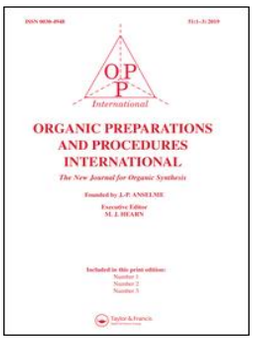

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OPPI BRIEF

A Facile and Practical One-Pot Synthesis of 2-[(Methylselenyl)Methyl]Benzoic Acid

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The structures of organo-selenium compounds are similar to those of organo-sulfur compounds, but they vary drastically in some of their properties. Because of the toxicity and enormously unpleasant odor of organo-selenium compounds, they have not been as well explored as could be justified. For example, organo-selenium compounds are reported as active antibacterial, antiviral, antifungal, anti-parastitic, anti-inflammatory and antihistamine agents.[1]

Recently, Liotta and his co-workers reported the use of phenyl selenide anion as the key reagent for the conversion of lactones to ω-vinylcarboxylic acids.[2] The choice of phenyl selenide anion as the ring-opening reagent seemed attractive for two reasons. First, a simple lactone possesses two sites which are potentially reactive to nucleophiles, the carbonyl carbon and the carbinolic carbon. Based on hard-soft acid-base theory, a soft nucleophile, such as phenyl selenide anion, should exhibit a preference for S_N2-type attack at the carbinolic carbon and thus generate ω-vinylcarboxylic acids.

An ample variety of aromatic acids have been used as key intermediates for the synthesis of 1,3,4-oxadiazole rings, which occupy a key place in medicinal chemistry due to their significant biological properties, including antimicrobial,[3] antituberculosis[4] and anticancer activity.[5] It is well-known that the combination of two or more types of heterocycles into one molecule may provide increased bioactivities due to the structural synergistic effect. The synthesis of 1,3,4-oxadiazoles bearing selenium requires aromatic acids containing selenium.[6] These acids are difficult to synthesize. In the course of our current research, we developed a new process for the preparation of an aromatic acid containing selenium, namely 2-[(methylselenyl)methyl]benzoic acid, by the S_N2-type cleavage of 2-benzofuran-1(3*H*)-one with methyl selenide anion generated from dimethyl diselenide. We observed good yield and purity.

Only two methods[7,8] are reported for the synthesis of 2-[(methylselenyl)methyl]-benzoic acid. But both the methods involved multistep protocols with expensive starting

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Table 1
Optimization of Reaction Conditions

Trial	Reagent	Solvent	Percentage Yield (%)	Yield obtained (g)	HPLC Purity (%)
1	NaH	DMF[a]	18.96	08.09	–
2	Na metal	THF[b]	28.80	12.30	–
3	$LiAlH_4$	THF[c]	24.12	10.30	–
4	$NaBH_4$	Methanol[d]	29.27	12.50	–
5	$NaBH_4$	Ethanol[e]	34.66	15.49	–
6	$NaBH_4$	THF[f]	50.13	21.41	–
7	$NaBH_4$ NaOH	$H_2O + THF$[g]	55.41	23.70	99.962

[a-g] See Experimental Section, optimization of reaction conditions, 0.18 mole scale.

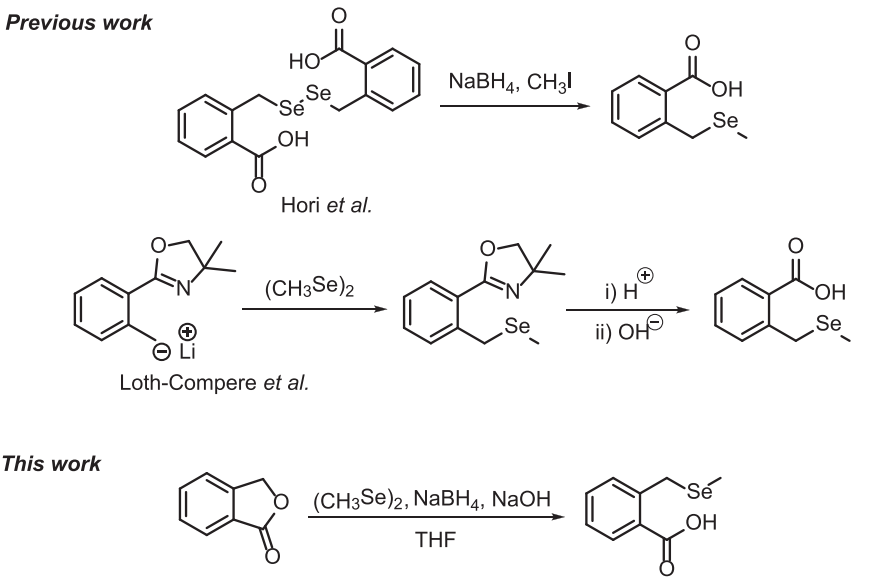
materials. Therefore, we explored a simple, effective and optimized process for its synthesis. Model reactions were conducted using dimethyl diselenide and different bases and solvents under mild conditions. The results of these studies are summarized in *Table 1*.

In the first method, dimethyl diselenide was treated with sodium hydride in dimethylformamide[9] to generate the methyl selenide anion which was then treated with 2-benzofuran-1(3*H*)-one to get methyl selenyl benzoic acid. But the sodium hydride used here requires caution, recovery of dimethyl formamide was difficult and the yield was also low. The reaction was repeated by replacing sodium hydride with sodium metal.[10] Though the yield was improved, the impurity profile remained the same. Moreover, sodium metal is difficult to handle, especially in scaled-up reactions. Sodium metal was then replaced with lithium aluminium hydride. But the process gave even more impurities and the yield was further reduced. The reaction conditions were further modified by employing sodium borohydride[11] in solvents such as methanol, ethanol and THF.[12] The optimum conditions used 1.5 mole-equiv of $NaBH_4$ and 0.5 mole-equiv of NaOH in THF-water medium (*Scheme 1*). A plausible mechanism is shown in *Scheme 2*.

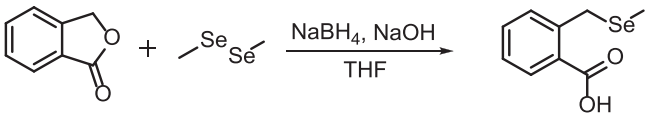
Previous reports on preparation of the title compound suffer from several disadvantages in chemical handling difficulties, high cost, multiple steps or complications in scale-up. The present method circumvents all these disadvantages. In conclusion, we have reported on a convenient synthesis of the title compound under mild conditions. Compared to previous methods, the preparation is simple to perform, gives good yields and produces pure product. Future work may explore the scope of this reaction. We hope that the process will aid in the wider exploration of selenium-based organic frameworks for new pharmacophores.

Experimental Section

Solvents and reagents were obtained from commercial sources and used without purification. Recrystallization was used for purification instead of column chromatography. Melting points were determined by the open capillary method and were uncorrected. IR spectra were obtained in KBr discs on a Shimadzu FT-IR 157 spectrometer. NMR spectra were recorded on a Bruker WH-200 (400 MHz) in DMSO-d_6 as solvent and TMS as an internal standard. Chemical shifts and coupling constants were expressed as ppm (δ) and



Scheme 1. The previous and present methods for the synthesis of the title compound.

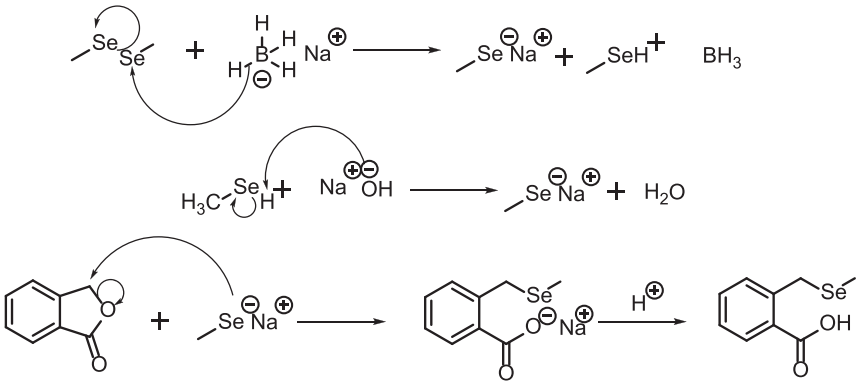


Scheme 2. Optimized synthesis of 2-[(methylselenyl)methyl]benzoic acid.

Hz (J) respectively. Mass spectra were recorded on a Jeolsx 102/Da-600 mass spectrometer/data system using argon/xenon (6 kV, 10mA) as the FAB gas. The accelerating voltage was 10 kV and spectra were recorded at room temperature. The elemental analyses (CHN) were performed using VARIO EL-III (Elemental Analysis system GmBH). The progress of the reactions was monitored by TLC on pre-coated silica gel G plates. All the spectral data of newly synthesized compounds were consistent with proposed structures. The purity of the samples was analysed by Agilent HPLC with UV detector. A complete protocol for the HPLC analysis was submitted for review by the editors and is available from the corresponding author upon request. ***Safety Notes***:[13,14] Throughout experiments, workers must use protective equipment, to include safety goggles, chemical splash eyewear, a half face respirator with organic vapor cartridge, safety shoes, nitrile hand gloves, disposable head caps, apron, laboratory fume hoods containing 50% sodium hydroxide solution, local exhaust ventilation, fire extinguisher, smoke/heat detector, a spill control kit containing sand, sodium bicarbonate, waste pan and broom.

Optimization of Reaction Conditions for 0.18 Mole Each of Furanone and Dimethyl Diselenide (Keyed to Notes a-g in *Table 1*)

a: 75 mL of DMF and 20.56 g (4.6 mole-equiv) of 60% NaH at room temperature. Product was isolated by adding 250 mL of ice cold water, followed by adjusting the pH to 3-4 by acetic acid and extraction with 75 mL of ethyl acetate.



Scheme 3. Plausible mechanism for the formation of 2-[(methylselenyl)methyl]benzoic acid.

b: 150 mL of THF and 8.57 g (2 mole-equiv) of Na metal at room temperature. Reaction mixture was completely distilled under reduced pressure and resulting solid was slowly added to 250 mL water, adjusted the pH to 3-4 by acetic acid and extracted with 75 mL of ethyl acetate.
c: 150 mL of THF and 8.10 g (2 mole-equiv) of $LiAlH_4$ at room temperature. Reaction mixture was completely distilled under reduced pressure and resulting solid was slowly added to 250 mL water, adjusted the pH to 3-4 by acetic acid and extracted with 3×75 mL of ethyl acetate.
d: 150 mL of methanol and 14.10 g (2 mole-equiv) of $NaBH_4$ at room temperature. Product was isolated by adding 250 mL of ice cold water, followed by adjusting the pH to 3-4 by acetic acid and extraction with 3×75 mL of ethyl acetate.
e: 150 mL of ethanol and 14.10 g (2 mole-equiv) of $NaBH_4$ at room temperature. Product was isolated by adding 250 mL of ice cold water, followed by adjusting the pH to 3-4 by acetic acid and extraction with 3×75 mL of ethyl acetate.
f: 125 mL of THF and 14.10 g (2 mole-equiv) of $NaBH_4$ at room temperature. Product was isolated by adding 250 mL of ice cold water, followed by adjusting the pH to 3-4 by acetic acid and extraction with 3×75 mL of ethyl acetate.
g: 125 mL of THF, 6.25 mL of H_2O, 3.72 g (0.5 mole-equiv) NaOH and 10.57 g (1.5 mole-equiv) of $NaBH_4$ at 45-50 °C. Product was isolated by adding 250 mL of ice cold water, followed by adjusting the pH to 3-4 by acetic acid and extraction with 162.5 mL of ethyl acetate at 60-65 °C.

Full Optimized Procedure for the Synthesis of 2-[(methylselenyl)methyl]benzoic Acid

In a 500 mL 3 necked round bottom flask, 125 mL of THF was taken and 35.2 g (0.18 mole) of dimethyl diselenide ((***Caution! See Safety Notes above***). All workers must be thoroughly instructed in working with selenium compounds prior to experiments.) under a nitrogen atmosphere. The reaction mass was chilled to 5-10 °C. Then, 10.67 g (0.29 moles) of sodium borohydride was added in 4 equal lots during one hour and was stirred for 3-4 hours. Color changes were observed from dark yellow to pale yellow along with the release of yellow vapors of methyl selenol (***Caution! See Safety Notes above***). The reaction mass was brought to room temperature, 3.71 g (0.093 mole) of sodium hydroxide dissolved in 6.0 mL of water was added and stirred for 15 minutes. To this reaction mass, 25 g (0.18 mole) of 2-benzofuran-1(3*H*)-one was added in 4 equal lots in one hour and stirred for 12-16 hours with TLC

monitoring (hexane:EtOAc, 3:2 (v/v)) followed by heating up to 40-45 °C for an hour. Then, THF was distilled out to 62 mL residual volume under reduced pressure. The resulting reaction mass was cooled to room temperature and then to 0-5 °C, followed by the addition of 250 mL of water and stirring for 30 minutes. The pH of the reaction mass was adjusted to 3.0-4.0 using acetic acid with the release of methyl selenol vapor (***Caution! See Safety Notes above***). to get the white precipitate of the product. The reaction mass was filtered, washed with water and drained.

In a three-necked round bottom flask, the wet crude material was taken and dissolved in 162.5 mL of ethyl acetate. The resulting solution was heated up to 65-68 °C and treated with 12.5 mL of 1% sodium bicarbonate solution with stirring to remove polar impurities. The organic layer was separated and washed with 125 mL of water. The aqueous layer was extracted with half the volume of ethyl acetate at 65-68 °C. The combined organic layers were decolorized using 1.25 g of 5% DCW charcoal at 65-68 °C and passed through a Hyflo® Super-Cel® bed (prepared by making a slurry of 3 g of the Hyflo® Super-Cel® with 50 mL of ethyl acetate followed by filtration over Whatman filter paper). Ethyl acetate was distilled out to 75 mL residual volume under vacuum distillation. Then, the reaction mass was chilled to 0-5 °C and maintained at this temperature for 2 hours. The solid formed was washed with a little chilled ethyl acetate followed by water. It was then dried *in vacuo* at 50-55 °C for 8 hours. The dried material was packed in a black polythene bag to avoid exposure to sunlight.

2-[(Methylselenyl)methyl]benzoic Acid

White crystalline solid; Yield: 55.41% (23.70 g); Mp.: 162-163 °C (Lit.: 164 °C)[8]; IR (KBr, ν/cm^{-1}): 3600 (O-H), 3068.85 (Ar-H), 2985.91, 2883 (C-H), 1678 (C = O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.87 (s, 3H, CH_3), 4.12 (s, 2H, CH_2), 7.31-7.32 (m, 2H, Ar-H), 7.45-7.48 (m, 1H, Ar-H), 7.85 (d, 1H, J= 8 Hz, Ar-H), 12.92 (s, 1H, -COOH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.8, 132.0, 131.3, 131.2, 129.8, 127.4, 127.1, 26.5, 4.4; MS (ESI-Q-Tof): m/z, calcd.for $C_9H_{10}O_2Se$ $[M-H]^+$: 228.98, Found: 228.80.

Anal. Calcd for $C_9H_{10}O_2Se$: C, 47.18; H, 4.40. Found: C, 47.12; H 4.39.

Acknowledgments

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