ISSN 1070-3632, Russian Journal of General Chemistry, 2018, Vol. 88, No. 5, pp. ????–????. © Pleiades Publishing, Ltd., 2018.
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5-Amino-Substituted Derivatives of 4-Nitrofurazane: Synthesis, Structure, and Biological Activity

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Received November 23, 2017

Abstract—New amination reactions of 5-chloro-4-nitrobenzofurazane with different amines were studied. The reactions of 5-chloro-4-nitrobenzofurazane with 2,4,6-trichloro-, *para*-acetyl-, and *para*-carboxyethylanilines gave the products of aromatic nucleophilic substitution of the chlorine substituent in the nitrogenous heterocycle, the composition and structure of which was established by chemical, physical, and physicochemical methods and X-ray diffraction analysis. The thermal stability was studied by synchronous thermogravimetry and differential scanning calorimetry (TG–DSC). The synthesized compounds showed a high antibacterial and antimycotic activity against human and animal pathogenic microflora.

Keywords: substituted anilines, 5-chloro-4-nitrobenzofurazane, nucleophilic aromatic substitution, heterocyclic compounds

DOI: 10.1134/S1070363218050092

Electrophilic–nucleophilic interactions are the most common processes in the synthetic organic chemistry of such nitrogenous heterocycles as substituted benzofurazanes and their oxides [1–10]. The methods for activation of aromatic heterocycles and, consequently, involvement them in nucleophilic aromatic substitution reactions are well known. The most used approach is the introduction of electron-acceptor substituents, for example, nitro groups, into such systems. 5-Chloro-4-nitrobenzofurazane is quite a reactive system containing an electrophilic benzofurazane ring which is prone to aromatic nucleophilic substitution (S_NAr) reactions due to the presence of an electron-acceptor substituent, specifically, nitro group. The amination of 5-chloro-4-nitrobenzofurazane with different amines occurs by the S_NAr mechanisms and leads to the products of aromatic nucleophilic substitution of the chlorine substituent in the six-membered ring with HCl elimination.

It is well known that substituted benzofurazanes and their oxides exhibit broad-range biological activity [1–5].

According to our previous findings gave unambiguous evidence showing that the reactions of dichlorodinitrobenzofuroxane and -furazane with different phosphines and amines in an alcohol–ether medium form exclusively the products of nucleophilic aromatic substitution of the Cl and NO_2 substituents in the nitrogenous heterocycle [6–10].

Aimed at extending the range of biologically active compounds, we reacted 5-chloro-4-nitrobenzo[*c*]-[1,2,5]oxadiazole **1** with such substituted anilines as *para*-acetyl-, *para*-carboxyethyl-, and 2,4,6-trichloroaniline in an ether–alcohol medium to synthesize the corresponding nucleophilic substitution products. The three reactions all gave monosubstituion products **3**, **5**, and **7**, respectively.

The reaction chloronitrobenzofurazane **1** with 2,4,6-trichloroaniline **2** at room temperature in a 1 : 3 ethanol–diethyl ether binary solvent resulted in the isolation of 4-nitro-*N*-(2,4,6-trichlorophenyl)benzo[*c*][1,2,5]oxadiazole-5-amine **3** (Scheme 1) as needle-like dark orange crystals, mp 138.4°C.

The composition and structure of the synthesized compound were confirmed by physical and physicochemical methods, including X-ray diffraction (XRD) analysis (Figs. 1 and 2). As seen from the figures, the trichlorophenylamino substituent in the aromatic ring of benzofurazane is orthogonal to the benzofurazane-ring plane due to steric strain.

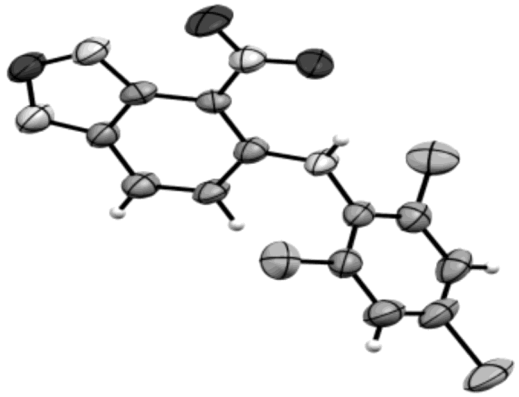


Fig. 1. General view of compound **3** in a crystal.

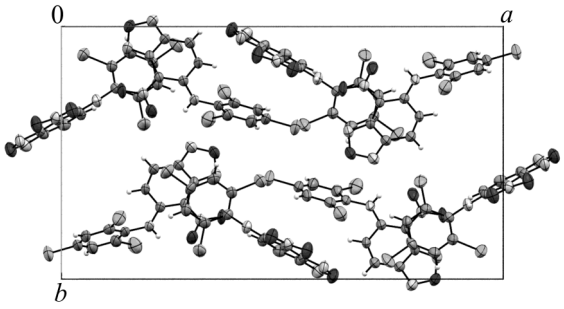


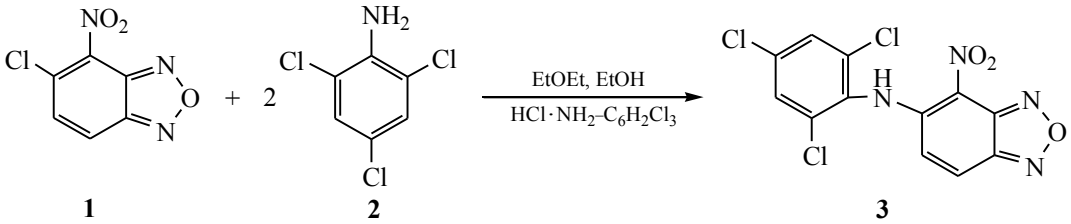
Fig. 2. Crystal packing of compound **3**.

Interesting results were obtained in the reactions 5-chloro-4-nitrobenzofurazane with two other structurally similar substituted anilines. Compound **1** readily reacts with ethyl *p*-aminobenzoate **4** in an alcohol–ether medium at room temperature to form product **5** (Scheme 2) as orange crystals, mp 260.3°C (TG–DSC data). The reaction of compound **1** with *p*-acetylaniline **6** in an alcohol–ether medium at room temperature gives product **7** (Scheme 3) as bright orange crystals, mp 257.3°C.

The composition and structure of compounds **5** and **7** were studied by elemental and XRD analysis and IR and NMR spectroscopy. Synchronous TG–DSC analysis revealed almost no weight loss up to the melting point, thereby providing evidence for a high thermal stability of the synthesized compounds. On the basis of the obtained compounds **5** and **7** were identified as the monosubstitution products ethyl {4-(4-nitrobenzo[*c*]-[1,2,5]oxadiazol-5-yl)amino}benzoate (**5**) and 1-{4-[(4-nitrobenzo[*c*][1,2,5]oxadiazol-5-yl)amino]phenyl}ethanone (**7**). Their IR spectra display absorption bands in the range 3450–3500 cm^{-1}, characteristic of the N–H bond in secondary amines, and a band at 1260 cm^{-1}, characteristic of the C–N bond in secondary amines. The strong band at 1700 cm^{-1} is assignable to the C=O bond and the bands around 1620 cm^{-1} provide evidence for the presence a benzofurazane C=N–O bond.

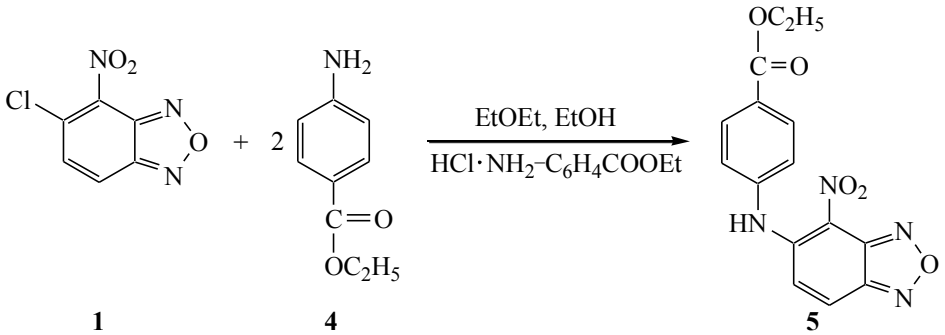
The structure of 1-{4-[(4-nitrobenzo[*c*][1,2,5]oxadiazol-5-yl)amino]phenyl}ethanone **7** was confirmed by XRD analysis (Figs. 3 and 4).

Scheme 1.



1 **2** **3**

Scheme 2.



1 **4** **5**

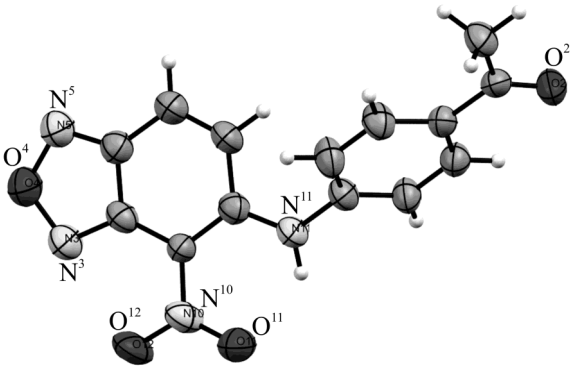


Fig. 3. General view of compound **7** in a crystal.

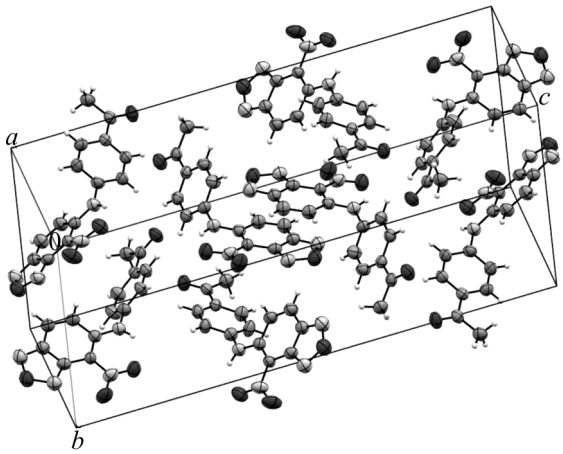


Fig. 4. Crystal packing of compound **7**.

Thus we found that the reactions of 5-chloro-6-nitrobenzofurazane with substituted anilines in an alcohol–ether medium involve nucleophilic substitution of the chlorine substituent in the furazane heterocycle. The characteristics of the synthesized compounds are listed in Table 1.

Products **3**, **5**, and **7** were tested for biological activity against pathogenic and conditionally pathogenic human and animal microflora. Compounds **3** and **7** showed the highest activity (Table 2), and they can be recommended for further study as a potential antiseptic and an antimycotic anti-inflammatory agents, respectively.

EXPERIMENTAL

The solvents were purified by standard procedures [11]. All starting reagents were used freshly distilled and identified by comparison of their physicochemical characteristics with published data.

The purity and thermal stability of the synthesized compounds were studied by synchronous thermal analysis (TG–DSC) on a NETZSCH STA 449C instrument in the temperature range from 20 to 400°C in an argon medium; heating rate 10 deg/min. The IR spectra were measured on a Thermo Avatar 360 FT-IR spectrometer in the range 500–3700 cm^{-1} for Nujol suspensions or in thin films between KBr plates. The NMR spectra were measured on a Bruker Avance III 400 spectrometer. The XRD patterns were obtained on a Bruker AXS APEX-II CCD instrument, MoK_α radiation (λ 0.71073 Å), at 293(2) K, using APEX2 [12] and SAINT software [13]. Absorption was included using SADABS software (version 2.10) [14]. Structure solution and least-squares refinement were performed using SHELXS97 [15] and SHELXL-2014 software [16].

Synthesis of compounds 3, 5, and 7 *(general procedure).* A 1 : 2 mixture of 5-chloro-4-nitrobenzofurazane in an alcohol–ether binary solvent was stirred at room temperature from 2 h to 2 weeks and then left to stand at room temperature for 2 weeks. Transparent crystals formed and were separated, washed with diethyl ether, and dried. The yields of the reaction products, spectral characteristics, and elemental analyses are listed in Table 1.

Scheme 3.

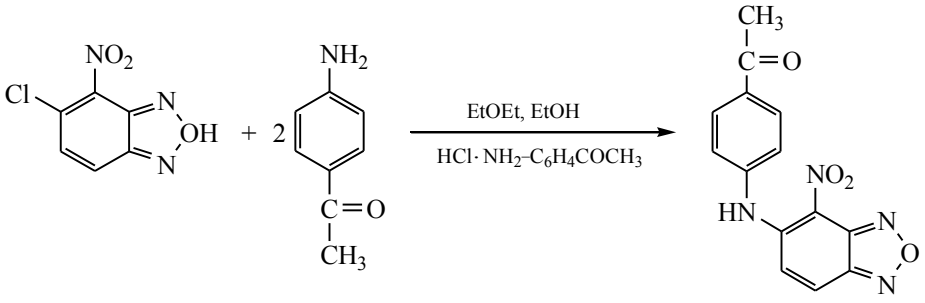


Table 1. Yields, melting points, and elemental analyses of compounds **3**, **5,** and **7**

Comp. no.	Yield, %	mp, °C	ν, cm^{-1}	Found, %			Formula	Calculated, %		
				C	H	N		C	H	N
3	61	138.4	3310 (NH), 1630 (C=N–O), 1523 (NO_2), 980 (N–O), 770 (C–Cl)	40.01	1.02	16.00	$C_{12}H_5Cl_3N_4O_3$	40.06	1.39	15.58
5	81	260.3	3450 (NH), 1700 (C=O), 1620 (C=N–O), 1523 (NO_2), 980 (N–O)	54.85	3.53	17.19	$C_{15}H_{12}N_4O_5$	54.88	3.66	17.07
7	80	257.3	3500 (NH), 1670 (C=O), 1620 (C=N–O), 1527 (NO_2), 980 (N–O)	56.13	3.09	18.56	$C_{14}H_{10}N_4O_4$	56.38	3.36	18.79

Table 2. Antimicrobial activity of compounds **3, 5**, and **7** and reference compounds (c = 50 μg/mL) estimated by the growth inhibition for pathogenic and conditionally pathogenic microflora (mm)

Compound	*Staphylococcus aureus*	*Escherihia coli*	*Pseudomonas aeruginosa*	*Bacillus subtilis*	*Candida albicans*
3	11	10	0	12	18
5	0	0	9	8	10
7	21	11	9	11	25
Penicillin	23	13	8	6	–
Nitrofungin	0	0	0	0	11

Crystals of compound **3** rhombic, $C_{12}H_5Cl_3N_4O_3$, crystal dimensions 0.090×0.272×0.886 mm^3, M 359.55 g/mol, space group $Pna2_1$, Z 8, a 24.850(8), b 14.148(4), c 7.959(3) Å, V 2798.2(16) $Å^3$, d_{calc} 1.707 g/cm^3, μ 0.672 mm^{-1}, collected reflections 25410 ($-32 \le h \le 33$, $-18 \le k \le 18$, $-10 \le l \le 10$), in the θ range from 1.64° to 28.43°, 6944 unique (R_{int} 0.0605) and 4509 observed reflections [$I \ge 2\sigma(I)$], 398 refinement parameters, R_1 0.0478, wR_2 0.0834, maximal residual electron density 0.249 (–0.232) $e/Å^3$. The crystal data were deposited at the Cambridge Crystallographic Data Center (CCDC 1563496).

Crystals of compound **7** rhombic, crystal dimensions 0.220×0.241×0.491 mm^3, M 298.26 g/mol, space group $Pbca$, Z 8, a 7.407(15), b 13.45(3), c 25.80(5) Å, V 2570.(9) $Å^3$, d_{calc} 1.541 g/cm^3, μ 0.117 mm^{-1}, collected reflections 20273 ($-9 \le h \le 9$,$-17 \le k \le 17$, $-34 \le l \le 33$), in the θ range from 3.03° to 28.27°, 3135 unique (R_{int} 0.1284) and 1407 observed reflections [$I \ge 2\sigma(I)$], 204 refinement parameters, R_1 0.0621, wR_2 0.1517, maximal residual electron density 0.325 (–0.410) $e/Å^3$. The crystal data were deposited at the Cambridge Crystallographic Data Center (CCDC 1563495).

The antimycotic and antibacterial activity of substituted benzofurazanes **5–7** was tested on the test cultures of pathogenic and conditionally pathogenic microflora: *Staphylococcus aureus* (ATCC 29213), *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853), *Bacillus subtilis* (B-10641), and *Candida albicans* (ATCC 885-653). The one-day cultures of microorganisms were washed out with saline solution from slant plain agars, standardized by McFarland turbidity standard no. 0.5 (1.5×10^8 CFU/mL), and inoculated on nutrient media using swab tubes, after which the test and reference compounds (Penicillin and Nitrofungin) were introduced into wells made in the inoculated nutrient medium. The nutrient medium was Sabouraud agar for *Candida* yeast-like fungi and Mueller–Hinton broth for conditionally pathogenic microflora. The dishes were incubated for 35°C for 24–48 h, and the bacterial growth inhibition zone diameter was then measured to an accuracy of 0.1 mm (Table 2).

ACKNOWLEDGMENTS

The work was funded by the subsidy allocated to the Kazan Federal University for the state assignment in the sphere of scientific activity (project no. 4.5888.2017/8.9).

REFERENCES

1. Kessel, D. and Belton, J.G., *Canser Res*., 1975, vol. 35, p. 3735.
2. Granik, V.G. and Grigor'ev, I.B., *Oksid azota (NO). Novyi put' k poisku lekarstv* [Nitrogen Oxide (NO). A New Approach to Drug Design], Moscow: Vuzovskaya Kniga, 2004.
3. Levinson, F.S., Evgen'ev, M.I., Ermolaeva, E.A., Efimov, S.I., and Falyakhov, I.F., Garipov, T.V., and Karimova, R.G*., Pharm. Chem. J*., 2003, vol. 37, no. 10, p. 522. doi 10.1023/B:PHAC.0000014855.66913.83
4. Macphee, D.G., Robert, G.P., Ternai, B., Ghosh, P., and Stephens, R., *Chem. Biol. Interact*., 1977, vol. 19, p. 77. doi 10.1016/0009-2797(77)90043-6
5. Ghosh, P., Ternai, B., and Whitehouse, M., *Med. Res. Rev*., 1981, vol. 1, p. 159. doi 10.1002/med.2610010203
6. Galkina, I.V., Takhautdinova, G.L., Tudriy, E.V., Yusupova, L.M., Falyakhov, I.F., Pozdeev, O.K., Shulaeva, M.P., Kipenskaya, L.V., Sakhibullina, V.G., Krivolapov, D.B., Litvinov, I.A., Galkin, V.I., and Cherkasov, R.A., *Russ. J. Org. Chem*., 2013, vol. 49, no. 4, p. 591. doi 10.1134/S1070428013040167
7. Galkina, I.V., Takhautdinova, G.L., Tudrii, E.V., Yusupova, L.M., Krivolapov, D.B., Litvinov, I.A., Cherkasov, R.A., and Galkin, V.I., *Russ. J. Org. Chem*., 2013, vol. 49, no. 4, p. 598. doi 10.1134/ S107428013040179
8. Galkina I.V., Tudriy E.V., Kataeva O.N., Usupova L.M., Luftmann H., and Galkin V.I., *Phosphorus, Sulfur, Silicon, Relat. Elem*., 2009, vol. 184, no. 4, p. 987. doi 10.1080/ 10426500902719636
9. Galkina, I.V., Tudrii, E.V., Berdnikov E.A., Yusupova, L.M., Levinson, F.S., Krivolapov, D.B., Litvinov, I.A., Cherkasov, R.A., and Galkin, V.I., *Russ. J. Org. Chem*., 2012, vol. 48, no. 5, p. 72. doi 10.1134/ S1070428012050156
10. Galkina, I.V., Takhautdinova, G.L., Tudrii, E.V., Yusupova, L.M., Sakhibullina, V.G., Krivolapov, D.B., and Galkin, V.I., *Uch. Zap. Kazansk. Univ. Ser. Estestv. Nauki*, 2013, vol. 155, book 1, p. 61.
11. Armagero, W.L.F., *Purification of Laboratory Chemicals*, Burlington: Butterworth–Heinemann, 2009.
12. *Bruker*. APEX2 Software Suite for Crystallographic Programs, Madison, Wis, USA: Bruker, 2009.
13. *Bruker.* Area Detector Control and Integration Software. Version 5.x. SMART and SAINT. Madison, Wis., USA: Bruker Analytical X-ray Instruments, 1996.
14. Sheldrick, G.M., *SADABS*. Program for Absorption Corrections, Göttingen, Germany: University of Göttingen, 1996.
15. Sheldrick, G.M., *Acta Crystallogr., Part A*, 2008, vol. 64, p. 112. doi 10.1107/S0108767307043930
16. Sheldrick, G.M., *Acta Crystallogr., Part C*, 2015, vol. 71, p. 3. doi 10.1107/S2053229614024218