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Dearomatization of oxa- or selenadiazolopyridines with neutral nucleophiles as an efficient approach to pharmacologically relevant nitrogen compounds

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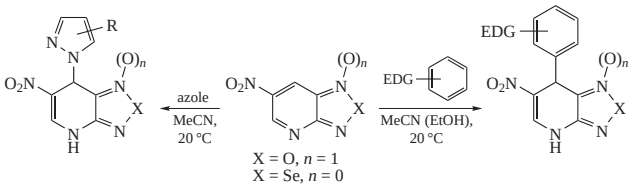
Highly electrophilic 6-nitro-4-azabenzofuroxan and 6-nitro-4-azabenzo[1,2,5]selenadiazole add π-excessive (het)arenes and other neutral nucleophiles at 7-position to give C–C- and N–C-bonded adducts, 1,4-dihydropyridines fused with furoxan or selenadiazole ring.



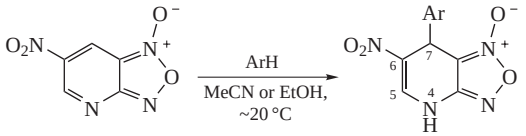
This work continues our ongoing project on synthesis of complex hybrid compounds combining several pharmacophoric moieties in the same molecule, interesting from the standpoint of design of novel pharmaceuticals.[1] In particular, approaches to polycyclic furoxan-containing potential nitric oxide donors comprising heterocyclic pharmacophoric fragments and biologically important furoxan ring have been elaborated.[2] Furoxans are considered as exogenic NO-donors and therefore extensively studied.[3]

Recently,[4] we have discovered that 6-nitro-4-azabenzofuroxan **1** reacts with CH-acids to afford carbon-bonded 1,4-adducts. In case of most acidic β-diketones, the reactions can proceed in the absence of bases, which would emphasize the highly electrophilic character of compound **1**.

Here we report on dearomatization of oxadiazolopyridine **1** with π-excessive (het)arenes. Related 6-nitro-4-azabenzo[1,2,5]selenadiazole **2** was also examined in reactions with both CH-acids and π-donor arenes. To the best of our knowledge, the reactions of fused pyridines with substituted anilines, phenols and π-donor azoles leading to 1,4-adducts have not been previously described. The only analogous example of the aniline adduct formation in reaction with benzonaphthiridine system was reported.[5]

We found that oxadiazolopyridine **1** readily reacted with π-excessive benzenoid compounds. Addition of equimolar amounts of a certain arene to its solution in MeCN or EtOH resulted in rapid formation of adducts **3a**–**d** after 15–20 min stirring at room temperature† (Scheme 1).

In products **3a**–**c**, a new bond was formed between C^7 of **1** and C^4 of the aniline. The yield of adduct with 2-naphthol was 51%. Anisole, 1,3-dimethoxybenzene and 2,4-dimethyl-6-nitroaniline did not give any adduct with substrate **1**.



1

3a Ar = 4-$H_2NC_6H_4$, 56%
3b Ar = 3-Me-4-$H_2NC_6H_3$, 55%
3c Ar = 4-$Me_2NC_6H_4$, 76%
3d Ar = 2-hydroxy-1-naphthyl, 51%

Scheme 1

Pyrazole and its derivatives bearing electron-donor groups afforded 1,4-adducts **4a**–**c** *via* N–C-bond formation (Scheme 2).† As expected, in case of *N*-methylpyrazole, formation of the adduct

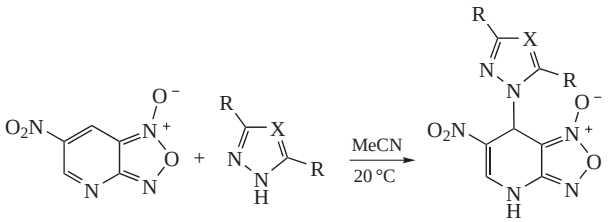
† 6-Nitro-4-azabenzofuroxan **1**[4] and 2,3-diamino-5-nitropyridine[6] were prepared as previously described.

6-Nitro-4-azabenzo[1,2,5]selenadiazole **2**. Selenium dioxide (1.22 g, 11 mmol) was added to a solution of 2,3-diamino-5-nitropyridine (1.7 g, 11 mmol) in EtOH (35 ml) and acetic acid (15 ml). The mixture was stirred under reflux for 4 h, cooled to room temperature and poured into water (200 ml). The precipitated product was filtered off and dried in air to give 1.49 g (59%) of compound **2** as brown solid, mp 123–124 °C. ^{1}H NMR (DMSO-d_6, 300.13 MHz) δ: 9.23 (s, 1H), 9.70 (s, 1H). ^{13}C NMR (DMSO-d_6, 75.47 MHz) δ: 127.5, 142.6, 149.1, 150.5, 165.2. IR (KBr, ν/cm^{-1}): 529, 739, 815, 1204, 1256, 1311, 1341, 1496, 1546, 1600, 3048, 3317. HRMS (ESI), *m*/*z*: 230.9425 $[C_5H_2N_4O_2Se + H]^+$ (calc., *m*/*z*: 230.9416).

Synthesis of compounds **3**–**5** *(general procedure).* A nucleophile (1 mmol) was added to a solution of compound **1** or **2** (1 mmol) in MeCN or EtOH (10 ml) and the mixture was stirred at room temperature for 30 min (for adducts with **1**) or 2–24 h (for adducts with **2**). The precipitated product was filtered off, washed with the same solvent (5 ml) and dried in air to give beige or brown solid adduct.

*7-(3,5-Dimethyl-4-nitro-1*H*-pyrazol-1-yl)-6-nitro-4,7-dihydro[1,2,5]oxadiazolo[3,4-*b*]pyridine 1-oxide* **4d**: yield 70%, mp 195–196 °C (decomp.). ^{1}H NMR (DMSO-d_6, 300.13 MHz) δ: 2.33 (s, 3H, Me), 2.86 (s, 3H, Me), 7.30 (s, 1H), 8.84 (s, 1H), 12.54 (br. s, 1H, NH). IR (KBr, ν/cm^{-1}): 471, 758, 832, 1006, 1174, 1239, 1312, 1363, 1486, 1568, 1583, 1643, 2848, 2977, 3087. HRMS (ESI), *m*/*z*: 346.0493 $[C_{10}H_9N_7O_6 + Na]^+$ (calc., *m*/*z*: 346.0507).

For characteristics of compounds **3a**–**d**, **4a**–**c**,**e**,**f** and **5a**–**g**, see Online Supplementary Materials.



1 **4a–f**

	R	X	Yield (%)
a	H	CH	30
b	Me	CH	65
c	Me	C–CH_2CO_2H	51
d	Me	C–NO_2	70
e	H	C–CHO	43
f	H	N	32

Scheme 2

did not occur. When unsubstituted imidazole was used, a complex mixture was formed, while 4-nitroimidazole, benzimidazole and benzotriazole were inert towards compound **1**.

Pyrazoles with electron-withdrawing substituents readily added to oxadiazolopyridine **1** with formation of products **4d**,**e** (see Scheme 2) which precipitated from the reaction mixture. However, their ^{1}H NMR spectra in DMSO-d_6 contained two sets of signals attributed to the expected adduct and the starting reactants. Similar phenomenon was observed in case of [1,2,4]triazole adduct **4f**. It seems likely that this was a result of reversibility of the transformations in DMSO-d_6 solution. Compound **4f** is poorly soluble in all common solvents used for NMR spectroscopy, therefore we were unable to record spectra in aprotic low-polar solvents. In DMSO solution, the adduct/reactants ratio was about 60:40. Interestingly that ^{1}H NMR spectrum recorded in CF_3COOD contained signals of only compound **1** (δ 8.75 and 9.38 ppm) and [1,2,4]triazole (8.99 ppm) indicating complete decay of the adduct into the starting compounds. Apparently, polar solvents favor reverse reaction characteristic of re-aromatization of the pyridine ring. We believe that the same situation arises in case of

‡ *Crystal data for* **4d**. X-ray diffraction data were collected on a Bruker APEX DUO diffractometer [λ(MoKα) = 0.71073 Å, ω-scans, $2\theta < 60.00°$]. Yellow crystals of $C_{10}H_9N_7O_6$ at 120(2) K are monoclinic, space group $P2_1/n$, a = 13.2684(8), b = 7.2207(5) and c = 13.7670(9) Å, β = = 100.0790(10)°, V = 1298.62(15) Å^3, Z = 4 (Z' = 1), d_{calc} = 1.653 g cm^{-3}. Intensities of 3783 independent reflections (R_{int} = 0.0407) out of 14844 collected were used in structure solution and refinement. The structure was solved by direct methods with SHELXT program[13] and refined by the full-matrix least-squares technique against F^2 in the anisotropic approximation. The analysis of Fourier maps revealed the disorder of pseudo-symmetric pyridofuroxan heterocyclic fragment by two positions, so that the nitro substituent of one component is superimposed by O–N–O fragment of the furoxan moiety of the second component; the superimposed fragments are apparently inverted, so the position of the saturated C(4) atom is almost the same on both components. The relative occupancy of the disordered positions was refined to be 0.76 : 0.24; the only restraints applied were restrictions on the anisotropic displacement parameters of the atoms of the minor component [EADP for C(4) and C(4′) atoms and ISOR for all other atoms]. Hydrogen atoms connected to nitrogen atoms were found from difference Fourier synthesis and refined isotropically. All other H atoms were placed in calculated positions and refined in the riding model with U_{iso}(H) equal to 1.5U_{eq}(C) and 1.2U_{eq}(C) of the connected methyl and other carbon atoms. The refinement converged to R_1 = 0.0411 [calculated for 2810 observed reflections with $I > 2\sigma(I)$], wR_2 = 0.0928 and GOF = 1.029. The refinement was performed with SHELX software package.[14]

CCDC 1837203 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

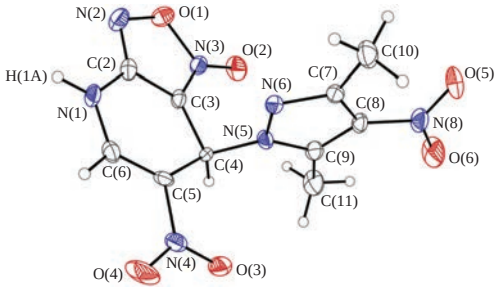
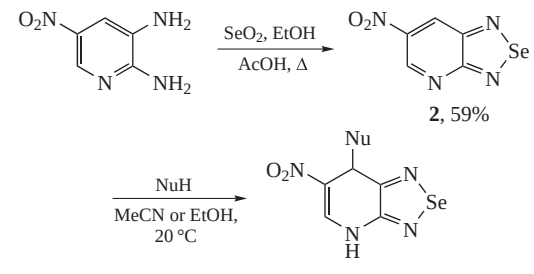


Figure 1 General view of molecule **4d** in crystal. Anisotropic displacement parameters are drawn with 50% probability, only the major component of the disordered heterocyclic moiety is shown.

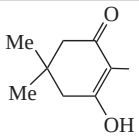
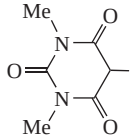
compounds **4d**,**e** with electron-withdrawing groups in pyrazole moieties.

The structure of product **4d** was confirmed by single-crystal X-ray diffraction (Figure 1).‡ In crystal, the pyridofuroxan fragment is disordered by two positions due to its pseudo symmetric geometry (Figure S1, see Online Supplementary Materials). The refined bond lengths and angles are typical of the corresponding fragments.

New 6-nitro-4-azabenzo[1,2,5]selenadiazole **2** was synthesized from 2,3-diamino-5-nitropyridine[6] (Scheme 3).† This compound readily added various nucleophiles at its pyridine moiety even in the absence of bases, which afforded products **5a**–**f**. ^{1}H NMR spectrum of adduct **5a** contains one set of signals which was attributed to the enol form. On the contrary, products **5b** and **5c** existed in DMSO-d_6 solution mainly in dioxo form. Adduct **5d** was formed upon treatment of compound **2** with equimolar amount of malononitrile in EtOH/H_2O mixture. 3,5-Dimethylpyrazole gave adduct **5g** in 62% yield, however this reaction was found to be reversible analogously to reactions of oxadiazolopyridine **1** with low-nucleophilic pyrazoles (see above).



5a–g

	Nu	Yield (%)
a		73
b		75
c	[MeC(O)]$_2$CH	95
d	(NC)CH	45
e	4-$Me_2NC_6H_4$	45
f	5-methoxy-3-indolyl	77
g	3,5-dimethyl-pyrazol-1-yl	62

Scheme 3

The new selenadiazole derivatives can be of special interest due to their potent biological properties since compounds of this class possess antibacterial, fungicidal and antioxidant activities[7,8] as well as high citotoxicity,[7] and are able to inhibit multiplication and to stimulate apoptosis of various types of cancer cells.[8,9] Antitumor activity of some [1,2,5]selenadiazoles exceeds that of standard medicinal preparations thus allowing one to consider them as potential cancer therapy agents.[9] In addition to substituents

at 7-position, compounds **3**–**5** contain NH-fragment which can serve as another derivatization point, in particular, for design of novel pharmaceuticals. Numerous examples were reported on acylation,[10] alkylation[11] and arylation[12] of N-unsubstituted 1,4-dihydropyridines.

In conclusion, reactions of 6-nitro-4-azabenzofuroxan and 6-nitro-4-azabenzoselenadiazole with π-excessive (het)arenes brought about C–C- and N–C-bonded 1,4-adducts, namely, 1,4-dihydropyridines fused with furoxan or selenadiazole ring. The resulting compounds combine pharmacologically important fragments in one molecule and therefore can be considered as prospective platforms for the design of pharmacology-oriented heterocyclic systems.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.11.025.

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