RSC Advances

COMMUNICATION

View Article Online
View Journal | View Issue

Published on 29 September 2014. Downloaded by University of Birmingham on 11/10/2014 15:04:38.

Cite this: *RSC Adv.*, 2014, **4**, 48959

Received 13th August 2014
Accepted 29th September 2014

DOI: 10.1039/c4ra08631g

www.rsc.org/advances

Highly efficient synthesis and antioxidant capacity of *N*-substituted benzisoselenazol-3(2*H*)-ones†

Agata J. Pacuła, Jacek Ścianowski* and Krzysztof B. Aleksandrzak

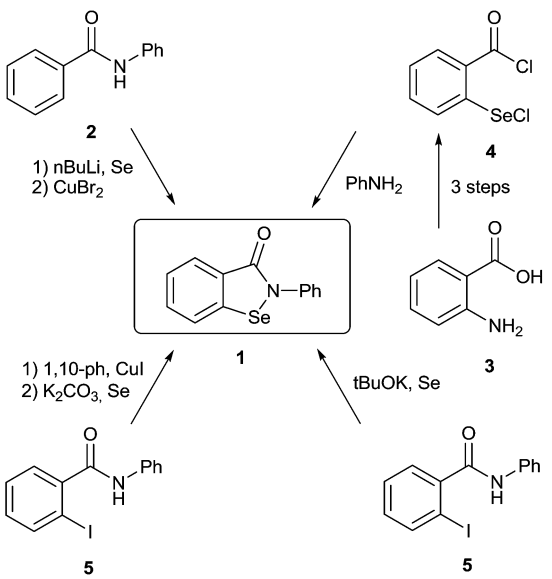
A new, general one step synthesis of *N*-substituted benzisoselenazol-3(2*H*)-ones based on the reaction of *o*-iodobenzamides with lithium diselenide, is described. A series of alkyl and aryl derivatives was obtained in high yields (up to 98%). Their GPx-like antioxidant activity, tested by NMR, showed a significantly higher activity than ebselen.

Oxidative stress is the cause of many frequently occurring diseases, involving the dysfunction of the cardiovascular system, neurodegeneration, aging, and cell damage leading to oncogenesis.[1] It can be defined as the imbalance between the production and destruction of free radicals in cells. Reactive oxygen species (ROS) cause damage that leads to apoptotic death. An increase of this process causes uncontrolled cell proliferation. Aerobic cells possess catalytic antioxidant systems as a natural defence against reactive oxygen and nitrogen species. Glutathione peroxidase (GPx), a selenoenzyme that reduces the excess of hydroperoxides, plays a major role in this process. Although the known GPx mimic, *N*-phenyl benzisoselenazol-3(2*H*)-one **1** (ebselen),[2] has been thoroughly studied, the search for more effective and less toxic analogues is currently one of the main topics of organoselenium chemistry.[3]

Selenium possesses several significant properties.[4] This essential micronutrient exhibits "insulin-like" activity – increased glucose and lipid metabolism is correlated with low selenium blood levels. Furthermore, it decreases the risk of cardiovascular disease by eliminating lipid peroxidation and influencing the role of inflammatory mediators. In mood disorders it protects neurons from oxidative stress and toxic effects of heavy metals by complexing them.[5]

Despite the biological importance of selenium, another advantage is its higher nucleophilicity and acidity than sulfur and ability to form long, weaker bonds with carbon atoms. Organoselenium compounds can be easy transformed into various reactive nucleophilic, electrophilic or radical reagents, *e.g.* addition of electrophilic selenium reagents to the double bonds and selenocyclization reactions were used to create new carbon–carbon, carbon–oxygen and carbon–nitrogen bonds. Chiral reagents make possible a stereoselective reactions.[6] Our previous work was focused on the synthesis of optically active terpenyl selenols, selenides, diselenides, and their applications in asymmetric synthesis.[7] Methodology presented in this work enables to obtain compounds exhibiting beneficial physiological and catalytic activities, and can not only be applied as catalysts in biological cycles but also as reagents in organic synthesis, fulfilling the requirements of green chemistry.[8]

Since the late 80's, four main methods for the synthesis of benzisoselenazol-3(2*H*)-ones have been developed (Scheme 1).



Scheme 1 Synthetic approaches to benzisoselenazol-3(2*H*)-one **1**.

Department of Organic Chemistry, Faculty of Chemistry, Nicolaus Copernicus University, 7 Gagarin Street, 87-100 Torun, Poland. E-mail: jsch@chem.umk.pl; Fax: +48 566542477; Tel: +48 566114532

† Electronic supplementary information (ESI) available: Experimental procedures and full characterization data. See DOI: 10.1039/c4ra08631g

Published on 29 September 2014. Downloaded by University of Birmingham on 11/10/2014 15:04:38.

The reaction of *N*-substituted benzamides **2** with *n*-butyllithium, selenium powder and copper bromide as an oxidant was reported by Engman *et al.*[9] Another methodology is the formation of the Se–N bond by the diazotization of anthranilic acid **3** and reaction with sodium diselenide that enables to form dibenzoic acid *o*-diselenide. This intermediate reacts with thionyl chloride to generate the corresponding chloride **4**, which reacts with aniline to give **1**. This route is most commonly used, however, the yields, are only moderate.[10] Two new methods were proposed by Kumar and co-workers.[11,12] In both cases *N*-substituted *o*-iodobenzamide **5** is used as a substrate. In the copper-catalyzed synthesis the catalyst is formed by the reaction of 1,10-phenantroline with copper iodide. In the presence of potassium carbonate as a base, CuI/L catalyses the Se–N coupling.[11] In the second method the substrate is treated with KSeO^{t}Bu formed *in situ* by the reaction of *t*BuOK with selenium (2 : 1). The authors report that benzisoselenazol-3(2*H*)-ones are obtained in higher yields due to the fact that in the previous method the catalyst was hard to separate from the product.[12]

In this paper we present, an efficient method for the synthesis of *N*-substituted benzisoselenazol-3(2*H*)-ones, and their antioxidant properties. Our starting material sodium selenide, was prepared *in situ* from sodium borohydride and elemental selenium.[7e] We assumed that applying NaSeNa as a reagent in the formation of the Se–N bond would enable us to synthesise benzizoselenazol-3(2*H*)-ones. However, only the iodo substituent was replaced by the hydrogen atom, and **6** was obtained (Scheme 2). A similar effect was observed when sodium sulfide was used.[13] Then sodium diselenide, formed from sodium hydroxide and elemental selenium in the presence of hydrazine hydride was used.[7b] In this case the only product was **1**. The efficiency of the reaction using lithium, sodium and potassium hydroxides was also tested. The highest yield was obtained when lithium hydroxide was applied (Scheme 2). This method for the synthesis of lithium diselenide is unknown in the literature. We have also tested the reaction of *N*-phenyl 2-chloro- and 2-bromobenzamide with in Li_2Se_2. Only 2-bromobenzamide yielded 21% of **1**.

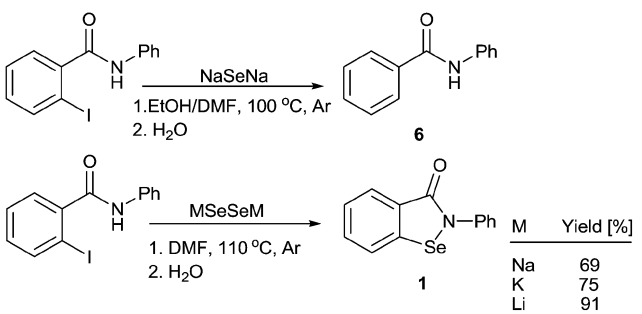
We assume, that the first step is the formation of diselenide **7** by the reaction of sodium diselenide with *o*-iodobenzamide. Then the present in the reaction mixture NaI/LiOH transforms the diselenide to the corresponding seleninic acid, and the elimination of water gives ebselen derivatives. To confirm our hypothesis *N*-cyclohexyl substituted diselenide **7** was prepared. Its reactions with LiOH, NaI, and a mixture of LiOH/NaI were carried out. Only the mixture gave the *N*-cyclohexyl benzisoselenazol-3(2*H*)-on **8** (Scheme 3).

On the other hand the reaction of **7** with commercial available KIO_3 also gave **8**.

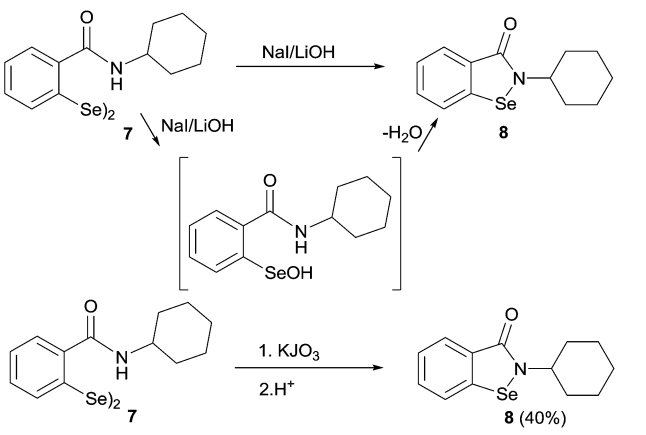
The developed method was efficient for a variety of substrates including alkyl derivatives with short **9** and **10**, long **11** or branched chains **12** and **13**, also cyclic **8**, and with additional aryl function **14** and **15**, also aryl derivatives with the naphthyl **16** and **17**, anthryl **18** and phenyl group substituted with nitro- **19**, bromo- **20**, iodo- **21** and methoxy-**22** substituents[14] (Scheme 4). Compounds **1**, **8**, **10**, **13**, **14**, **20**, **21** have established biological activity.[15]

The evaluation of the antioxidant activity was based on the method proposed by Iwaoka and co-workers with 10% of the catalyst.[16] Benzisoselenazol-3(2*H*)-ones were oxidized by hydrogen peroxide to seleninic acid which catalyses the transformation of dithione **23**, bearing two thiol groups to a disulfide–dithiotreitol **24**. The reaction rate was measured by ^{1}H NMR analysis. The result can show not only the antioxidative potential of the compound but also the ability to catalyse the formation of S–S bonds in proteins.[17] The decrease in the concentration of the substrate was measured after 3, 5, 15, 30 and 60 minutes for each compound (see ESI†). Comparing to ebselen, the alkyl analogues with one to four carbon chains exhibit higher reactivity, and when long and branched *N*-substituted derivatives are used the reaction rate decreases significantly – the concentration of the substrate after 60 minutes is still about 80–90%. Among aryl analogues only those with the *p*-nitro, *p*-iodo and *p*-methoxy phenyl group are stronger catalysts than ebselen. The *p*-iodo substituted derivative enables to finish the reaction after 5 minutes. For the most active compounds **15**, **19**, **21**, **22** the test was performed with 5% of the catalyst (Fig. 1).

According to this study, the obtained benzisoselenazol-3(2*H*)-ones are much stronger catalysts than ebselen. Using catalysts containing *N*-phenyl group substituted in *para* position with NO_2 or I **21**, **19**, after 2 hours we have observed 100%



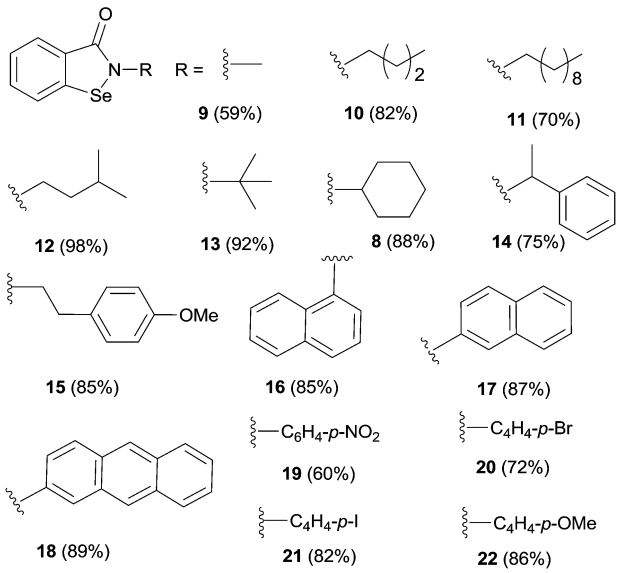
Scheme 2 Reaction of *o*-iodobenzamide with Na_2Se and Na_2Se_2.



Scheme 3 Plausible mechanism of the benzizoselenazolo-3-(2*H*)-nes formation.

 This journal is © The Royal Society of Chemistry 2014

Published on 29 September 2014. Downloaded by University of Birmingham on 11/10/2014 15:04:38.



Scheme 4 Alkyl and aryl benzizoselenazol-3(2*H*)-on analogues.

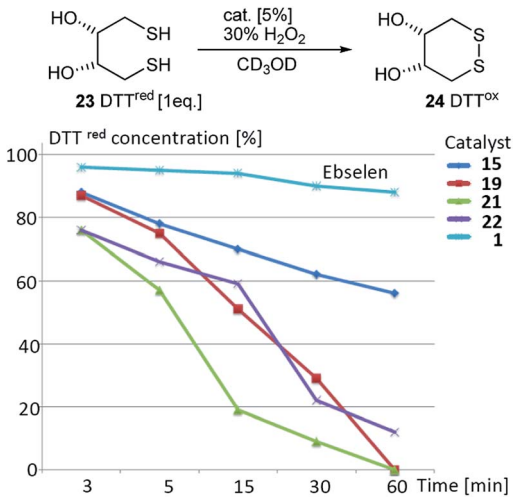


Fig. 1 Reactivity of the tested "ebselen-like" catalysts.

transformation of **23** to **24**. Also good result was obtained for *p*-methoxy group, near 90% of conversion. In the same time unsubstituted phenyl group gave only 10% change of concentration of **23**.

Conclusions

A new method for the preparation of benzisoselenazol-3(2*H*)-one analogues has been developed. A wide range of *N*-alkyl and *N*-aryl derivatives have been obtained. A plausible mechanism for the formation of ebselen derivatives was proposed. All compounds were tested by the NMR assay that highlighted the higher activity of alkyl and aryl analogues as compared to ebselen. The aryl derivatives substituted in the *para* position shown the highest antioxidant activity.

Notes and references

1 M. Iwaoka, Antioxidant Organoselenium Molecules, in *Organoselenium Chemistry: Between Synthesis and Biochemistry*, ed. C. Santi, Bentham Science Publishers, 2014, p. 361.

2 M. J. Parnham and H. Sies, *Biochem. Pharmacol.*, 2013, **86**, 1248.

3 (*a*) G. Mugesh, W.-W. du Mont and H. Sies, *Chem. Rev.*, 2001, **101**, 2125; (*b*) B. J. Bhuyan and G. Mugesh, Biological and Biochemical Aspects of Selenium Compounds, in *Organoselenium Chemistry: Synthesis and Reactions*, ed. T. Wirth, WILEY-VCH, 2012, p. 361; (*c*) D. Pietrella, Antimicrobial Activity of Organoselenium Compounds, in *Organoselenium Chemistry: Between Synthesis and Biochemistry*, ed. C. Santi, Bentham Science Publishers, 2014, p. 328; (*d*) B. K. Sarma and G. Mugesh, *J. Am. Chem. Soc.*, 2005, **127**, 11477; (*e*) K. P. Bhabak and G. Mugesh, *Chem.–Eur. J.*, 2009, **15**, 9846; (*f*) K. Selvakumar, P. Shah, H. B. Singh and R. J. Butcher, *Chem.–Eur. J.*, 2011, **17**, 12741; (*g*) K. Satheeshkumar and G. Mugesh, *Chem.–Eur. J.*, 2011, **17**, 4849; (*h*) V. P. Singh, H. B. Singh and R. J. Butcher, *Eur. J. Org. Chem.*, 2011, 5485; (*i*) K. Bijian, Z. Zhang, B. Xu, S. Jie, B. Chen, Sh. Wan, J. H. Wu, T. Jiang and A. A. Alaoui-Jamali, *Eur. J. Med. Chem.*, 2012, **48**, 143; (*j*) C. Santi, R. Di Lorenzo, C. Tidei, L. Bagnoli and T. Wirth, *Tetrahedron*, 2012, **68**, 10530; (*k*) M. Zielińska-Błajet, P. J. Boratyński, J. Palus and J. Skarżewski, *Tetrahedron*, 2013, **69**, 10223; (*l*) I. J. Kade, B. D. Balogun and J. B. T. Rocha, *Chem.-Biol. Interact.*, 2013, **206**, 27; (*m*) Z. Luo, L. Liang, J. Sheng, Y. Pang, J. Li, L. Huang and X. Li, *Bioorg. Med. Chem.*, 2014, **22**, 1355.

4 (*a*) J. He, D. Li, K. Xiong, Y. Ge, H. Jin, G. Zhang, M. Hong, Y. Tian, J. Yin and H. Zeng, *Bioorg. Med. Chem.*, 2012, **20**, 3816; (*b*) Z. Luo, J. Sheng, Y. Sun, Ch. Lu, J. Yan, A. Liu, H. Luo, L. Huang and X. Li, *J. Med. Chem.*, 2013, **56**, 9089; (*c*) F. Mao, J. Chen, Q. Zhou, Z. Luo, L. Huang and X. Li, *Bioorg. Med. Chem.*, 2013, **23**, 6737.

5 D. Bartolini, S. Ciffolilli, M. Piroddi, G. Murdolo, C. Tortoioli and F. Galli, Biochemistry and Nutrition of Selenium: From Inorganic Forms to Endogenous Proteins, in *Organoselenium Chemistry: Between Synthesis and Biochemistry*, ed. C. Santi, Bentham Science Publishers, 2014, p. 268.

6 (*a*) J. Ścianowski and Z. Rafiński, Electrophilic Selenium Reagents: Addition to Double Bonds and Selenocyclizations, in *Organoselenium Chemistry: Between Synthesis and Biochemistry*, ed. C. Santi, Bentham Science Publishers, 2014, p. 8; (*b*) C. Santi and C. Tidei, Addition Reactions with Formation of Carbon–Sulfur and Carbon Selenium Bonds, in *Comprehensive Organic Synthesis*, ed. A. G. Molander and P. Knochel, Elsevier, Oxford, 2nd edn, 2014, vol. 7, p. 605.

7 (*a*) J. Ścianowski, *Tetrahedron Lett.*, 2005, **46**, 3331; (*b*) J. Ścianowski, Z. Rafiński and A. Wojtczak, *Eur. J. Org. Chem.*, 2006, **14**, 3216; (*c*) Z. Rafiński, J. Ścianowski and A. Wojtczak, *Tetrahedron: Asymmetry*, 2008, **19**, 223; (*d*)

Published on 29 September 2014. Downloaded by University of Birmingham on 11/10/2014 15:04:38.

Z. Rafiński and J. Ścianowski, *Tetrahedron: Asymmetry*, 2008, **19**, 1237; (*e*) J. Ścianowski, Z. Rafinski, A. Wojtczak and K. Burczyński, *Tetrahedron: Asymmetry*, 2009, **20**, 2871; (*f*) Z. Rafinski, J. Ścianowski and A. Wojtczak, *Lett. Org. Chem.*, 2009, **6**, 321; (*g*) J. Ścianowski, Z. Rafiński, A. Szuniewicz and A. Wojtczak, *Tetrahedron*, 2009, **65**, 10162; (*h*) J. Ścianowski, J. Rafalski, A. Banach, J. Czaplewska and A. Komoszyńska, *Tetrahedron: Asymmetry*, 2013, **24**, 1089.

8 (*a*) C. Santi, R. Di Lorenzo, C. Tidei, L. Bagnoli and T. Wirth, *Tetrahedron*, 2012, **68**, 10530; (*b*) C. Tidei and C. Santi, Selenium and "Bio-Logic" Catalysis: New Bioinspired Catalytic Reactions, in *Organoselenium Chemistry: Between Synthesis and Biochemistry*, ed. C. Santi, Bentham Science Publishers, 2014, p. 345; (*c*) A. L. Braga, R. S. Schwab and O. E. D. Rodrigues, Eco-Friendly Access and Application of Organoselenium Reagents: Advances Toward Green Chemistry, in *Organoselenium Chemistry: Between Synthesis and Biochemistry*, ed. C. Santi, Bentham Science Publishers, 2014, p. 197; (*d*) C. W. Nogueira, G. Zeni and J. B. T. Rocha, *Chem. Rev.*, 2004, **104**, 6255.

9 L. Engman and A. Hallberg, *J. Org. Chem.*, 1989, **54**, 2964.

10 A. Welter, L. Christiaens and W.-P. Ferdinand, *Eur. Pat.* Appl. EP 44453, 1982, Chem. Abstr., 1982, 96, 199699v.

11 (*a*) S. J. Balkrishna, B. S. Bhakuni, D. Chopra and S. Kumar, *Org. Lett.*, 2010, **12**, 5394; (*b*) S. J. Balkrishna, B. S. Bhakuni and S. Kumar, *Tetrahedron*, 2011, **67**, 9565.

12 S. J. Balkrishna, Sh. Kumar, K. G. Azad, B. S. Bhakuni, P. Panini, N. Ahalawat, R. S. Tomar, R. M. Detty and S. Kumar, *Org. Biomol. Chem.*, 2014, **12**, 1215.

13 A. A. Vasil'er and L. Engman, *J. Org. Chem.*, 1998, **63**, 3911.

14 Lithium diselenide was prepared *in situ* from lithium hydroxide and elemental selenium (3 : 1) under argon atmosphere. Hydrazine hydrate (0.6 equiv.) was added, the mixture was heated to 110 °C and stirred for 15 minutes until the reagent was formed. After adding the *N*-substituted *o*-iodobenzamide the reaction was heated for 20 h. Colour change from dark brown to light orange was observed. Brine was added and the mixture was stirred at room temperature for additional 20 h. The formation of white precipitate was observed. The crude product was filtered under reduced pressure, washed with water, dried on air and purified using column chromatography (silica gel–DCM).

15 (*a*) M. Pietka-Ottlik, H. Wojtowicz-Mlochowska, K. Kolodziejczyk, E. Piasecki and J. Mlochowski, *Chem. Pharm. Bull.*, 2008, **56**, 1423; (*b*) M. Pietka-Ottlik, P. Potaczek, E. Piasecki and J. Mlochowski, *Molecules*, 2010, **15**, 8214; (*c*) K. P. Bhabak, A. A. Vernekar, S. R. Jakka, G. Roy and G. Mugesh, *Org. Biomol. Chem.*, 2011, **9**, 5193; (*d*) J. Mlochowski, K. Kloc, L. Syper, A. D. Inglot and E. Piasecki, *Liebigs Ann. Chem.*, 1993, **12**, 1239; (*e*) J. Mlochowski, R. J. Gryglewski, A. D. Inglot, A. Jakubowski, L. Juchniewicz and K. Kloc, *Liebigs Annales*, 1996, **11**, 1751.

16 F. Kumakura, B. Mishra, K. I. Priyadarsini and M. Iwaoka, *Eur. J. Org. Chem.*, 2010, 440.

17 K. Arai, F. Kumakura and M. Iwaoka, *FEBS Open Bio*, 2012, **2**, 60.

 This journal is © The Royal Society of Chemistry 2014