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Selenazolium salts as catalysts in oxidation reactions

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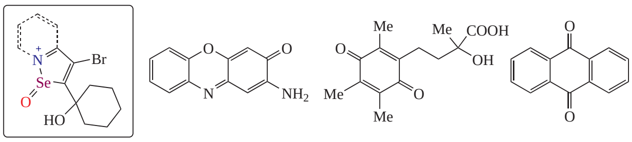
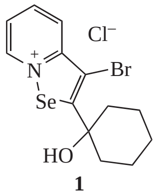
Selenazolium salts promote mild oxidation of 2-aminophenol, hydroquinone, Trolox-C, and anthracene with hydrogen peroxide.



Reduction and oxidation reactions represent very important processes for a life existence. Almost all intra and extra cell functions are based on reduction and oxidation of bioactive molecule or metal in enzyme center. In a long list of various elements (Fe, Cu, Zn, Mg, *etc.*) found in active centers of enzymes, the only one, namely, selenium, is not coordinated, but covalently bonded in enzyme structure. Selenium is incorporated in proteins generally in the form of selenocysteine which is a unique 21st amino acid.[1,2] Selenium-containing compounds exhibit significant ability to modulate various redox enzymes activity including glutathione peroxidases family, glutathione reductase, thioredoxin system, *etc.* by the depletion and formation of cellular glutathione, modulation of NADPH level and stimulation of oxygen consumption. The interaction of these compounds with glutathione suggests potentially important role for them in therapy of oncological diseases.[3–5]

Recently, we have elaborated methods for the preparation of stable fused selenazolium salts, systems with a Se–N$^+$ bond.[6] These compounds exhibit Gpx-like properties by oxidizing sulfur-containing natural amino acids, however, thiol oxidation is only the tip of the iceberg. In continuation of our research in the field of selenium chemistry,[7–9] here we present our results for the use of selenazolium salts as catalysts in oxidation reactions.

The first reaction we studied was oxidation of 2-aminophenol. In organisms, 2-aminophenols can be oxidized by phenoxazinone synthase (PHS, 2-aminophenol : oxygen oxidoreductase).[10] It seems to participate in a mechanism to protect mammalian tissue from oxidative damage[11] and forms the core structure of certain antibiotics.[12] It is also considered to contribute to the activity of phenoxazinone antibiotics, allowing the compounds to intercalate nucleic acids, which is why so many phenoxazinones are effective anticancer agents,[13] for example, Actinomycin D. Phenoxazinone systems occur in natural compounds such as antibiotics, insect pigments, fungal metabolites, and 2-aminophenoxazin-3-one derivatives exhibit antitumor, antimicrobial, and antiviral activity *in vitro* and *in vivo*.[14,15] Synthetically, 2-aminophenol can be successfully oxidized with hydrogen peroxide in the presence of 5 mol% of ebselen as the catalyst in *tert*-butanol.[16] The reaction was terminated by addition of a pinch of Pt/C.



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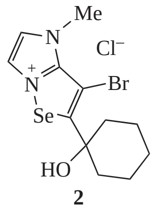

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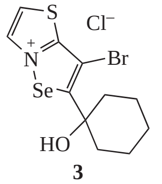

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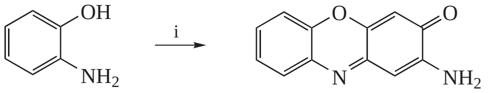
Our concern was put on improving the ability of selenazolopyridinium salts to serve as catalysts in the same reaction. Selenazolopyridinium **1**, selenazoloimidazolinium **2**, and selenazolothiazolinium **3** salts were chosen in purpose to find which of them exhibits better catalytic properties. Attempts were started in *tert*-butanol in the presence of only 2 mol% of **1** (Scheme 1). After 12 h of stirring at room temperature, we noticed full conversion, and Questiomycin A (2-amino-3*H*-phenoxazin-3-one) **5** was isolated in 76% yield. Next, we optimized reaction media using different solvents (*e.g.* methanol, ethanol, 2-propanol, acetonitrile, DMF) and found that acetonitrile was more appropriate solvent as the yield of **5** increased to almost quantitative (98%),[†] and the reaction time was shortened to 4 h. It was also possible to reduce catalyst loading to 1 mol%, but the full conversion time increased to 2 days and the product yield decreased by 12%. This experiment establishes that selenazolopyridinium salts exhibit PHS-like activity. Other selenazolium salts **2** and **3** showed lower catalytic activity under the same reaction conditions (62–78% yields), possibly because of lower stability of these heterocyclic systems compared with **1**.

1,4-Hydroquinone **6** useful as cosmetic skin lightener inrgedient was the second investigated substrate. It can be readily oxidized with H_2O_2 in the presence of silver oxide or copper complexes with the formation of *p*-benzoquinone **7**.[17,18] Herein we found that selenazolium salts can also be used as catalysts for this purpose, providing quinone **7** quantitatively in 30 min. Therefore, we studied



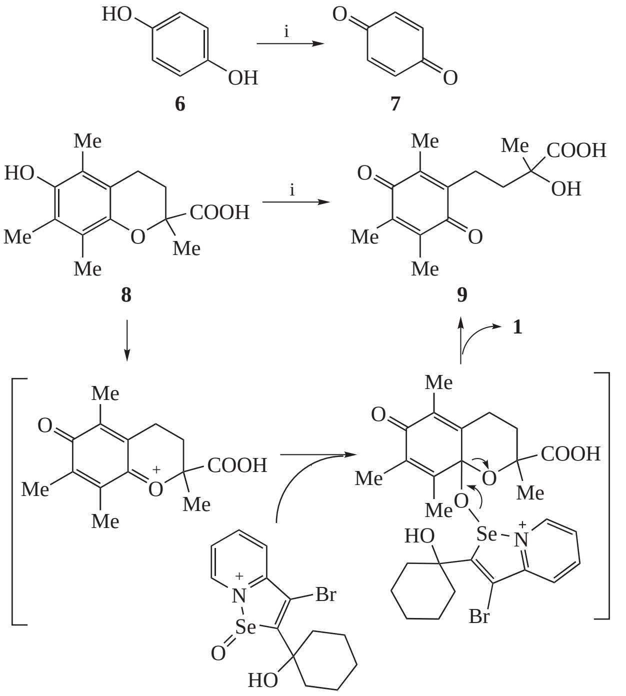
4

5
Questiomycin A

Scheme 1 *Reagents and conditions:* i, **1**, **2** or **3** (2 mol%), H_2O_2, MeCN, room temperature.

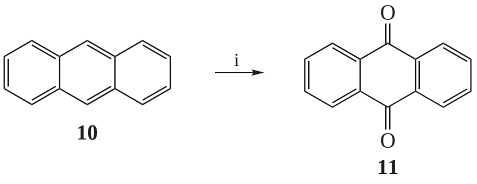
[†] *Oxidation of 2-aminophenol.* Hydrogen peroxide (25% aq., 0.1 ml) was added to a solution of 2-aminophenol **2** (0.109 g, 1 mmol) and catalyst **1** (8 mg, 2 mol%) in MeCN (5 ml). After 4 h of stirring, ascorbic acid (0.1 g) was added and the solvent was evaporated. The crude product was purified by flash chromatography to give 2-amino-3*H*-phenoxazin-3-one **5**.[15] Yield 104 mg (98%). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 6.32 (s, 1H), 6.35 (s, 1H), 6.83 (br. s, 2H), 7.35–7.39 (m, 1H), 7.43–7.52 (m, 2H), 7.67–7.71 (m, 1H). MS (ESI), *m*/*z*: 213 [M + 1]. No product formation was detected after 4 h of stirring in the absence of **1**.

whether selenazolium salts can catalyze vitamin E (α-tocopherol) oxidation (*cf.* ref. 19). Trolox-C **8** was chosen as a water-soluble analogue of vitamin E. In fact, it was almost completely oxidized by hydgrogen peroxide into quinoidal form **9** in methanol at room temperature in the presence of 5 mol% of **1** in 1 h of stirring.[‡] Notably, overnight stirring of Trolox-C with **1** in methanol leaved it unchanged. In addition, overnight oxidation of Trolox-C with H_2O_2 in the absence of selenazolium **1** under the same reaction conditions afforded the **8**:**9** mixture in a ratio of 55:45. The plausible mechanism is presented in Scheme 2.



Scheme 2 *Reagents and conditions:* i, **1** (5 mol%), H_2O_2, MeOH, room temperature.

Anthracene **10** is readily oxidized with hydrogen peroxide to anthracene-9,10-dione **11** in the presence of metal salts and complexes[20–22] at elevated temperature (Scheme 3). When ebselen is used as a catalyst, the yield of **11** is low (23%), while dimeric 9,9′-bianthracene-10,10′(9*H*,9′*H*)-dione, the major oxidation product (51%), is formed by free radical mechanism.[23] However, the use of **1** provided formation of **11** in 78% yield on carrying out the reaction in methanol at 40 °C in only 4 h.[§]



Scheme 3 *Reagents and conditions:* i, **1** (5 mol%), H_2O_2, MeOH, 40 °C.

In summary, we have found that fused selenazolnium salts can serve as catalysts for the preparation of Questiomycin A. These compounds promote hydroquinone, Trolox-C and even anthracene oxidation with hydrogen peroxide in almost quantitative yields under close to physiological conditions. In most cases, these catalysts provide better yields compared with well-known ebselen. It opens a possibility to continue our studies moving focus of investigations from flask to *in vitro* experiments with malignant and normal cells.

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[‡] *Oxidation of Trolox-C.* Hydrogen peroxide (25% aq., 0.4 ml) was added to a solution of compound **8** (0.25 g, 1 mmol) and catalyst **1** (20 mg, 5 mol%) in methanol (40 ml). After 1 h of stirring, ascorbic acid (0.2 g) was added and the solvent was evaporated. The crude product was purified by flash chromatography to afford 2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dien-1-yl)butanoic acid **9**. Yield 240 mg (91%). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.28 (s, 3H), 1.52 (ddd, 1H, *J* 4.3, 12.2, 25.7 Hz), 1.68 (ddd, *J* 5.2, 18.2, 25.7 Hz), 1.93 (s, 6H), 1.94 (s, 3H), 2.26–2.34 (m, 1H), 2.50–2.29 (m, 2H). MS (ESI), *m*/*z*: 267 [M + 1]. Oxidation without a catalyst resulted in a **8**:**9** (55:45) mixture after overnight stirring.

[§] *Oxidation of anthracene.* Hydrogen peroxide (25% aq., 0.3 ml) was added to a solution of anthracene **10** (0.178 g, 1 mmol) and catalyst **1** (20 mg, 5 mol%) in methanol (50 ml). After 4 h of stirring at 40 °C, ascorbic acid (0.2 g) was added and the solvent was evaporated. The crude product was purified by flash chromatography to give anthracene-9,10-dione **11**. Yield 160 mg (78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.76–7.90 (m, 4H, Ar), 8.30–8.41 (m, 4H, Ar). GC-MS, *m*/*z*: 208.1 $[M]^+$. No product formation was detected after 4 h of stirring in the absence of **1**.