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REACTION OF 3-(4-CHLORO-FURAZANYL-3-N(O)N-AZOXY)-4-NITROFURAZAN WITH WEAK BASES

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When 3-(4-chlorofurazanyl-3-N(O)N-azoxy)-4-nitrofurazan reacts with weak bases and nucleophiles, we observe selective attack on the carbon atom bonded to the nitro group; we do not observe products formed by substitution of the chlorine.

Keywords: azoxyfurazans, nitrofurazans, furazans, chlorofurazans, nucleophilic substitution.

Despite the fact that an activated halogen atom is the customary leaving group in nucleophilic (hetero)aromatic substitution reactions, far fewer papers have been devoted to halofurazans [1, 2] than to their more accessible nitro analogs [3-11]. Data from study of the chemistry of nitrofurazans [12] and also other furazan derivatives suitable for nucleophilic substitution reactions [13] have been generalized in recent reviews.

In S_N2 reactions, as a leaving group the nitro group has mobility similar to fluorine and is significantly more effective than chlorine [14-16]. At the same time, specific properties are intrinsic to nitro compounds that occasionally complicate the desired direction of the reaction [17]. This first of all involves the ability of nitro compounds to exhibit oxidation properties in a reaction, where reagents such as thiols or aniline are mainly consumed in secondary processes. Secondly, the nitrite ion formed during substitution of the nitro group can compete with the nucleophile available in the reaction mixture, which also gives rise to secondary products. The latter phenomenon, however, can be used in synthesis of some phenols and derivatives of diphenyl ether [18]. For nitrofurazans containing an electron-acceptor substituent, formation of difurazanyl ether derivatives is the major reaction when they are treated with weak bases and nucleophiles [4-6, 10].

Using this reaction, we have synthesized chromophore macrocyclic difurazanyl ethers by intermolecular condensation of 4,4'-dinitroazofurazan (**1**) in the presence of bases [5]. Attempts to prepare N-oxides of these macrocycles under similar conditions, starting from an azoxy analog of compound **1** such as 4,4'-dinitroazoxyfurazan (**2**), proved to be unsuccessful [10]. Moreover, we observed conversions due to nonselective attack on the carbon atoms bonded to the nitro group closest to the N-oxide moiety of the azoxy group (direction **A**) and bonded to the N(O) atom of the azoxy group (direction **B**), which yielded a mixture of linear difurazanyl ethers. Products from substitution of the nitro group far away from the N-oxide moiety (direction **C**) were not observed in this case [10].

Thus in compound **2**, the relative nucleofugacity of the nitro group closest to the N-oxide moiety of the azoxy group is significantly higher than for the remote nitro group. This observation encouraged us to study the reactivity of a compound in which the nitro group closest to the N-oxide moiety is replaced by a less mobile leaving group. In this case, for a compound with the same reactivity for centers **A** and **C**, as a result of the reaction we might expect formation of macrocycles similar to what we see in the case of compound **1** [5].

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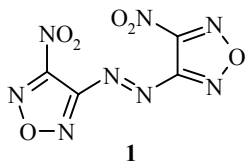

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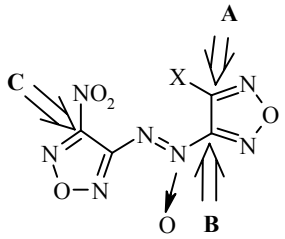


2, **3**

2 X = NO_2, **3** X = Cl

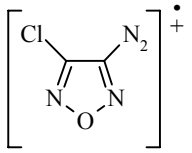
In this paper, we present our data from a study of the reactivity of 3-(4-chlorofurazanyl-3-N(O)N-azoxy)-4-nitrofurazan (**3**) [11]. This compound contains a less active chlorine at center **A** as a potential leaving group.

When compound **3** was refluxed in acetonitrile in the presence of $NaNO_2$ for more than 2 h, 65% of the starting compound remained unchanged. The products were separated by chromatography. Analysis of the ^{14}N NMR spectra for all the fractions clearly showed the absence of any nitrofurazans other than the starting material **3**. In this case, three chlorine-containing products were formed. Two of them were identified as monoethers **4** and **5** (yields 6% and 11% respectively). The third product (7% yield) was the diether **6** (Scheme 1). We note that in this case, we did not observe either macrocycle **7** (the formation of which might be expected in analogy to the reactions of compound **1** in [5]) or linear ether **8** (compare with the reaction of compound **2** in [10]). We also used chromatography/mass spectrometry to look for 4,4'-dichlorodifurazanyl ether (**9**) in the reaction mixture, since attack on the center **B** might give such an ether in analogy to the reactions of compound **2** [10], but we did not observe traces of ether **9**.

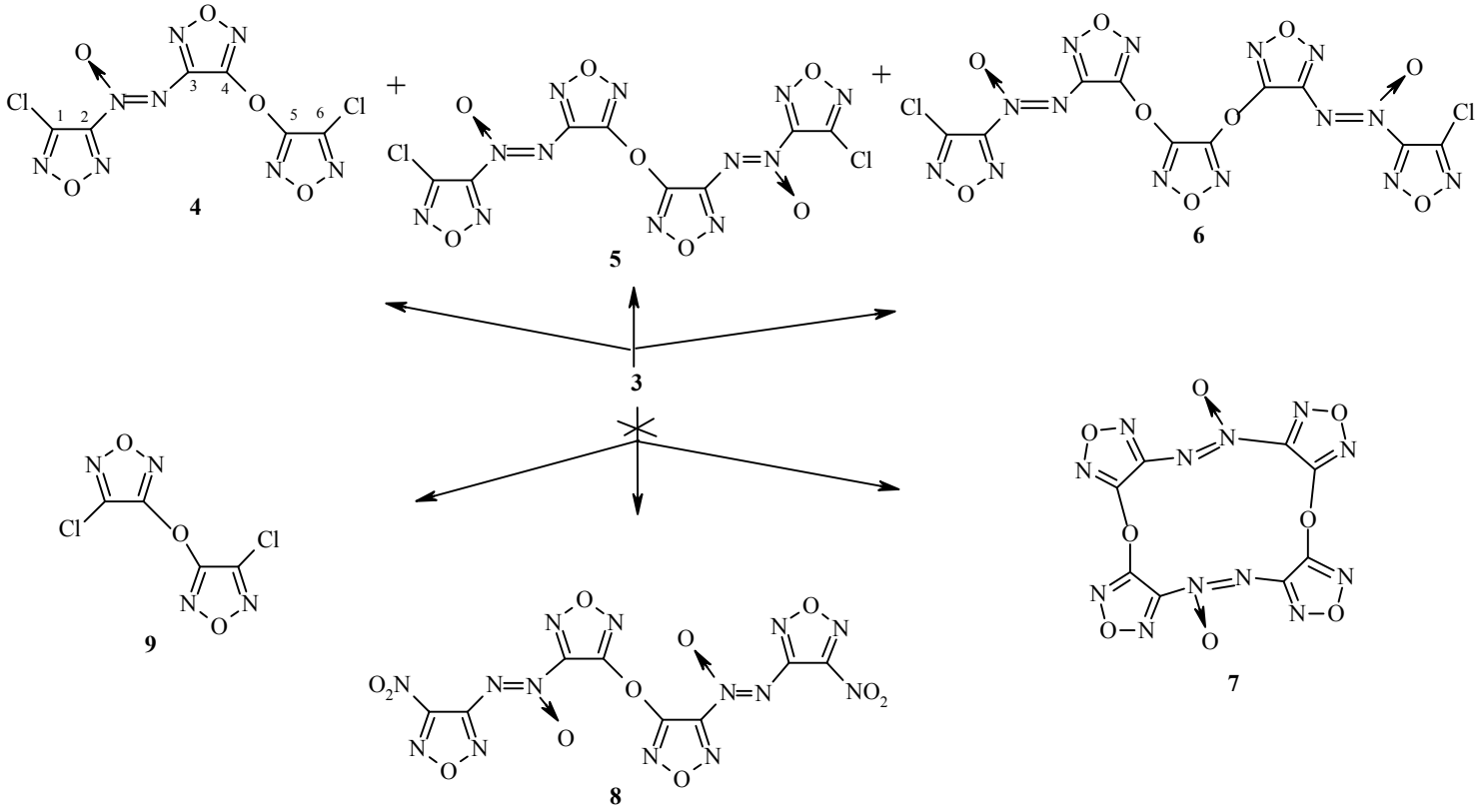
We must note that a compound such as 4,4'-dichloroazoxyfurazan [11], which does not contain a nitro group, remains unchanged under analogous conditions.

In contrast to compound **2**, compound **3** does not react with Li_2CO_3 or Na_2CO_3 in boiling acetonitrile; the starting compound is recovered in quantitative yield after boiling for 1 h. When compound **3** was stirred with K_2CO_3 in acetonitrile at 81°C, we detected the presence of 34% starting compound **3**, 11% ether **4**, and 22% ether **5** from GLC and chromatography/mass spectrometry of the reaction mass. The remainder of compound **3** was used up in formation of a mixture of hydroxy derivatives (chromatography/mass spectrometer data), and attempts at preparative separation of the mixture were unsuccessful.

After chromatographic separation and purification, the structures of the compounds obtained were proven by spectral methods and elemental analysis. In the mass spectra of all the compounds, there are relatively intense molecular ion peaks in the form of triplets, which is typical of compounds containing two chlorine atoms [19]. Fragmentation usually begins with elimination of an oxygen atom from the azoxy group [M^+ - O], followed by elimination of an NO molecule from the furazan ring [M^+ - O - NO]. Both chlorine atoms are present in the primary fragmentary ions, which is clearly supported by their multiplet appearance (see the experimental section). A typical feature of the spectra for all the compounds is the presence of a fragmentary ion appearing as a doublet of peaks with a difference of 2 mass units, *m*/*z* 131 and 133, probably of the following structure:



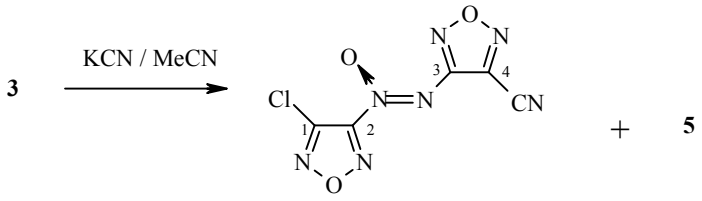
Scheme 1



The ^{13}C and ^{14}N NMR data we obtained previously for isomeric azoxyfurazans [7] and chlorofurazans [11] allow us to unambiguously make assignments in the spectra of the compounds obtained. For example, for compound **4** we observe the presence of six signals; the chemical shifts of the carbon atoms bonded to chlorine atoms appear in the region 139-142 ppm. The signal from the carbon atom on the azoxy group is broadened by a $^{13}C–^{14}N$ interaction. The ^{14}N NMR spectrum is characterized by a single singlet at -70.7 ppm, confirming the presence of an azoxy group.

We showed earlier that upon reaction of nitrofurazans with various weak bases, including KCN, only the difurazanyl ether derivatives are formed [4, 10]. In contrast, from compound **3** under analogous conditions we unexpectedly obtained the cyano derivative (Scheme 2). So reaction of chloride **3** with KCN in CH_3CN at 20°C leads to a mixture of 3-(4-chlorofurazanyl-3-N(O)N-azoxy)-4-cyanofurazan (**10**) and ether **5** in 2:3 ratio. The products were easily separated by chromatography. The yield of compound **10** was 12%. Replacing KCN by NaCN allows us to increase the yield up to 23%. The maximum yield of the cyano derivative **10** (61%) was achieved in reaction of compound **3** with KCN under phase transfer catalysis conditions in a liquid – liquid system (CH_2Cl_2–water) in the presence of benzyl triethyl ammonium chloride. The starting compound is completely consumed at room temperature in 7 h. The study showed that when we use a liquid–solid system (CH_2Cl_2–KCN), in the same time period only 20% of the starting compound **3** is consumed (monitored by GLC). In this case, ether **5** is always formed as a secondary product.

Scheme 2



10

As in all the cases described above, the reaction with cyanide ion occurred exclusively at the carbon atom bonded to a nitro group (direction **C**); we did not observe any products formed by substitution of the halogen.

The structure of the cyano derivative **10** was supported by the ^{13}C and ^{14}N NMR data, mass spectroscopy, and the IR spectrum taken altogether. Thus in the IR spectrum we see a low-intensity band at 2265 cm^{-1} for the conjugated nitrile group. The ^{13}C NMR chemical shift at 105.7 ppm is typical of a cyano group on a furazan ring [3, 4, 7]. In the ^{14}N NMR spectrum, we observed a single chemical shift at -68.2 ppm, belonging to the N(O) atom of the azoxy group. In the mass spectrum, the molecular ion, appearing as a doublet of peaks with a difference of 2 mass units and intensity ratio 3:1, identifies the presence of one chlorine atom in the compound [19].

Compound **10**, like all the halofurazans mentioned above, is highly volatile and easily sublimes. Even working briefly with these compounds caused allergic reactions in personnel.

Thus substituting one of the nitro groups in compound **2** by a chlorine atom is accompanied by a significant change in the reactivity; the regioselectivity of nucleophilic attack primarily changes. All the studied reagents substitute only the nitro group in compound **3**, yielding a chlorine-containing product. The fact that in this case no chlorine substitution products are formed means that extended and more in-depth study of the reactivity of various halofurazans is required.

EXPERIMENTAL

The melting points were determined on a Kofler apparatus. The ^{13}C and ^{14}N NMR spectra, based on the natural isotope content, were obtained on a Bruker AM-300 spectrometer (75 MHz and 21 MHz respectively). The chemical shifts in the ^{14}N NMR spectra are given on the δ scale, with nitromethane as the external standard. The mass spectra were recorded on a Finnigan MAT INCOS-50 and a Varian MAT CH-111 (electron impact, 70 eV). The IR spectra were recorded on a Specord IR-75 spectrometer (for the solids, in KBr disks; for the liquids, in a thin film). The course of the reaction and the purity of the products were monitored by TLC, eluent CH_2Cl_2–pentane, 1:1, on Silufol UV-254 plates (the spots were visualized by UV; the spots can also be visualized by spraying the plates with a 5% diphenylamine solution in hexane followed by heating or irradiation by a UV lamp; azoxyfurazans appear as dark spots). For preparative chromatography, we used SiO_2 100/160 mesh (Armenia). GLC analysis was carried out on a Biokhrom-1 chromatograph (flame ionization detector, capillary column, helium as the carrier gas). The starting compound **3** was obtained by the procedure described earlier in [11].

Reaction of 3-(4-Chlorofurazanyl-3-N(O)N-azoxy)-4-nitrofurazan (3) with $NaNO_2$. Sodium nitrite (0.138 g, 20 mmol) was added all at once to a solution of compound **3** (0.262 g, 1 mmol) in absolute acetonitrile (5 ml). The mixture obtained was stirred while boiling under reflux for ~2 h (monitored by TLC). After cooling, the reaction mass was diluted with water and extracted with CH_2Cl_2 (4 × 15 ml). The combined extracts were washed with water, dried with $MgSO_4$, filtered, and evaporated down on a rotary evaporator. The residue was chromatographed on a column, eluent CH_2Cl_2–pentane, 1:1.

First Fraction: the starting compound **3**, yield 65%; mp 26-27°C.

Second Fraction: 4-(4-chlorofurazanyl-3-N(O)N-azoxy)-4-chlorodifurazanyl ether (**4**), yield 6%; oil. Mass spectrum, *m*/*z* (I_{rel}, %): 338, 336, 334 (15) [M^+], 320, 318 (5) [M^+ - O], 242, 241 (56), 240 (24), 239 (78), 229-227, 217-215, 133 (71), 131 (100). ^{13}C NMR spectrum (acetone-d_6), δ, ppm: 139.2 (C-1), 141.8 (C-6), 146.6 (C-3), 157.3, 158.7 (C-4, C-5), 158.9 (C-2). ^{14}N NMR spectrum ($CDCl_3$), δ, ppm ($\Delta\nu_{1/2}$, Hz): -70.7 (N→O, $\Delta\nu_{1/2}$ = 60). Found, %: C 21.42; Cl 21.07; N 33.50. $C_6Cl_2N_8O_5$ (335.02). Calculated, %: C 21.51; Cl 21.16; N 33.45.

Third Fraction: 4,4'-bis(4-chlorofurazanyl-3-N(O)N-azoxy)difurazanyl ether (**5**), yield 11%; mp 99-101°C. Mass spectrum, *m*/*z* (I_{rel}, %): 450, 448, 446 (7) [M^+], 429 [M^+ - O] (3), 413 [M^+ - 2O] (2), 329, 327 (7), 285-283, 256, 254 (9), 229 (26), 227 (39), 215 (15), 199 (11), 171 (38), 133 (69), 131 (100), 114 (21), 112 (37). IR spectrum, ν, cm^{-1}: 1580, 1510, 1470, 1305, 1245, 1110, 1010, 925, 860, 750. ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 141.8 (C-1), 146.6 (C-3), 156.5 (C-2), 157.5 (C-4). ^{14}N NMR spectrum ($CDCl_3$), δ, ppm ($\Delta\nu_{1/2}$, Hz): -70.9 (N→O, $\Delta\nu_{1/2}$ = 76). Found, %: C 21.54; Cl 15.94; N 37.52. $C_8Cl_2N_{12}O_7$ (447.07). Calculated, %: C 21.49; Cl 15.86; N 37.60.

Fourth Fraction: 3,4-bis[4-(4-chlorofurazanyl-3-N(O)N-azoxy)furazanyl-3-oxy]furazan (**6**), yield 7%; mp 49-51°C. Mass spectrum, *m*/*z* (I_{rel}, %): 530 (1) [M^+], 513 (7) [M^+ - O], 433, 432 (10), 430 (14), 329, 327 (30), 268, 267 (22), 241, 227 (19), 198 (11), 133 (62), 131 (90), 83 (100). IR spectrum, ν, cm^{-1}: 1575, 1560, 1510, 1480, 1310, 1245, 1205, 1110, 1100, 980. Found, %: C 22.65; Cl 13.38; N 36.86. $C_{10}Cl_2N_{14}O_9$ (531.10). Calculated, %: C 22.62; Cl 13.35; N 36.92.

Reactions of Compound 3 with Alkali Metal Carbonates were carried out analogously, using an equimolar ratio of the reactants.

3-(4-Chlorofurazanyl-3-N(O)N-azoxy)-4-cyanofurazan (10). A. NaCN (2.45 g, 50 mmol) was added to a solution of compound **3** (2.62 g, 10 mmol) in acetonitrile (20 ml) and the mixture was vigorously stirred for 1 h at room temperature and then for 7 h while boiling under reflux. After cooling, the reaction mass was diluted with a ten-fold volume of methylene chloride and then washed with water. The solution obtained was dried with $MgSO_4$, filtered, and evaporated down. The residue was chromatographed on a column with SiO_2, eluent CH_2Cl_2–pentane, 1:1.

First Fraction: compound **10**, yield 23%; mp 41-42°C. Mass spectrum, *m*/*z* (I_{rel}, %): 242, 240 [M^+], 226, 224 [M^+ - O], 213, 211 [M^+ - NO], 155, 153, 135, 122, 98, 73, 68. IR spectrum, ν, cm^{-1}: 2265 (C≡N), 1570, 1545, 1490, 1430, 1305, 1245, 1175, 1110, 1020, 925, 870. 13C NMR spectrum (CDCl3), δ, ppm: 105.7 (C≡N), 130.6 (C-4), 141.9 (C-1), 154.5 (C-3), 156.3 (C-2). ^{14}N NMR spectrum ($CDCl_3$), δ, ppm ($\Delta\nu_{1/2}$, Hz): -68.1 (N→O, $\Delta\nu_{1/2}$ = 40). Found, %: C 24.94; Cl 14.72; N 40.51. $C_5ClN_7O_3$ (241.55). Calculated, %: C 24.86; Cl 14.68; N 40.59.

Second Fraction: compound **5**, yield 35%. This compound is identical to the compound described above according to its characteristics.

B. A solution of KCN (1.24 g, 20 mmol) in water (10 ml) and benzyl triethyl ammonium chloride (0.25 g) was added with vigorous stirring to a solution of compound **3** (2.62 g, 10 mmol) in methylene chloride (30 ml). The reaction mixture obtained was stirred vigorously at room temperature for 7 h. The organic layer was separated, washed with water, dried with $MgSO_4$, filtered, and evaporated down. According to chromatographic data, the residue contained 61% compound **10** and 17% compound **5**.

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