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Hydroperoxide Oxidation of Azomethines and Alkylarenes Catalyzed by Ebselen

by M. Giurg, H. Wójtowicz and J. Młochowski*

Institute of Organic Chemistry, Biochemistry and Biotechnology, Wrocław University of Technology, Wyb. Wyspiańskiego 27, 50-375 Wrocław, Poland

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2-Phenyl-1,2-benzisoselenazol-3(2H)-one (ebselen), known as glutathione peroxidase mimic, is found as an efficient catalyst for hydrogen peroxide and *tert*-butyl hydroperoxide oxidation of the azomethine group in azines, aldoximes, and methyl or methylene group in alkylarenes. Depending on the substrate used and the reaction conditions, the major products are aldehydes, ketones, carboxylic acids or their derivatives. It is postulated that ebselen is involved in the free-radical oxidation mechanism.

Key words: azomethines, alkylarenes, ebselen, hydroperoxides, oxidation

Oxidation of organic compounds with hydroperoxides, particularly with hydrogen peroxide and *tert*-butyl hydroperoxide, is a current problem of synthetic organic chemistry, because both of these oxidants are easily available, cheap, ecologically friendly and useful for a large-scale synthesis [1,2]. Unfortunately their activity toward many organic substrates is too low. For this purpose the oxygen-transfer catalysts, making oxidation more effective, must be used. Selenium compounds such as selenium(IV) oxide, diaryl diselenides and areneseleninic acids have been reported during last three decades as efficient hydrogen peroxide catalysts as well as *tert*-butylhydroperoxide activators [3–7].

Previously we presented 2-nitro- and 2,4-dinitrobenzeneseleninic acid and di(2-nitrophenyl) diselenide as oxygen-transfer catalysts, when 30% hydrogen peroxide was used as a stoichiometric oxidant. Benzeneperoxyseleninic acids, formed *in situ*, were postulated as the active intermediates [8]. These catalysts were successfully applied in our laboratory for styrene epoxidation [9], conversion of the oximes to carboxylic acid esters [10], conversion of 1,1-dimethylhydrazones into nitriles [11], the Baeyer-Villiger oxidation of aromatic and α,β-unsaturated aldehydes and ketones [12,13]. Moreover, it was found that selenium(IV) oxide efficiently catalyzed hydrogen peroxide oxidation of aliphatic, aromatic and heteroaromatic aldehydes to carboxylic acids [14], and that some diaryl diselenides catalyzed oxidation of sulfides into sulfoxides [15] and oxidative conversion of cycloalkanones into cycloalkanecarboxylic acids [16]. Most recently our attention has been directed to 2-phenyl-1,2-benzisoselenazol-3(2H)-one (ebselen) as the oxygen-transfer catalyst, since

* Author for correspondence. E-mail: Mlochowski@kchf.ch.pwr.wroc.pl

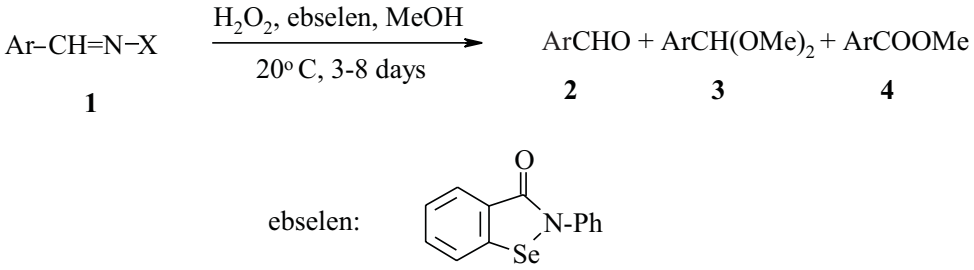
it has been known that this compound is able to interact with oxygen species in the living cells in a manner similar to the action of selenium containing enzyme, glutathione peroxidase. Although role of ebselen in the biomimetic oxidation of thiols into disulfides was fully explained [17–20], its effectiveness as catalyst for oxidation of other functional groups was limited to few reactions only, such as oxidation of sulfides to sulfoxides, conversion of aromatic 1,1-dimethylhydrazones into nitriles, regeneration of parent ketones from ketazines [21] and oxidation of various aromatic aldehydes to carboxylic acids [22].

RESULTS AND DISCUSSION

In this work we provide the evidence that hydroperoxides in the presence of catalytical amounts of ebselen might be used as a reagent for oxidation of azomethine group in azines or oximes and methyl or methylene group in alkylarenes. The hydroperoxides used as the stoichiometric oxidants were 30% hydrogen peroxide and 80% *tert*-butylhydroperoxide.

Azomethine derivatives of benzaldehydes, such as azine **1a** and oximes **1b**–**d**, oxidized with hydrogen peroxide in methanol gave parent aldehydes **2a**–**d**, their dimethylacetals **3a**–**c** and methylbenzoates **4a**–**d**. The esters **4** were main products with oximes as substrates. The results were similar for the oxime **2c** having strong electron-withdrawing and for oxime **2d** having electron-donating substituent in the *para* position of the aromatic ring (Scheme 1, Table 1).

Scheme 1



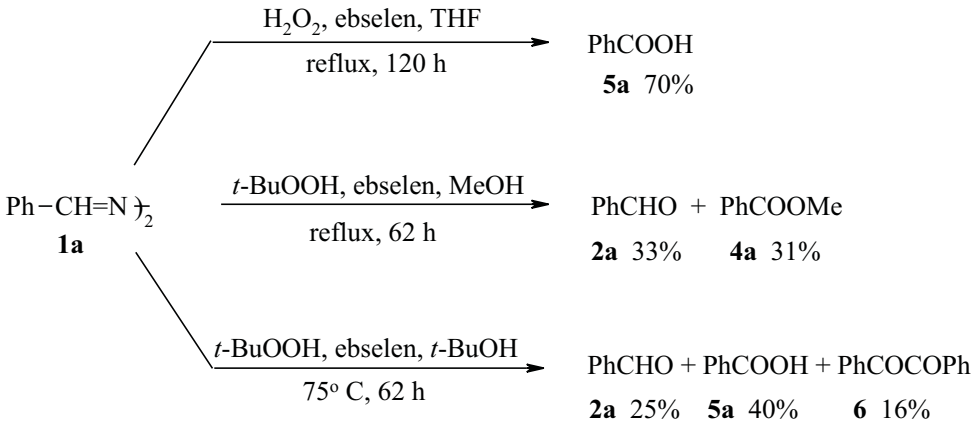
Other experiments carried out on the azine **1a** have shown that the result of the reaction depended on the oxidant used and on the reaction conditions, particularly on the solvent since methanol (and other primary and secondary alkanols) could participate in the reaction [10]. The products, other than these listed in Table 1, such as benzoic acid **5a** and benzil **6** were also formed (Scheme 2).

Ketazines **7a** and **7b** were oxidized with hydrogen peroxide exclusively to parent ketones **8a** and **8b**, while oxidation of azine **9** derived from 2-acetylpyridine gave the mixture of expected ketone **10** and condensed triazole **11** (Scheme 3).

Table 1. The results of the oxidation of aldazine **1a** and aldoximes **1b**–**d** with H_2O_2-ebselen.

Substrate	Ar	X	Reaction	Products, yield, %		
1–**4**			time, h	**2**	**3**	**4**
a	C_6H_5	-N=CHC_6H_5	62	30	32	30
b	C_6H_5	-OH	140	10	0	82
c	4-$NO_2C_6H_4$	-OH	180	25	5	70
d	4-$MeOC_6H_4$	-OH	130	30	0	62

Scheme 2

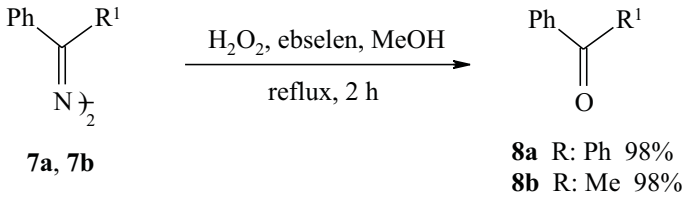


On the other hand, when azine **9** was oxidized with cerium(IV) ammonium nitrate (CAN), both of the compounds **10** and **11** were produced. Since CAN is well known one-electron oxidant generating free radicals [23,24], it seems possible that free-radical mechanism is involved in the hydroperoxide oxidation of azines catalyzed by ebselen. The side condensation reaction leading to benzil (**6**) and results of oxidation of alkylarenes **12** seem to confirm this hypothesis. The role of ebselen is evident, because no reaction progress was observed when azines or alkylarenes were treated with hydrogen peroxide or *tert*-butyl hydroperoxide without this catalyst.

Toluene (**12a**) and five other alkylarenes (**12b-f**) were oxidized with *tert*-butyl hydroperoxide in the presence of ebselen to benzaldehyde (**13a**) and ketones **13b**–**f**. (Scheme 4, Table 2). Although the methyl group in toluene remained resistant toward oxidation and benzaldehyde was formed only in low yield, the benzylic methylene group in alkylarenes **12b**–**f** was oxidized to carbonyl group more efficiently. The experiments with ethylbenzene (**12b**) have shown that although during long period con-

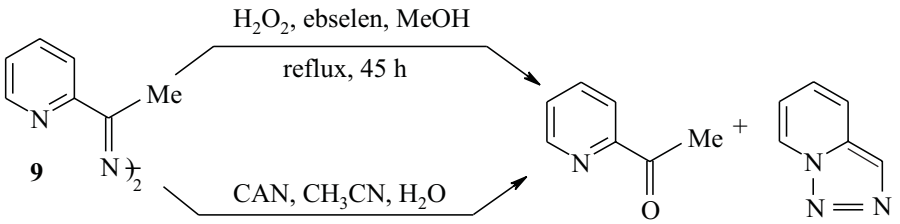
version of the substrate increased, side reactions took place and chemoselectivity of the main reaction decreased. Similar effect was observed when the oxidant was used in a larger excess. The reaction time, given in Table 2, was optimized for each substrate. No reaction was observed when catalysts such as titanosilicate TS-1, selenium(IV) oxide and even ebselen were used for hydrogen peroxide oxidation of toluene.

Scheme 3



7a, **7b**

8a R: Ph 98%
8b R: Me 98%

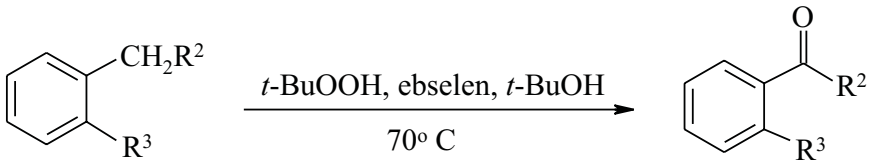


10 58%
75%

11 42%
23%

In conclusion, we can say that ebselen is an effective catalyst for hydrogen peroxide and *tert*-butyl hydroperoxide oxidation of aldazines to aldehydes and carboxylic acids as well as ketazines to ketones, and in particular cases to the products of oxidative cyclization, such as triazine **11**. The oximes oxidized with hydrogen peroxide–ebselen system in methanol gave methyl carboxylates as major products. In another reaction, using *tert*-butyl hydroperoxide in the presence of ebselen, methyl and benzylic methylene groups in alkylarenes are converted to carbonyl groups. Most probably the ebselen is involved in a free-radical mechanism. To our knowledge this is a rare example of free-radical oxidation promoted by organoselenium compound.

Scheme 4



12 **13**

Table 2. The results of the oxidation of alkylarenes **12** with *t*-BuOOH-ebselen.

Substrate **12**	R^2	R^3	Reaction time, h	Conversion %	Yield[a] %
a	H	H	48	14	71
b	Me	H	24	60	92
			48	92	52
c	Ph	H	48	80	95
d			48	93	98
e	$-CH_2CH_2-$		48	60	59
f	$-CH_2CH_2CH_2-$		64	56	45

[a] Yield based on the converted substrate.

EXPERIMENTAL

General: *tert*-Butyl hydroperoxide 80% solution in di-*tert*-butyl peroxide/water 3:2 (Fluka), hydrogen peroxide 30% solution in water (POCh) and cerium(IV) ammonium nitrate 98% (Fluka) were used as oxidants. The ebselen was synthesized in the way reported in [25]. Azines and aldoximes (with E configuration) were obtained according to procedures described earlier [26,27]. Other reagents and solvents were purchased from Aldrich or Fluka.

The reaction products presented in Table 1 and 2 were analyzed using Hewlett-Packard 5890/II apparatus with capillary column HP-1 (25 m, 0.22 mm). All compounds were identified by comparison of their MS spectra (Hewlett-Packard 5971a) with data reported in the library NBS 49 K and 75K or by comparison with the retention times and MS spectra of authentic samples.

Oxidation of aldazine 1a and aldoximes 1b–d with H_2O_2-ebselen. The mixture of aldazine **1a** (0.24 g, 2.0 mmol) or aldoxime **1b–d** (2.0 mmol), methanol (15 ml), hydrogen peroxide (0.80 ml, 8.0 mmol) and ebselen (0.027 g, 0.1 mmol) was magnetically stirred at room temperature for periods given in Table 1. The reaction mixture was treated with a pinch of Pt/C and then poured into the solution of sodium hydrogen carbonate (2.5 g) and sodium chloride (7.5 g) in water (75 ml). The products were extracted with chloroform (3 × 25 ml) and the layers were separated. The organic layer was dried over anhydrous sodium sulfate and analyzed by gas chromatography and the products were identified by mass spectrometry (GC-MS system).

Oxidation of aldazine 1a with *tert*-butyl hydroperoxide. The mixture of aldazine **1a** (1.04 g, 5.0 mmol), methanol or *tert*-butanol (10 ml), *tert*-butyl hydroperoxide (2.2 ml, 17.6 mmol) and ebselen (0.070 g, 0.25 mmol) was magnetically stirred under gentle reflux (methanol), or at 75°C (*tert*-butanol) for 62 h. After the reaction was completed the mixture was worked up and analyzed as described above.

Oxidation of aldazine 1a to benzoic acid (5a). To the solution of aldazine **1a** (1.04 g, 5.0 mmol) in tetrahydrofuran (7.5 ml) 30% hydrogen peroxide (2.5 ml, 25 mmol) and ebselen (0.068 g, 0.25 mmol) were added. The reaction mixture was magnetically stirred and slowly heated to gentle reflux maintained for 120 h. During the reaction additional portions of hydrogen peroxide (0.5 ml) were added after each 24 h period. When the reaction was completed, the mixture was treated with a pinch of Pt/C and then the solution of sodium hydrogen carbonate (2.5 g) and NaCl (7.5 g) in water (100 ml) was added until evolution of carbon dioxide ceased. The solution was washed with chloroform (10 ml and 2 × 5 ml) and the aqueous layer was acidified with concentrated hydrochloric acid (pH 1-2) then the acid **5a** was extracted with chloroform (50 ml and 4 × 20 ml). The combined extracts were dried over anhydrous sodium sulfate, the solvent was removed *in vacuo*. Crude **5a** was obtained as a residue (0.98 g, 80% yield). Recrystallization from ethanol-water gave pure benzoic acid m.p. 122–123°C (0.85 g, 70% yield).

Oxidation of ketazine 9 with H_2O_2-ebselen. To the solution of ketazine **9** (1.19 g, 5.0 mmol) in methanol (15 ml), ebselen (0.070 g, 0.25 mmol) and hydrogen peroxide (2.7 ml, 27 mmol) were added. The mixture was gently refluxed for 45 h, poured to the solution of sodium hydrogen carbonate (2.5 g) and sodium chloride (7.5 g) in water (75 ml) and was shaken. The organic products were isolated by extraction

with dichloromethane (25 ml and 5 × 10 ml) and separated by silica gel (70–230 mesh) column chromatography using ethyl acetate (freshly distilled over potassium carbonate) as an eluent. 2-Acetylpyridine (**10**) was eluted as a first fraction (0.705 g, 58% yield) and 3-methyl-[1,2,3]triazolo[1,5-a]pyridine (**11**) (m.p. 81–84°C, ref. [28] 84–85°C, ^{1}H NMR and IR spectra identical to these reported in ref. [29]) as the next fraction (0.282 g, 42% yield).

Oxidation of ketazine 9 with cerium(IV) ammonium nitrate. The solution of ketazine **9** (0.95 g, 4.0 mmol) and cerium ammonium nitrate (5.6 g, 10 mmol) in acetonitrile (33 ml) and water (18 ml) was poured into 250 ml round-bottom flask and magnetically stirred at room temperature for 16 h. After the reaction was completed acetonitrile was evaporated *in vacuo*, to the concetrate water (40 ml) was added and the solution was treated with sodium hydrogen carbonate (5.0 g, 60 mmol). The formed solid was filtered off, washed with water (100 ml) and dichloromethane (50 ml). The filtrates were collected, water layer was separated and extracted with dichloromethane (5 × 25 ml). All dichloromethane solutions were combined, dried over anhydrous sodium sulfate, concentrated *in vacuo* to a small volume (*ca* 5 ml). The products were separated as described above. 2-Acetylpyridine (**10**) (0.730 g, 75% yield) and triazole (**11**) (0.122 g, 23% yield) were isolated in this way.

Oxidation of alkylarenes 12 with *tert*-butyl hydroperoxide – ebselen. The solution of alkylarene **12** (5 mmol), *tert*-butylhydroperoxide (1.26 ml, 10 mmol) and ebselen (0.058 g, 0.25 mmol) in *tert*-butanol (10 ml) was stirred under reflux for the period given in Table 2. The solvent was evaporated *in vacuo*, the residue was dissolved in dichloromethane and the solution was analyzed using gas chromatography and the products **13** were identified by comparison of their MS spectra with data reported in the library.

REFERENCES

1. Młochowski J. and Said S.B., *Polish J.Chem*., **71**, 140 (1997).
2. Jones A.K. and Wilson T.E., in *Encyclopedia of Reagents for Organic Synthesis*, Paquette L.A. (ed.), J. Wiley and Sons, Chichester 1995, p 880.
3. Paulmier C., *Selenium Reagents and Intermediates in Organic Synthesis*, Pergamon Press, Oxford 1986.
4. Liotta D. and Monahan III R., *Science*, **231**, 356 (1986).
5. Młochowski J., *Phosphorus, Sulfur and Silicon*, **136–138**, 191 (1998).
6. Nishibayashi Y. and Uemura S., *Topics in Current Chem*., **208**, 234 (2000).
7. Młochowski J., Brząszcz M., Giurg M. and Wójtowicz H., *Wiad. Chem*., **55**, 9 (2001).
8. Syper L. and Młochowski J., *Tetrahedron*, **43**, 207 (1987).
9. Kubicz E. and Młochowski J., *J. Frakt. Chem*., **333**, 243 (1991).
10. Said S.B., Skarżewski J. and Młochowski J., *Synth. Commun*., **22**, 1851 (1992).
11. Said S.B., Skarżewski J. and Młochowski J., *Synthesis*, 223 (1989).
12. Syper L., *Tetrahedron*, **43**, 2853 (1987).
13. Syper L., *Synthesis*, 167 (1989).
14. Brząszcz M., Kloc K., Maposah M. and Młochowski J., *Synth. Commun*., **30**, 4425 (2000).
15. Palus J. and Młochowski J., *Polish J. Chem*., **72**, 1931 (1998).
16. Giurg M. and Młochowski J., *Synth. Commun*., **29**, 2281 (1999).
17. Fisher H. and Dereu N., *Bull. Soc. Chim. Belg*., **96**, 757 (1987).
18. Engman L., Stern D., Cotgreave I.A. and Anderson C.M., *J. Am .Chem. Soc*., **114**, 9737 (1992).
19. Back T.G. and Dyck B.P., *J. Am. Chem. Soc*., **119**, 2077 (1997).
20. Mugesh G., du Mont W.-W. and Sies H., *Chem. Rev*., **101**, 2125 (2001).
21. Młochowski J., Giurg M., Kubicz E. and Said S.B., *Synth. Commun*., **26**, 291 (1996).
22. Wójtowicz H., Brząszcz M., Kloc K. and Młochowski J., *Tetrahedron*, **57** 9743 (2001).
23. Jacob P., Collery P.S., Shulgin A.T. and Castagnoli N., Jr., *J. Org. Chem*., **41**, 3627 (1976).
24. Skarżewski J., *J. Chem. Research (S)*, 410, (1980).
25. Młochowski J., Kloc K., Syper L., Inglot A.D. and Piasecki E., *Liebigs Ann. Chem*., 1239 (1993).
26. Młochowski J. and Giurg M., *Polish J. Chem*., **68**, 2333 (1994).
27. Giurg M. and Młochowski J., *Polish J. Chem*., **71**, 1093 (1997).
28. Bower J.B. and Ramage G.R., *J. Chem. Soc*., 4506 (1957).
29. Mori H., Sakamoto K., Mashito S., Matsuoka Y., Matsubayashi and Sakai K., *Chem. Pharm. Bull*., **41**, 1944 (1993).