Nitropyrazoles

22*. On reactivity of 3,5-dinitro-4-(phenylsulfonyl)pyrazole and its *N*-methyl derivative

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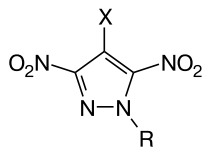
3,5-Dinitro-4-(phenylsulfonyl)pyrazole (**5**) obtained by oxidation of 3,5-dinitro-4-(phenylthio)pyrazole with 30% H_2O_2 in AcOH was involved into nucleophilic substitution reaction with thiophenol, which proceeded with substitution of the phenylsulfonyl group at position 4. *N*-Methyl-3,5-dinitro-4-(phenylsulfonyl)pyrazole obtained by methylation of **5** with dimethyl sulfate was involved into nucleophilic substitution reaction with thiophenol, *p*-bromophenol, and morpholine with the regioselective substitution of the nitro group at position 5 to form 5-R-3-nitro-4-(phenylsulfonyl)pyrazoles.

Key words: pyrazole, nitro group, nitropyrazoles, 3,5-dinitropyrazoles, (phenylsulfonyl)-nitropyrazoles, nucleophilic substitution, nucleophiles, regioselective substitution, methylation.

Earlier, taken nucleophilic substitution in 3,4,5-trinitro-1*H*-pyrazole **1** and its *N*-methyl derivative **2** as an example, we have found that traditional regioselectivity of nucleophilic substitution (at position 3 or 5) depends on the ability of trinitropyrazole derivatives to form an N-anion under the reaction conditions: for the first time, a possibility of nucleophilic substitution of the nitro group at position 4 of the trinitropyrazole N-anion was demonstrated on a wide body of examples.[2]

At the same time, practical application of trinitropyrazole derivatives **1** and **2** for the directed functionalization of the pyrazole ring by nucleophilic substitution of an NO_2 group is limited by the necessity of using certain precautions when the starting compounds **1** and **2** are handled on a multigram scale (see Ref. 3).

Recently, we have found that 4-chloro-3,5-dinitropyrazole derivatives **3** and **4** can serve as convenient starting compounds for the selective functionalization of position 4 in 3,5-dinitropyrazoles. However, regioselectivity of the nucleophilic substitution in these compounds did not change in going from the N anion of NH pyrazole **3** to its *N*-methyl derivative **4**. In all the cases occurs the substitution of the Cl atom at position 4 (see Ref. 4).



1—4

Compound	X	R	Compound	X	R
1	NO_2	H	**3**	Cl	H
2	NO_2	Me	**4**	Cl	Me

Thus, the direction of nucleophilic substitution in 4-X-3,5-dinitropyrazoles was found to depend not only on the ability to form an anion under the reaction conditions, but also on the nature of the leaving group at position 4.

In this connection, investigation of regularities of nucleophilic substitution in dinitropyrazoles containing, besides NO_2 groups, an additional leaving group seems an actual problem.

In the present work, we studied nucleophilic substitution in 3,5-dinitro-4-(phenylsulfonyl)-1*H*-pyrazole (**5**) and its *N*-methyl derivative, 1-methyl-3,5-dinitro-4-(phenylsulfonyl)-1*H*-pyrazole (**6**).

Dinitropyrazole **5** was obtained by the oxidation of 3,5-dinitro-4-(phenylthio)pyrazole **7** with 30% H_2O_2 in acetic acid (Scheme 1). As typical representatives of N-, O-, and S-nucleophiles we have chosen morpholine, *p*-bromophenol, and thiophenol. The reaction was carried out in water in the temperature range 20—90 °C. In the case of morpholine, we used a three-fold excess of the latter, in the case of phenol and thiophenol, the reaction was carried out using two equivalents of NaOH as a deprotonating agent. Thus, the conditions of the reaction of dinitropyrazole **5** with nucleophiles were completely the same as in nucleophilic substitution in pyrazoles **1** and **3** (see Refs 2 and 4).

It was found that under indicated conditions, only thiophenol was involved into the reaction with (phenyl-

* For Part 21, see Ref. 1.

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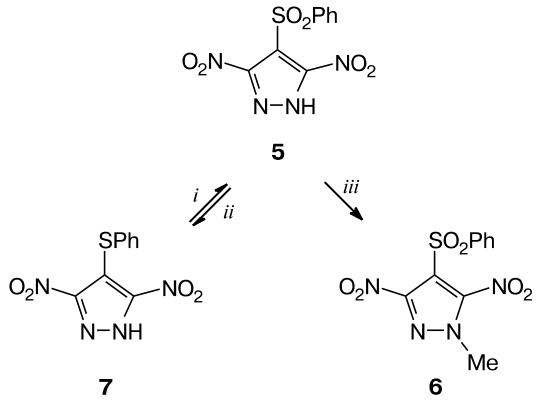
sulfonyl)pyrazole **5**, which led to the formation of phenyl substituted derivative **7** in 90% yield (see Scheme 1). *p*-Bromophenol and morpholine did not give the reaction.

Scheme 1



i. 30% H_2O_2—AcOH, 60 °C, 12 h, 70%; *ii*. PhSH (1 equiv.)/NaOH (2 equiv.), H_2O, 25 °C, 7 h, 90%; *iii*. Me_2SO_4 (1.2 equiv.)/$NaHCO_3$ (2 equiv.), H_2O, 25 °C, 7 h, 75%

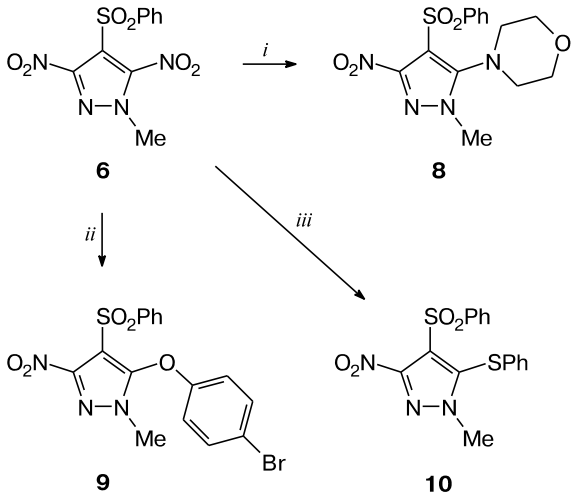
Thus, a conclusion can be drawn that the regioselectivity of nucleophilic substitution in 3,5-dinitro-4-(phenylsulfonyl)pyrazole **5** is the same as in 4-X-3,5-dinitropyrazoles **1** (X = NO_2) and **3** (X = Cl). Namely, the 4-$PhSO_2$ group is the group which undergoes the selective replacement as a result of formation of an anion under the reaction conditions.* However, the reactivity of pyrazole **5** (to be exact, of its N-anion) is considerably lower than that of anions of pyrazoles **1** and **3**, which give the nucleophilic substitution reaction with O- and N-nucleophiles, as well.

The simplest nonionizable representative of 3,5-dinitro-4-(phenylsulfonyl)pyrazoles, 1-methyl-3,5-dinitro-4-(phenylsulfonyl)pyrazole **6**, was obtained upon the action of dimethyl sulfate on pyrazole **5** in water in the presence of $NaHCO_3$ in 75% yield (see Scheme 1).

We used morpholine, *p*-bromophenol, and thiophenol as model N-, O-, and S-nucleophiles. The reaction with morpholine (3 equiv.) was carried out in methanol at room temperature. The complete conversion was reached within 10 h and the yield of the substitution product **8** was 76% (Scheme 2). In the case of *p*-bromophenol and thiophenol, which were used in a small excess (1.1 equiv.), the reaction was performed in a mixture of water—acetonitrile at room temperature during 10 h, using 1.1 equiv. of NaOH as a deprotonating agent. The yields of the substitution products **9** and **10** were 82 and 86%, respectively (see Scheme 2).

Analysis of the ^1H and ^{13}C NMR spectra of compounds **8**—**10** showed that all the spectra still have the signals

Scheme 2



i. N O (3 equiv.), MeOH, 25 °C, 10 h; *ii*. *n*-BrC_6H_4OH (1.1 equiv.)/NaOH (1.1 equiv.), MeCN/H_2O, 25 °C, 10 h; *iii*. PhSH (1.1 equiv.)/NaOH (1.1 equiv.), MeCN/H_2O, 25 °C, 10 h.

corresponding to the $PhSO_2$ group. Moreover, the substitution of the NO_2 group rather than the $PhSO_2$ group was confirmed by mass spectra and elemental analysis. The choice between substitution of the 3-NO_2 or 5-NO_2 group was made in favor of position 5 based on the analysis the ^{13}C NMR spectra of 5-substituted 3-nitropyrazoles.[6] It is known[7] that in the NMR spectra of nitropyrazoles, the signals for the carbon atoms are arranged in the following order C(3) ≥ C(5) > C(4). In the NMR spectra of compounds **8**—**10**, the most downfield signal for the carbon atom is broadened because of the quadruple relaxation on the ^{14}N nuclei of the NO_2 group and, therefore, is attributable to the fragment C(3)—NO_2.

In conclusion, we found yet another example in the series of 4-X-3,5-dinitropyrazoles, regioselectivity of nucleophilic substitution in which changes depending on the ability to form an anion under the reaction conditions.

Experimental

Melting points were measured on a Boetius heating stage and were not corrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-300 spectrometer in [$^2H_6$]DMSO at 298 K. ^1H and ^{13}C chemical shift are given relative to $SiMe_4$. Mass spectra were recorded on a Finnigan MAT INCOS 50 (direct injection, EI, 70 eV) and Bruker MicroOTOF II instruments. Reaction progress and purity of compounds were monitored by TLC on Merck Silicagel 60 F_{254} plates. Elemental analysis was performed on a Perkin Elmer Series II 2400 instrument.

3,5-Dinitro-4-(phenylthio)-1*H*-pyrazole (7) was obtained according to the known procedure.[2c]

* It is obvious that the pK_a value for compound **5** is lower than the pK_a value of 3,5-dinitropyrazole (see Ref. 5: pK_a = 3.15).

3,5-Dinitro-4-(phenylsulfonyl)-1*H*-pyrazole (5). Pyrazole **7** (12.5 g, 0.047 mol) was added to a solution of 30% H_2O_2 (25 mL) in AcOH (200 mL). The mixture was kept for 12 h at 60 °C, the solvent was evaporated at reduced pressure, the residue was recrystallized from EtOH—H_2O to obtain the product (9.8 g, 70%) with m.p. 191—193 °C. Found (%): C, 36.42; H, 2.05; N, 19.01. $C_9H_6N_4O_6S$. Calculated (%): C, 36.25; H, 2.03; N, 18.79. ^{1}H NMR, δ: 7.65 (m, 3 H, Ph); 8.05 (m, 2 H, Ph). ^{13}C NMR, δ: 107.15 (C(4)); 127.56 (CH); 129.23 (CH); 133.70 (CH); 141.30; 154.54 (C(3,5)). MS: m/z = 298 $[M]^+$.

Reaction of compounds 5 with S-nucleophiles. Sodium hydroxide (0.12 g, 3 mmol) was added to a solution of pyrazole **5** (0.89 g, 3 mmol) in H_2O (10 mL) and the mixture was stirred for 10 min. A solution prepared from NaOH (0.12 g, 3 mmol) and thiophenol (0.34 mL, 3.3 mmol) in H_2O (10 mL) was added to the solution obtained. The mixture was stirred for 7 h at room temperature, acidified with 20% H_2SO_4 to pH 1, a precipitate formed was filtered off, dried, and recrystallized from a mixture of MeOH—H_2O to obtain compound **7** (0.72 g, 90%) with m.p. 155—156 °C (see Ref. 2c).

1-Methyl-3,5-dinitro-4-(phenylsulfonyl)-1*H*-pyrazole (6). The compound **5** (0.89 g, 3 mmol) was added to a solution of $NaHCO_3$ (0.50 g, 6 mmol) in H_2O (10 mL), followed by stirring during 10 min. After addition of Me_2SO_4 (0.34 mL, 3.6 mmol), the mixture was stirred for 7 h at room temperature. A precipitate formed was filtered off, dried in air, and recrystallized from MeCN to obtain the product (0.70 g, 75%) with m.p. 155—157 °C. Found (%): C, 38.68; H, 2.77; N, 18.13. $C_{10}H_8N_4O_6S$. Calculated (%): C, 38.46; H, 2.58; N, 17.94. ^{1}H NMR, δ: 4.12 (s, 3 H, NMe); 7.77 (m, 3 H, Ph); 8.15 (m, 2 H, Ph). ^{13}C NMR, δ: 41.35 (NMe); 112.62 (C(4)); 128.29 (CH); 129.82 (CH); 135.23 (CH); 138.66; 144.52 (C(5)); 150.05 (C(3)). MS: m/z = 312 $[M]^+$.

4-[1-Methyl-3-nitro-4-(phenylsulfonyl)-1*H*-pyrazole-5-yl]-morpholine (8). Morpholine (0.53 mL, 6 mmol) was added to a solution of pyrazole **6** (0.62 g, 2 mmol) in MeOH (15 mL), the mixture was kept during 10 h at room temperature. The solvent was evaporated at reduced pressure, the solid residue was washed with water on the filter and recrystallized from a mixture of MeOH—H_2O to obtain the product (0.53 g, 76%) with m.p. 163—165 °C. Found (%):C, 48.05; H, 4.64; N, 16.10. $C_{14}H_{16}N_4O_5S$. Calculated (%): C, 47.72; H, 4.58; N, 15.90. ^{1}H NMR, δ: 3.23 (t, 4 H, J = 4.4 Hz); 3.72 (t, 4 H, J = 4.4 Hz); 3.94 (s, 3 H, NMe); 7.68 (m, 3 H, Ph); 8.05 (m, 2 H, Ph). ^{13}C NMR, δ: 36.75 (NMe); 49.47; 66.37; 108.13 (C(4)); 126.87 (CH); 129.31 (CH); 133.76 (CH); 141.31; 150.84 (C(3)); 151.04 (C(5)). MS: m/z = 352 $[M]^+$.

Reaction of compound 6 with O- and S-nucleophiles (general procedure). *p*-Bromophenol or thiophenol (1.1 mmol) was added to a solution of NaOH (1.1 mmol) in H_2O (5 mL), the mixture was stirred for 10 min, followed by addition of pyrazole **6** (1 mmol)) in CH_3CN (7 mL). After stirring of the reaction mixture for 10 h at room temperature, the solvent was evaporated *in vacuo*, the solid residue was washed with water on the filter and recrystallized from a mixture of MeOH—H_2O.

5-(4-Bromophenoxy)-1-methyl-3-nitro-4-(phenylsulfonyl)-1*H*-pyrazole (9). The yield was 82%, m.p. 135—137 °C. Found (%): C, 43.98; H, 2.82; N, 9.70. $C_{16}H_{12}BrN_3O_5S$. Calculated (%): C, 43.85; H, 2.76; N, 9.59. ^{1}H NMR, δ: 3.75 (s, 3 H, NMe); 7.15 (m, 2 H, Ph); 7.55 (m, 4 H, Ph); 7.72 (m, 3 H, Ph). ^{13}C NMR, δ: 36.24 (NMe); 105.13 (C(4)); 116.38 (C(Br)); 118.32 (CH_{Ph}); 127.09 ($CH_{Ph—SO2}$)); 129.16 ($CH_{Ph—SO2}$); 132.82 (CH_{Ph}); 134.10 ($CH_{Ph—SO2}$); 140.26 (C—SO_2); 148.64 (C(5)); 149.18 (C(3)); 155.37 (C—O—Ph). MS: m/z = 437, 439 (1 : 1) $[M]^+$.

1-Methyl-3-nitro-4-(phenylsulfonyl)-5-(phenylthio)-1*H*-pyrazole (10). The yield was 86%, m.p. 123—125 °C. Found (%): C, 51.36; H, 3.61; N, 11.33. $C_{16}H_{13}N_3O_4S_2$. Calculated (%): C, 51.19; H, 3.49; N, 11.19. ^{1}H NMR, δ: 3.88 (s, 3 H, NMe); 7.20 (m, 2 H, Ph); 7.34 (m, 3 H, Ph); 7.62 (m, 2 H, Ph); 7.71 (m, 1 H, Ph); 7.89 (m, 2 H, Ph). ^{13}C NMR, δ: 38.71 (NMe); 118.91 (C(4)); 126.30 (CH); 127.83 (CH); 128.62 (CH); 129.07 (CH); 129.38 (CH); 131.32; 134.28 (CH); 138.28 (C(5)); 140.02; 151.63 (C(3)). MS: m/z = 375 $[M]^+$.

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