Ebselen-like catalysts – new approach

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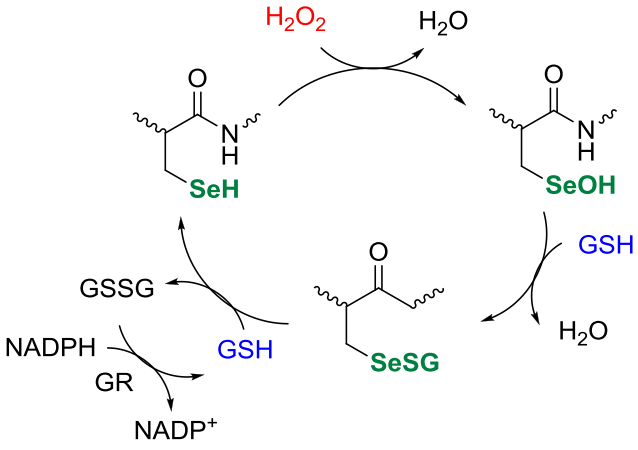
Abstract: Ability to eliminate reactive oxygen species is one of the most promising features of organoselenium compounds in medicinal chemistry. Ebselen (*N*-phenyl-1,2-benzisoselenazol-3(2H)-one) is a well known GPx mimic with proven antioxidant capacity. However, side effects, and in some cases only moderate activity, leave the search for new highly effective benzisoselenazolone analogues still open. In this work, we present an efficient methodology for the synthesis of ebselen derivatives. Lithium diselenide formed *in situ* reacts with *N*-substituted *o*-iodobenzamides to give the products in high yield - up to 98%. All synthesised compounds were also tested for their antioxidant activity in an NMR assay using dithiothreitol as substrate. The obtained results led us to the conclusion that *N*-phenyl analogues with *p*-methoxy, *p*-nitro and *p*-iodo moieties are the most active ones.

Keywords: ebselen, benzisoselenazol-3(2H)-ones, antioxidant activity, dithiothreitol

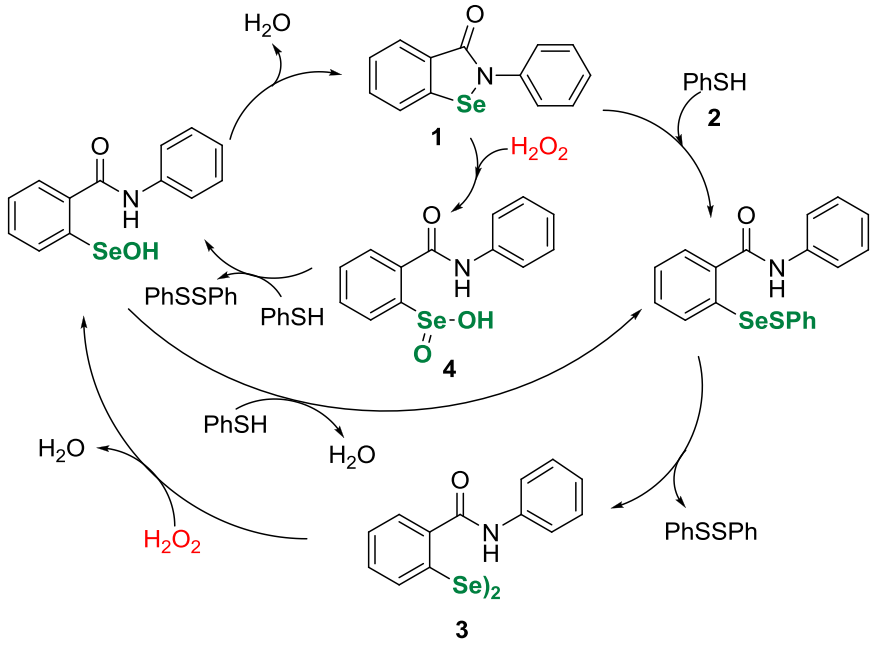
Introduction

Glutathione peroxidase (GPx) is a selenoenzyme that keeps the amount of free radicals in physiological concentrations and supports the redox homeostasis in living organisms. The excess of reactive oxygen and nitrogen species is associated with various cell dysfunctions and the process of aging. Cancer, stroke, diabetes, neurological and cardiovascular diseases are the effects of disrupted redox regulations [1]. In the catalytic cycle, selenocysteine residue eliminates the peroxide in cooperation with intracellular thiols, mostly glutathione GSH (Scheme 1).



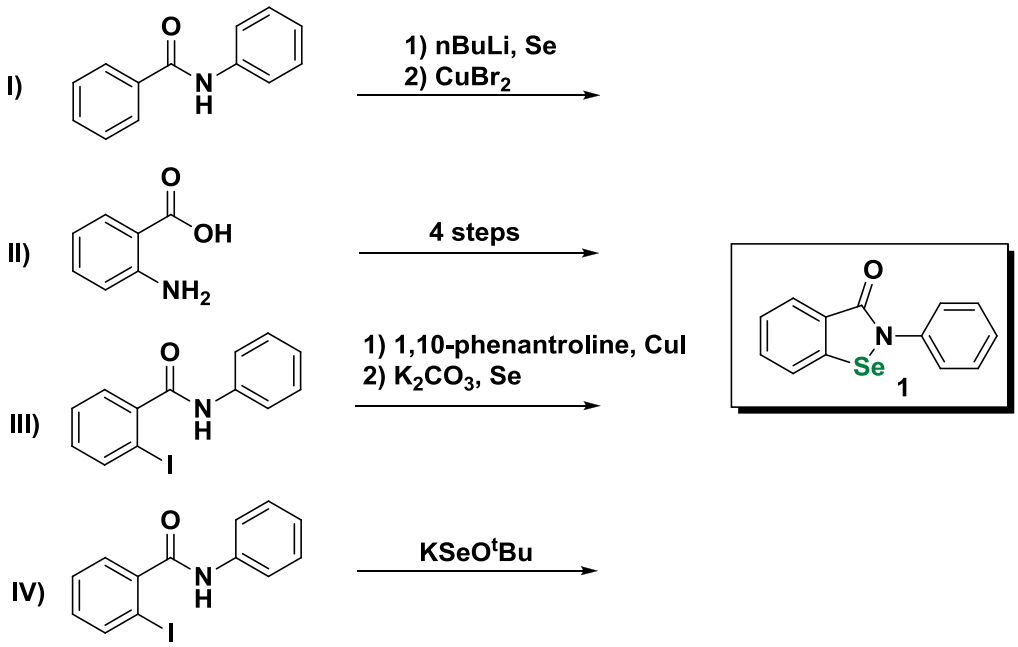
Scheme 1. Catalytic elimination of peroxides

Ebselen **1** mimics GPx by acting as an artificial selenocysteine. Benizoselenazol-3(2H)-one **1** reacts with two equivalents of thiol **2** to form the diselenide **3** which reduces the peroxide. Ebselen can also react directly with H_2O_2 generating the seleninic acid **4** (Scheme 1) [2].



Scheme 1. Catalytic peroxide reduction by ebselen

Ebselen **1** can be synthesized by four methodologies: *ortho*-lithiation of benzanilide, than addition of Se, and $CuBr_2$ **I** [3], multistep synthesis from anthranilic acid **II** [4], formation of Se-N bond catalyzed by 1,10-phenanthroline/copper iodide **III** [5] and reaction of *o*-iodobenzamide with $KSeO^tBu$ **IV** [6] (Scheme 2).

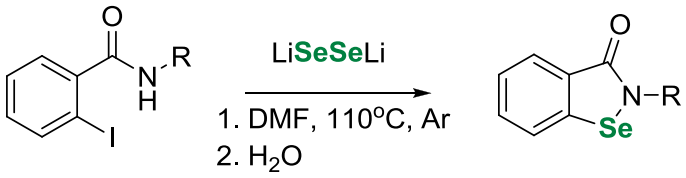


Scheme 2. Methods of ebselen synthesis

In this communication we present a new one step, metal free route for the synthesis of benzisoselenazol-3(2H)-one analogues in high yields. All of the synthesized compounds were also tested for their potential antioxidant activity.

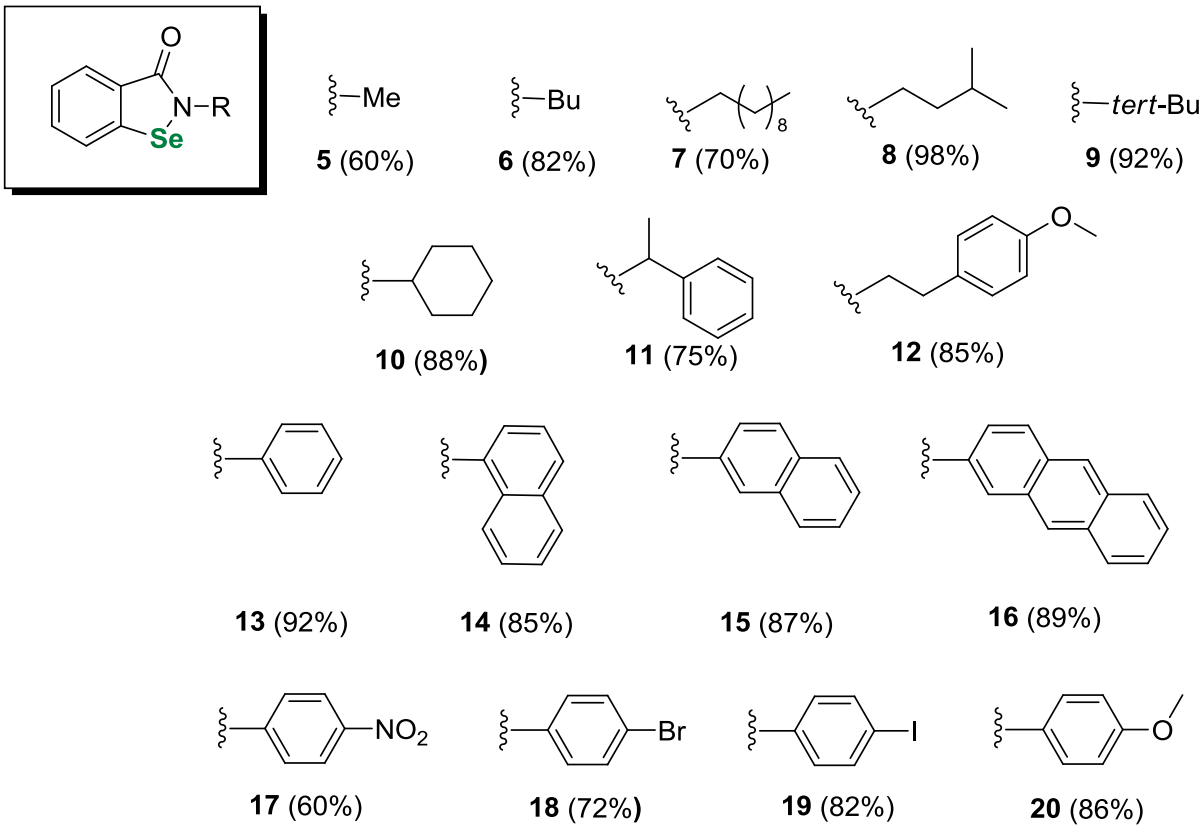
Results and discussion

The method developed in our research group is based on the reaction of o-iodobenzamide with lithium diselenide (Scheme 3) [7].



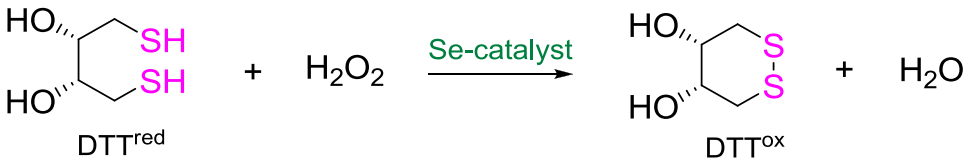
Scheme 3. New method to synthesize ebselen derivatives

By applying this method we were able to synthesize a wide range of aryl and alkyl 1,2-benzisoselenazol-3(2H)-one analogues in high yields (60-98%) (Scheme 4).



Scheme 4. Synthesized alkyl and aryl analogues

The antioxidant activity was tested by the method proposed by Iwaoka and co-workers [8]. Benzisoselenazol-3(2H)-one oxidized by hydrogen peroxide transforms the dithiothreitol **21** to dithione **22**. The rate of the reaction is measured from the changes in the ^{1}H NMR spectrum (Scheme 5).



	Substrate concentration [%]				
Catalyst [0.1 equiv.]	**3 min**	**5 min**	**15 min**	**30 min**	**60 min**
5	78	65	35	11	0
6	81	59	41	32	29
7	98	97	94	91	85
8	77	58	42	28	13
9	97	96	94	93	91
10	75	69	62	55	44
11	85	74	55	35	11
12	0	0	0	0	0
13 (Ebselen)	84	75	64	58	52
14	99	98	97	96	95
15	87	83	78	71	62
16	96	94	91	89	88
17	25	7	5	0	0
18	86	83	79	75	71
19	42	0	0	0	0
20	64	41	5	0	0

Scheme 5. Activity of the tested catalysts

Reactions where we had observed a total conversion of the substrate, after 15 minutes or less, were repeated using 0.05 equivalent of the selenium catalyst. Compounds **12**, **17**, **19** and **20** were the most active ones (Scheme 6).

	Substrate concentration [%]				
Compound [0.05 equiv.]	**3 min**	**5 min**	**15 min**	**30 min**	**60 min**
12	88	78	70	62	56
17	87	75	51	29	0
19	76	57	19	9	0
20	76	66	59	22	12
13 (Ebselen)	96	95	94	90	88

Scheme 6. Results for the most active catalysts

After 60 minutes only 12% of dithiotreitol was oxidized when ebselen was used as catalyst. Compounds with *N*-phenyl *p*-nitro and *p*-iodo moieties made the substrate react in a quantitative amount in equal time.

Conclusion

Methodology presented in this work provides an efficient tool in the synthesis of benzisoselenazolone derivatives. Ebselen is an efficient radical scavenger so all of the obtained products were also tested for their antioxidant capacity. We showed that *N*-phenyl derivatives with *p*-iodo, *p*-methoxy and *p*-nitro moieties in 5% concentration were significantly more effective catalysts.

References

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