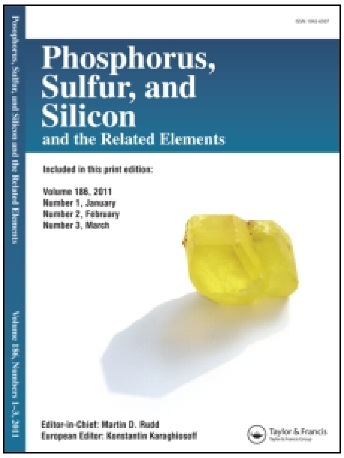

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Developments in the Chemistry of Selenaheterocyclic Compounds of Practical Importance

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Developments in the Chemistry of Selenaheterocyclic Compounds of Practical Importance

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The progress in chemistry of the compounds having selenaheterocyclic ring system is presented. The review is concentrated on the benzisoselenazol-3(2H)-ones, their aza-analogues, bezo[b]selenophenes, 1,3,2-benzothiaselenazoles, 1,3-benzothiaselenoles, 1,3,2-benzodiselenazoles and 1,2,4-benzoselenadiazinones. The methods for their synthesis are reported. Some of them, particularly the benzisoselenazol-3(2H)-ones, are indicated as biological response modifiers and effective catalysts for hydroperoxide oxidation of different groups of organic compounds.

Keywords Antimicrobials; catalysis; oxidation; selenium; virucides

INTRODUCTION

The interest in the chemistry and use of different organoselenium compounds, among them selenaheterocycles, expanded rapidly during last three decades and a lot of works concerned in this field have been published. There are many reports and some reviews dealing with selenaheteroaromatic compounds and their nonaromatic analogues of practical importance as prospective pharmaceuticals,[1–6] reagents and catalysts,[6–8] and materials for electronics.[9–12] Several of these works have been recently done in our laboratory, and we present them briefly in this review.

Our research interest has been focused on 2-phenylbenzisoselenazol-3(2*H*)-one **1** (R = Ph), named ebselen, because this compound, as well as other cyclic selenenamides, interact with the bioactive oxygen species in the manner similar to that of enzyme glutathione peroxidase. The

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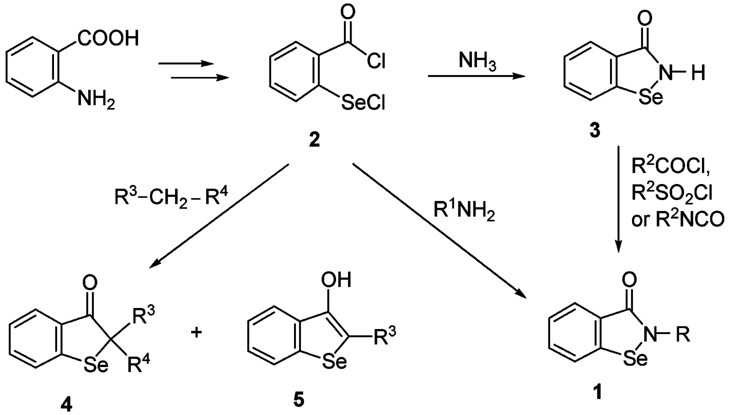
synthetic effort was directed to the modification of the leading ebselen molecule by introduction of the different substituents on the nitrogen atom or to the condensed benzene ring, by replacement this ring by the pyridine moiety as well as by variation of the heterocyclic ring.

N-Substituted benzisoselenazol-3(2H)-ones **1** were obtained on two ways (Scheme 1). The amines, amino acids, aminoalkanols and other compounds having primary amino group treated with 2-(chloroseleno)benzoyl chloride 2 underwent tandem selenenylation-acylation resulted in the heterocyclic ring formation.[13–15] The alternative route was based on the reaction of unsubstituted benzisoselenazol-3(2H)-ones **3** with acid chlorides, sulfonyl chlorides or isocyanates.[16,17] Activated methylene group in 1,3-dicarbonyl and related compounds also underwent selenenylation-acylation. Depending on the substrate used, the benzo[b]selenophenones **4** or 3-hydroxybenzo[b]selenophenes **5** were produced.[18,19]



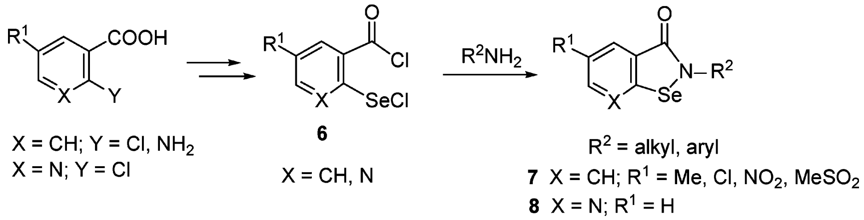
R = alkyl, aryl, heteroaryl, hydroxyalkyl, acyl, carboxyalkyl, sulfonyl, carbamoyl

R^3,R^4 = CN, COMe, COPh, COOEt, $P(O)(OEt)_2$; R^3–R^4 = $COCH_2(CH_2)_nCO$, n = 1,2

SCHEME 1

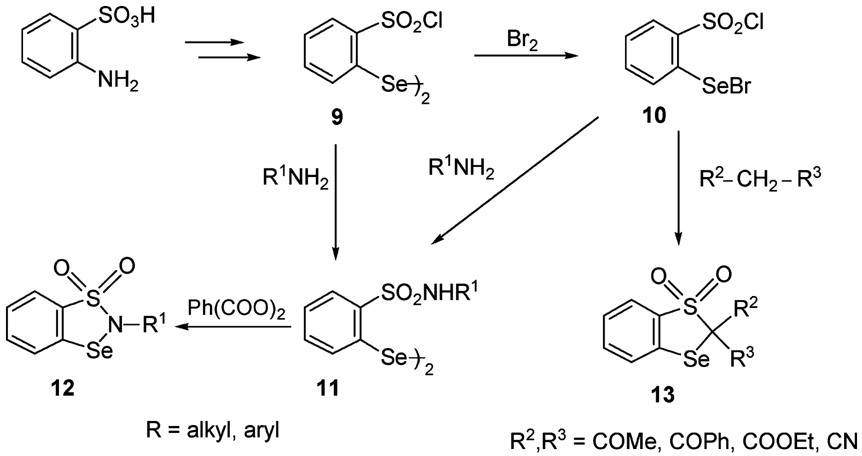
Starting from 5-substituted 2-aminobenzoic acid or from 2-chloro-3-carboxypyridine the dichlorides **6** were obtained. Treated with primary amines they gave the 5-substituted benzisoselenazol-3(2H)-ones **7** [20] or 7-azabenzisoselenazol-3(2H)-ones **8** (Scheme 2).[21,22]

Other analogues of ebselen, having the sulfonyl group instead of carbonyl group are the 1,3,2-benzothiaselenazole 1,1-dioxides **12**. Their synthesis started from sulfanilic acid converted to the diselenide **9** which treated with bromine gave the 2-(bromoseleno)benzenesulfonyl chloride **10**. The reaction of **9** or **10** with primary amines followed by oxidation of the resulted diselenides **11** with the benzoyl



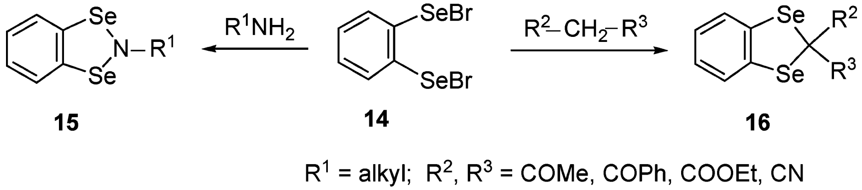
SCHEME 2

peroxide lead to the final products **12**.[23,24] Another new group of compounds containing selenium and sulfur in the heterocyclic ring are the 1,3-benzothiaselenole 1,1-dioxides 13. They were obtained by selenenylation-sulfonylation of the active methylene compounds with bromochloride **10** (Scheme 3).[25]



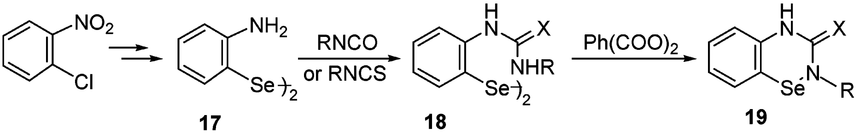
SCHEME 3

Selenaheterocycles having two selenium atoms in the ring are the 1,3,2-benzisoselenazoles **15** and 1,3-benzo-(2*H*)-diselenoles **16**. They were prepared from 1,2-di(bromoseleno)benzene 15 and primary amines or active methylene compounds (Scheme 4).[25,26]



SCHEME 4

The compounds **19** having previously unknown six-membered 1,2,4-benzoselenadiazine ring system were synthesized from 2-chloronitrobenzene. It was converted to the bis (2-aminophenyl) diselenide **17** and then to the urea or thiourea derivatives **18** which were oxidatively cyclized to the final products by treatment with benzoyl peroxide (Scheme 5).[26]



17 **18** **19**

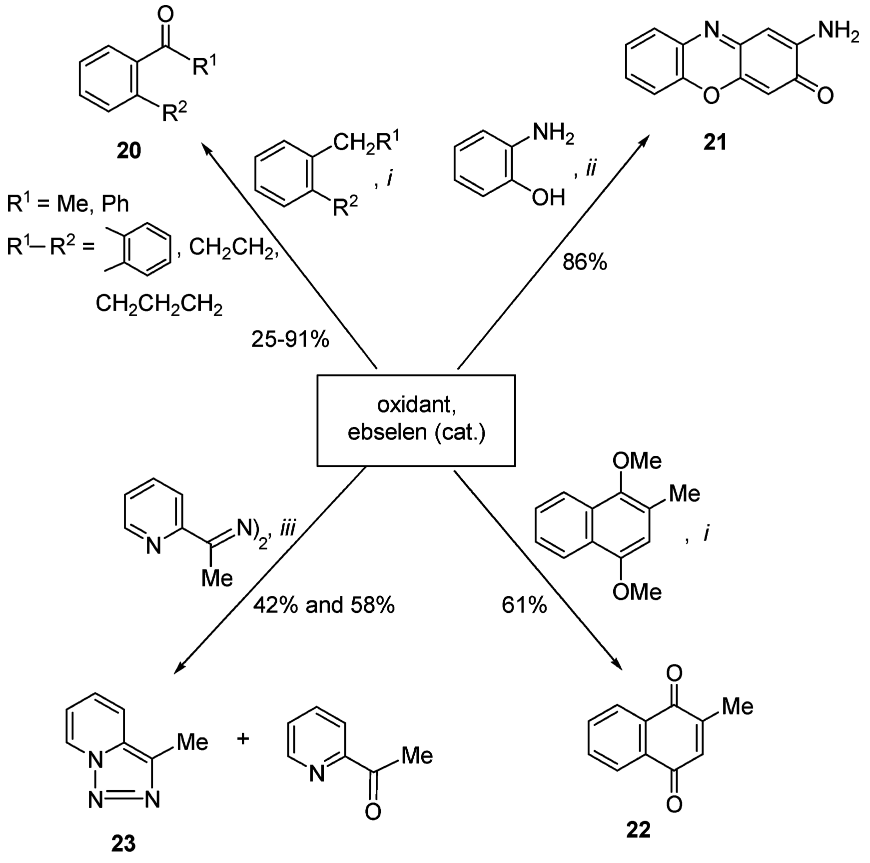
X = O, R = alkyl; X = S, R = Ph

SCHEME 5

The selenaheterocyclic compounds obtained in our laboratory were tested biologically *in vitro* mainly as virucides and antimicrobials. The 7-azabenzisoselenazol-3(2H)-ones **8** and their methiodides were found in the antiviral assay to be strong inhibitors of cytopathic activity of HSV-1 and EMCV viruses (MIC = 0.4–6.0 μg/ml). Ebselen and the *p*-chloroebselen exhibited strong inhibitory activity against growth of fungi *Saccaromyces cerevisiae and Candida albicans* strains.Among the compounds tested in vitro against bacteria, yeasts and filamentous fungi the broadest spectrum of activity was observed for the 2-methyl-7-azabenzisoselenazol-3(2H)-one (**8**, R = Me) having minimum inhibitory dose values in the range 2.0–32.0 μg/ml. The compounds having no selenanamide Se-N moiety in the ring and these where selenium was replaced by sulfur were inactive. It supports the hypothesis that the activity is due to the reactivity of Se-N bond with the essential thiol groups of biomolecules present in the living cells. It was shown that benzisoselenazol-3(2H)-ones easily reacted with tiols. The heterocyclic ring was cleaved and selenosulfides were formed as the stable compounds or underwent spontaneous disproportionation to diselenides and disulfides.[27,28]

Extending our study on the chemical properties of selenaheterocyclic compounds we found that ebselen and its analogues treated with a large excess of 30% aqueous hydrogen peroxide formed unstable hydroperoxyselenuranes. These hydroperoxides were the active intermediates involved in hydrogen peroxide or *t*-butyl hydroperoxide (TBHP) oxidation of organic compounds catalyzed by benzisoselenazol-3(2H)-ones.[29] We provided the evidence that ebselen is one of the most versatile oxygen-transfer catalyst among organoselenium compounds in several reactions where stoichiometric oxidants was hydrogen peroxide or TBHP.

There were: selective oxidation of sulfides to sulfoxides,[30]oxidation of the oximes, in the presence of primary or secondary alcohols to esters,[31] oxidative conversion of *N*, *N*-dimethylhydrazones or benzylamines into nitriles,[30,32] regeneration of the parent ketones from azines,[33] dehydrogenation of tetraisoquinoline to isoquinoline,[32] epoxidation of cyclooctene,[34] and oxidation of aromatic aldehydes to arenecarboxylic acids with avoiding of the Baeyer-Villiger rearrangement.[29] In all of these reactions, the catalyst was used in 5% molar amount. These reactions have a practical value since procedures are simple and the products can be isolated in high to excellent yields. The reaction conditions and the results suggest the ionic mechanisms.



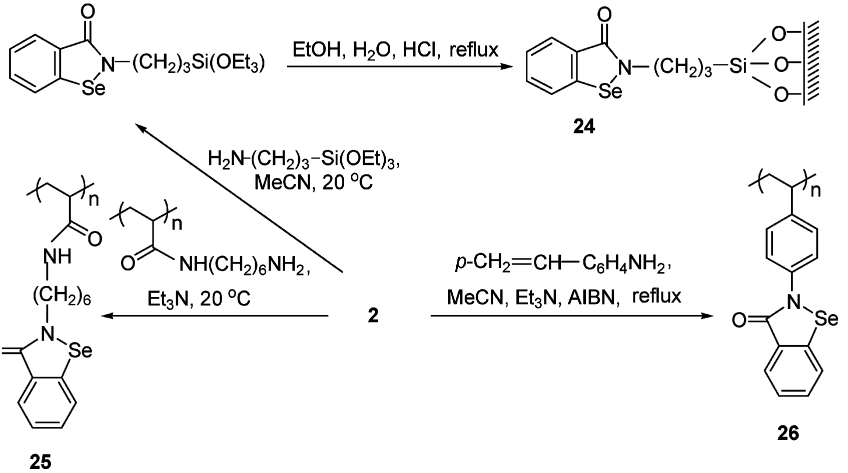
i, TBHP, *t*-BuOH, reflux; *ii*, H_2O_2, *t*-BuOH, 20°C; *iii*, H_2O_2, MeOH, reflux

SCHEME 6

Other reactions, presented in Scheme 6, show that free-radical mechanisms can also take place, and that oxidation proceeds via cation-radicals. Catalyzed by ebselen TBHP oxidation of alkylarenes to alkyl aryl ketones **20**,[33] oxidative coupling of 2-aminophenol to phenoxazinone **21**,[35] oxidative demethylation of 2-methyl-1,4-dimethoxynaphthalene to quinone **22**,[36] and formation of condensed triazole **23** from the azine derived from 2-acetylpyridine,[33] gave results similar to these when one-electron oxidants such as, Ce(IV), Ag(II) or Mn(III) were the reagents.

Previously, we reported that some other 2-substituted benzisoselenazo-3(2*H*)-ones **1** and their open-chain analogues the 2-(carbamoyl)phenyl diselenides also exhibited appreciable catalytic activity.[7,8] In this work, the 1,3,2-benzothiaselenazole 1,1-dioxides **12** were found as the effective catalysts for oxidation of cycloalkanones to cycloalkanecarboxylic acids and 2-methyl-1,4-dimethoxynaphthalene to 2-methyl-1,4-naphthoquinone **22**.

Since heterogenization of homogenous catalysts by their covalent binding to solid support has received recently considerable attention,[37--39] we undertook the effort to immobilize the benzisoselenazol-3(2H)-ones on the silica and polymer. The silica-supported catalyst **24** named Halicat, was simply obtained from 2-(chloroseleno)benzoyl chloride **2** (Scheme 7), and successfully used for hydroperoxide oxidation of sulfides, aromatic aldehydes and alkylarenes. Its activity was similar to activity of ebselen but the catalyst could be easily separated from the reaction mixture by filtration



SCHEME 7

and reused several times.[40,41] Other heterogenous catalysts were the benzisoselenazolon-3(2H)-ones **25** and **26** covalently immobilized on the polymer support.[4,42] The studies on their catalytical properties are in progress.

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