# Nitropyrazoles
## 11.* Isomeric 1-methyl-3(5)-nitropyrazole-4-carbonitriles in nucleophilic substitution reactions. Comparative reactivity of the nitro group in positions 3 and 5 of the pyrazole ring

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With reactions of isomeric 1-methyl-3-nitro- and 1-methyl-5-nitropyrazole-4-carbonitriles with anionic *S*-, *O*-, and *N*-nucleophiles (RSH, PhOH, and 3,5-dimethyl-4-nitropyrazole in the presence of $K_2CO_3$ or MeONa), it was shown that for *N*-substituted 3(5)-nitropyrazoles, the nitro group in position 5 is much more reactive than in position 3.

**Key words:** nitropyrazoles, nucleophilic substitution, anionic nucleophiles.

Earlier,[2] we demonstrated that the introduction of a nitro group into a pyrazole ring enables one to develop efficient synthetic techniques for the pyrazole series and estimate the electronic effects of some fragments in pyrazole-containing systems.

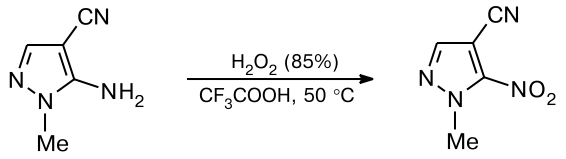
An important line in improving the methodology of synthesis from nitropyrazoles is to investigate nucleophilic substitution for the nitro groups in positions 3(5) and develop selective introduction of substituents into either position.

In a pyrazole ring, positions 3 and 5 are most liable to a nucleophilic attack;[3] these positions are not equivalent in *N*-substituted pyrazoles. A halogen (chlorine or bromine) atom in position 5 is much more reactive than in position 3 (*e.g.*, see lit.[4]), despite more considerable steric hindrances to nucleophilic substitution for the Hal(5) atom, especially in 4-substituted pyrazoles.

Nucleophilic substitution for the nitro group in position 5 of *N*-substituted pyrazoles was illustrated with a number of examples (see lit.[5]). However, relevant data for 3-nitropyrazoles are lacking. Because the steric effects of halogen atoms and a nitro group differ, the relative reactivity of the $NO_2$ group in positions 3 and 5 is *a priori* not obvious. In the present work, the nitro groups in positions 3 and 5 were compared in reactivity by using isomeric 1-methyl-5-nitropyrazole-4-carbonitrile (**1**) and 1-methyl-3-nitropyrazole-4-carbonitrile (**2**); the presence of the electron-withdrawing CN group in position 4 facilitates nucleophilic substitution.

Nitrile **1** was prepared by the oxidation of 5-amino-1-methylpyrazole-4-carbonitrile with 85% $H_2O_2$ in trifluoroacetic acid (Scheme 1). The starting amine was synthesized according to a known procedure.[6]

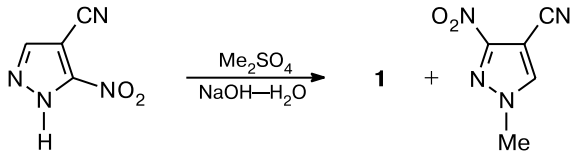
**Scheme 1**




**1**

Isomeric nitrile **2** was prepared through the methylation of 3(5)-nitropyrazole-4-carbonitrile with dimethyl sulfate in aqueous alkali followed by separation of isomers **1** and **2** by column chromatography (Scheme 2). The starting 3(5)-nitropyrazole-4-carbonitrile was synthesized according to a known procedure.[7]

**Scheme 2**




**2**

**1** : **2** = 1 : 4.5

*S*-Nucleophiles ($PhS^-$, $PhCH_2S^-$, $PhNHCOCH_2S^-$, $CH_3COS^-$, $EtOCSS^-$), *O*-nucleophiles ($PhO^-$, $MeO^-$), and an *N*-nucleophile (3,5-dimethyl-4-nitropyrazole an-

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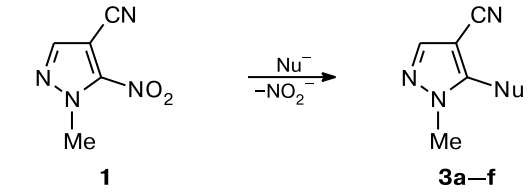
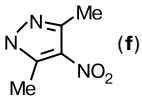
ion) were used. Except for potassium ethylxanthate and sodium methoxide, all nucleophiles were generated *in situ* by treating a conjugated acid (corresponding to the nucleophilic species) with $K_2CO_3$. For the reactivity estimates to be compared, equal concentrations of nitrile **1** in different solvents were employed. The molar ratio of **1** to $Nu^-$(NuH) was always 1 : 1.

In the presence of potassium carbonate, nitrile **1** actively reacts with thiophenol and benzylmercaptan (Scheme 3). In DMF, the reaction is completed over several minutes at room temperature; in acetonitrile, heating is required. For instance, the reactions of nitrile **1** with PhSH and $PhCH_2SH$ in the presence of $K_2CO_3$ in boiling $CH_3CN$ were completed over ~40 min.

**Scheme 3**




Nu = PhS (**a**), $PhCH_2S$ (**b**), $PhNHCOCH_2S$ (**c**), PhO (**d**), MeO (**e**),  (**f**)

Under analogous conditions (boiling $CH_3CN$, $K_2CO_3$), an *N*-phenylthioglycolamide anion is substituted for the nitro group much more slowly than thiophenol and benzylmercaptan. The complete conversion (TLC monitoring) is reached in 8 h. However, the reaction duration in boiling ethanol is only 2 h.

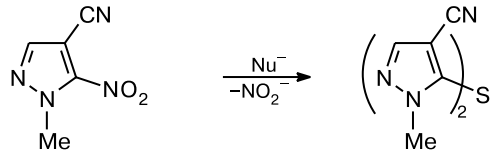
The other *S*-nucleophiles are even less reactive in the substitution reaction than an *N*-phenylthioglycolamide anion. For instance, nitrile **1** completely reacts with thioacetic acid in the presence of $K_2CO_3$ in boiling ethanol over 4 h, while its reaction with potassium ethylxanthate requires six hours.

It should be noted that the last two nucleophiles yield sulfide **3g** instead of the expected substitution product (Scheme 4). Analogous substitution reactions for halogens were reported earlier.[8]

Nitrile **1** completely reacts with sodium methoxide in DMF over ~30 min. The reaction of nitrile **1** with phenol in boiling $CH_3CN$ in the presence of $K_2CO_3$ is completed over 8 h; *i.e.*, the reactivity of phenol is nearly the same as that of *N*-phenylthioglycolamide (see Scheme 3).

3,5-Dimethyl-4-nitropyrazole is also capable of replacing, in the presence of $K_2CO_3$, the nitro group in nitrile **1**, although the reaction proceeds comparatively slowly (boiling acetonitrile, 12 h; see Scheme 3). The

**Scheme 4**

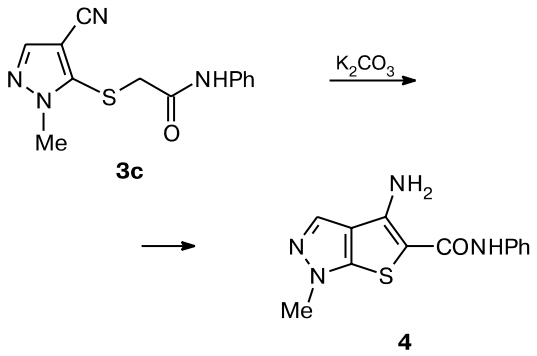



Nu = EtOCSS, MeCOS

reaction conditions and the yields and characteristics of compounds **3a**—**g** are given in Tables 1 and 2.

When heated in ethanol with an additional mole of $K_2CO_3$, compound **3c** containing an *N*-phenylthioglycolamide residue undergoes cyclization into the corresponding thieno[2,3-*c*]pyrazole (**4**) (Scheme 5); the data for this compound are presented in Tables 3 and 4.

**Scheme 5**




The same *S*-, *O*-, and *N*-nucleophiles were used in reactions with nitrile **2** under the reaction conditions of

**Table 1.** Conditions for the replacement of the nitro group in nitrile **1**

| Compound | Solvent | Conversion time of nitrile **1** | *T*/°C | Yield (%) | M.p. /°C |
|---|---|---|---|---|---|
| **3a** | DMF | ~3 min | 25 | 45 | 18—20[a] |
| | $CH_3CN$ | ~40 min | 80 | 57 | |
| **3b** | DMF | ~3 min | 25 | 42 | Oil[a] |
| | $CH_3CN$ | ~40 min | 80 | 58 | |
| **3c** | $CH_3CN$ | ~8 h | 80 | 72 | 155 (from EtOH) |
| | $C_2H_5OH$ | ~2 h | 78 | 75 | |
| **3d** | $CH_3CN$ | ~8 h | 80 | 72 | 125 (from EtOH) |
| **3e** | DMF | ~30 min | 25 | 37 | 103 (from EtOH) |
| **3f** | $CH_3CN$ | ~12 h | 80 | 71 | 114 (from EtOH) |
| **3g** | $C_2H_5OH$ | ~4 h | 78 | 48[b] | 191 (from EtOH) |
| | | ~6 h | 78 | 39[c] | |

[a] Purified by column chromatography.
[b] The reaction with $CH_3COSH + K_2CO_3$.
[c] The reaction with EtOCSSK.

**Table 2.** Characteristics of the products obtained by replacement of the nitro group in nitrile **1**

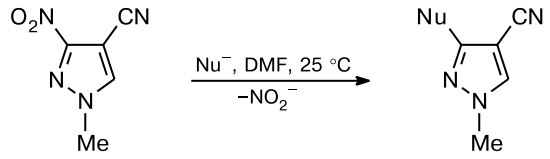
| Compound | Found / Calculated (%) | | | | Molecular formula | $^1$H NMR ($(CD_3)_2SO$), δ | IR, ν/cm$^{-1}$ | MS, *m/z*, $[M]^+$ |
|---|---|---|---|---|---|---|---|---|
| | C | H | N | S | | | | |
| **3a** | 61.37<br>61.37 | 4.37<br>4.21 | 19.63<br>19.52 | 14.73<br>14.90 | $C_{11}H_9N_3S$ | 8.21 (s, CH); 7.37, 7.25 (both m, Ph);3.87 (s, Me) | 2232 (CN) | 215 |
| **3b** | 62.93<br>62.86 | 5.06<br>4.84 | 19.24<br>18.33 | 13.81<br>13.98 | $C_{12}H_{11}N_3S$ | 8.04 (s, CH); 7.24, 7.10 (both m, Ph); 4.12 (s, $CH_2$); 3.58 (s, Me) | 2232 (CN) | 229 |
| **3c** | 57.49<br>57.34 | 4.57<br>4.44 | 19.58<br>20.57 | 11.05<br>11.77 | $C_{13}H_{12}N_4OS$ | 10.16 (s, NH); 8.11 (s, CH); 7.48 (d, Ph); 7.29, 7.05 (both t, Ph); 3.92 (s, Me); 3.76 (s, $CH_2$) | 2244 (CN); 1688 (CO) | 272 |
| **3d** | 65.60<br>66.32 | 4.47<br>4.55 | 20.81<br>21.09 | —<br> | $C_{11}H_9N_3O$ | 7.96 (s, CH); 7.46, 7.29 (both t, Ph); 7.23 (d, Ph); 3.72 (s, Me) | 2228 (CN) | 199 |
| **3e** | 52.57<br>52.55 | 5.21<br>5.14 | 30.41<br>30.64 | —<br> | $C_6H_7N_3O$ | 7.76 (s, CH); 4.20, 3.56 (both s, Me) | 2228 (CN) | 137 |
| **3f** | 48.50<br>48.78 | 4.07<br>4.09 | 33.72<br>34.13 | —<br> | $C_{10}H_{10}N_6O_2$ | 8.33 (s, CH); 3.75 (s, NMe) 2.54, 2.51 (both s, Me) | 2240 (CN) | 246 |
| **3g** | 48.82<br>49.17 | 3.09<br>3.30 | 34.01<br>34.40 | 13.05<br>13.13 | $C_{10}H_8N_6S$ | 8.18 (s, CH); 3.99 (s, Me) | 2228 (CN) | 244 |

**Table 3.** Reaction conditions for the synthesis of compounds **4**, **5a**, and **5e**

| Compound | Solvent | τ/h | *T*/°C | Yield (%) | M.p./°C |
|---|---|---|---|---|---|
| **4** | EtOH | 12 | 80 | 86 | 140 (from MeOH) |
| **5a** | DMF | 170 | 25 | 17 | Oil* |
| **5e** | DMF | 48 | 25 | 23 | 111 (from MeOH) |

* Purified by column chromatography.

**Scheme 6**




**2** **5a,e**

Nu = PhS (**a**), MeO (**e**)

nitrile **1**. However, substitution in 4-cyano-1-methyl-3-nitropyrazole (**2**) was successful only with thiophenolate and methylate anions in DMF (Scheme 6). In the reaction with sodium methoxide, its complete conversion requires approximately two days, whereas nitrile **1** is fully consumed over 30 min under analogous conditions. With thiophenol at 25 °C, the conversion of compound **2** was not completed even in a week (*vs.* ~3 min for nitrile **1** under analogous conditions); yet the substitution product was isolated. The data for products **5a** and **5e** are given in Tables 3 and 4.

No reaction of nitrile **2** with benzylmercaptan and *N*-phenylthioglycolamide in DMF or $CH_3CN$ in the pres-

**Table 4.** Characteristics of compounds **4**, **5a**, and **5e**

| Compound | Found / Calculated (%) | | | | Molecular formula | $^1$H NMR ($(CD_3)_2SO$), δ | IR, ν/cm$^{-1}$ | MS, *m/z*, $[M]^+$ |
|---|---|---|---|---|---|---|---|---|
| | C | H | N | S | | | | |
| **4** | 56.96<br>57.34 | 4.42<br>4.44 | 19.94<br>20.57 | 11.56<br>11.77 | $C_{13}H_{12}N_4OS$ | 9.03 (s, NH); 7.88 (s, CH) 7.75 (m, Ph); 7.37 (s, $NH_2$); 7.30, 7.05 (both m, Ph); 3.90 (s, Me) | 2244 (CN); 1612 (CO) | 229 |
| **5a** | 61.20<br>61.37 | 4.01<br>4.21 | 19.12<br>19.52 | 14.65<br>14.90 | $C_{11}H_9N_3S$ | 8.62 (s, CH); 7.46, 7.28 (both m, Ph); 3.92 (s, Me) | 2238 (CN) | 215 |
| **5e** | 53.03<br>52.55 | 5.15<br>5.14 | 29.37<br>30.64 | —<br> | $C_6H_7N_3O$ | 8.26 (s, CH); 3.89, 3.74 (both s, Me) | 2236 (CN) | 137 |

ence of potassium carbonate occurs at room temperature; on heating (*e.g.*, at 60 °C), the resulting mixture is difficult to separate (TLC) and contains no product of nitro group substitution. Nitrile **2** does not react with 3,5-dimethyl-4-nitropyrazole or phenoxide anions under the reaction conditions of nitrile **1** (boiling acetonitrile, $K_2CO_3$). Nor does nitrile **2** react with these nucleophiles in DMF at 100 °C.

Thus, with isomeric nitriles **1** and **2** as examples, we showed that in 3(5)-nitropyrazoles, the nitro group in position 5 is much more reactive than in position 3 as regards nucleophilic substitution reactions. Apparently, this difference is due to the significantly higher positive $\pi$-charge in the pyrazoles in position 5,[9] though a more precise answer calls for further investigations into both the electron density distribution in nitriles **1** and **2** and the energies of formation of the corresponding 3- and 5-*ipso*-σ-complexes.

## Experimental

$^1$H NMR spectra were recorded on Bruker AC-200, Bruker WM-250, and Bruker AC-300 instruments. Chemical shifts are referenced to $Me_4Si$. IR spectra were recorded on a Specord M-80 instrument (KBr pellets). Mass spectra were recorded on a Varian MAT CH-6 instrument. The course of the reactions was monitored and the purity of the compounds was checked by TLC on Silufol UV-254 plates.

**1-Methyl-5-nitropyrazole-4-carbonitrile (1).** Dropwise addition of 85% $H_2O_2$ (50 mL) to $CF_3COOH$ (75 mL) was followed by addition of 5-amino-1-methylpyrazole-4-carbonitrile (15 g, 0.123 mol) in portions at no higher than 30 °C. The reaction mixture was kept at 45—50 °C for 3 h, cooled, and poured into ice water (300 mL). The precipitate that formed slowly was filtered off, washed with cold water to a neutral reaction, and dried to give a dark yellow product (8 g, 42%), m.p. 127 °C (from ethanol). Found (%): C, 39.08; H, 2.53; N, 36.38. $C_5H_4N_4O_2$. Calculated (%): C, 39.48; H, 2.65; N, 36.83. $^1$H NMR ($(CD_3)_2SO$), δ: 8.35 (s, CH); 4.20 (s, $CH_3$). IR, ν/cm$^{-1}$: 2252 (CN); 1536 ($NO_2$); 1344 ($NO_2$). MS, *m/z*: 152 $[M]^+$.

**1-Methyl-3-nitropyrazole-4-carbonitrile (2).** Dimethyl sulfate (27.5 mL) was added dropwise to a solution of 3-nitropyrazole-4-carbonitrile (26.5 g, 0.174 mol) in 3.5% NaOH (320 mL) at no higher than 30 °C. After the precipitation was completed, the solution was stirred for an additional 1 h. The precipitate was filtered off, washed with cold water to a neutral reaction, and dried to give a mixture of 1-methyl-5-nitropyrazole-4-carbonitrile (**1**) and 1-methyl-3-nitropyrazole-4-carbonitrile (**2**); the total yield was 26 g (86%), **1** : **2** = 1 : 4.5 ($^1$H NMR data). Column chromatography of the mixture on silica gel in chloroform gave pure 1-methyl-3-nitropyrazole-4-carbonitrile **2** (20 g) as light yellow crystals, m.p. 92 °C. Found (%): C, 39.86; H, 2.74; N, 36,03. $C_5H_4N_4O_2$. Calculated (%): C, 39.48; H, 2.65; N, 36.83. $^1$H NMR ($(CD_3)_2SO$), δ: 8.81 (s, CH); 4.05 (s, $CH_3$). IR, ν/cm$^{-1}$: 2244 (CN); 1540 ($NO_2$); 1348 ($NO_2$). MS, *m/z*: 152 $[M]^+$.

**Substitution for the nitro group in 1-methyl-5-nitropyrazole-4-carbonitrile (1) and 1-methyl-3-nitropyrazole-4-carbonitrile (2) (general procedure).** ***A.*** Nitrile **1** or **2** (0.38 g, 2.5 mmol) was dissolved in 10 mL of DMF. A corresponding conjugated acid (or its salt for sodium methoxide) (2.5 mmol) and potassium carbonate (0.38 g, 2.75 mmol) were successively added (the latter was not used in the reactions with sodium methoxide). The reaction mixture was stirred under the conditions specified in Tables 1 and 3. After the reaction was completed, the mixture was poured into water and acidified to pH 4. The product was extracted with ether (3 to 4 × 10—15 mL, TLC). The extracts were combined, washed with dilute HCl and water, and dried over $MgSO_4$. The ether was removed and the residue was either recrystallized from ethanol or purified by column chromatography on silica gel in ethyl acetate—hexane (1 : 4).

***B.*** Nitrile **1** (0.38 g, 2.5 mmol) was dissolved in 10 mL of acetonitrile (ethanol). A corresponding conjugated acid (or its salt for potassium *O*-ethylxanthate) (2.5 mmol) and potassium carbonate (0.38 g, 2.75 mmol) were successively added (the latter was not used in the reactions with potassium ethylxanthate). The reaction mixture was stirred under the conditions specified in Table 1. After the reaction was completed, the solvent was removed and the residue was dissolved in water. The undissolved part was filtered off and recrystallized from ethanol.

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