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ONE-POT SYNTHESIS OF ARYL SELENONIC ACIDS AND SOME UNEXPECTED BYPRODUCTS

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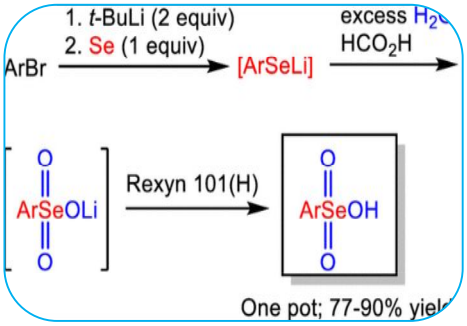
ABSTRACT:

Synthesis of aryl selenonic acids from various aryl bromides by a one-pot method involving metalation, selenation, and oxidation with hydrogen peroxide, followed by ion exchange, afforded pure products in 79–92% yields. The first example of a cyclic selenonic ester was found to be an O-hydroxymethyl derivative readily dehydrated, while two minor byproducts were isolated and shown by X-ray crystallography to be mixed salts of aryl selenonic acids.



KEYWORDS: *One-pot synthesis, selenonic acids*

INTRODUCTION

Benzeneseleninic acid (1a) and its anhydride 2a, as well as various analogues, have been extensively studied and used in a wide range of synthetically useful oxidations. Some of these processes use catalytic amounts of selenium compounds in the presence of inexpensive and environmentally friendly stoichiometric co-oxidants such as hydrogen peroxide. These include conversion of alcohols to aldehydes or ketones, phenols to quinones, dehydrogenation of steroidal ketones, α,β-unsaturated compounds of lactones and lactams, epoxidation and dihydroxylation of alkanes, and Baer-Villiger oxidation. In the latter three cases, the corresponding peroxyseleninic acid was proposed as the active oxidant.

In contrast, although the corresponding selenonic acids were first reported over a century ago, they have been studied less frequently and have found little use as synthetic reagents. This is largely due to difficulties in their preparation and characterization, which led to errors and uncertainties in identifying their structures in earlier work. For example, in 1909 Doughty reported the preparation of 4a by heating selenic acid (H_2SeO_4) in benzene at 115ºC for 95 h. Subsequently, a more efficient variation of this process used selenium trioxide and benzene in liquid sulfur dioxide to obtain the same product. However, in 1964, Petzold and Leinig repeated Doty's earlier work and demonstrated the presence of both Se(IV) and Se(VI) in the product by the Bunsen test. On this basis, they suggested that the product was actually the selenoniumselenonate salt 5a, formed by protonation of 1a by 4a. Many other early reports of selenonic acid were based on the oxidation of diselenides or seleninic acid with oxidants such as nitric acid or potassium permanganate. The products are usually either isolated as their metal salts or obtained by treating the latter with a strong acid such as perchloric acid.

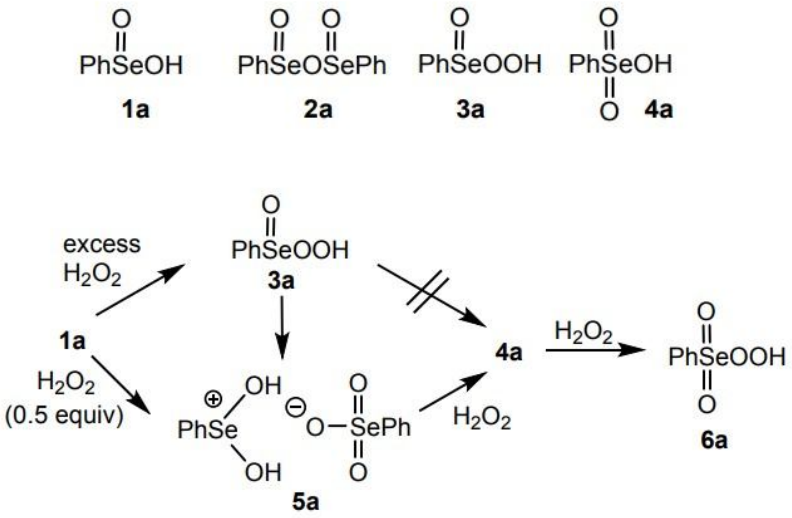
Purification and characterization often fell short of the methods available at the time. In recent examples, Abdo and Knapp prepared sodium and triethylammonium salts of selenonic acid derivatives

of carbohydrates. Perfluoro analogues and p-chlorobenzeneselenonic acid have also been reported. In general, the preparation of selenonic acids is hampered by their strong acidity and water solubility, difficulty in separating the free acid from byproduct metal salts, their high polarity which usually hinders chromatographic purification on common adsorbents such as silica gel, and their hygroscopic nature. Furthermore, the diselenide and seleninic acid precursors of selenonic acid are not always readily available, resulting in the need for alternative processes based on more common starting materials.

More recently, we have reported that, contrary to previous reports, the epoxidation of cyclooctene with benzeneseleninic acid (1a) and hydrogen peroxide mainly proceeds via the stepwise formation of the selenoniumselenonate salt 5a, followed by 4a and finally the proposed peroxyselenonic acid 6. Epoxidation with 6a thus generated proved to be significantly faster than with peroxyseleninic acid 3a . Furthermore, Cyper and Mlochowski isolated peroxyseleninic acid 3a and indicated that it isomerized to selenonic acid 4a when heated in acetonitrile. However, we found that this reaction, which also proceeded in solution at room temperature and was accompanied by oxygen evolution, actually produced 4a and not 5a, which was confirmed by the X-ray structure of the product. It also confirmed the earlier structure proposed by Petzold and Leinig, based on their Bunsen test, of the product obtained by the Dottie method. As 4a alone fails to effect epoxidation, its further conversion to the postulated peroxyselenonic acid 6a with hydrogen peroxide is essential for epoxidation.

Thus, 6a appears to be the most active oxidant species in this redox manifold, but it has proven to be too unstable to isolate. Given the difficulties in preparing selenonic acids and their incomplete characterization in previous work, we now report a new protocol for the prepn., with a newly discovered and unexpected role in the epoxidation of certain alkenes 4a and 6a of a series of different selenonic acids.

Oxidation pathways for the reaction of benzeneseleninic acid (1a) with hydrogen peroxide



RESULT AND DISCUSSION:

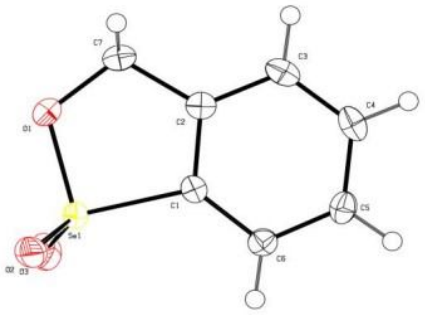
Synthesis of arylselenonic acids 4a-4l was achieved at room temperature from a series of aryl bromides by metalation with t-butyllithium in THF solution at -80ºC, addition of powdered selenium and oxidation of the resulting selenolates with hydrogen peroxide. Presence of formic acid. The lithium selenonates were then extracted with water and passed through a short column of Rexin 101(H) ion exchange resin to produce free selenonic acid. Aqueous solutions of 4 were dried under vacuum to afford the final products in high purity state. Although some selenonic acids have been prepared by further oxidation of selenic acids or diselenides, usually with harsh oxidants, the advantage of the

present method is that it starts from more widely available aryl bromides for products where the corresponding diselenides and selenic acids are not readily available.

During optimization studies of the preparation of 4b, it was found that t-butyllithium was more effective than n-butyllithium in the metalation-selenation sequence, as the latter resulted in significant formation of the corresponding aryl n-butyl selenides. A low temperature also proved necessary to avoid decomposition of the products as well as to avoid the reaction of t-butyllithium with the solvent THF. Although the overall stoichiometry of the process required only three equivalents of hydrogen peroxide to convert lithium selenolates to selenonic acid 4, a total of 4 or 5 equivalents of hydrogen peroxide were added in two portions to achieve complete oxidation. Attempts were made to catalyze the formation of selenonic acid with several acids. Acetic acid had little effect and was difficult to remove from the product, while trifluoroacetic acid caused significant degradation. However, formic acid increased the rate by ca. Threefold, affordable products of high purity and easily extracted from the product. Although the exact reason for the beneficial effects of formic acid is not clear, one possibility is that it protonates the selenic acid intermediate, thereby activating it for further attack by hydrogen peroxide.

The results showed that various aryl selenonic acids could be obtained in good to high (80–95%) yields with products containing electron-donating and -withdrawing substituents (4h, 4i) located at the ortho, meta, or para -position. Naphthalene (4j) and biphenyl (4k) derivatives were also obtained without difficulty. Attempts to prepare 2-(hydroxymethyl) benzeneselenonic acid (4l) by the usual method led to the formation of the cyclic selenonate ester 4m by dehydration of 4l. The Se NMR spectrum of 4m in $CDCl_3$ revealed a signal at 1121.5 ppm, well below the resonance of selenonic acids 4a-4k. Crystallization of 4m by slow evaporation from water produced crystals suitable for X-ray crystallography, which clearly confirmed its structure. When 4m was dissolved in D2O, the NMR spectra were quite different from those in $CDCl_3$, including a Se signal at 1025.1 ppm, which was consistent with the selenonic acid structure 4l and indicated that the dehydration was reversible. Although cyclic seleninate esters containing Se(IV) are well known, to our knowledge, cyclic selenonate esters have not been reported previously.

ORTEP diagram of cyclic selenonate ester 4m. For details, see the Supporting Information

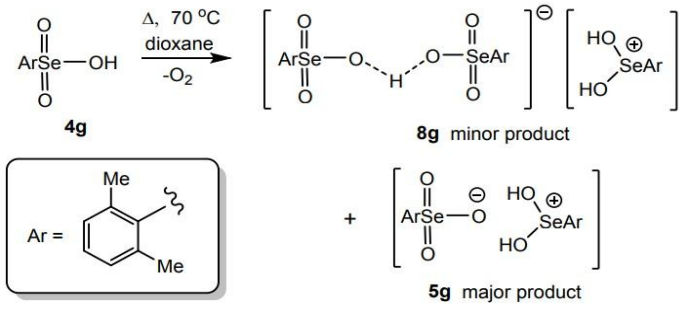


The above selenonic acid proves to be stable at or below room temperature and can be stored in the refrigerator for at least several weeks. However, during the optimization study, several unexpected byproducts were also observed. An attempt to recrystallize a sample of crude 4b from dichloromethane delivered a small amount of the salt 7b instead of 4b. Its Se NMR spectrum revealed signals at 1302.710 and 1029.5 ppm, which are characteristic of selenious and selenonic acid species, respectively, and the X-ray crystal structure confirmed that it is a salt obtained by protonation of selenonic acid (H2SeO3). Acid 4b. The formation of 7b in this event was attributed to the small amount of excess unreacted elemental selenium remaining after the selenation step and then converted to selenious acid by hydrogen peroxide oxidation, followed by protonation by the main product, selenonic acid 4b. Alternatively, it is conceivable that the selenious acid was formed during the process by oxidative C-Se

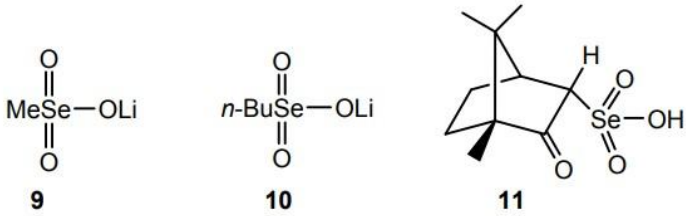
bond cleavage of the arylseleno intermediate. Compounds prepared by typical procedures and listed in the experimental section are free from selenious acid based on 77Se NMR and HRMS spectra of the final products, a result indicating that care must be taken to ensure that the selenation step is permissible. Go to perfection and avoid the use of excess selenium in the preparation of products 4.

When a sample of 2,6-dimethylbenzeneselenonic acid (4g) was heated to 75°C in dioxane, then cooled to room temperature, 6g of the salt crystallized slightly and its structure was determined by X-ray crystallography. Interestingly, the structure contains a dimeric hydrogen bridged selenonate ion and a protonated seleninic acid cation. Although this was similar to the 1:1 salt 5a in Scheme 1 , the 2:1 stoichiometry in 6g was unexpected. However, evaporation of the mother liquor and examination of the residue by NMR spectroscopy in CDCl3 revealed the presence of the corresponding 1:1 salt 5g as the major product. This experiment shows that heating selenonic acid 4 can readily cause oxygen loss to form the corresponding seleninicacid 1 followed by its protonation by 4 to give more stable mixed Se(IV)–Se(VI) salts such as 6g and 3g.

Thermal decomposition of selenonic acid 4g to produce mixed Se(IV)-Se(VI) salts



Attempts to extend the process shown in Scheme 2 to produce free alkyl selenonic acids became more difficult because of their decomposition upon treatment with rexin 101(H), which was necessary to liberate the free acids from their lithium salts. However, crude lithium methane- and n-butaneselenonates can be prepared by modifying the general process. Similarly, hydrogen peroxide oxidation of the corresponding diselenide in the presence of HCl-diethyl ether yielded endo-3-camphorselenonic acid (11) in solution, but it decomposed when isolation was attempted.



CONCLUSION:

The procedure described here provides a one-pot method for the preparation and characterization of various aryl selenonic acids from the corresponding readily available aryl bromides. The cyclic selenonic ester 4m appears to be the first example of its class. During early attempts to prepare selenonic acids 4b and 4g several unexpected salts 7b, 4g, and 5g were formed by protonation of Se(IV) oxyacids by strong Se(VI) acids 4g.

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