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Hydroperoxide Oxidation of Benzylamines Catalyzed by Selenium Compounds*

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Selenium(IV) oxide, poly(bis-1,2-phenylene) diselenide, bis[2-(N-benzisoselenazol-3(2H)-onyl]diselenide and particularly 2-phenyl-1,2-benzisoselenazol-3(2H)-one (ebselen), were employed as the catalysts for hydrogen peroxide and *t*-butyl hydroperoxide oxidation of benzylamines. A reaction of primary amines proceeded *via* hydroxylamine and oxime, and the nitriles accompanied by imines, carboxylic acids and aldehydes were the final products. The secondary amines produced mainly the nitrones, while tetrahydroisoquinoline was dehydrogenated to isoquinoline.

Key words: amines, dehydrogenation, ebselen, hydroperoxides, oxidation

Oxidation of amines is an useful way for synthesis of a variety nitrogen-containing organic compounds. The reaction leads to different products depending on the nature of the oxidizing agents and a type of amine [1]. Among the oxidants the selenium compounds were successfully used [2,3]. The oxidation of primary and secondary amines with benzeneseleninic anhydride [4–6] or alternatively with benzeneseleninic chloride [7], or with diphenylselenium bis(trifluoroacetate) [8] affords imines. The imines can be hydrolyzed to ketones, oxidized further to nitriles or converted into α-cyanoamines. Oxidation of indolines with seleninic acid or with seleninic anhydride affords the corresponding indoles [9]. More recently the secondary amines were oxidized to nitrones with hydrogen peroxide in the presence of selenium(IV) oxide [10,11].

Among the oxidants employed in modern organic synthesis hydrogen peroxide and *t*-butyl hydroperoxide (TBHP) have the prominent position. Both of them are commercially available and cheap non-polluting reagents of low molecular weight containing a high amount of an active oxygen [12–15]. Since they are only moderately active toward most organic substrates many catalysts, among them selenium compounds are used. Although catalyzed hydroperoxide oxidation of various groups of organic compounds has been extensively studied the selenium promoted hydrogen peroxide oxidation of amines is limited only to a few examples mentioned above [10,11] and to our knowledge the oxidation with TBHP in the presence of selenium compounds has not been previously investigated.

* Dedicated to Prof. M. Szafran on the occasion of his 70th birthday.

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Our particular interest has been focused on 2-phenylbenzisoselenazol-3(2H)-one (**8**) named ebselen because this compound, as well as other cyclic selenenamides and related diselenides, are known as glutathione mimics reacting with bioactive oxygen species [16]. In our previous works we presented these compounds as efficient catalysts for hydrogen peroxide oxidation of N,N-dimethylhydrazones to nitriles, azines into parent carbonyl compounds and sulfides to sulfoxides [17,18]. Most recently ebselen was found as an effective catalyst for TBHP oxidation of aromatic aldehydes to arenecarboxylic acids [19], epoxidation of cyclooctene [20] and conversion of 1,4-dimethoxyarenes into *p*-quinones [21]. Oxidation of azomethine group in azines, aldoximes, and methyl or methylene group in alkylarenes by this reagent afforded, depending on the substrate used and the reaction conditions, aldehydes, ketones, carboxylic acids or their derivatives [22].

RESULTS AND DISCUSSION

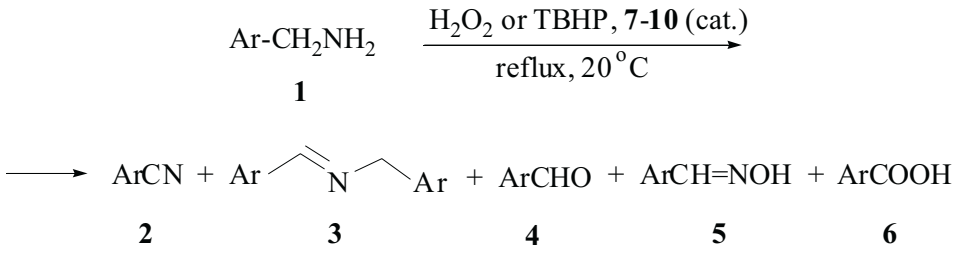
In the work presented here ebselen and three other selenium compounds were used as the catalysts for hydroperoxide oxidation of primary and secondary benzylamines. Four primary amines: unsubstituted benzylamine (**1a**), benzylamines substituted in the aromatic ring (**1b**, **1c**) and 3-aminomethylpyridine (**1d**), and three N-substituted benzyl amines: N-methylbenzylamine (**1e**), dibenzylamine (**1f**) and 1,2,3,4-tetrahydroisoquinoline (**1g**) were taken as the model substrates.

The catalysts were selenium(IV) oxide (**7**), ebselen (**8**) and two diselenides **9** and **10**. Poly(bis-1,2-phenyl) diselenide (**9**) has been recently found as an efficient catalyst for preparative hydrogen peroxide oxidation of different aromatic aldazines, aldoximes and tosylhydrazones to arenecarboxylic acids [23]. The previously unknown bis[2-(N-benzisoselenazol-3(2H)-one)] diselenide **10** was designed as the new catalyst having both diselenide and benzisoselenazol-3(2H)-one moiety in the same molecule. It was obtained by the tandem selenylation-acylation of the recently reported 2,2′-diselenobisaniline [24] with 2-(chloro-seleno)benzoyl chloride synthesized from anthranilic acid in the way referred in [25].

The stoichiometric oxidants were 30% aqueous hydrogen peroxide and 80% *t*-butyl hydroperoxide. It is known that both these peroxides are able to generate the active intermediates from selenium compounds. There is an evidence that the electrophilic center localized on the selenium atom and or the nucleophilic center localized on the oxygen atom of the selenahydroperoxide group are involved in the reaction mechanism. The intermediate derived from selenium(IV) oxide is peroxyselenic(IV) acid **7a** or its ester [26], while diselenides produce areneperoxyseleninic acids (like **9a**) or their derivatives [27]. Hydroperoxyselenurane (**8a)** was postulated to be intermediate generated from ebselen [19] thus it seems to be possible that both hydroperoxyselenurane and peroxyseleninic acid moieties are present in the active species formed by the compound **10.**

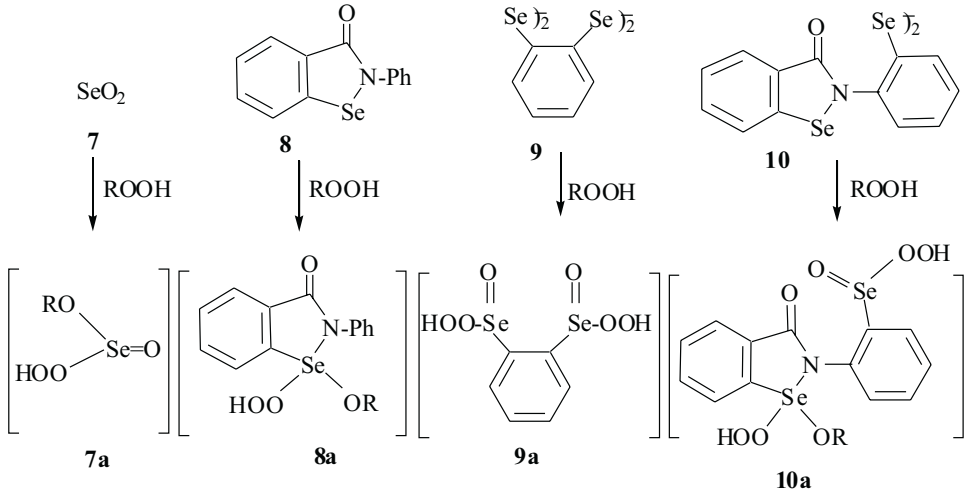
In all experiments the catalyst **7** and **8** was used in 5 % mol amount (related to the substrate) or these having four selenium atoms in the molecule (**9**,**10**) were taken in 1.2 % mol amount. The reaction was carried out in *t*-butanol under reflux during 20 h, while conversion of the substrate was completed. After the reaction finished, the mixture was analyzed using gas chromatography and products were identified by GC/MS or isolated preparatively.

Scheme 1



Ar = C_6H_5 (**1a**); 4-ClC_6H_4 (**1b**); 2-$CH_3OC_6H_4$ (**1c**); 3-Py (**1d**)

Scheme 2



R = H, *t*-Bu

The results of the oxidation of primary amines **1a–d** are presented in Table 1. Benzylamine (**1a**) oxidized with two equivalents of hydrogen peroxide produced a mixture of compounds **2–5,** where imine **3** was a major product. When six equivalents of the oxidant were used benzonitrile (**2**) and benzaldoxime (**5**) were mainly produced. The ebselen (**8**) was less effective catalyst and the conversion of the substrate was very low for two equivalents of hydrogen peroxide (entry 3) , although when six equivalents of the oxidant were used the conversion of the substrate was completed and benzonitrile (**2a**) was the major product (entry 4). Since selectivity of the oxidation of amine **1a** with H_2O_2-SeO_2, TBHP-SeO_2 and H_2O_2-ebselen was low in further experiments TBHP in the presence of ebselen (**8**), **9** and **10** was used as the oxidant for the amines **1a–d** (entries 6–17). Although the results varied depending on the substrate and catalyst they made the evidence that most effective and selective catalyst was ebselen (**8**) and corresponding nitriles **2a–d** were obtained in satisfactory to high preparative yields 66–82%.

Table 1. Oxidation of primary benzylamines **1a–d**.

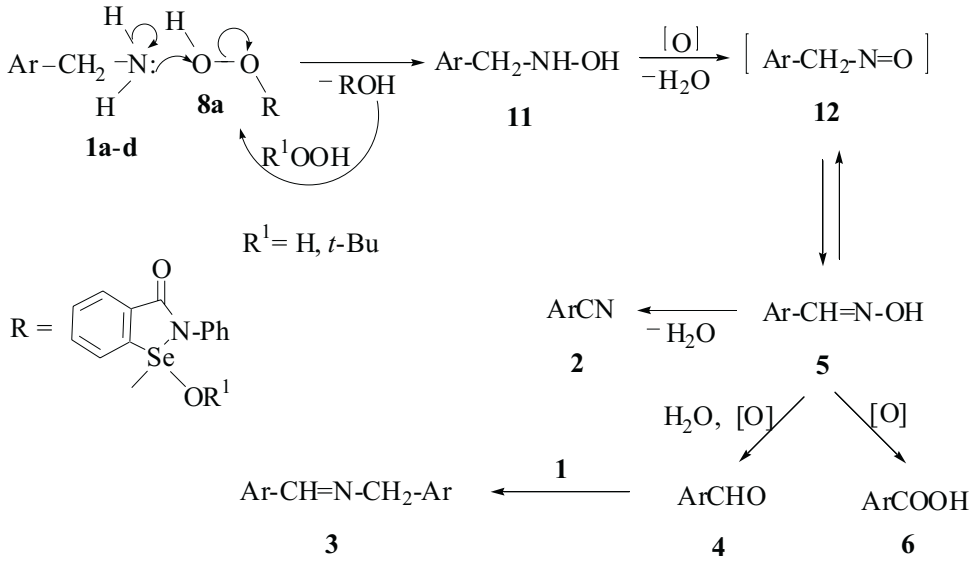
Entry	Substrate	Oxidant	Catalyst	Products, yield[a] %				
				2	**3**	4	**5**	**6**
1	**1a**	H_2O_2[b]	7	8	65	8	7	–
2		H_2O_2	7	36	20	–	38	–
3		H_2O_2[b]	8	–	4[c]	–	–	–
4		H_2O_2	8	60	14	5	6	–
5		TBHP	7	–	65	13	–	–
6		TBHP	8	75(71)	–	–	–	8
7		TBHP	9	6	23	47	–	–
8		TBHP	10	68	–	–	–	10[d]
9	**1b**	TBHP	8	90(82)	–	–	–	7
10		TBHP	9	50	–	–	–	25
11		TBHP	10	74	–	–	–	11
12	**1c**	TBHP	8	79(72)	–	–	–	–
13		TBHP	9	52	–	–	–	30
14		TBHP	10	72	–	–	–	3
15	**1d**	TBHP	8	62(66)	–	–	–	25
16		TBHP	9	57	16	–	–	25
17		TBHP	10	43	22	–	–	16

[a]Yields determined by GC. Data in parentheses are referred to isolated yields. [b]Two equivalents of the oxidant were used. [c]The substrate was recovered in 95% yield. [d]Benzamide was also produced in 10% yield.

The possible mechanism of the oxidation of primary amines with hydroperoxides in the presence of ebselen (**8**) involves formation of hydroperoxyselenurane **8a** as an active intermediate. The first step of the reaction lead to the oxime (**5**) *via* highly reactive hydroxylamine **11** and nitroso compound **12** analogously as it has been postulated when benzylamines were oxidized with hydrogen peroxide in the presence

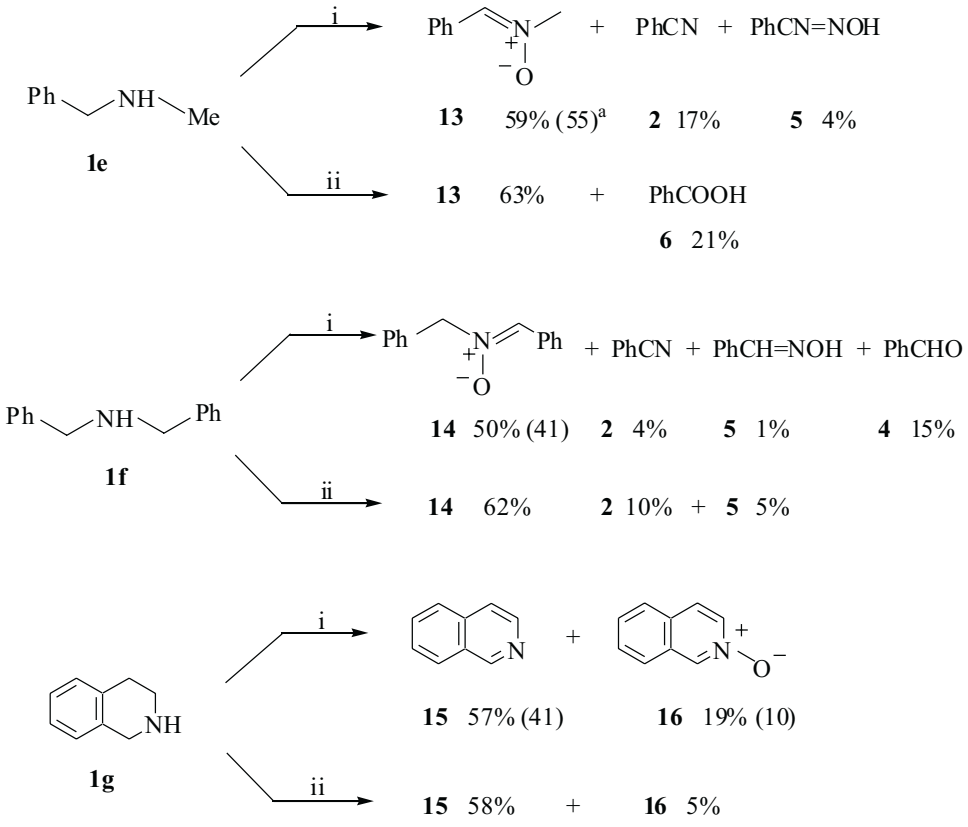
of sodium wolframate [28], peroxotungstophosphate [29] or methyltrioxorenium [30]. According to known reactions the oximes (**5**) can be subsequently dehydrated to the nitriles (**2**), converted to the parent aldehydes (**4**) or oxidized to arenecarboxylic acids (**6**). In some cases formed aldehyde **4** reacting with starting substrate **1** gave aldimine **3**.

Scheme 3



The results of the oxidation of N-substituted benzylamines with hydrogen peroxide or TBHP in the presence of **8** are presented in Scheme 4. N-Methylbenzylamine (**1e**) and dibenzylamine (**1f**) produced the nitrones (**13** and **14**) as the major products similarly as it was reported earlier when secondary amines were oxidized with H_2O_2-SeO_2 [10,11]. Most probably the reaction proceeds *via* dehydrogenation of the amine and subsequent N-oxidation of intermediate imine. The main reaction is accompanied by cleavage of C–N bond resulted in formation of the nitrile (**2**), aldehyde (**4**), oxime (**5**) and carboxylic acid (**6**) in the similar manner as described for primary amines in Scheme 3. Surprisingly, tetrahydroisoquinoline (**1g**) was dehydrogenated to isoquinoline (**15**) in contrast to the earlier work [31], where 3,4-dihydroisoquinoline N-oxide was a product of hydroxyalkylflavine by catalyzed oxidation of **1g** with hydrogen peroxide. To our knowledge we present the first example of aromatization of tetrahydroisoquinoline by hydroperoxides.

Scheme 4



i = TBHP, **8** (cat.) *t*-BuOH, reflux, 20 h
ii = H_2O_2, **8** (cat.) *t*-BuOH, reflux, 20 h
[a] Data in parentheses are referred to isolated yields.

CONCLUSIONS

The results described herein demonstrate that oxidation of primary benzylamines using hydrogen peroxide or *tert*-butyl hydroperoxide with selenium catalyst, particularly ebselen, provides nitriles as the major products, while oxidation of the secondary amines gave nitrones. In the same reaction conditions 1,2,3,4-tetrahydroisoquinoline is aromatized to isoquinoline. Since all these compounds are produced in satisfactory yields and can be easily isolated the reaction has a practical value.

EXPERIMENTAL

The reaction products, presented in Table 1 and Scheme 3, were analyzed using Hewlett-Packard 5990/II apparatus with capillary column HP-1 (25 m, 0.22 mm). The products were identified by comparison of their MS spectra (Hewlett-Packard 5971A) with date reported in the library NBS 49K and 75K, or their melting points (Digital Melting Point Apparatus Electrothermal IA 91100) by analysis of their ^{1}H NMR data ($CDCl_3$ or DMSO-d_6, TMS, Bruker DRX 300 spectrometer). Hydrogen peroxide (30% aqueous solution), *tert*-butylhydroperoxide (80% in di-*tert*-butylperoxide/water 3:2), *tert*-butanol, selenium(IV) oxide (**7**) and amines (**1a–g**) were purchased from Aldrich and Fluka. The catalysts **8** and **9** were obtained in the ways reported in [25] and [23] respectively.

Synthesis of bis[2-(N-benzisoselenazol-3(2H)-one)] diselenide (10). To a vigorously stirred, cooled on ice/salt bath solution of bis(2-aminophenyl) diselenide (0.428 g. 1.25 mmol) obtained according to ref. [24] and triethylamine (0.557 g, 5.5 mmol) in dry dichloromethane (20 ml) the solution of (2-chloroseleno)benzoyl chloride [25] (0.635 g, 2.50 mmol) in dry dichloromethane (25 ml) was added dropwise over 40 min. The reaction was continued for additional 2 h, while the mixture warmed to room temperature. The solvent was evaporated *in vacuo* and product **10** was isolated from the residue by silica gel chromatography (chloroform-methanol 50:1) and finally recrystallized from THF. Yield 80%. Pale yellow prisms. M.p. 129–130°C (with decomp.). IR (KBr) 1607 cm^{-1} (CO). ^{1}H NMR (DMSO-d_6): 7.29–7.42 (m, 6H, ArH); 7.50 (t, 2H, J = 7.5 Hz, ArH); 7.69–7.74 (m, 4H, ArH); 7.92 (d, 2H, J = 7.5 Hz, ArH); 8.12 (d, 2H, J = 8.1 Hz, ArH). Anal. Calcd for $C_{26}H_{16}N_2O_2Se_4$ (704.26): C, 44.34; H, 2.29; N, 3.98; Found: C, 39.32; H, 2.72; N, 3.80.

Oxidation of benzylamines 1a–g. General procedure. The solution of amine **1a–g** (5 mmol) in *tert*-butanol (8 ml), 30% hydrogen peroxide (3.1 ml, 30 mmol) or *tert*-butyl hydroperoxide (3.8 ml, 30 mmol) and a catalyst **7** (0.028 g, 0.25 mmol), **8** (0.068 g, 25 mmol), **9** (0.029 g, 0.06 mmol) or **10** (0.044 g, 0.06 mmol) were magnetically stirred under reflux for 20 h. (TLC control of the reaction progress shown that after this time all substrates were completely converted). After the reaction finished solvent was evaporated *in vacuo*, the residue was dissolved in water (50 ml) and extracted with dichloromethane (3×20 ml). The combined extracts were dried over anhydrous sodium sulfate and dichloromethane was removed *in vacuo*. The residue was analyzed and identified by GC/MS. In some experiments (Table 1, entries 6, 9, 12, 15) the nitriles **2a–d** were isolated by silica gel chromatography (dichloromethane). In the same way the nitrones **13** and **14**, isoquinoline **15** and its N-oxide **16** were isolated using chloroform (for **13** and **14**) and ethyl acetate (for **15** and **16**) as an eluent. All isolated products were identified by their comparison with authentic sample (TLC, M.p., IR, ^{1}H NMR).

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