Characteristic features of nucleophilic substitution in the series of 4-RSO_2-6-nitro-1-phenyl-1*H*-indazoles and benzo[*d*]isoxazoles

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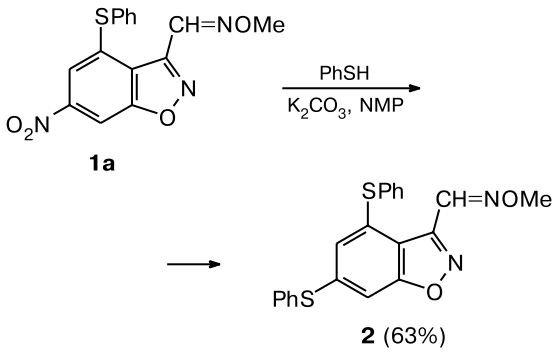
Oxidation of 3-substituted 4-R-6-nitro-1-phenyl-1*H*-indazoles and benzo[*d*]isoxazoles (R = Ph, CH_2CO_2Me) gave the corresponding sulfones treatment of which with PhSH—K_2CO_3 in *N*-methylpyrrolidone results in replacement of only the RSO_2 group in position 4 with the 6-NO_2 group remaining intact, contrary to the known sequence of nucleophilic substitution for *meta*-arranged nucleofuges.

Key words: 1*H*-indazoles, benzo[*d*]isoxazoles, nitro compounds, sulfones, nucleophilic substitution.

Previously, we reported the synthesis of 3-substituted 4,6-dinitrobenzo[*d*]isoxazoles[1] and 1-aryl-4,6-dinitro-1*H*-indazoles[2,3] on the basis of picrylacetaldehyde. It was found that the nitro group in position 4 of these compounds is highly active and can be replaced under mild conditions on treatment with a broad range of anionic O-, N-, and S-nucleophiles (thiols, phenols, or alcohols in the presence of inorganic bases or NaN_3).[1—3] The reactions are regiospecific, the nitro group in position 6 remains intact even with a large excess of the nucleophile. The 6-NO_2 group in the products of nucleophilic substitution of the 4-NO_2 group is not replaced either; under more drastic reaction conditions (temperature rise above 100 °C), the starting nitro compounds decompose.

The only exception is 6-nitrobenzo[*d*]isoxazole **1a**, which reacts with PhSH in the presence of K_2CO_3 under rather drastic conditions (100 °C, in *N*-methylpyrrolidone (NMP)) to give the product of replacement of the 6-nitro group, namely, bis-sulfide **2** (Scheme 1).

Scheme 1



1a

2 (63%)

Apparently, for the majority of mononitro benzo[*d*]isoxazole and 1*H*-indazole derivatives we prepared previously, the electrophilicity of the heteroaromatic system does not suffice for the replacement of the 6-NO_2 group. We suggested that the introduction of a strong electron-withdrawing substituent that would still be less efficient than the leaving NO_2 group into position 4 of the benzo[*d*]isoxazole or indazole nucleus would enhance the mobility of the 6-NO_2 group, and it could be possible to replace this group on treatment with nucleophiles. As such substituent, we chose the RSO_2 group. Indeed, it has been shown recently[4] that in the benzene series with *meta*-located $PhSO_2$ and NO_2 groups, only the NO_2 group is replaced on treatment with PhSH (in the presence of K_2CO_3), while the $PhSO_2$ group activates the *meta*-arranged NO_2 group virtually in the same way as the nitro group, as follows from comparison of the conditions of NO_2 replacement in *meta*-dinitro and *meta*-nitro(phenylsulfonyl) derivatives of benzene.

Starting from the previously synthesized[1,3] sulfides **1a—c**, we prepared 6-nitro-4-RSO_2 derivatives of the benzo[*d*]isoxazole and 1*H*-indazole, in particular, compounds **1a—c** were oxidized to the corresponding sulfones on treatment with 30% aqueous H_2O_2 in the CF_3COOH medium (Scheme 2).

In the resulting sulfones, we studied the direction of nucleophilic substitution taking the reaction of nitrosulfones **3a—c** with benzenethiol as an example.

We found that on treatment of sulfonyl derivatives **3a—c** with PhSH in the presence of K_2CO_3 in NMP, only the 4-RSO_2 group is replaced to give previously described[1,3] sulfides **1a,b** (Scheme 3).

The reaction proceeds under mild conditions (20 °C) and regiospecifically (the nitro group in position 6 re-

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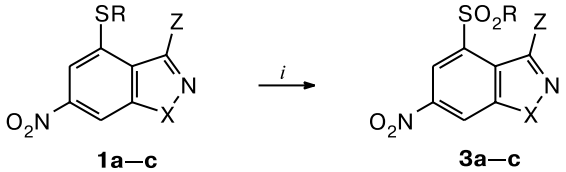
Scheme 2

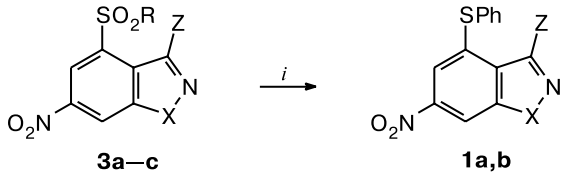


1a—c **3a—c**

Compound	R	Z	X	Yield **3** (%)
a	Ph	CH=NOMe	O	91
b	Ph	CN	NPh	98
c	CH_2CO_2Me	CN	NPh	92

i. H_2O_2, CF_3COOH, 20 °C, 1 h.

Scheme 3



3a—c **1a,b**

Starting compound	Product	Yield of **1** (%)
3a	**1a**	64
3b	**1b**	74
3c	**1b**	94

i. PhSH, K_2CO_3, NMP, 20 °C.

mains intact). The rate of replacement of the sulfonyl group in compounds **3a,c** is comparable with the rate of replacement of the 4-NO_2 group in the dinitro derivatives of the benzo[*d*]isoxazole[1] and 1*H*-indazole[3] series (the reactions with PhSH under identical conditions proceed to completion in 24 h), while in compound **3b**, this rate was somewhat lower (full conversion of the starting sulfonyl derivative required 48 h).

The formation of only one of the two possible substitution products was demonstrated by ^{1}H NMR of the crude reaction product. The compounds obtained were identified by a set of physicochemical methods, and products **1a,b** were also compared with the specimens synthesized previously. The key characteristics (m.p., NMR spectra, and so on) of the resulting phenylthio derivatives coincide with those for the obtained previously specimens.

Thus, we demonstrated that nucleophilic substitution in 3-substituted 4-RSO_2-6-nitro-1-phenyl-1*H*-indazoles and 4-RSO_2-6-nitrobenzo[*d*]isoxazoles proceeds regiospecifically with replacement of only the 4-RSO_2 group.

This reaction pathway unusual for the benzene fragment is, apparently, related to the strong influence of the annelated heterocycle and its substituent in position 3, as is the case for 4,6-dinitrobenzo-annelated five-membered aromatic heterocycles.[1—3,5] To elucidate specific reasons, separate structural studies and calculations are required.

Experimental

^{1}H NMR spectra were recorded on a Bruker AC-200 instrument and ^{13}C NMR spectra were run on a Bruker AM-300 spectrometer. The chemical shifts (δ) are referred to Me_4Si. The spin-spin coupling constants are given in Hz. All samples for NMR spectroscopy were prepared in a 1 : 1 DMSO-d_6—CCl_4 mixture. IR spectra were measured on a Specord M-80 instrument in KBr pellets. Mass spectra were recorded on a Kratos MS-30 mass spectrometer (EI, 70 eV, *m/z*). The course of the reactions was monitored and the purity of substances was checked by TLC on Silufol UV-254 plates. The solvents were not specially purified.

4,6-Bis(phenylthio)benzo[*d*]isoxazole-3-carboxaldehyde *O*-methyloxime (2). A mixture of compound **1a** (0.58 g, 1.83 mmol), benzenethiol (0.19 mL, 1.83 mmol), K_2CO_3 (0.26 g, 1.83 mmol), and 6 mL of NMP were stirred for 10 h at 100 °C. The reaction mixture was poured in water and acidified to pH 2, the precipitate was filtered off and recrystallized from EtOH to give 0.47 g (63%) of compound **2**. M.p. 113—114 °C (EtOH). Found (%): C, 64.11; H, 4.15; S, 16.25. $C_{21}H_{16}N_2O_2S_2$. Calculated (%): C, 64.26; H, 4.11; S, 16.34. ^{1}H NMR, δ: 4.05 (s, 3 H, OCH_3); 6.60 (s, 1 H, H(5)); 7.20 (s, 1 H, H(7)); 7.30—7.50 (m, 10 H, Ph); 8.50 (s, 1 H, CH=N). ^{13}C NMR, δ: 62.41, 105.50, 116.25, 123.30, 128.95, 129.24, 132.91, 129.43, 129.90, 130.57, 130.80, 133.77, 134.34, 138.10, 142.95, 151.02, 164.10. MS: 392 $[M]^+$. IR, ν/cm^{-1}: 1040, 1060 (C=C), 1580 (C=N).

Preparation of sulfones 3a—c (general procedure). A 30% solution of H_2O_2 (2 mL) was added to a solution of 6 mmol of the corresponding sulfide in 20 mL of CF_3COOH and the mixture was stirred for 1 h at 20 °C. The reaction mixture was poured in water and the precipitate was filtered off, washed with water, and dried at 100 °C.

6-Nitro-4-(phenylsulfonyl)benzo[*d*]isoxazole-3-carboxaldehyde *O*-methyloxime (3a). M.p. 132—134 °C. Found (%): C, 49.98; H, 3.31; S, 8.83. $C_{15}H_{11}N_3O_6S$. Calculated (%): C, 49.86; H, 3.07; S, 8.87. ^{1}H NMR (DMSO-d_6), δ: 4.03 (s, 3 H, OCH_3); 7.60—7.80 (m, 3 H, Ph); 7.90 (d, 2 H, Ph, $^3J_{H,H}$ = 7.3 Hz); 8.65 (s, 1 H, CH=N); 8.80 (s, 1 H, H(5)); 9.20 (s, 1 H, H(7)). MS: 330 $[M - OCH_3]^+$.

3-Cyano-6-nitro-1-phenyl-4-(phenylsulfonyl)-1*H*-indazole (3b). M.p. 207—209 °C. Found (%): C, 58.99; H, 3.15; S, 8.08. $C_{20}H_{12}N_4O_4S$. Calculated (%): C, 59.40; H, 2.99; S, 7.93. ^{1}H NMR (DMSO-d_6), δ: 7.60—7.90 (m, 8 H, Ph); 8.20 (m, 2 H, Ph); 8.80 (s, 1 H, H(5)); 8.90 (s, 1 H, H(7)).

Methyl 2-[(3-cyano-6-nitro-1-phenyl)-1*H*-indazole-4-yl)sulfonyl]acetate (3c). M.p. 185—187 °C. Found (%): C, 51.05; H, 3.15; S, 7.85. $C_{17}H_{13}N_4O_6S$. Calculated (%): C, 51.00; H, 3.02; S, 8.01. ^{1}H NMR (DMSO-d_6), δ: 3.67 (s, 3 H, OCH_3); 4.98 (s, 2 H, CH_2); 7.60—7.90 (m, 5 H, Ph); 8.70 (s, 1 H, H(5)); 8.90 (s, 1 H, H(7)). ^{13}C NMR (DMSO-d_6), δ: 113.1, 115.5, 120.3, 123.0, 125.3, 130.9, 131.0, 132.8, 137.8, 140.1, 146.9, 163.5. IR, ν/cm^{-1}: 1724 (CO_2Me), 1540, 1340 (NO_2), 1168 (SO_2). MS: 400 $[M]^+$.

Preparation of sulfides 1a,b (general procedure). A mixture of 1 mmol of particular sulfone **3a—c**, PhSH (0.1 mL, 1 mmol),

K_2CO_3 (0.14 g, 1 mmol), and 6 mL of NMP was stirred for 24—48 h at 20 °C (TLC monitoring). The reaction mixture was poured in water and acidified to pH 2, and the precipitate was filtered off, recrystallized from EtOH, and dried at 80 °C.

6-Nitro-4-(phenylthio)benzo[*d*]isoxazole-3-carboxaldehyde *O*-methyloxime (1a). M.p. 117—118 °C (EtOH). Found (%): C, 54.54; H, 3.43; S, 9.62. $C_{15}H_{11}N_3O_4S$. Calculated (%): C, 54.70; H, 3.37; S, 9.74. ^{1}H NMR, δ: 4.05 (s, 3 H, OMe); 7.50—7.60 (s, 6 H, Ph, H(5)); 8.57 (s, 1 H, CH=N); 8.74 (s, 1 H, H(7)). 13C NMR (δ: 62.68, 104.00, 117.89, 121.76, 129.89, 130.45, 133.63, 135.64, 138.21, 149.21, 151.87, 162.81. The sample was identical to that prepared previously.[1]

3-Cyano-6-nitro-1-phenyl-4-phenylthio-1*H*-indazole (1b). M.p. 196—198 °C (EtOH). ^{1}H NMR, δ: 7.50—7.80 (m, 11 H, Ph, H(5)); 8.42 (s, 1 H, H(7)). The sample was identical to that prepared previously.[3]

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