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Electrophilic Aromatic Selenylation: New OPRT Inhibitors

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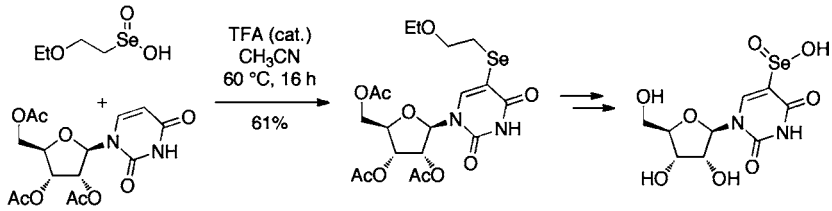
ABSTRACT



2-Ethoxyethaneseleninic acid reacts with electron-rich aromatic substrates to deliver, by way of the selenoxides, the (2-ethoxyethyl)seleno ethers, which can in turn be transformed into a diverse set of aryl-selenylated products. Among these, a family of 5-uridinyl derivatives shows submicromolar inhibition of human and malarial orotate phosphoribosyltransferase.

A wide assortment of selenium-based reagents allows the introduction of Se into organic structures by both nucleophilic and electrophilic pathways, and the resulting organoselenium products can be oxidized, reduced, or otherwise converted to useful targets that may or may not retain Se.[1] Despite the toxic nature of organoselenium derivatives in general, many of these have shown marked biological and enzyme inhibitory activities that may find important applications.[2] Electrophilic introduction of Se is commonly performed by using selenenyl chlorides and their relatives, and is mostly limited to ArSe-X examples. We recently demonstrated that alkaneseleninic acids ($RSeO_2H$) react as electrophiles toward electron-rich aromatic rings such as phenols and indoles.[3,4] We have now modified this reaction to allow the incorporation of the versatile 2-ethoxyethaneselenenyl substituent, and show that tranformations of the latter can, in the case of 5-selenylated uridine, produce products that are inhibitory to malarial and human orotate phosphoribosyltransferase.

2-Ethoxyethaneseleninic acid (**1**, Scheme 1), prepared from bromoethyl ethyl ether, reacts with uridine triacetate **2** under acidic conditions (catalytic trifluoroacetic acid) to give as the major product the 5-selenylated nucleoside **3**.[5] The 5-selenylated pyrimidines **4**−**6** were prepared analogously.

Would this selenylation reaction work in aqueous solution? Water-soluble nucleosides did indeed give the 5-selenylated

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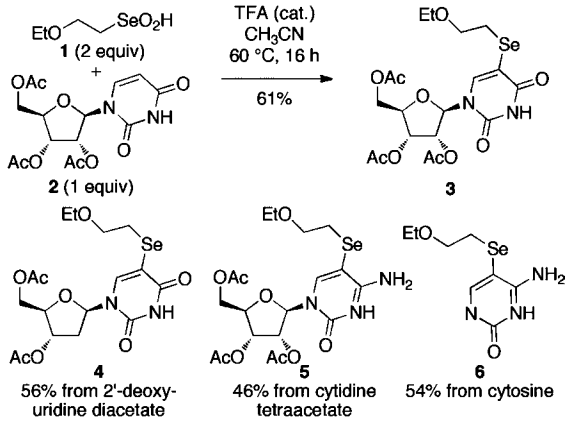
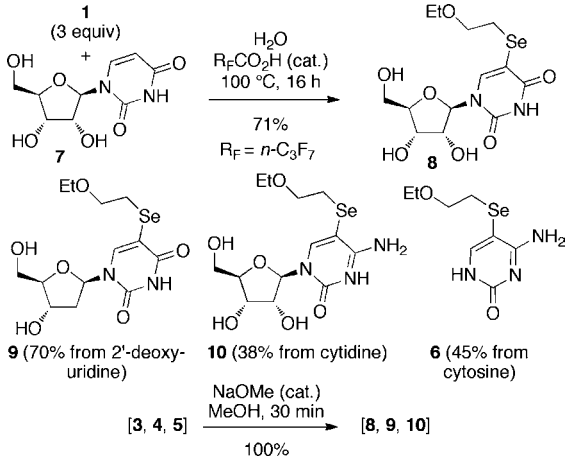
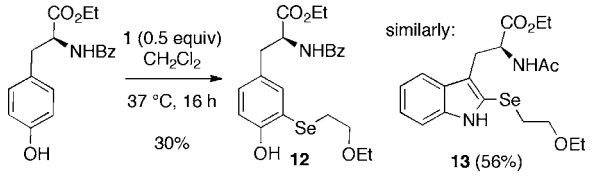
Scheme 1. Electrophilic Selenylation with $EtOCH_2CH_2SeO_2H$



Scheme 2. Selenylation in Aqueous Solution



Scheme 3. Selenylation of Tyrosine and Tryptophan Derivatives

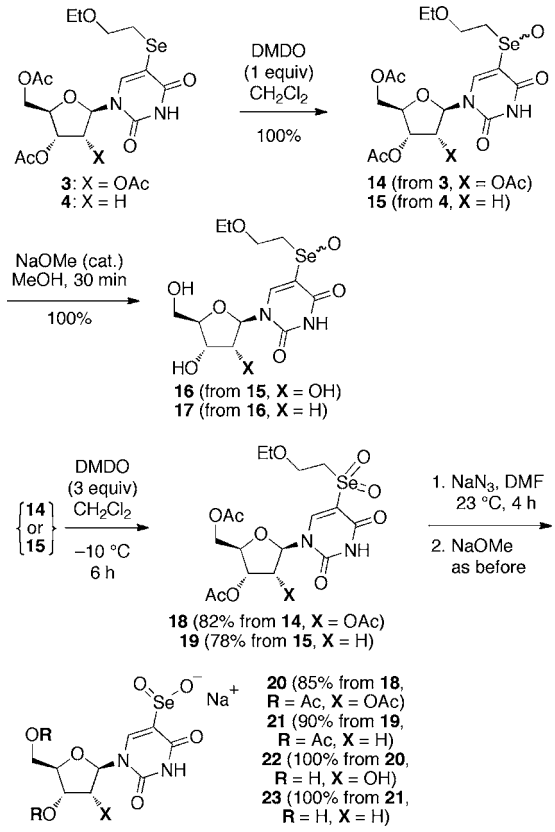


products **8**, **9**, and **10**, and cytosine gave **6**, when the reaction was performed in the presence of heptafluorobutanoic acid (bp 120 °C), Scheme 2. Deacetylation of the nucleoside triacetates from Scheme 1 confirmed their structures.

More reactive aromatic rings, such as those contained in tyrosine and tryptophan, selenylated more easily, even without added acid catalyst (Scheme 3). Less reactive rings, such as those in phenylalanine derivatives, did not selenylate.

By altering the oxidation state and substitution at Se, selenoethers can be transformed to a variety of related organoselenium species. Thus, DMDO oxidation of **3**

Scheme 4. Oxidation of 5-Selenylated Nucleosides



(Scheme 4) led cleanly to the stable selenoxide **14** (two diasteriomers at Se) or, with additional reagent, the selenone **18**. Retro-ene elimination of ArSeOH,[6] normally spontaneous at 23 °C, is suppressed by the β heteroatom in the ethoxyethyl chain.[7] Nucleophilic dealkylation of **18** with sodium azide[8] gave the uridine 5-seleninic acid **20**. Respective deacetylation of **14** and **20** gave the triols **16** and **22**, and, in the analogous 2′-deoxy series, **15** and **21** gave diols **17** and **23**.

Because of the susceptibility of phenols to oxidation, comparable transformations of **12** could only be accomplished following protection of the phenolic −OH (Scheme 5). The selenoxide **25** and selenone **26** were prepared as before, and dealkylation gave the seleninate **27**. Analogous oxidation of **13** was unsuccessful.

Careful purification of product mixtures and identification of minor products allowed some insight into the mechanism of selenylation (Scheme 6). Reaction of **2** gave, in addition to **3**, the diselenides **28**, **29**, and **30**. By subjecting selenoxide **14** to the same conditions, we were able to isolate selenoether **3** and a different mix of **28**, **29**, and **30**. Diselenide **28** results from reductive coupling[9] of ArSeOH, the product of retro-ene elimination from **14**, and **29** and **30** result from reductive

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(7) Tiecco, M.; Testaferri, L.; Tingoli, M.; Marini, F. *J. Org. Chem.* **1993**, *58*, 1349–1354, and references cited therein.

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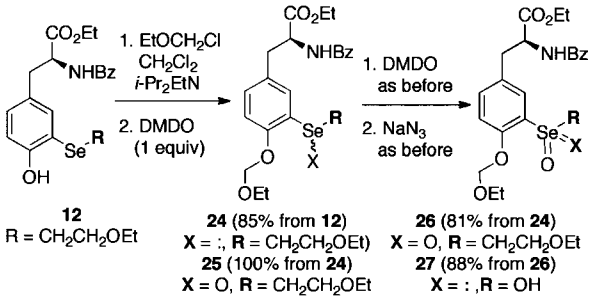
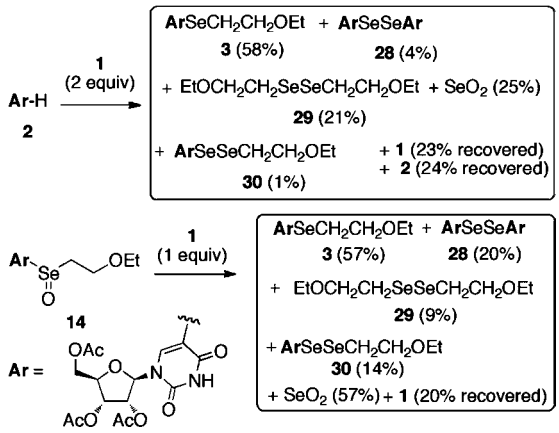
Scheme 5. Oxidation of Selenylated Tyrosine Derivative



Scheme 6. Full Product Analysis of Selenylation Reactions

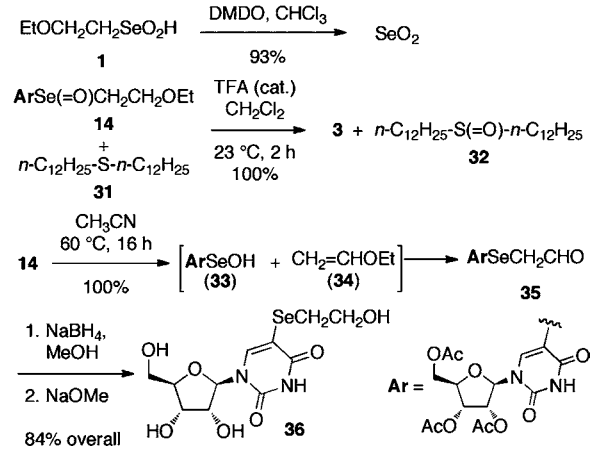


coupling of **1** and diselenide scrambling,[10] respectively. These results strongly implicate selenoxide **14** as an intermediate in the selenylation of **2**. Formation of **14** could arise from initial addition of electrophilic $EtOCH_2CH_2Se(OH)_2^+$, followed by loss of water. Reduction of **14** to **3** evidently occurs in part by co-oxidation of seleninate **1** to 2-ethoxyethaneselenonic acid, which then decomposes to 2-ethoxyethanol and SeO_2. The latter was isolated in both reactions, and identified unambiguously by ^{77}Se NMR.

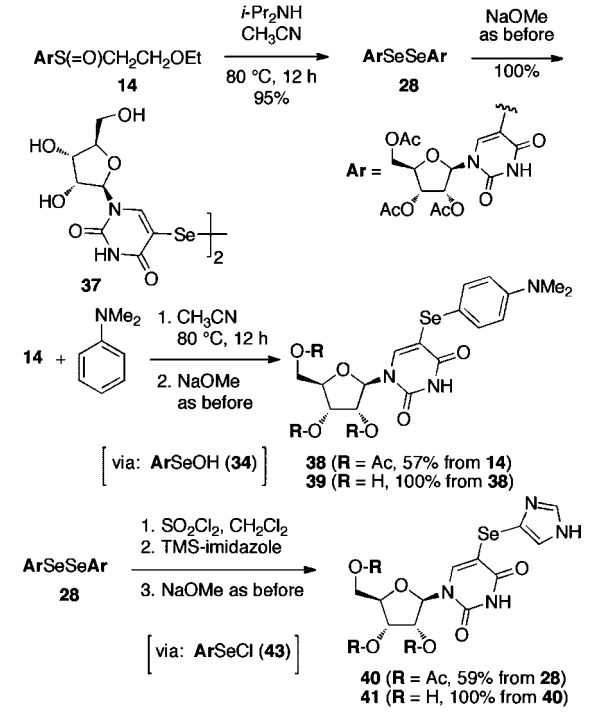
Several control reactions (Scheme 7) provide further support for the intermediacy of **14**. Purposeful oxidation of seleninate **1** with DMDO gave SeO_2, as expected. Redox reaction of **14** with didodecyl disulfide (**31**) led to sulfoxide **32** along with **3** (catalytic TFA was required for this reaction), illustrating the ease with which O may be transferred from the selenoxide. However, adding **31** to the reaction of **1** and **2** did not improve the yield, but rather blocked the selenylation by reducing **1**. Finally, thermolysis of **14** in the absence of acid or a reducing agent gave the aldehyde **35**, presumably by way of the retro-ene reaction, followed by efficient readdition of the selenenic acid **33** to alkene **34**.[11] Reduction of **35** and then deacetylation gave the tetrol **36**.

(9) Reich, H. J.; Wollowitz, S.; Trend, J. E.; Chow, F.; Wendelborn, D. F. *J. Org. Chem.* **1978**, *43*, 1697–1705.
(10) Pleasants, J. C.; Guo, W.; Rabenstein, D. L. *J. Am. Chem. Soc.* **1989**, *111*, 6553–6558.

Scheme 7. Control Reactions for the Selenylation Mechanism



Scheme 8. Transformations of ArSeOH



The thermolytic formation of **33** under mild conditions allowed its interception by *i*-Pr_2NH (Scheme 8), providing not the selenenamide,[12] but rather the diselenide **28**. Alternatively, **33** was trapped by dimethylaniline[13] to give the (mixed) diarylselenide **38**, and **28** was oxidatively cleaved and then coupled to *N*-trimethylsilylimidazole[14] to provide **38**. Respective deacetylation gave 5-selenylated uridines **37**, **39**, and **41**.

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Orotate phosphoribosyltransferase (OPRT) is an essential enzyme for the de novo biosynthesis of pyrimidine nucleotides, promoting the attachment of orotic acid to phosphoribosylpyrophosphate.[15] This is the only pathway for pyrimidine nucleotide production in *Plasmodium falciparum*, the major causative agent of malaria.[16] Furthermore, new ways of interrupting nucleotide synthesis in rapidly proliferating human cancer cells may offer alternative therapy options for this disease. The 5-selenated nucleosides were evaluated as competitive inhibitors of malarial and human OPRTs. Six of the relatively nonpolar uridine derivatives (**8**, **10**, **36**, **37**, **39**, and **41**) reached submicromolar K_i values for human OPRT (*Hs*OPRT), and three of these (**37**, **39**, and **41**) were also submicromolar inhibitors of *P. falciparum* OPRT (*Pf*OPRT) (Table 1). The most active nucleoside, diselenide **37**, is particularly interesting as it may represent a prototype for OPRT inhibitiors that can bind to both subunits of a homodimeric active site. Synthetic access to the selenylated nucleosides also provides new opportunities for investigating the inhibition of additional nucleoside processing enzymes, including pyrimidine nucleoside kinases, thymidine kinase, thymidylate synthetase, thymidine phosphorylase, and orotidine monophosphate decarboxylase.

Table 1. Inhibition of OPRTs by Selenylated Nucleosides

compd	K_i, μM (*Pf*OPRT)	K_i, μM (*Hs*OPRT)
6	2.15 ± 0.75	1.14 ± 0.48
8	1.30 ± 0.33	0.26 ± 0.03
10	1.44 ± 0.44	0.44 ± 0.10
16	6.10 ± 1.60	2.40 ± 0.39
22	10.82 ± 1.98	5.89 ± 1.31
36	1.54 ± 0.47	0.72 ± 0.21
37	0.16 ± 0.02	0.16 ± 0.03
39	0.75 ± 0.21	0.24 ± 0.10
41	0.92 ± 0.28	0.91 ± 0.27

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Supporting Information Available: Details of the enzymatic evaluation, and the preparation and spectroscopic characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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