Reactions of 4,6-dinitrobenzo[*c*]isoxazoles with nucleophiles

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Reactions of nucleophiles with 3-R-4,6-dinitrobenzo[*c*]isoxazoles (anthranils) were studied. Reactions of 4,6-dinitroanthranil (R = H) with anionic O- and S-nucleophiles (phenols and benzenethiols in the presence of K_2CO_3) do not result in displacement of the nitro groups. The malonodinitrile anion (C-nucleophile) attacks the C(3) atom with opening of the isoxazole ring followed by recyclization into 2-amino-5,7-dinitroquinoline-3-carbonitrile *N*-oxide. The 5-NO_2 group in the latter is smoothly replaced under the action of benzenethiol and 4-chlorophenol in the presence of K_2CO_3. In the case of 3-substituted anthranil (R = $COCH_3$), one nitro group (4-NO_2) is replaced under the action of benzenethiol and NaN_3.

Key words: 2,4,6-trinitrotoluene, 4,6-dinitrobenzo[*c*]isoxazole, anthranils, nucleophilic substitution, 4,6-dinitroquinoline *N*-oxide.

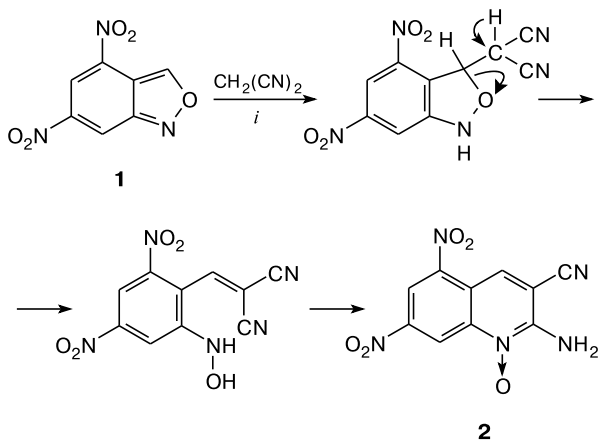
Benzo[*c*]isoxazoles (2,1-benzoisoxazoles, or anthranils) are widely used for synthetic purposes (including the preparation of useful biologically active compounds[1]). Among nitroanthranils, 4,6-dinitroanthranils are of particular interest because their benzene fragment can be functionalized not only by modification of the nitro groups and their *ipso*-substitution but also by nucleophilic substitution of the hydrogen atom (S_NH) that is *ortho* to the nitro group. The S_NH reaction is favored by the formation of stable anionic σ^H-adducts of nucleophiles with the benzene ring.[2—5] Some substituted 3-R-4,6-dinitroanthranils are known.[6—11] Recently, we have developed a preparative method for the synthesis of the first member of the series (unsubstituted 4,6-dinitroanthranil) from 2,4,6-trinitrotoluene (TNT).[12]

It is known that various five-membered aromatic heterocycles annulated with 4,6-dinitrobenzene usually smoothly react with anionic nucleophiles to give, through displacement of the 4-NO_2 group, the corresponding *ipso*-substitution products.[13—16]

In the present work, we studied reactions of 4,6-dinitroanthranil (**1**) with anionic O- and S-nucleophiles (phenols and benzenethiols in the presence of a base). However, the reaction did not occur under conditions accepted as standard for this type of reactions (K_2CO_3, *N*-methylpyrrolidone (*N*-MP), 20—50 °C). An increase in the temperature to 90 °C resulted in the decomposition of the starting compound. Apparently, this is due to the instability of 3-unsubstituted anthranils under basic conditions at elevated temperatures.[1]

3-Unsubstituted anthranils are known[17] to react with malonodinitrile in the presence of an organic base, giving quinoline *N*-oxide derivatives. The initial step of the reaction is believed[18] to involve addition of the malonodinitrile anion to the C(3) atom of anthranil. We found that 4,6-dinitroanthranil (**1**) readily reacts with malonodinitrile in boiling ethanol in the presence of piperidine (Pip), quantitatively yielding earlier unknown 2-amino-5,7-dinitroquinoline-3-carbonitrile *N*-oxide (**2**) (Scheme 1).

Scheme 1



i. Pip/EtOH, reflux.

Room-temperature reactions of compound **2** with benzenethiol and 4-chlorophenol in the presence of K_2CO_3 in *N*-MP and with sodium azide in DMF involve displacement of one nitro group to give the corresponding substitution products in high yields (Scheme 2).

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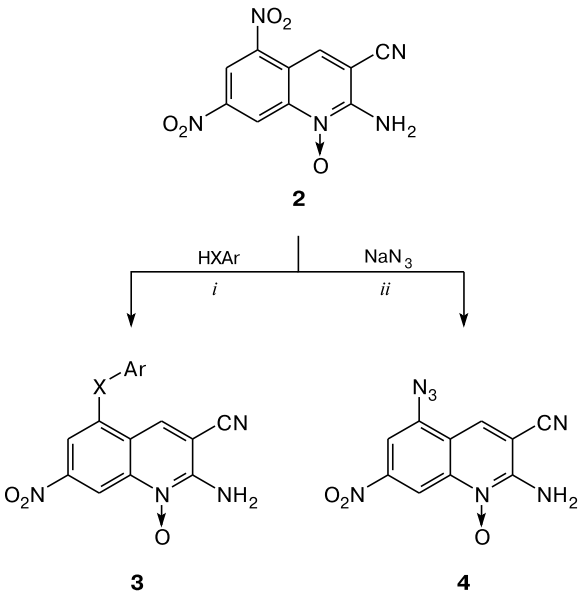
Scheme 2



XAr = SPh (**a**), *p*-OC_6H_4Cl (**b**)

i. K_2CO_3, *N*-MP, ~20 °C; *ii*. DMF, ~20 °C.

The displacement of the 5-NO_2 group in the reactions with benzenethiol and 4-chlorophenol was confirmed by a NOE experiment, which revealed couplings of the H(4) and H(6) protons of the quinoline system with the H(2) and H(6) protons, respectively, of benzenethiol and 4-chlorophenol.

3-Acetyl-4,6-dinitroanthranil[6] possessing a substituent in the position 3 is stable under basic conditions at elevated temperatures; its reactions with anionic nucleophiles proceed with displacement of one nitro group (Scheme 3).

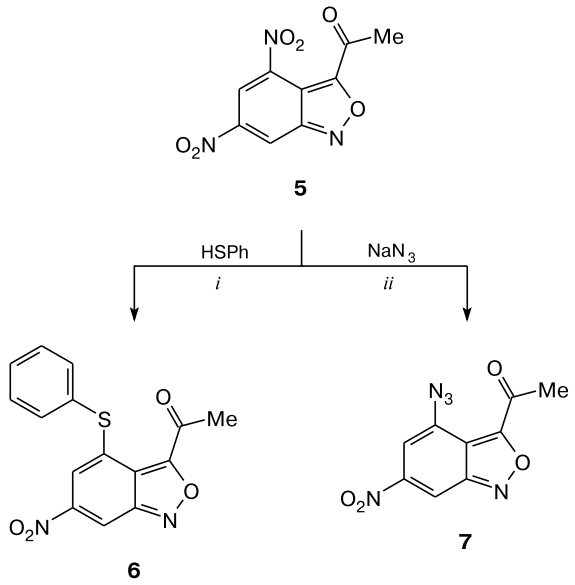
The displacement of the 4-NO_2 group in a reaction with benzenethiol was confirmed by a NOE experiment, which revealed couplings of the acetyl protons and the H(5) proton of the anthranil fragment with the H(2) and H(6) protons of benzenethiol.

Experimental

^{1}H NMR spectra were recorded on a Bruker AC-200 instrument in DMSO-d_6. Chemical shifts δ are referenced to $SiMe_4$. The mass spectrum was recorded on a Kratos MS-30 instrument (70 eV). The melting points of the compounds obtained were measured on a Boetius hot-stage microscope according to the Kofler procedure (heating rate 4 deg min^{-1}).

2-Amino-5,7-dinitroquinoline-3-carbonitrile *N*-oxide (2). Malonodinitrile (0.17 g, 2.4 mmol) and several drops of piperidine were added to a solution of 4,6-dinitroanthranil (**2**) (0.5 g, 2.4 mmol) in ethanol (5 mL). The reaction mixture was refluxed for ~20 h and poured into water. The precipitate that formed was filtered off and dried. The yield of compound **2** was 98%, m.p. >320 °C. ^{1}H NMR (DMSO-d_6), δ: 9.31, 8.79, 8.70 (all s, 1 H, H(6), H(7), H(4)); 8.52 (s, 2 H, NH_2). MS, *m/z*: 275 [M^+]. Found (%): C, 43.25; H, 1.96; N, 25.21. $C_{10}H_5N_5O_5$. Calculated (%): C, 43.56; H, 1.83; N, 25.45.

Scheme 3



i. K_2CO_3, *N*-MP, 50 °C; *ii*. DMF, 50 °C.

Replacement of the nitro group in 2-amino-5,7-dinitroquinoline-3-carbonitrile *N*-oxide (2) (general procedure). A nucleophilic component (2.54 mmol) was added to a solution of 2-amino-5,7-dinitroquinoline-3-carbonitrile *N*-oxide (**2**) (0.7 g, 2.54 mmol) in *N*-MP (7 mL) (or DMF for NaN_3). Phenols and benzenethiols were added together with K_2CO_3 (0.39 g, 2.54 mmol). The reaction mixture was stirred at room temperature for 6 h and poured onto ice. The precipitate that formed was filtered off and washed with cold acetone.

2-Amino-7-nitro-5-(phenylthio)quinoline-3-carbonitrile *N*-oxide (3a). Yield 86%, m.p. 252—254 °C. ^{1}H NMR (DMSO-d_6), δ: 8.56 (s, 1 H, H(4)); 8.02 (s, 1 H, H(8)); 7.35—7.57 (m, 7 H, Ar, NH_2); 7.12 (s, 1 H, H(6)). Found (%): C, 56.55; H, 3.07; N, 16.81. $C_{16}H_{10}N_4O_3S$. Calculated (%): C, 56.80; H, 2.98; N, 16.56.

2-Amino-5-(4-chlorophenoxy)-7-nitroquinoline-3-carbonitrile *N*-oxide (3b). Yield 81%, m.p. 305 °C (decomp.). ^{1}H NMR (DMSO-d_6), δ: 8.72, 8.68 (both s, 1 H, H(8), H(4)); 8.40 (s, 2 H, NH_2); 7.60, 7.35 (both d, 2 H, AA´BB´, *p*-PhCl, J = 8.5 Hz); 7.25 (s, 1 H, H(6)). Found (%): C, 53.62; H, 2.59; N, 15.47. $C_{16}H_{10}ClN_4O_4$. Calculated (%): C, 53.87; H, 2.54; N, 15.71.

2-Amino-5-azido-7-nitroquinoline-3-carbonitrile *N*-oxide (4). Yield 85%, m.p. >320 °C. ^{1}H NMR (DMSO-d_6), δ: 8.68 (s, 1 H, H(4)); 8.28—8.40 (m, 3 H, H(8), NH_2); 7.93 (s, 1 H, H(6)). Found (%): C, 43.95; H, 2.02; N, 36.37. $C_{10}H_5N_7O_3$. Calculated (%): C, 44.29; H, 1.86; N, 36.15.

Replacement of the 4-nitro group in 1-(4,6-dinitro[*c*]isoxazol-3-yl)ethanone (5) (general procedure). A nucleophilic component (0.4 mmol) was added to a solution of 1-(4,6-dinitro-[*c*]isoxazol-3-yl)ethanone (**5**) (0.1 g, 0.4 mmol) in *N*-MP (1 mL) (or DMF for NaN_3). Benzenethiol was added together with

K_2CO_3 (0.054 g, 0.4 mmol). The reaction mixture was stirred at 50 °C for 2 h and poured onto ice. The precipitate that formed was filtered off, washed with water, and recrystallized from EtOH.

1-(6-Nitro-4-(phenylthio)benzo[*c*]isoxazol-3-yl)ethanone (6). Yield 76%, m.p. 138—141 °C. ^{1}H NMR (DMSO-d_6), δ: 8.58 (s, 1 H, H(7)); 7.70—7.55 (m, 5 H, SPh); 7.34 (s, 1 H, H(5)); 2.78 (s, 3 H, CH_3). Found (%): C, 58.12; H, 3.45; N, 8.72. $C_{15}H_{10}N_2O_4S$. Calculated (%): C, 57.32; H, 3.21; N, 8.91.

1-(4-Azido-6-nitrobenzo[*c*]isoxazol-3-yl)ethanone (7). Yield 70%, m.p. 150 °C (decomp.). ^{1}H NMR (DMSO-d_6), δ: 8.96 (s, 1 H, H(7)); 7.94 (s, 1 H, H(6)); 2.84 (s, 3 H, CH_3). Found (%): C, 44.13; H, 2.24; N, 27.89. $C_9H_5N_5O_4$. Calculated (%): C, 43.73; H, 2.04; N, 28.33.

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