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Superelectrophilic nature of 4,6-dinitrobenzo[*c*]isoxazole (4,6-dinitroanthranil) in [4+2]-cycloaddition reactions and σ^H-complex formation

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4,6-Dinitrobenzo[*c*]isoxazole (4,6-dinitroanthranil) acts as a dienophile and heterodiene in [4+2]-cycloaddition reactions, and its behaviour in σ^H-complex formation reactions has been examined.

Nitrobenzannelated heterocycles such as 4,6-dinitrobenzofuroxan (DNBF), 4,6-dinitrobenzofurazan (DNBZ) and 4-nitrobenzodifuroxan (NBDF) (Figure 1), possess a very high electrophilicity (superelectrophilicity).[1]

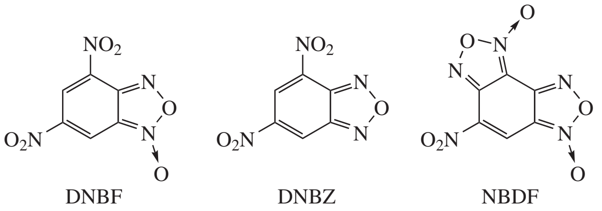


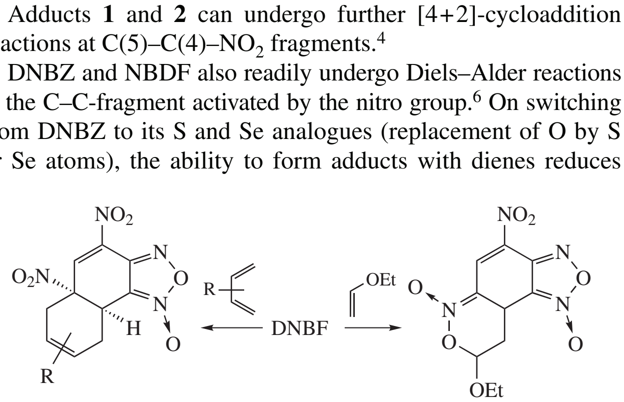
Figure 1

For example, DNBF forms very stable zwitterionic σ-complexes at a benzene fragment even with very weak C-nucleophiles – benzene derivatives with electron-donating substituents and π-electron-rich aromatic heterocycles (indoles, pyrroles, thiophenes, *etc.*).[2]

DNBF is a stronger electrophile than the 4-nitrophenyldiazonium cation.[2,3] Such a high electrophilicity characterizing the ability to add nucleophiles to the benzene ring results in a considerable decrease in the aromaticity of the benzene fragment.[4] Thus, DNBF forms the adducts with different dienes at the C(6)–C(7) bond under mild conditions. The reactions proceed regio- and stereoselectively[4,5] (Scheme 1, adduct **1**). Moreover, the C(7)–C(6)–NO$_2$ fragment can also act as a heterodiene affording adducts with nucleophilic dienophiles, for example, with ethyl vinyl ether[4(b)] (Scheme 1, adduct **2**).

Adducts **1** and **2** can undergo further [4+2]-cycloaddition reactions at C(5)–C(4)–NO$_2$ fragments.[4]

DNBZ and NBDF also readily undergo Diels–Alder reactions at the C–C-fragment activated by the nitro group.[6] On switching from DNBZ to its S and Se analogues (replacement of O by S or Se atoms), the ability to form adducts with dienes reduces substantially, while less electrophilic mononitro benzofuroxans do not undergo Diels–Alder reactions at all[7] at least with common dienes.



Scheme 1

The characteristic example of the influence of the electrophilicity of aromatic nitro compounds on the ability to undergo Diels–Alder reaction is the behaviour of 2-aryl-4,6-dinitrobenzotriazole-1-oxides: in this series, only 2-(2,4,6-trinitrophenyl)-4,6-dinitrobenzotriazole-1-oxide bearing the most electrophilic aryl substituent is able to undergo [4+2]-cycloaddition reactions.[7]

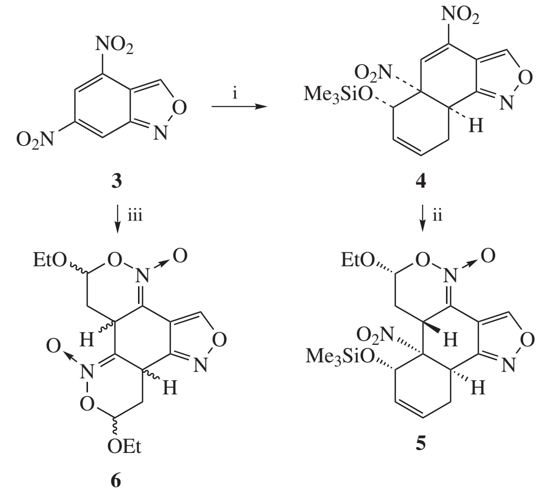
We studied the behaviour of another analogue of DNBZ – 4,6-dinitroanthranil **3** (4,6-dinitrobenzo[*c*]isoxazole) – the product of formal replacement of the nitrogen atom with the =CH fragment. Recently, a preparative method for the synthesis of compound **3** was developed in our laboratory.[8]

One could expect that, on the replacement of the N_{sp^2} atom with the much less electron-withdrawing HC_{sp^2} fragment, the electrophilicity of the molecule would decrease considerably and the C(3) atom must be bonded with the strong electron-withdrawing substituent for the successful Diels–Alder reaction at the C–C–NO$_2$ fragment.[†] However, it was found that even 3-unsubstituted 4,6-dinitroanthranil undergoes [4+2]-cycloaddition reactions under mild conditions by its *meta*-dinitrophenylene fragment.

We found that 4,6-dinitroanthranil **3** reacts with 1-(trimethylsilyloxy)buta-1,3-diene at room temperature in chloroform at the C(6)–C(7) bond (Scheme 2). The reaction proceeds in accordance with normal electron demands with high regio- and stereoselectivity giving rise to product **4** in good yield. It is interesting that, despite a large excess of the diene, the C(5)–C(4)–NO$_2$ fragment of adduct **4** remains intact, and it does not react with one more diene molecule. At the same time, compound **4** readily reacts as a heterodiene with ethyl vinyl ether (on stirring in chloroform at room temperature for 24 h) to give adduct **5** in 65% yield (Scheme 2).

On the interaction of 4,6-dinitroanthranil **3** with ethyl vinyl ether, bis-adduct **6** was isolated in 47% yield after stirring at room temperature in chloroform for 4 h (Scheme 2). In this case, a mixture of diastereomers (a ratio of 9:1) was obtained, as determined by ^{1}H NMR data (double series of signals was observed). Here, both of the nitro olefin fragments of anthranil **3** act as heterodienes towards the nucleophilic ethyl vinyl ether.

[†] 3-Unsubstituted anthranils are known to undergo [4+2]-cycloaddition reactions in another way: the isoxazole moiety acts as a diene towards strong electrophilic dienophiles (dialkyl acetylenedicarboxylates and maleimide).[9]



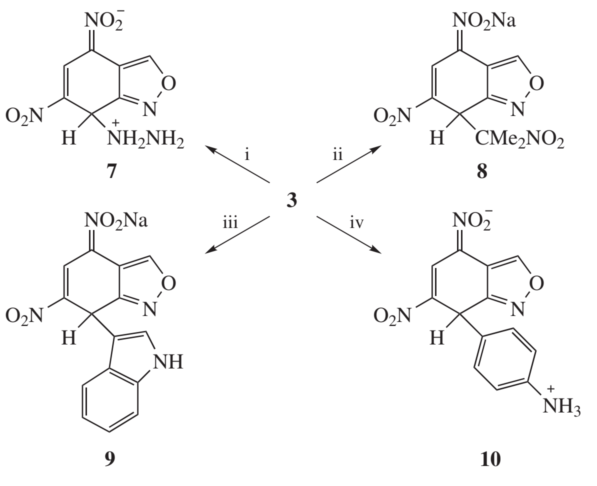
Scheme 2 *Reagents and conditions*: i, 1-(trimethylsilyloxy)buta-1,3-diene (5 equiv.), $CHCl_3$, 20 °C, 2 h; ii, ethyl vinyl ether (52 equiv.), $CHCl_3$, 20 °C, 24 h; iii, ethyl vinyl ether (175 equiv.), 20 °C, 4 h.

A feature of 4,6-dinitroanthranil **3** that characterizes it as a superelectrophile is the ability to form stable zwitterion σ^{H}-adducts even with very weak neutral C-nucleophiles – aniline and indole (Scheme 3, compounds **9**, **10**). Stronger nucleophiles such as hydrazine and the sodium salt of 2-nitropropane react similarly. Addition products **7**–**10** of the corresponding nucleophile at the 7-position of the dinitrobenzo[*c*]isoxazole system were obtained (Scheme 3).

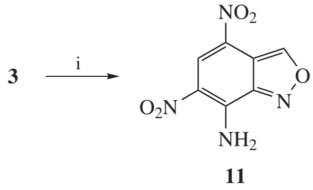
Note that compounds **7**–**10** are stable. They were isolated as crystals on cooling (**7** and **10**), evaporation to dryness (**8**) or pouring into water (**9**), and they can be stored at room temperature. Decomposition was observed only on heating above 120–160 °C. In the UV-VIS spectra of compounds **7**–**10**, there are intense absorption bands at 500–520 nm.

The ability of compound **3** to add nucleophiles at the 7-position allowed us to carry out the direct functionalization of 4,6-dinitroanthranil, which was shown taking its amination under oxidative nucleophilic substitution of hydrogen conditions as an example (Scheme 4). The complex $AgPy_2MnO_4$ (see ref. 10) was used as an oxidant, and amine **11** was synthesised in excellent yield.

The structures of the polycyclic compounds obtained were proved by NMR spectroscopy, mass spectrometry and microanalysis.[‡] Stereochemistry of compounds **4** and **5** was determined on the basis of 2D heteronuclear correlation NMR spectra (NOESY, COSY, HSQC and HMBC).



Scheme 3 *Reagents and conditions*: i, $N_2H_4 \cdot H_2O$ (15 equiv.), EtOH, 20 °C, 0.5 h; ii, $NaCMe_2NO_2$ (1.2 equiv), 2-nitropropane, 20 °C, 3 h; iii, indole (1 equiv.), $NaHCO_3$ (1 equiv.), dioxane–H_2O, 20 °C, 24 h; iv, $PhNH_2$ (1 equiv.), MeOH, 20 °C, 2 h.



Scheme 4 *Reagents and conditions*: i, $AgPy_2MnO_4$ (1.5 equiv.), NH_3 (7 N solution in MeOH), –10–+10 °C, 24 h.

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[‡] ^{1}H NMR spectra were recorded on a Bruker DRX-500 spectrometer.

For **4**: yield 70%, mp 177–179 °C. ^{1}H NMR ($CDCl_3$) δ: 0.14 (s, 9H), 1.93 (dd, 1H, *J* 11.2 Hz, *J* 6.0 Hz), 2.85 (m, 1H), 4.50 (m, 1H), 4.84 (d, 1H, *J* 6.0 Hz), 5.94 (m, 1H), 6.06 (m, 1H), 6.95 (s, 1H), 8.84 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 284, 30.8, 68.1, 68.5, 91.8, 105.6, 124.5, 132.9, 144.5, 155.7, 160.9. Found (%): C, 48.10; H, 4.41. Calc. for $C_{14}H_{17}N_3O_6Si$ (%): C, 47.85; H, 4.88.

For **5**: yield 65%, mp 220–222 °C. ^{1}H NMR ($CDCl_3$) δ: 0.12 (s, 9H), 1.27 (m, 3H), 2.11 (dd, 1H, *J* 9.3 Hz, *J* 8.8 Hz), 2.38 (m, 1H), 2.79 (m, 1H), 2.97 (m, 1H), 3.27 (t, 1H, *J* 6.5 Hz), 3.72 (m, 1H), 4.07 (m, 1H), 4.39 (t, 1H, *J* 8.2 Hz), 4.71 (d, 1H, *J* 5.1 Hz), 5.42 (dd, 1H, *J* 3.6 Hz, *J* 3.0 Hz), 9.05 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 0.1, 14.9, 26.9, 29.5, 32.1, 33.5, 65.8, 66.4, 92.4, 102.7, 107.4, 111.3, 125.4, 129.4, 130.5, 156.8, 161.1. HRMS, *m*/*z*: 424.1530 (calc. for $C_{18}H_{25}N_3O_7Si$: 424.1535).

For **6**: yield 47% (the mixture of diastereomers), mp 209–211 °C. ^{1}H NMR ($CDCl_3$) δ (major isomer): 1.15–1.35 (m, 6H), 1.5–1.7 (m, 1H), 2.00 (m, 1H), 3.20–3.30 (m, 1H), 3.60–3.75 (m, 2H), 3.90–4.15 (m, 5H), 5.50–5.65 (m, 2H), 9.22 (s, 1H).

For **7**: yield 75%, mp > 130 °C (decomp.). ^{1}H NMR ([$^2H_6$]DMSO) δ: 4.18 (br. s, 4H), 5.19 (s, 1H), 8.55 (s, 1H), 8.92 (s, 1H).

For **8**: yield 72%, mp > 160 °C (decomp.). ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.26 (s, 6H), 5.45 (s, 1H), 8.62 (s, 1H), 8.97 (s, 1H).

For **9**: yield 37%, mp > 120 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 7.16 (m, 3H), 7.26 (m, 1H), 7.59 (d, 2H, ^3J 8.8 Hz), 8.32 (s, 1H), 8.67 (s, 1H), 10.49 (s, 1H), 12.31 (br. s, 1H).

For **10**: yield 17%, mp > 120 °C (decomp.). ^{1}H NMR ([$^2H_6$]DMSO) δ: 3.42 (br. s, 4H), 5.64 (s, 1H), 7.22 (d, 2H, ^3J 9.0 Hz), 7.31 (d, 2H, ^3J 9.0 Hz), 8.65 (s, 1H), 8.91 (s, 1H).

For **11**: yield 95%, mp > 260 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 8.74 (s, 1H), 9.96 (br. s, 1H), 10.14 (br. s, 1H), 10.16 (s, 1H).