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Unusual reaction of 4-nitrobenzofurazan with amines

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The treatment of 4-nitrobenzofurazan with secondary amines resulted in the formation of 4-amino-5,7-bis(dialkylamino)-benzofurazans, as established by X-ray diffraction analyses; this is the first example of S_N^H reaction with synchronous alteration of three functions.

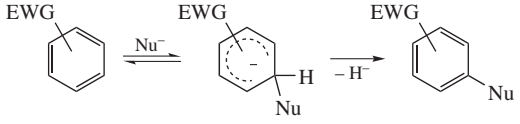
Nucleophilic (hetero)aromatic substitution of hydrogen (S_N^H) is a powerful tool in organic synthesis.[1] In most cases, this process is especially effective for selective C–C, C–N, C–O and C–S bond formation, and many nitro(het)arenes and activated heterocycles have been functionalized by the S_N^H technique. This process consists of the addition of a nucleophile to nitroarenes followed by oxidative aromatization of the initially formed anionic σ-complex (Scheme 1). The ease of the oxidation was found to depend inversely on the electron deficiency of the parent molecule.[1,2] For example, adducts from 4-nitrobenzofuroxan were more easily oxidized than those from 4,6-dinitrobenzofuroxan. However, the oxidative pathway is not clear, it may be that the solvent, air, or the starting molecule itself plays an active role in the oxidation process.

In contrast to classical nucleophilic aromatic substitution ($S_N^{ipso}Ar$), usually accompanied by HHal, HNO_2 or RSO_3H elimination, at S_N^H reactions a water molecule is typically released, that is fascinating to create environmentally friendly processes.

Nitrobenzofuroxans have received much attention[3] since the neutral 10-π-electron-deficient heteroaromatic compounds exhibited an extremely high electrophilic character[2(b),4] relative to many covalent nucleophilic addition and substitution processes.

Surprisingly, only a few publications have reported on the S_N^H reaction of benzofurazan derivatives. Thus, anthra[1,2-*c*]furazan-6,11-dione[5,6(a)] and anthra[2,3-*c*]furazan-5,10-dione[6(b)] readily reacted with sulfite ions,[5] ammonia, primary and secondary amines[6] giving corresponding 4-substituted derivatives; 4-nitrobenzofurazan **1** underwent facile competitive monoaddition of anionic nucleophiles (MeO^-,[7(a)] mononitroalkane anions,[2(b),7(b),(c)] sulfite ions[7(d)]) to the 5- or 7-positions under experimental conditions. All reactions led to relatively stable intermediated anionic σ-adducts.

To expand the usefulness of benzofurazan chemistry,[8] as well as to provide a predicting tool, we undertook a study of this S_N^H reaction. We found that 4-nitrobenzofurazan **1** can be induced to undergo smooth S_N^H reactions to secondary amines, with simultaneous reduction of the nitro group to the amino group.



EWG = electron-withdrawing group

Scheme 1

When compound **1** was treated at room temperature with a deficiency of morpholine (1 mol) in DMF for 0.5 h, a complex reaction ensued, in which starting **1** and four new compounds were fixed by TLC. The same four products were observed when the nitrobenzofurazan **1** was treated with morpholine (4 mol) in dioxane for 1 h. With more morpholine (5 mol) at room temperature for 48 h, the reaction was less complex and two products were isolated by careful chromatography (Scheme 2). The first product (11%) was identified as 4-nitro-7-morpholino-benzofurazan **2a**.† The second major (48%) product **3a** was found to have a molecular formula of $C_{14}H_{19}N_5O_3$, suggesting that two morpholine moieties have been incorporated and that the new product has arisen *via* the nitro group reduction.† Mass spectral analysis of the product gave a parent ion at *m*/*z* 305, consistent with molecular formula specified above. In addition, mass spectrum shows significant peaks due to loss of a NO moiety (*m*/*z* 275) from the molecular ion and then of a morpholine group (*m*/*z* 188) as might be expected from the benzofurazan

† All spectroscopic and analytical data were consistent with the structures assigned. The identity of products **2a–d** was confirmed by NMR spectra, elemental analysis, melting points, HRMS and comparison with the published data.

For **2a**: mp 227–228 °C (lit.,[10(a)] 225–226 °C).

For **2b**: mp 170–171 °C (lit.,[10(a)] 169–170 °C).

For **2c**: mp 116–117 °C (lit.,[10(b)] 115–116 °C).

For **2d**: mp 210–211 °C (lit.,[10(c)] 210 °C).

For **3a**: mp 204–205 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.82 (m, 4H), 3.23 (m, 4H), 3.79 (m, 8H), 5.15 (br. s, 2H, NH_2), 6.52 (s, 1H). ^{13}C NMR ([$^2H_6$]DMSO) δ: 50.1, 50.2 (CH_2–N), 65.9, 66.5 (CH_2–O), 109.3 (C^4), 120.9 (C^6), 129.5 (C^3), 131.3 (C^5), 144.1 (C^2), 145.8 (C^1). MS, *m*/*z* (%): 305 $[M]^+$ (100). Found (%): C, 55.14; N, 22.91; H, 6.30. Calc. for $C_{14}H_{19}N_5O_3$ (305.34) (%): C, 55.07; N, 22.94; H, 6.27.

For **3b**: mp 136–137 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.38 (m, 12H), 2.66 (m, 4H), 3.61 (m, 8H), 4.37 (br. s, 2H, NH_2), 6.46 (s, 1H). ^{13}C NMR ([$^2H_6$]DMSO) δ: 23.3, 23.4, 24.8, 25.7 (CH_2–C), 50.4, 50.9 (CH_2–N), 108.8 (C^4), 119.2 (C^6), 130.6 (C^3), 133.2 (C^5), 144.1 (C^2), 145.5 (C^1). MS, *m*/*z* (%): 301 $[M]^+$ (100). Found (%): C, 63.83; N, 23.13; H, 7.72. Calc. for $C_{16}H_{23}N_5O$ (301.39) (%): C, 63.76; N, 23.24; H, 7.69.

For **3c**: mp 158–160 °C, MS, *m*/*z* (%): 329 $[M]^+$ (100), 314 $[M – Me]^+$ (20), 313 $[M – NH_2]^+$ (17), 299 $[M – NO]^+$ (10), 284 $[M – Me – NO]^+$ (10). Found (%): C, 65.71; N, 21.19; H, 8.30. Calc. for $C_{18}H_{27}N_5O$ (329.45) (%): C, 65.62; N, 21.26; H, 8.26.

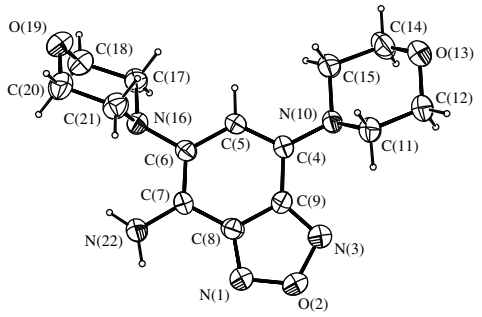
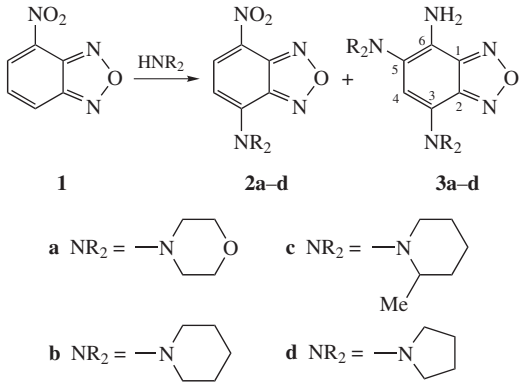


Figure 1 Molecular structure of **3a**.

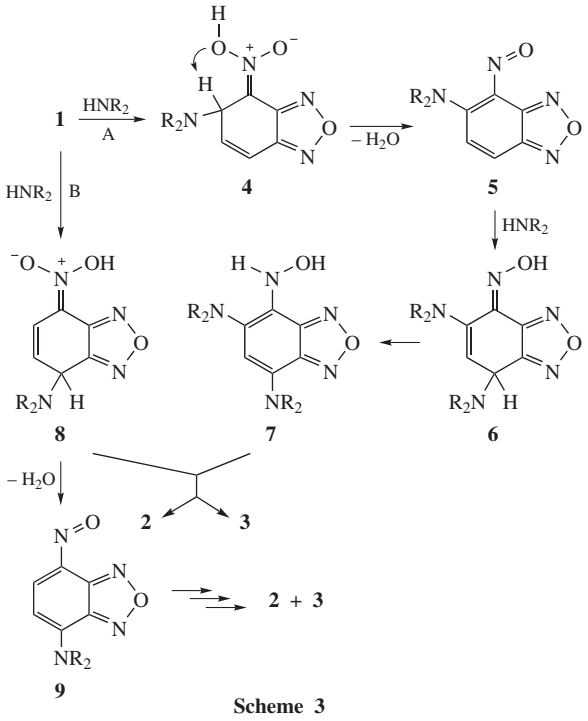
structure. ^{1}H NMR analysis clearly indicated the presence of the amino group and two morpholine fragments. In order to characterize the product unambiguously, a single crystal X-ray determination was carried out (Figure 1).‡ The molecular dimensions of the benzofurazan unit of **3a** fall within the ranges of other benzofurazans that have been examined by X-ray crystallography.[8(*b*),9]

We found that the reaction of nitrobenzofurazan **1** with other secondary amines (Scheme 2) in dioxane at 20 °C behaves similarly, producing corresponding disubstituted aminobenzofurazans **3b**,**c** (35–50%) along with nitro products **2b**,**c** (12–15%). A related reaction occurred using pyrrolidine resulting, however, in the formation of a complex mixture, from which desired amine **3d** was isolated in low yield (8%).

Thus, the behavior of 4-nitrobenzofurazan **1** in S_N^H reaction was found to dramatically differ from that of 4-nitrobenzofuroxan, where the nitro group was preserved in the product and only a nucleophile added to the substrate at 7-position.[2(*a*),11] The reduction of the furoxan to furazan ring was also described.[11(*a*)]



Scheme 2



Scheme 3

The formation of amine **3** can be best rationalized through σ-complex formation. As depicted in Scheme 3, two possibilities can be envisaged, pathways A and B. Both pathways differ only in position of the first amine molecule addition. These pathways, nevertheless, afford finally product **3**. Aromatization of σ-complexes (**4**, **6** and **8**) can proceed *via* both intramolecular redox reactions (as, for example, at transformation **4** → **5**), and intermolecularly (as, for example, at transformation **7** + **8** → **2** + **3**). Nitroso§ intermediates **5** and **9** added on next amine molecule, followed by redox transformation.

Note that special experiments showed that compound **2a** did not react with morpholine under the similar conditions, as well as it could not be transformed into product **3a**.

The participation of the nitro group in intramolecular redox process at S_N^H reaction for nitrotriazolopyrimidines was described recently;[13] at this the reduction of nitro to amino group and introduction of a nucleophile to basic molecule took place.

In summary, note that we have discovered the first example of S_N^H reaction with synchronous alteration of three functions. This unusual reaction is likely to be useful for multicentral modification of benzofurazans.

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‡ *X-ray diffraction data*. Compound **3a**, $C_{14}H_{19}N_5O_3$, M = 305.34, monoclinic, space group $P2_1/c$, a = 11.216(2), b = 17.002(3) and c = 7.955(4) Å, β = 101.69(2)°, V = 1485.5(8) Å^3, Z = 4, d_{calc} = 1.365 g cm^{-3}. Cell parameters and intensities of 3008 independent reflections (1341 with $I \geq 2\sigma$) were measured on an Enraf-Nonius CAD-4 diffractometer in the $\omega/2\theta$-scan mode, $\theta \leq 74.21°$, using CuKα radiation with a graphite monochromator. Data were corrected for an absorption effect [μ(Mo) = 8.21 cm^{-1}]. The structure was solved by a direct method using the SIR[14(*a*)] program and refined by the full matrix least-squares using the SHELXL97[14(*b*)] program. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were calculated and refined as riding atoms. The final residuals were $R(F_0^2)$ = 0.054, $R_w(F_0^2)$ = 0.119. All calculations were performed on PC using WinGX[14(*c*)] program. Cell parameters, data collection and data reduction were performed on Alpha Station 200 computer using MoLEN[14(*d*)] program. All figures were made using the program PLATON.[14(*e*)]

CCDC 694600 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2008.

§ Recently, the possibility of nitrosobenzenes participation in S_N^H reaction was described.[12]

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