]^-$: 234.9515; found: 234.9510.

When the above process was scaled up to 1.87 g (10.0 mmol) of 4-bromoanisole and 0.790 g (10.0 mmol) of selenium powder, 2.12 g (90%) of product **4b** were obtained.

In a separate experiment, where a small excess (<5%) of selenium was present, recrystallization of the crude product from dichloromethane resulted in the formation of a crystalline precipitate of salt **7b**, the structure of which was determined by X-ray crystallography (see Figure 3).

The following products were prepared similarly, starting with 1.00 mmol of the corresponding aryl bromide. In the case of compounds **4e**, **4h**, and **4m**, a second portion of 2 mmol of hydrogen peroxide was added instead of the usual 1 mmol in order for the reaction to go to completion.

3-Methoxybenzeneselenonic Acid (4c). The product was isolated (205 mg, 87%) as a clear oil. ^1H NMR (400 MHz, D_2O): δ 7.51 (t, J = 8.1 Hz, 1 H), 7.38 (dt, J = 7.8, 1.3 Hz, 1 H), 7.34 (dd, J = 2.6, 1.6 Hz, 1 H), 7.19 (ddd, J = 8.4, 2.6, 1.0 Hz, 1 H), 3.79 (s, 3 H). $^{13}C\{^1H\}$ NMR (101 MHz, D_2O): δ 159.9, 143.9, 131.4, 120.1, 118.1, 110.8, 55.9. $^{77}Se\{^1H\}$ NMR (76 MHz, D_2O): δ 1024.0. HRMS (ESI) m/z calcd for $C_7H_7O_4{}^{80}Se$ $[M - H]^-$: 234.9515; found: 234.9510.

4-Tolueneselenonic Acid (4d).[11a,15a,b] The product was isolated (189 mg, 86%) as an off-white solid. Mp: 64−70 °C (dec) (lit.[11a] mp 66−73 °C). ^1H NMR (400 MHz, D_2O): δ 7.67 (d, J = 8.4 Hz, 2 H), 7.39 (d, J = 8.0 Hz, 2 H), 2.32 (s, 3 H). $^{13}C\{^1H\}$ NMR (101 MHz, D_2O): δ 145.5, 139.9.0, 130.8, 125.6, 20.7; $^{77}Se\{^1H\}$ NMR (76 MHz, D_2O): δ 1025.3. HRMS (ESI) m/z calcd for $C_7H_7O_3{}^{80}Se$ $[M - H]^-$: 218.9566; found: 218.9565.

2-Tolueneselenonic Acid (4e).[15a] The product was isolated (184 mg, 84%) as colorless, hygroscopic crystals. Mp: 54−58 °C. ^1H NMR (400 MHz, D_2O): δ 7.81 (d, J = 8.1 Hz, 1 H), 7.48 (t, J = 7.5 Hz, 1 H), 7.37−7.31 (m, 2 H), 2.55 (s, 3 H). $^{13}C\{^1H\}$ NMR (101 MHz, D_2O): δ 141.5, 136.5, 133.4, 132.4, 126.5, 126.1, 18.6. $^{77}Se\{^1H\}$ NMR (76 MHz, D_2O): δ 1023.2. HRMS (ESI) m/z calcd for $C_7H_7O_3{}^{80}Se$ $[M - H]^-$: 218.9566; found: 218.9564.

3-Tolueneselenonic Acid (4f).[15a] The product was isolated (172 mg, 79%) as a clear oil. ^1H NMR (400 MHz, D_2O): δ 7.58−7.54 (m, 2 H), 7.42−7.41 (m, 2 H), 2.28 (s, 3 H). $^{13}C\{^1H\}$ NMR (101 MHz, D_2O): δ 142.8, 141.2, 134.6, 130.0, 125.8, 122.6, 20.5. $^{77}Se\{^1H\}$ NMR (76 MHz, D_2O): δ 1025.2. HRMS (ESI) m/z calcd for $C_7H_7O_3{}^{80}Se$ $[M - H]^-$: 218.9566; found: 218.9562.

2,6-Dimethylbenzeneselenonic Acid (4g). The product was isolated (179 mg, 77%) as an off-white solid. Mp dec from 109 °C. ^1H NMR (400 MHz, D_2O): δ 7.33 (t, J = 7.5 Hz, 1 H), 7.18 (d, J = 7.5 Hz, 2 H), 2.63 (s, 6 H). $^{13}C\{^1H\}$ NMR (101 MHz, D_2O): δ 142.6, 138.0, 132.7, 131.0, 21.2. $^{77}Se\{^1H\}$ NMR (76 MHz, D_2O): δ

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1030.9. HRMS (ESI) m/z calcd for $C_8H_9O_3{}^{80}Se$ $[M - H]^-$: 232.9722; found: 232.9721.

In a separate experiment, a solution of 111 mg (0.476 mmol) of **4g** in dioxane was heated at 70 °C in an oil bath for 3.5 h. When cooled to room temperature, a small amount of salt **8g** crystallized and was collected and subjected to X-ray crystallography (Figure 4). The supernatant liquid was evaporated in vacuo, and the residue was triturated with D_2O to afford mainly unreacted **4g** in the D_2O solution, while the remaining off-white solid was identified as the 1:1 salt **5g** (49.8 mg, 46%). Mp: dec from 121 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 11.77 (s, 2 H), 7.37−7.29 (m, 2 H), 7.14 (m, 4 H), 2.77 (s, 12 H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 142.7, 140.4, 138.8, 137.8, 133.5, 132.7, 131.0, 130.4, 21.9, 19.9. $^{77}Se\{^1H\}$ NMR (76 MHz, $CDCl_3$): δ 1176.1, 1036.9.

*4-Fluorobenzeneselenonic Acid (**4h**).*[15e] The product was isolated (178 mg, 80%) as a clear colorless oil. ^1H NMR (400 MHz, D_2O): δ 7.82 (dd, J = 8.9, 5.0 Hz, 2 H), 7.28 (dd, J = 8.8, 8.9 Hz, 2 H). $^{13}C\{^1H\}$ NMR (101 MHz, D_2O): δ 165.3 (d, J = 253.1 Hz), 138.6, 128.6 (d, J = 9.7 Hz), 117.4 (d, J = 23.2 Hz). $^{19}F\{^1H\}$ NMR (377 MHz, D_2O): δ −104.3. $^{77}Se\{^1H\}$ NMR (76 MHz, D_2O): δ 1021.4. HRMS (ESI) m/z calcd for $C_6H_4FO_3{}^{80}Se$ $[M - H]^-$: 222.9315; found: 222.9315.

*4-(Trifluoromethyl)benzeneselenonic Acid (**4i**).* The product was isolated (228 mg, 83%) as a white solid. Mp: dec from 46 °C. ^1H NMR (400 MHz, D_2O): δ 7.98 (d, J = 8.4 Hz, 2 H), 7.90 (d, J = 8.4 Hz, 2 H). $^{13}C\{^1H\}$ NMR (101 MHz, D_2O): δ 145.8, 134.0 (q, J = 33.0 Hz), 126.9 (q, J = 3.8 Hz), 126.1, 122.6 (q, J = 272.4 Hz). $^{19}F\{^1H\}$ NMR (377 MHz, D_2O): δ −63.2. $^{77}Se\{^1H\}$ NMR (76 MHz, D_2O): δ 1020.4. HRMS (ESI) m/z calcd for $C_7H_4F_3O_3{}^{80}Se$ $[M - H]^-$: 272.9283; found: 272.9289.

*Naphthalene-1-selenonic Acid (**4j**).*[15d] The product was isolated (206 mg, 81%) as an orange-brown solid. Mp: dec from 94 °C. ^1H NMR (400 MHz, D_2O): δ 8.45 (d, J = 8.5 Hz, 1 H), 8.12 (d, J = 7.4 Hz, 1 H), 8.05 (d, J = 8.3 Hz, 1 H), 7.90 (d, J = 8.2 Hz, 1 H), 7.66 (t, J = 7.7 Hz, 1 H), 7.56 (t, J = 7.6 Hz, 1 H), 7.51 (t, J = 7.8 Hz, 1 H). $^{13}C\{^1H\}$ NMR (101 MHz, D_2O): δ 138.7, 134.2, 133.8, 128.6, 128.2, 127.1, 127.0, 126.5, 124.3, 123.2. $^{77}Se\{^1H\}$ NMR (76 MHz, D_2O): δ 1020.9. HRMS (ESI) m/z calcd for $C_{10}H_7O_3{}^{80}Se$ $[M - H]^-$: 254.9566; found: 254.9565.

*1,1′-Biphenyl-3-selenonic Acid (**4k**).* The product was isolated (220 mg, 78%) as a viscous orange oil. ^1H NMR (400 MHz, D_2O): δ 8.02 (s, 1 H), 7.86 (d, J = 7.8 Hz, 1 H), 7.79 (d, J = 8.5 Hz, 1 H), 7.65 (t, J = 7.9 Hz, 1 H), 7.60 (d, J = 7.0 Hz, 2 H), 7.44 (t, J = 7.3 Hz, 2 H), 7.38 (t, J = 7.3 Hz, 1 H). $^{13}C\{^1H\}$ NMR (101 MHz, D_2O): δ 143.7, 142.7, 138.6, 132.3, 130.8, 129.3, 128.6, 127.1, 124.5, 123.9. $^{77}Se\{^1H\}$ NMR (76 MHz, D_2O): δ 1024.3. HRMS (ESI) m/z calcd for $C_{12}H_9O_3{}^{80}Se$ $[M - H]^-$: 280.9722; found: 280.9720.

*2-(Hydroxymethyl)benzeneselenonic Acid (**4l**) and Cyclic Selenonate Ester **4m**.* The cyclic selenonate ester **4m** was isolated (177 mg, 82%) by the usual method as a white solid. Crystallization by slow evaporation from water gave colorless needles. Mp: 65−67 °C. The structure was confirmed by single crystal X-ray diffraction (Figure 2). NMR spectra were recorded in $CDCl_3$ (dried over 3 Å molecular sieves). ^1H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 8.0 Hz, 1 H), 7.86 (td, J = 7.6, 1.1, Hz, 1 H), 7.74 (td, J = 7.7, 1.1 Hz, 1 H), 7.59 (d, J = 7.8 Hz, 1 H), 5.62 (s, 2 H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 137.2, 135.1, 133.6, 131.0, 125.0, 124.0, 70.2. $^{77}Se\{^1H\}$ NMR (76 MHz, $CDCl_3$): δ 1116.5. HRMS (ESI) m/z calcd for $C_7H_7O_3{}^{80}Se$ $[M + H]^+$: 218.9555; found: 218.9555.

When **4m** was dissolved in D_2O, it afforded the hydrated form **4l**. ^1H NMR (400 MHz, D_2O): δ 7.83 (d, J = 7.2 Hz, 1 H), 7.61−7.56 (m, 2 H), 7.44−7.40 (m, 1 H), 4.89 (s, 2 H). $^{13}C\{^1H\}$ NMR (101 MHz, D_2O): δ 140.4, 138.5, 133.7, 129.5, 128.4, 126.4, 60.0. $^{77}Se\{^1H\}$ NMR (76 MHz, D_2O): δ 1021.9. HRMS (ESI) m/z calcd for $C_7H_7O_4{}^{80}Se$ $[M - H]^-$: 234.9515; found: 234.9513.

*Lithium Methaneselenonate (**9**).* Selenium (79 mg, 1.0 mmol) was suspended in 10 mL of dry THF and cooled to −78 °C. Methyllithium (1.6 M, 0.66 mL, 1.05 mmol) was added dropwise, and the reaction mixture was stirred at −78 °C for 10 min, after which the cold bath was removed, and the mixture was stirred at room temperature for an additional 15 min. Hydrogen peroxide (50%, 0.57 mL, 10 mmol) was added, and the reaction was stirred at room temperature for 4 h. The solvent was removed in vacuo with no heating to give crude **9** as a white solid. Mp: dec from 103 °C; ^1H NMR (400 MHz, D_2O): δ 3.28; $^{13}C\{^1H\}$ NMR δ 42.6; $^{77}Se\{^1H\}$ NMR (76 MHz, D_2O): δ 1044.9. The crude product can be stored for at least several days at −5 °C, but it decomposed upon treatment with Rexyn 101(H) resin, resulting in a mixture of selenious acid and unreacted methaneselenonic acid as the major and minor products, respectively. $^{77}Se\{^1H\}$ NMR (76 MHz, D_2O): δ 1300.3 (H_2SeO_3, major), 1040.0 (CH_3SeO_3H, minor).

*Lithium Butaneselenonate (**10**).* The crude lithium salt **10** was prepared in the same manner as **9** to afford a white solid, which could be stored at −5 °C for several days, but decomposed upon treatment with Rexyn 101(H) resin. Mp: dec from 106 °C. ^1H NMR (400 MHz, D_2O): δ 3.55 (t, J = 7.7 Hz, 2 H), 1.94 (pentet, J = 7.7 Hz, 2 H), 1.54 (pentet, J = 7.4 Hz, 2 H), 0.96 (t, J = 7.4 Hz, 3 H). $^{13}C\{^1H\}$ NMR (101 MHz, D_2O): δ 59.1, 24.8, 21.2, 12.6. $^{77}Se\{^1H\}$ NMR (76 MHz, D_2O): δ 1061.6.

*endo-3-Camphorselenonic Acid (**11**).* *endo*-3-Camphor diselenide[28] (230 mg, 0.50 mmol) was dissolved in 10 mL of dichloromethane, and hydrogen peroxide (50%, 0.17 mL, 3.0 mmol) was added, followed by $HCl{\cdot}OEt_2$ (2.0 M, 0.5 mL, 1 mmol). The reaction was allowed to stir at room temperature for 15 min, during which time the yellow color of the diselenide was discharged. The product selenonic acid was found to be stable in solution for several hours but rapidly decomposed upon attempted isolation. A freshly prepared product obtained by evaporation of volatile material in vacuo at room temperature had the following properties. ^1H NMR (400 MHz, $CDCl_3$): δ 7.56 (br s, 1 H), 4.75 (s, 1 H), 2.71 (s, 1 H), 2.10−2.00 (m, 1 H), 2.00−1.88 (m, 1 H), 1.83−1.70 (m, 1 H), 1.70−1.57 (m, 1 H), 0.98 (s, 3 H), 0.90 (s, 3 H), 0.87 (s, 3 H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 205.4, 82.9, 59.4, 47.4, 46.6, 30.1, 23.3, 19.9, 18.9, 9.6. $^{77}Se\{^1H\}$ NMR (76 MHz, $CDCl_3$): δ 1052.1. HRMS (ESI) m/z calcd for $C_{10}H_{15}O_4{}^{80}Se$ $[M - H]^-$: 279.0141; found: 279.0140.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01369.

^1H, ^{13}C, ^{77}Se, and ^{19}F NMR spectra of compounds **4a**−**4m**, **5g**, and **9**−**11** (Figures S1−S53), along with X-ray crystallographic data for compounds **4m**, **7b**, and **8g** (Figures S54−S56 and Tables S1−S3) (PDF)

Accession Codes

CCDC 2088126−2088128 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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