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Nitropyrazoles
8.* 3(5)-Amino-4-nitropyrazole: convenient synthesis and study of nitration

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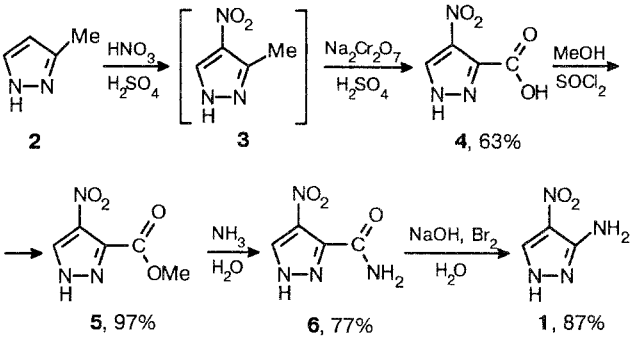
A new preparative method for the synthesis of 3(5)-amino-4-nitropyrazole starting from accessible 3(5)-methylpyrazole has been elaborated. Nitration of the former affords 3(5)-nitramino-4-nitropyrazole or 1,4-dinitro-3-aminopyrazole, depending on the reaction conditions.

Key words: 3(5)-amino-4-nitropyrazole, aminonitropyrazoles, nitration.

3(5)-Aminopyrazoles are multipurpose key compounds in the syntheses of pyrazole-containing compounds of various types, including condensed structures.[2] Moreover, the presence of a nitro group in the pyrazole ring is useful for the functionalization of pyrazoles both by virtue of transformations of this group and due to its activating effect on the endocyclic NH fragment and certain substituents in the ring.[3,4]

In this respect, the simplest *N*-unsubstituted pyrazoles simultaneously containing a 3(5)-amino group and a nitro group in the cycle attract interest. 3(5)-Amino-4-nitropyrazole (**1**), which is useful, *e.g.*, for the preparation of antitumor drugs,[5] is among these compounds. However, the known methods for its synthesis[6–8] have low efficiency since they are multi-stage, and the precursors are not easily accessible. Therefore, the elaboration of new, more efficient approaches to the synthesis of aminonitropyrazole **1** seems to be an urgent problem.

We synthesized compound **1** starting from commercially available 3(5)-methylpyrazole (**2**).[9] Its nitration at position 4 followed by transformation of the methyl group to an amino group by the scheme:



* For communication 7, see Ref. 1.

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We succeeded in the elaboration of a procedure for the synthesis of 4-nitropyrazole-3(5)-carboxylic acid (**4**) without the isolation of intermediate 3(5)-methyl-4-nitropyrazole (**3**). Compound **3** was oxidized with potassium or sodium bichromate in the nitration mixture immediately following the nitration of **2**. The yield of acid **4** with respect to the original methylpyrazole **2** was 63%.

Acid **4** does not enter the Schmidt reaction and thus cannot be directly transformed to aminonitropyrazole **1** by the action of HN_3. Aminonitropyrazole **1** was obtained as follows. Acid **4** was transformed to methyl ester **5**, which was converted to amide **6** by the action of ammonia. Amide **6** smoothly rearranges under the conditions of the Hoffman reaction to give amine **1**. The overall yield of compound **1** with respect to five stages exceeds 40%. Its structure was confirmed by ^1H, ^{13}C, ^{14}N, and ^{15}N NMR and mass spectroscopy and by comparison with an authentic sample.

The ^{13}C NMR data made it possible to establish that the proton in the pyrazole ring of compound **1** is localized at a ring nitrogen atom located far from the amino group. For example, the ^{13}C NMR chemical shift for the unsubstituted carbon atom in pyrazole **1** (C—H, 134.96 ppm) corresponds to the C-5 position, whereas the chemical shift for the carbon atom bonded with the amino group (C—NH_2, 147.83 ppm) corresponds to the C-3 position. This kind of dependence of the chemical shifts of C atoms on their position in the pyrazole ring has been reported in the literature.[10]

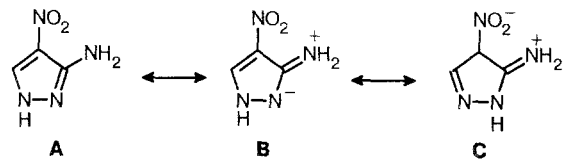
In order to roughly assess the reactivity of compound **1**, its NH-acidity (pK_a) and basicity (pK_{BH+}) were determined* spectrophotometrically in water at 20 °C. The pK_{BH+} value was determined both for the first ($pK_{BH(1)+}$) and the second ($pK_{BH(2)+}$) protonation steps of pyrazole **1**. For comparison, the acidity and basicity of 3-nitro-4-aminopyrrazole (**7**) recently synthesized by us[11] were also determined. The results are presented in Table 1, along with the literature data[12] on the acidity and basicity of 4-nitropyrazole (**8**) and 3-nitropyrazole (**9**).

It is known that 3(5)-aminopyrazoles are protonated not at the amino group but at the neighboring nitrogen atom of the cycle, whereas 4-aminopyrazoles are protonated at the amino group.[13] Hence, in the case of compound **1**, $pK_{BH(1)+}$ determines the basicity of the cycle (more strictly, the cyclic N-2 atom), while $pK_{BH(2)+}$ corresponds to the basicity of the 3-amino group bonded with the protonated cycle. It follows that the basicity of the amino group itself in compound **1** is within $-0.35 > pK_{BH(2)+(NH2)} > -3.70$; using some analogies with benzene derivatives,[14] it may be estimated as $-1.5 \div -2$. In turn, the basicity of compound **7** ($pK_{BH+} = 1.75$) is determined by the basicity of the 4-amino group. The difference by several orders of magnitude between the basicity of the amino groups in isomers **1** and **7** and the sharp decrease in the basicity of the cycle on passage from aminonitropyrazole **1** to 4-nitropyrazole **8** (see Table 1) indicates that the 3-amino group in compound **1** is in very strong conjugation with the pyrazole cycle (+M effect) and thus structure (**B**) significantly contributes to the resonance hybrid **1**. As a result, protonation occurs at the N-2 atom.

Table 1. Acidity and basicity of aminonitro- and nitropyrazoles

Compound	pK_a	$pK_{BH(1)+}$	$pK_{BH(2)+}$
1	9.73 ± 0.03	−0.35 ± 0.05	−3.70 ± 0.05
		−0.47 ± 0.05*[13]	
7	9.50 ± 0.03	1.75 ± 0.03	—
8	9.67*[12]	−1.96*[12]	
9	9.81*[12]	−4.66*[12]	

* Literature data.



Evidently, the contribution of structure **C** is not high, since, although this conjugation between the amino and nitro group is possible both in aminonitropyrazole **1** and in its isomer **7**, the difference in basicity of the amino groups is very high.

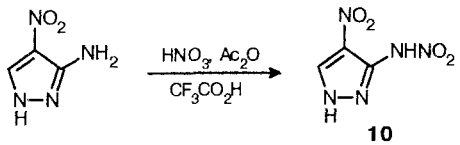
A comparison of the NH-acidity of pyrazoles **1** and **8** (Table 1) indicates that the introduction of a 3-amino group into compound **8** has almost no effect on the acidity. In our opinion, this is an evidence that the conjugation between the 3-amino group and the 4-nitropyrazolate anion is insignificant. An analogous phenomenon is observed in the case of the pair of 3-nitrosubstituted pyrazoles, **7** and **9**, where the difference in NH-acidity is very small (see Table 1). The explanation for this fact is similar to that for the pair of compounds **1** and **8**.

A convenient test for the behavior of aminonitropyrazole **1** in electrophilic substitution reactions is the nitration of this compound. It is known that, depending on the nitrating agent, the nitro group enters different positions of a *N*-unsubstituted pyrazole cycle to give either *C*- or *N*-nitropyrazoles.[3] Compound **1** can also undergo nitration at the exocyclic amino group to give the respective nitramine. If nitration of aminonitropyrazole **1** at the endocyclic nitrogen atom is performed, the resulting *N*-nitro derivative may be of interest for the

* The determination was carried out by V. I. Gulevskaya (Institute of Organic Chemistry of the RAS).

functionalization of **1** by nucleophilic substitution of the *N*-nitro group (*cf.* Ref. 3).

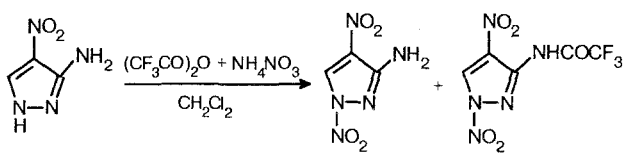
We found that the action of various acid nitrating mixtures results in nitration of only the exocyclic amino group to give 3(5)-nitramino-4-nitropyrazole (**10**). The formation of product **10** occurs even in the HNO_3 + $(CH_3CO)_2O$ + CF_3COOH mixture (actually, a solution of acetyl nitrate in CF_3COOH), which, as shown for other examples,[1] is very efficient for the *N*-nitration of endocyclic nitrogen atoms in *N*-unsubstituted pyrazoles (*cf.* Ref. 3).



10

This direction of nitration may be explained by the fact that cycle protonation (at the N-2 nitrogen atom, see above) occurs initially in acid media, and nitration involves the amino group. The structure of compound **10** was confirmed by NMR spectral data (see Experimental). The ^1H NMR spectrum displays a signal for H-5 (8.81 ppm) and a broadened singlet at 12.6 ppm, whose chemical shift corresponds to the acid proton at the cyclic N atom. The ^{14}N NMR spectrum contains signals for the $C—NO_2$ group (−32.9 ppm) and the $N—NO_2$ group (−21.7 ppm). The signals for the nitro groups were assigned on the basis of the ^{13}C NMR data. Under the conditions of ternary heteronuclear resonance ^{13}C-{^1H,^{14}N(−32.9 ppm)}, broadening of the signal for the C-4 atom (130.04 ppm) is removed. This indicates that the nitro group with a chemical shift of −32.9 ppm is located at the C-4 atom.

Nitration of compound **1** at the cyclic nitrogen atom can be performed in CH_2Cl_2 in the absence of an acid if trifluoroacetyl nitrate is used (formed by the treatment of $(CF_3CO)_2O$ with NH_4NO_3).[15] This confirms the above assumption on the effect of an acid on the direction of nitration of compound **1**. It should be emphasized that *N*-nitration of **1** proceeds strictly regioselectively: only 3-amino-1,4-dinitropyrazole (**11**) is formed from the two possible isomers, *i.e.*, nitration proceeds only at the nitrogen atom located far from the amino group (N-1). Along with *N*-1-nitration, partial trifluoroacetylation at the amino group also occurs to give 1,4-dinitro-3-(trifluoroacetylamino)pyrazole (**12**). The mixture of products **11** and **12** was separated, and the hitherto unknown compounds **11** and **12** were isolated as individual compounds.



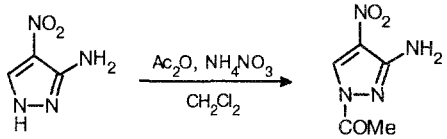
11 **12**

The structure of the 1,4-dinitro derivatives was determined as follows. The ^{14}N NMR spectra of these compounds contain a signal with a −64÷65 ppm chemical shift corresponding to the nitro group at the cyclic nitrogen atom ($N—NO_2$). The position of the nitro group in products **11** and **12** can be easily revealed from ^{13}C NMR spectra, where the chemical shift for the unsubstituted carbon atom (C—H) corresponds to the C-5 position, while the chemical shift of the carbon atom bonded with the amino group corresponds to the C-3 position.

It could be expected that nitration of aminonitropyrazole would occur *via* electrophilic attack at the N-2 nitrogen atom (the protonation site, *vide supra*). However, 1-nitrosubstituted pyrazoles are actually formed, and their formation is probably under thermodynamic control.

If trifluoroacetyl nitrate ($(CF_3CO)_2O$ + NH_4NO_3) acts on aminonitropyrazole **1** in the presence of a small amount of CF_3COOH, compound **12** becomes the main reaction product. Pyrazole **12** readily loses the trifluoroacetyl and nitro groups upon treatment with 20% aqueous H_2SO_4 (at ~20°C) to give the original pyrazole **1**. Moreover, pyrazole **11** readily undergoes hydrolyzation to give **1** even in the absence of an acid.

A weaker nitration agent, acetyl nitrate (Ac_2O + NH_4NO_3), does not afford any products of nitration of compound **1** in CH_2Cl_2 in the absence of an acid. Instead, the product of *N*-acetylation at the cyclic nitrogen atom, 1-acetyl-3-amino-4-nitropyrazole (**13**), is formed in 30 % yield.



13

In this case, electrophilic substitution also occurs only at the N-1 atom of the pyrazole ring. The structure of the acetylation product **13** was determined similarly to the above proof for compounds **11** and **12**.

The employment of other non-acid nitration agents, *viz.*, $Cu(NO_3)_2$ + Ac_2O, $AgNO_3$ + AcCl in CH_3CN, or NO_2BF_4 in CH_2Cl_2, as well as the use of the 1-trimethylsilyl derivative of pyrazole **1** as the object of nitration by NO_2BF_4 in CH_2Cl_2 (*cf.* Ref. 16) does not result in nitration of compound **1** at the cyclic nitrogen.

Experimental

^1H, ^{13}C, and ^{14}N NMR spectra were recorded on a Bruker AM-300 spectrometer. The chemical shifts are given relative to Me_4Si (^1H, ^{13}C) or CH_3NO_2 (^{14}N). IR spectra were obtained on a Specord M-80 spectrophotometer in KBr pellets. Mass spectra were recorded on a Varian MAT CH-6 spectrometer. The reactions and the purity of compounds were monitored by TLC on Silufol UV-254 plates.

4-Nitropyrazole-3-carboxylic acid (4). 3(5)-Methylpyrazole **2** (50 g, 0.61 mol) and then HNO_3 (d = 1.5, 60 mL, 1.4 mol) were added at <40°C with stirring to conc. H_2SO_4 (120 mL). The temperature was increased to 100°C over 1 h, the mixture was kept at 100°C for 4 h and cooled to ~20°C, and 500 mL of conc. H_2SO_4 was added. Then, $Na_2Cr_2O_7 \cdot 2H_2O$ or $K_2Cr_2O_7$ (183 g, 0.62 mol) was added portionwise at a temperature not exceeding 60°C, and the mixture was stirred for 10 h at 60°C and poured onto 2 kg of ice. The precipitate was filtered off, washed with water, and dried in the air to give 60 g (63%) of acid **4**, m.p. 206—208°C (from water).

3-Methoxycarbonyl-4-nitropyrazole (5). Acid **4** (50 g, 0.32 mol) was dissolved in MeOH (150 mL), then $SOCl_2$ (23 mL) was added dropwise, and the mixture was refluxed for 3 h. The reaction mixture was evaporated to dryness to give product **5** (53 g, 97%, m.p. 119—120°C (from water)) used without further purification.

4-Nitropyrazole-3-carboxamide (6). A solution of ester **5** (53 g) in 25% aqueous ammonia (500 mL) was kept for 15 h at ~20°C. The precipitate was filtered off, washed with cold water, and dried in the air to give 38 g (77%) of amide **6**, m.p. 305—306 °C (from water).

3-Amino-4-nitropyrazole (1). Bromine (3.1 mL, 0.06 mol) was added at 0°C with stirring to a solution of NaOH (12 g, 0.3 mol) in H_2O (80 mL), and then amide **6** was added portionwise. The mixture was kept for 1 h at 0°C, heated to 50—55°C, kept for 1.5 h, cooled to ~20°C, acidified with conc. HCl to pH 5—6, and cooled to 0°C. The precipitate was washed with water and dried in a vacuum desiccator over P_2O_5 to give 5.6 g (87%) of compound **1**, m.p. 241—242°C (from water).

3(5)-Nitramino-4-nitropyrazole (10). Pyrazole **1** (0.64 g, 0.005 mol) was dissolved in CF_3COOH (5 mL), then HNO_3 (d = 1.5, 2.1 mL, 0.05 mol) and Ac_2O (0.94 mL, 0.01 mol) were added at 0°C. The mixture was stirred for 3 h at 0—5°C, then poured onto ice, and extracted with ether, and the ether extract was dried with $MgSO_4$. Evaporation of the solvent afforded 0.75 g (80%) of compound **10**, t.dec. ≥125°C (from 1,2-dichloroethane). ^1H NMR (acetone-d_6), δ: 8.81 (s, H-5); 12.57 (br.s, N—H). ^{13}C NMR (acetone-d_6), δ: 130.04 (d, J = 4.55 Hz, C-4); 132.17 (d, J = 200.1 Hz, C-5); 138.88 (d, J = 6.8 Hz, C-3). ^{14}N NMR (acetone-d_6), δ: −32.9 (s, $\nu_{1/2}$ = 20 Hz, C-NO_2); −21.7 (s, $\nu_{1/2}$ = 63 Hz, N—NO_2). Found (%): C, 21.36; H, 1.66. $C_3H_3N_5O_4$. Calculated (%): C, 20.82; H, 1.75.

Nitration of 3-amino-4-nitropyrazole 1 in a neutral medium. Dry NH_4NO_3 (0.8 g, 0.01 mol) was added to a suspension of compound **1** (1.28 g, 0.01 mol) in abs. CH_2Cl_2 (10 mL), then $(CF_3CO)_2O$ (5 mL, 0.035 mol) was slowly added at 0—5°C. After 30 min, the mixture was heated to ~20°C and kept for 2 h. The reaction mixture was poured into ice water, and the organic layer was separated, washed with water, and dried with $MgSO_4$. The solvent was evaporated, and the residue (0.9 g) was recrystallized from EtOH to give 0.25 g (15%) of 3-amino-1,4-dinitropyrazole (**11**), t.dec. ≥155°C. ^1H NMR (acetone-d_6), δ: 9.91 (s, H-5). ^{13}C NMR (acetone-d_6), δ: 128.24 (d, J = 212.13 Hz, C-5); 130.83 (d, J = 3.33 Hz, C-4); 150.28 (d, J = 8.0 Hz, C-3). ^{14}N NMR (acetone-d_6), δ: −64.6 (1-NO_2); −26.6 (4-NO_2). IR, ν/cm^{-1}: 3104, 1652, 1552, 1512, 1368, 1352, 1284, 1244. MS (EI, 70 eV), m/z: 173 $[M]^+$. After recrystallization the mother liquor was concentrated, and the residue was recrystallized from $CHCl_3$ to give 0.6 g (22%) of 3-(trifluoroacetylamino)-1,4-dinitropyrazole (**12**), m.p. 149°C. ^1H NMR (acetone-d_6), δ: 9.70 (s, H-5); 10.92 (br.s, NH). ^{13}C NMR (acetone-d_6), δ: 116.42 (q, J = 287.27 Hz, CF_3); 127.49 (d, J = 211.66 Hz, C-5); 130.57 (d, J = 2.41 Hz, C-4); 137.64 (d, J = 8.5 Hz, C-3); 156.0 (q, J = 31.7 Hz, CO). ^{14}N NMR (acetone-d_6), δ: −65.2 (s, $\nu_{1/2}$ = 71 Hz, 1-NO_2), −25.2 (s, $\nu_{1/2}$ = 49 Hz, 4-NO_2). IR, ν/cm^{-1}: 3390, 3160, 1756, 1652, 1560, 1525, 1370, 1290, 1178. MS (EI, 70 эВ), m/z: 224 $[M-NO_2+H]^+$.

1-Acetyl-3-amino-4-nitropyrazole (13). Dry NH_4NO_3 (0.4 g, 0.005 mol) was added to a suspension of aminonitropyrazole **1** (0.64 g, 0.005 mol) in abs. CH_2Cl_2 (5 mL). The reaction mixture was cooled to 10°C, and freshly distilled Ac_2O was slowly added dropwise. The temperature was gradually increased to 20°C, and the suspension was kept for 20 h. The residue was filtered off, and the filtrate was concentrated. The dry residue was recrystallized from water to give 0.27 g (30%) of compound **13**, m.p. 183°C. ^1H NMR (acetone-d_6), δ: 2.59 (s, 3 H, CH_3); 8.11 (s, 1 H, H-5); 8.26 (br.s, 2 H, NH_2). ^{13}C NMR (acetone-d_6), δ: 23.00 (q, J = 130.5 Hz, CH_3); 118.17 (s, C-4); 138.53 (d, J = 197.4 Hz, C-5); 148.55 (d, J = 3.2 Hz, C-3); 174.36 (q, J = 6.9 Hz, CO). ^{14}N NMR (acetone-d_6), δ: −18.61 (s, $\nu_{1/2}$ = 125 Hz, 4-NO_2). ^{15}N NMR (acetone-d_6), δ: −302.62 (t, J = 94.6 Hz, NH_2). IR, ν/cm^{-1}: 3416, 3312, 1724, 1640, 1528, 1444, 1368, 1292. MS (EI, 70 eV), m/z: 170 $[M]^+$.

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