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Synthesis and antioxidant activity of silicon analogue of butylhydroxytoluene

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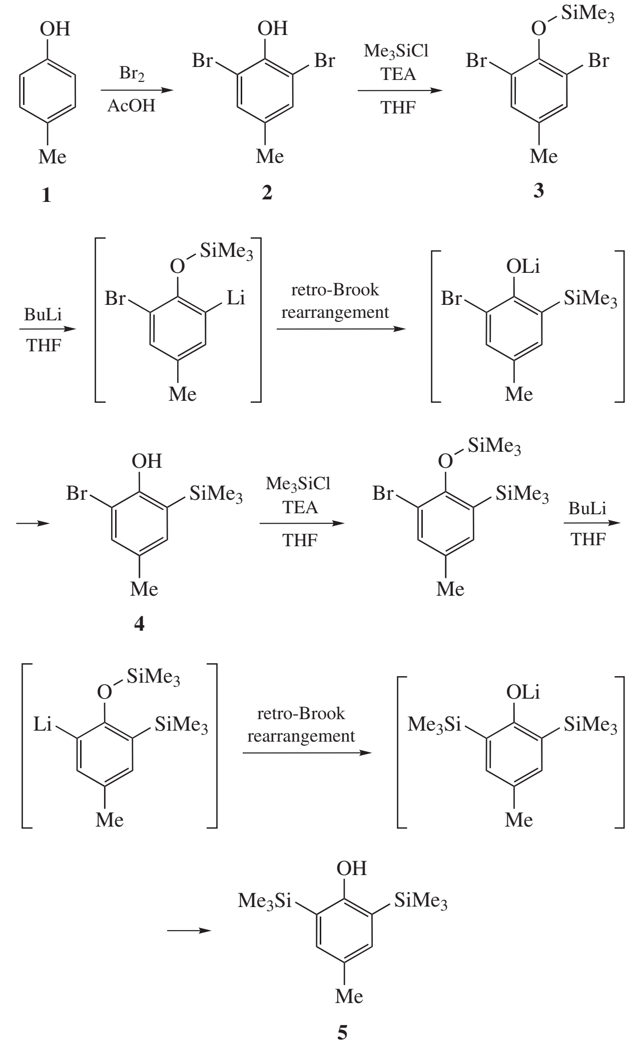
Effect of a silicon analogue of butylated hydroxytoluene, 2,6-bis(trimethylsilyl)-*p*-cresol, on the non-enzymatic formation of NO in *in vitro* experiments under the artificial nitrosative stress conditions was demonstrated.

Antioxidants are compounds that inhibit oxidation reactions by neutralizing free radicals which form in their course. A class of oxygen-containing free radicals are known as reactive oxygen species (ROS) and includes the hydroxyl radical (HO$^\bullet$), superoxide anion ($^\bullet O_2^-$) and hydrogen peroxide (H_2O_2). ROS are highly toxic oxidants and are formed during the metabolism of oxygen.[1] ROS accumulation may cause cells injury through the destruction of lipids, proteins, nucleic acids, sugars and other cellular components.[2] Many diseases such as cancer, atherosclerosis, Alzheimer's and Parkinson's diseases, rheumatoid arthritis and coronary heart disease are associated with oxidative damage of biomolecules.[3–5] The use of antioxidants can prevent radical-induced damage and thus allow one to stave off and treat the above mentioned diseases.[6,7] In addition, antioxidants are also widely used in food, cosmetics, synthetic polymers and many other industrial processes.[8]

One of the particular classes of antioxidants is the group of natural and synthetic phenols. The ability of phenolic compounds to quench free radicals arises due to both their acidity (ability to donate protons) and their delocalized π-electrons characteristic of benzene rings (ability to transfer electrons while remaining relatively stable). The most famous representatives of phenolic antioxidants are butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA) and *tert*-butylated hydroxyquinine (TBHQ). These compounds are widely used as food and cosmetic additives. In spite of this, their application is under question because of possible side effects for human health and also they are suspected of being responsible for carcinogenesis and liver damage.[9–11]

Introduction of silicon into biologically active compounds often leads to the increase in activity, decrease in toxicity, prolongation of the action and increase in lipophilicity. Sila-substitution (C/Si exchange) of existing drugs is an approach to search for new drug-like candidates that have beneficial biological properties.[12] Thus, it is possible to assume that the replacement of *tert*-butyl group in BHT by bioisosteric trimethylsilyl one can cause increase in the antioxidant activity.

The main purpose of this work was to study the influence of the replacement of *tert*-butyl group by the bioisosteric trimethylsilyl one on antioxidant activity using BHT (Scheme 1).[†] Note that the synthesis of various TMS-substituted phenols and the investigations of the transformations of these organosilicon aroxyls were previously reported.[13–18]



Scheme 1

[†] All solvents were purified before the use. THF was distilled from sodium/benzophenone and triethylamine was distilled from KOH. All reagents were obtained from Aldrich Chemical Co. The reactions were monitored by TLC using Fluka silica gel (60 F 254) plates (0.25 mm). Column

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Silicon derivative **5** was prepared in five steps from 4-methylphenol **1** (see Scheme 1). 2,6-Dibromo-4-methylphenol **2** was obtained by treatment of starting **1** with bromine in acetic acid.[19] Reaction of compound **2** with chlorotrimethylsilane in THF using triethylamine as a base gave its TMS ether **3** in good yield (89%). Lithiation of compound **3** with 1 equiv. of BuLi at –78 °C in THF followed by heating to room temperature caused the retro-Brook rearrangement with the formation of compound **4** in 93% yield.[20] The final product **5** was obtained in good yield by the repeating silylation of **4** with subsequent retro-Brook rearrangement. The ^{1}H NMR spectrum of compound **5** showed singlets at δ 0.32 (SiMe), 2.27 (Ph*Me*), 4.83 (OH) and 7.15 (Ph). Structure of compound **5** has also been confirmed by IR, ^{13}C, ^{29}Si NMR spectroscopy and elemental analysis.

Antioxidant activity of the silicon analogue of BHT **5** was investigated with the use of two solvents, DMSO and ethanol.[‡] The type of activity and the ability to inhibit non-enzymatic formation of nitrogen monoxide was found to preferably depend on structural properties of compounds because the change of the solvent does not lead to a breach of anti- and prooxidant activities of compounds.

Table 1 Antioxidant activity of 2,6-bis(trimethylsilyl)-4-methylphenol **5** in comparison with various antioxidants on the photoproduction model of NO.

Compound	Antioxidant activity (%) (in DMSO)
Butylhydroxytoluene	31.20 ± 2.34
2,6-Bis(trimethylsilyl)-4-methylphenol	52.90 ± 3.47
2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4*H*-chromen-4-one (Quercetin)	75.50 ± 5.64
2-Ethyl-6-methyl-3-hydroxypyridine (Mexidol)	20.10 ± 1.15
6-Hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid (Trolox)	8.80 ± 0.48
2-[2-(2,6-Dichlorophenylamino)phenyl]acetic acid (Diclofenac)	43.30 ± 3.17
(±)-5-Benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylic acid, 2-amino-2-(hydroxymethyl)-1,3-propanediol (Ketorolac)	32.20 ± 2.62

Investigation of antiradical activity parameters on the photoproduction model of NO showed a significant difference between the test compounds (Table 1). In comparison with the control, quercetin has the largest value of antiradical activity. At the same time, compound **5** inhibits the formation of nitrogen monoxide up to 52.9% which significantly exceeds the value of antiradical activity for BHT (31.2%). Widely used in clinical practice antioxidant Mexidol inhibits oxidation of ascorbate up to 20.1%, while Trolox (water-soluble analogue of vitamin E) inhibits oxidation of ascorbate only to 8.8%.

In conclusion, the silicon analogue of BHT **5** exhibits the highest inhibition of the formation of active form of nitrogen monoxide among the investigated non-natural alkylphenols. This may be related to the influence of silicon on delocalized π-electrons, that promotes the increased mobility of hydrogen atom in the phenolic group. Finally, as it is known it causes the high antiradical activity of alkylphenols. Note that famous analgesics Diclofenac and Ketorolac inhibit oxidation of ascorbate up to 43.3% and 32.2%, respectively. The results obtained are useful in search for new antioxidants, in particular organoelement ones.

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chromatography was carried out using Merck 60 (230–400 mesh) silica gel. Visualization was made with UV light. ^{1}H NMR spectra were recorded on a Bruker WP 250 SY spectrometer (250.13 MHz). ^{13}C and ^{29}Si NMR spectra were recorded on a Bruker DRX500 spectrometer. Chemical shifts are reported relative to chloroform (δ 7.25 ppm for ^{1}H NMR and 77.00 ppm for ^{13}C).

(2,6-Dibromo-4-methylphenoxy)trimethylsilane **3**. Triethylamine (9.11 g, 0.09 mol) was added to a stirred solution of 2,6-dibromo-4-methylphenol **2** (20 g, 0.075 mol) in THF (100 ml) at 0 °C followed by dropwise addition of chlorotrimethysilane (8.97 g, 0.083 mol). The mixture was stirred at room temperature for 2 h. The solvent was removed *in vacuo* and the residue was diluted with hexanes (150 ml). The solid precipitate was filtered off and washed with hexane. The filtrate was concentrated *in vacuo* to afford compound **3** as colourless oil, yield 89%. IR (CsI, ν/cm^{-1}): 2956, 1469, 1286, 1254, 922, 877, 850, 761, 739. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 0.36 (s, 9H, SiMe), 2.23 (s, 3H, Ph*Me*), 7.27 (s, 2H, Ph). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 1.24, 19.95, 115.60, 132.76, 133.35, 148.27. ^{29}Si NMR (59 MHz, CDCl$_3$) δ: 24.7. Found (%): C, 35.59; H, 4.29; Br, 47.56; Si, 8.09. Calc. for $C_{10}H_{14}Br_2OSi$ (%): C, 35.52; H, 4.17; Br, 47.26; Si, 8.31.

2-Bromo-4-methyl-6-trimethylsilylphenol **4**. A 1.6 M solution of BuLi in hexane (18.75 ml, 0.03 mol) was added dropwise to a stirred solution of compound **3** (10 g, 0.03 mol) in absolute THF (40 ml) at –80 °C under argon. The mixture was stirred at –80 °C for 1 h, then it was warmed to room temperature and 80 ml of water acidified with acetic acid was added under stirring. The aqueous layer was extracted twice with dichloromethane and washed with water. The extracts were dried (Na$_2$SO$_4$), the solvent was evaporated *in vacuo* to give compound **4** as colourless oil, yield 93%. IR (CsI, ν/cm^{-1}): 3523, 2954, 1564, 1450, 1392, 1321, 1246, 1234, 1176, 1078, 908, 840, 766, 744. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 0.30 (s, 9H, SiMe), 2.26 (s, 3H, Ph*Me*), 5.54 (s, 1H, OH), 7.07 (d, 1H, Ph, *J* 1.8 Hz), 7.27 (d, 1H, Ph, *J* 1.8 Hz). ^{13}C NMR (75 MHz, CDCl$_3$) δ: –1.15, 20.21, 110.06, 126.57, 130.88, 133.06, 135.04, 153.84. ^{29}Si NMR (59 MHz, CDCl$_3$) δ: –3.14. Found (%): C, 46.35; H, 5.78; Br, 30.68; Si, 10.53. Calc. for $C_{10}H_{15}BrOSi$ (%): C, 46.33; H, 5.83; Br, 30.83; Si, 10.83.

2,6-Bis(trimethylsilyl)-4-methylphenol **5**. *Step 1.* (2-Bromo-4-methyl-6-trimethylsilylphenoxy)trimethylsilane was prepared similarly to **3**. Colourless oil, yield 83%. IR (CsI, ν/cm^{-1}): 2954, 2900, 1435, 1389, 1265, 1248, 1211, 1086, 930, 887, 847, 768, 748. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 0.29 (s, 9H, SiMe), 0.38 (s, 9H, SiMe), 2.25 (s, 3H, Ph*Me*), 7.07 (d, 1H, Ph, *J* 2.4 Hz), 7.34 (d, 1H, Ph, *J* 2.4 Hz). ^{13}C NMR (75 MHz, CDCl$_3$) δ: –0.16, 2.41, 20.12, 113.59, 131.82, 132.45, 135.11, 135.17, 154.74. ^{29}Si NMR (59 MHz, CDCl$_3$) δ: –3.47, 19.26. Found (%): C, 47.26; H, 7.09; Br, 24.15; Si, 16.71. Calc. for $C_{13}H_{23}BrOSi_2$ (%): C, 47.12; H, 7.00; Br, 24.11; Si, 16.95. *Step 2.* Compound **5** was prepared similarly to **4**. Colourless oil, yield 74%. IR (CsI, ν/cm^{-1}): 3604, 3024, 2958, 2900, 1577, 1412, 1311, 1250, 1173, 856, 837. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 0.32 (s, 18H, SiMe), 2.27 (s, 3H, Ph*Me*), 4.83 (s, 1H, OH), 7.15 (s, 2H, Ph). ^{13}C NMR (75 MHz, CDCl$_3$) δ: –0.5, 20.6, 123.9, 129.1, 137.1, 163.1. ^{29}Si NMR (59 MHz, CDCl$_3$) δ: –5.96. Found (%): C, 62.27; H, 9.70; Si, 21.84. Calc. for $C_{13}H_{24}OSi_2$ (%): C, 61.84; H, 9.58; Si, 22.25.

[‡] Antioxidant activity was estimated by the degree of the inhibition of active form of NO *in vitro* according to reported method,[21] which is based on the ability of sodium nitroprusside to autoxidate under the action of light with the formation of NO.[22] NO induction was caused by the action of light (40 W) on samples with sodium nitroprusside. Irradiation was carried out for 60 min at 20 °C. The incubation mixture contained 4 ml 0.001% solution of sodium nitroprusside, 0.5 ml 0.01% solution of sodium ascorbate and 0.5 ml solution of the test compounds (solvents – DMSO and ethanol) with a finite value of the titer in the total incubation mixture equal to 0.03 mg ml^{-1}. BHT was used as a comparative drug.

The efficiency of inhibition of the formation of NO was determined by the inhibition of oxidation of ascorbate by recording the change in optical density of solution at 264 nm on an SF-26 spectrophotometer. Antioxidant activity was expressed in percentage inhibition of oxidation of ascorbate. In parallel, a control sample that did not contain drugs was tested. The optical density of solutions was measured before and after incubation. Mathematical processing of the results was carried out by the methods of variational statistics using the Student's *t*-test.[23]

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