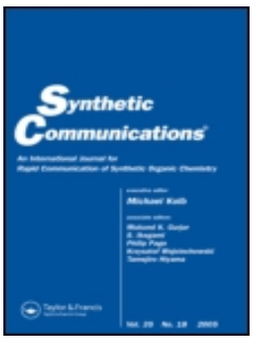

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Synthesis and investigation of antimicrobial activity of compounds derived from benzo[C][1,2,5]oxadiazole-1-oxides and phenolates

Elena A. Chugunova[a], Nurgali I. Akylbekov[b], Alexandra D. Voloshina[a], Natalia V. Kulik[a], Vladimir V. Zobov[a], Vasily M. Babaev[a], Nikolai V. Gavrilov[b], and Alexander R. Burilov[a]

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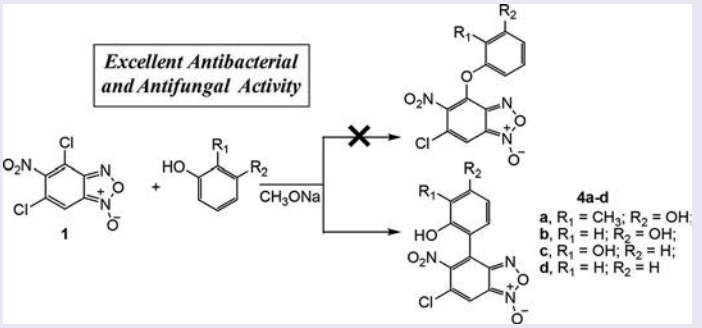
ABSTRACT

(Di)chloro(di)nitrobenzofuroxans form substitution products involving carbon atoms with phenolates in isopropyl alcohol medium. In the case of 4,6-dinitro-5,7-dichlorobenzofuroxan, besides replacement of one chlorine atom and the formation of *C*-bonded product, we observed the hydrolysis of the second chlorine and replacement of it by hydroxyl group. Products of reaction of 4,6-dichloro-5-nitrobenzofuroxan with phenolates display excellent antimicrobial activity and have dual action, both against bacteria and fungi.

GRAPHICAL ABSTRACT



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KEYWORDS
Antimicrobial activity; benzofuroxan; *C*-bonded product; dual action; phenolates

Introduction

It is known that benzofuroxan derivatives belong to one of the most important classes of heterocycles and possess interesting properties in theoretical and applied areas.[1–3] There is considerable interest in this organic scaffold because of its ability to release nitric oxide (NO) molecules under physiological conditions in medicinal and biological areas.[4,5] Another reason for the growing interest is the instability of NO aqueous solutions; it is necessary to find compounds that will be able to generate NO in situ (NO donors or NO releasing agents). Benzofuroxan derivatives display typical NO-dependent activities both in vitro and in vivo, and the possibility of modulating NO release by changing the

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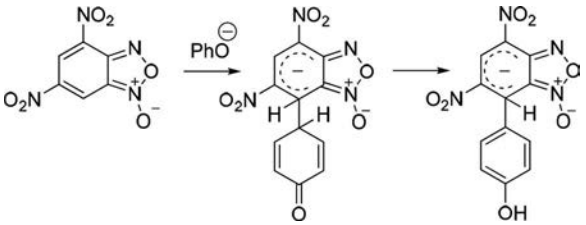
substituent on the ring makes them versatile tools in designing NO donor/drug hybrids.[6] Indeed, particular attention has been devoted to complexed molecules containing benzofuroxanyl and other biologically active subunits.

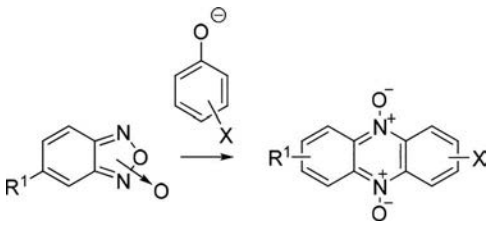
Phenolic compounds are widely distributed in plants and, due to their antioxidant activity, present potential beneficial health effects. As well as delaying autoxidation of unsaturated lipids in products, they also show significant antimicrobial activity.[7] Pioneering work on the antimicrobial activity of synthetic phenolic antioxidants was published by Ward and Ward.[8] Such phenolic compounds (including synthetic antioxidants) display high antimicrobial activity against several bacteria. It is also has been shown that phenolic compounds like catechol and coumarin display bactericidal and fungicidal activities.[9] Branen et al.[10] found that phenolic antioxidants exert inhibitory properties against several types of bacteria.[11] The antimicrobial activity of phenolic antioxidants appears to depend on the presence of a hydroxyl group on the molecule, the lipid solubility of the compound, and the degree of steric hindrance.

We realized that it would be of interest to synthesize novel compounds containing both systems, benzofuroxan—able to release NO—and phenol derivatives—acting as free radical traps and showing high antioxidant and antimicrobial activity.

It was well established by Buncel et al.[12] that, due to the powerful electron-withdrawing N-oxide group of 4,6-dinitrobenzofuroxan, it reacts with phenoxide ion to give a carbon-bonded reaction adduct at C-7. The oxygen-bonded adduct was not observed.

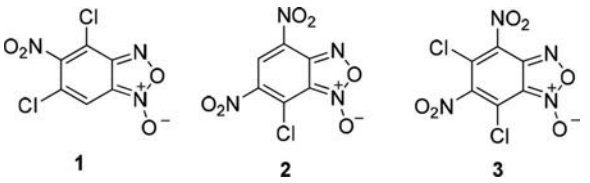


According to another literature source, phenolate anions and benzo[1,2-*c*]1,2,5-oxadiazole *N*-oxides (benzofuroxans) react to afford phenazine N_5,N_{10}-dioxide derivatives.[13,14] These compounds are known to have high antibacterial activity.[15]



These results prompted us to use structurally similar (di)chloro(di)nitrobenzofuroxan derivatives, namely 4,6-dichloro-5-nitrobenzofuroxan **1**, 7-chloro-4,6-dinitrobenzofuroxan

2, and 4,6-dinitro-5,7-dichlorobenzofuroxan **3**, in the reaction with different *N*- and *S*-nucleophiles.[16–18]

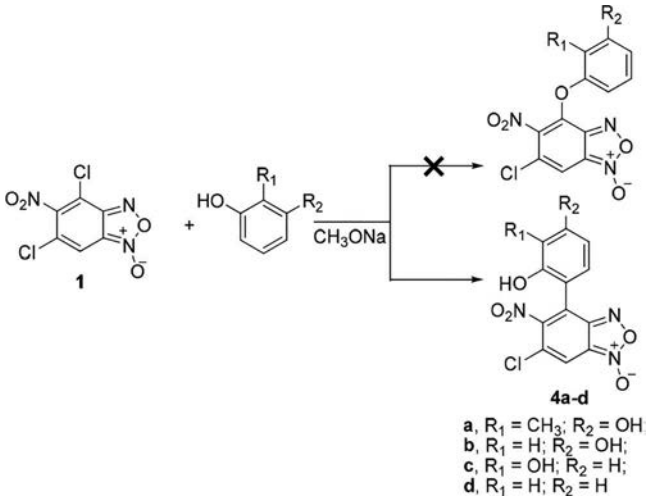


Herein, we present the results of our research involving the interaction of 4,6-dichloro-5-nitrobenzofuroxan **1**, 7-chloro-4,6-dinitrobenzo-furoxan **2**, and 4,6-dinitro-5,7-dichloro-benzofuroxan **3** with phenolats such as phenol, resorcinol, methylresorcinol, and pyrocatechin.

Results and discussion

Chemistry

It is known that benzofuroxans are not stable in alkalis, so we used sodium methoxide, prepared by reaction of sodium in excess of methanol for obtaining of phenol, resorcinol, methylresorcinol, and pyrocatechin anions. Reaction of phenol, resorcinol, methylresorcinol, and pyrocatechin with freshly prepared sodium methoxide was carried out by heating to 50 °C for 30 min to obtain the corresponding sodium salt. Interaction of salts with 4,6-dichloro-5-nitrobenzofuroxan were performed at ratios of 1:1 and 2:1, but regardless of the reactant ratio, the reactions took place with the sole formation of the mono-substitution product (Scheme 1). On the basis of ^{1}H NMR, mass spectrometry, and elemental analysis we have established the structure of the reaction products (Figs. S1 and S2, Supporting



Scheme 1. Reaction between 4,6-dichloro-5-nitrobenzofuroxan and phenolates.

Information). The structures of obtained compounds are different from expected ones, oxygen-bonded substitution products. Instead of three signals characteristic for *O*-bonded product (two doublets and a triplet) we can see on the ^{1}H NMR spectra only two signals—two doublets—that confirm the *C*-bonded structure (Fig. S1, Supporting Information). An unusual reaction, apparently, can be explained by the fact that the hydroxy group of phenol strongly activates the aromatic ring to give substitution products involving carbon atoms.

As depicted in Fig. S2, SI, the electrospray ionization–mass spectra (ESI-MS) of compound **4a** show a series of peaks. The signals appear at *m/z* 336.0 and 673.1, which is attributed to $[M-H]^-$ and $[2M-H]^-$ respectively. The isotopic patterns for all peaks are in good agreement with the predicted isotopic distribution patterns.

Similar behavior is observed in the reaction of 7-chloro-4,6-dinitrobenzofuroxan **2** with methylresorcinol (Scheme 2, Fig. S3, S4, SI).

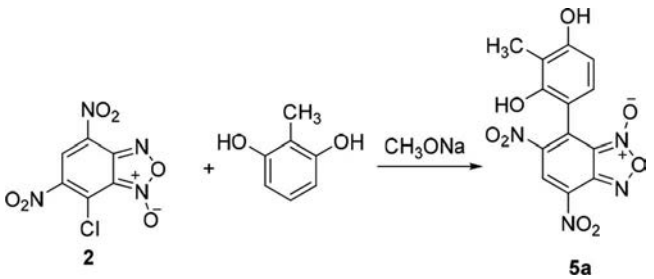
In the case of 4,6-dinitro-5,7-dichlorobenzofuroxan **3**, besides replacement of one chlorine atom and the formation of *C*-bonded product, we observed the hydrolysis of the second chlorine and replacement of it by hydroxyl group (singlet at 4.08 ppm) (Scheme 3, Fig. S5, S6, SI).

Thus, as a result of our experiments we developed the method of synthesis of phenol-containing benzofuroxans.

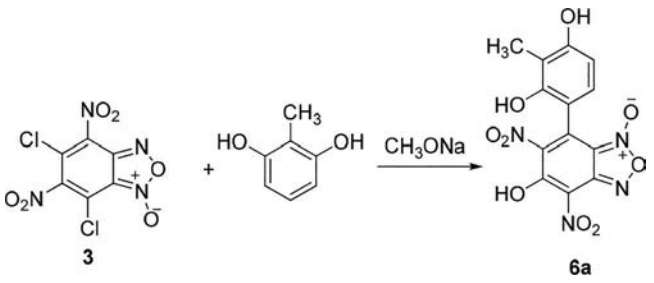
Biological activity

All the target compounds were evaluated for their antibacterial and antifungal activity against several pathogenic representative Gram-negative bacteria [*Pseudomonas aeruginosa* (Pa) 9027 and *Escherichia coli* (Ec) F-50], Gram-positive bacteria [*Staphylococcus aureus* (Sa) 209p, *Bacillus cereus* (Bc) 8035], molds [*Aspergillus niger* (An) BKMF-1119, *Trichophyton mentagrophytes var. gypseum* (Tm) 1773], and yeast [*Candida albicans* (Ca) 885-653]. The minimal inhibitory concentration (MIC) was determined by the broth dilution methods against the aforementioned strains and defined as the lowest concentration that exhibited no growth. The activities of compounds **4a–4c** are collected in Table SI along with those of reference drugs nitroxoline, ciprofloxacin, ofloxacin, norfloxacin, and ketoconazole. Compounds **4d, 5a**, and **6a** exhibited no activity under the circumstances that were tested.

Compounds **4a–c** display excellent activity against *Staphylococcus aureus* 209p strain and is more active compared to nitroxoline (MIC = 3.9 μg/mL). Compound **4a** is more active against *Staphylococcus aureus* 209p (MIC 0.19 μg/mL) than the reference drug



Scheme 2. Reaction between 4,6-dinitro-7-chlorobenzofuroxan and methylresorcinol.



Scheme 3. Reaction between 4,6-dinitro-5,7-dichlorobenzofuroxan and methylresorcinol.

ciprofloxacin (0.25 μg/mL) and more active against *Candida albicans* (MIC 3.1 μg/mL) than the reference drug ketoconazole (3.9 μg/mL), so this compound has dual action—against both Gram-positive bacteria and fungi, whereas the activity against Gram-negative bacteria was not satisfactory.

Conclusion

As a result of reactions with the phenolic derivatives it was found that (di)chloro(di)-nitrobenzofuroxans form substitution products involving carbon atoms with phenolates in isopropyl alcohol medium. Products **4a**–**4c** display excellent antimicrobial activity, whereas **4a** is active both against bacteria and fungi.

Materials and methods

Chemistry

The initial benzofuroxan derivatives **1**–**3** were synthesized according to the known procedures.[19–21]

General procedure for the synthesis of compounds

A suspension of sodium methoxide was prepared (Na, 0.023 mg, 0.001 mol, in 5.0 mL of anhydrous methanol) at room temperature. After complete dissolution of sodium the corresponding phenol (0.001 mol) was added and the mixture was stirred at 50 °C for 30 min. Benzofuroxan (0.001 mol) in 5 ml of anhydrous methanol at room temperature was added; the reaction mixture was stirred at room temperature for 2 h and precipitated in distilled water with a few drops of hydrochloric acid; and the solid was filtered, washed with cold water, and dried in vacuum (0.06 mm Hg) at 40°C to constant weight.

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