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The specific reactivity of 3,4,5-trinitro-1*H*-pyrazole

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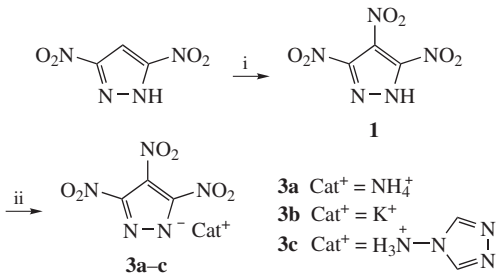
Nitration of 3,5-dinitropyrazole with HNO_3–H_2SO_4 mixture gives 3,4,5-trinitro-1*H*-pyrazole, which in reaction with ammonia, amines or thiols under mild conditions undergoes regioselective nucleophilic substitution of the 4-positioned nitro group.

Previously,[1] we have reported on the synthesis of N-unsubstituted all-carbon nitrated pyrazole (3,4,5-trinitro-1*H*-pyrazole, **1**) by the oxidation of 5-amino-3,4-dinitropyrazole with highly concentrated hydrogen peroxide in concentrated sulfuric acid. Here we describe an alternative approach to compound **1** by nitration of 3,5-dinitropyrazole **2** with HNO_3–H_2SO_4 mixture (Scheme 1). In contrast to our present results, Herve *et al.*[2] report that HNO_3–H_2SO_4 mixture is not sufficient for the nitration of the 3,5-dinitropyrazole **2** and compound **1** is formed only upon addition of excess of 60% oleum to the standard nitration mixture.

Trinitropyrazole **1** is a strong NH-acid ($pK_a = 0.05$) well soluble both in water and in a wide range of organic solvents including diethyl ether, ethyl acetate, dioxane, THF, alcohols, acetonitrile, DMF and DMSO. Being such a strong acid, pyrazole **1** forms stable salts of type **3** (see Scheme 1)† not only with strong bases (NH_3, KOAc, **3a**,**b**) but also with weak bases like *N*-amino-1,2,4-triazole (**3c**) ($pK_{BH^+} = 3.23$[3]).



Scheme 1 *Reagents and conditions*: i, HNO_3 (15 equiv.)–H_2SO_4 (30 equiv.), 90–100 °C, 10 h; ii, MeOH, room temperature, 2 h, base (1 equiv.): **a**, NH_3, **b**, KOAc, or **c**, *N*-amino-1,2,4-triazole.

† The structures of all compounds were established by ^{1}H, ^{13}C, $^{14(15)}$N NMR as well as special correlation NMR techniques such as HMBC, HSQC and NOESY in DMSO-d_6 on a Bruker AC-300 or Bruker DRX-500 spectrometer and confirmed by IR-spectroscopy, mass-spectrometry on a KRATOS MS-30 or MicrOTOFII instrument, and elemental composition data. All the compounds contain the bands 1325, 1520 cm^{-1} (NO_2) in their IR spectra, and the appropriate $[M]^+$ in their mass spectra.

*3,4,5-Trinitro-1*H*-pyrazole* **1**. A solution of **2** (18.6 g, 0.12 mol) in a mixture of H_2SO_4 (d = 1.824, 186 ml) and HNO_3 (d = 1.51, 75 ml) was kept at 90–100 °C for 10 h. The resulting mixture was poured into ice-water (1 dm^3), and extracted with ethyl acetate (2×300 ml). The organic layer was separated, washed with water and dried with $MgSO_4$. The solvent was then removed, and the residue was crystallized from toluene. Yield, 20.7 g (87%), mp 186 °C (lit.,[1] mp 182–184 °C, lit.,[2] mp 187.8 °C).

3a: yield 89%, mp 195–198 °C. ^{13}C NMR, δ: 122.06 (C^4), 146.90 (C^3, C^5).

3b: yield 95%, mp 199–201 °C. ^{13}C NMR, δ: 122.03 (C^4), 147.24 (C^3, C^5).

3c: yield 90%, mp 165 °C. ^{13}C NMR, δ: 122.06 (C^4), 143.97, 146.91 (C^3, C^5).

N-Unsubstituted 3,4,5-trinitropyrazole **1** is prone to unusually react with nucleophiles. It readily reacts with excess of ammonia or aliphatic amines under very mild conditions (in water at room temperature) as well as with thiols in the presence of inorganic bases, affording compounds **4**‡ and **5**,§ respectively (Scheme 2). The latter are the products of 2-positioned nitro group substitution.

Trinitropyrazole **1** is easily hydrolyzed by $NaHCO_3$ solution, with the corresponding hydrolysis product being isolated as the disodium salt **6**¶ (Scheme 2).

It should be of note that formation of products **4**–**6** is the first example of the regioselective nucleophilic substitution of the 4-positioned nitro group in the pyrazole ring. Previously, only the substitution of a nitro group at 3- or 5-position in 3(5),4-dinitropyrazoles was documented.[4] Obviously, the first

‡ *Synthesis of 3,5-dinitro-4-NR'R''-1*H*-pyrazoles* **4a**–**h** *(general procedure)*. To the solution of trinitropyrazole **1** (0.5 g, 2.5 mmol) in water (5 ml), the appropriate amine (10 equiv. in case of **4a**,**b** and 3 equiv. in case of **4c**–**h**) was added and the reaction mixture was left for 10 h at ambient temperature. The precipitate was filtered off, washed with cold MeOH, suspended in 3 ml of water and acidified with 20% H_2SO_4 to pH 1. The resulting precipitate was filtered off, dried and crystallized from EtOH–H_2O (1:1).

4a: yield 80%, mp 166–168 °C. ^{13}C NMR, δ: 128.96 (C^4), 138.84 (C^3, C^5). ^{14}N NMR (acetone-d_6) δ: –25.15 ($\nu_{1/2}$ 80 Hz, NO_2). IR (KBr, ν/cm^{-1}): 3460, 3320, 3190, 1650, 1525, 1350. UV [λ/nm (ε)]: 260 (12000), 400 (9600) in H_2O; 306 (16200), 400 (8400) in aq. NaOH; 222 (12400) in aq. H_2SO_4. pK_a = 3.42, pK_{BH^+} = –5.43. MS (ESI), m/z: 172.0117 (calc. for $C_3H_2N_5O_4^-$: 172.0112).

4b: yield 87%, mp 170–171 °C. ^{1}H NMR, δ: 3.00 (s, 3H). ^{13}C NMR, δ: 33.31 (Me), 129.83 (C^4), 139.39 (C^3, C^5). MS (ESI), m/z: 186.0272 (calc. for $C_4H_4N_5O_4^-$: 186.0269).

4c: yield 80%, mp 170–172 °C. ^{1}H NMR, δ: 1.92 (m, 4H), 3.36 (m, 4H). ^{13}C NMR, δ: 25.44, 51.92, 125.17 (C^4), 141.39 (C^3, C^5).

4d: yield 74%, $T_{decomp.}$ 238 °C. ^{1}H NMR, δ: 3.22 (m, 4H), 3.75 (m, 4H). ^{13}C NMR, δ: 50.79, 66.43, 126.22 (C^4), 143.50 (C^3, C^5).

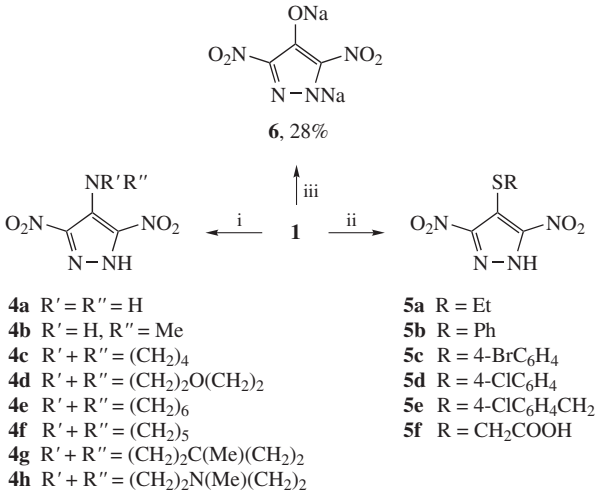
4e: yield 87%, mp 188–190 °C. ^{1}H NMR, δ: 1.65 (m, 8H), 3.24 (m, 4H). ^{13}C NMR, δ: 27.60, 29.00, 53.74, 128.14 (C^4), 144.15 (C^3, C^5).

4f: yield 89%, mp 166–168 °C. ^{1}H NMR, δ: 1.61 (m, 6H), 3.12 (m, 4H). ^{13}C NMR, δ: 22.68, 25.94, 51.90, 127.60 (C^4), 143.06 (C^3, C^5).

4g: yield 74%, mp 138–139 °C. ^{1}H NMR, δ: 0.93 (d, 3H), 1.30 (m, 2H), 1.55 (m, 1H), 1.64 (m, 2H), 3.08 (m, 2H), 3.21 (m, 2H). ^{13}C NMR, δ: 21.14, 28.02, 30.22, 34.02, 43.29, 51.25, 127.51 (C^4), 146.86 (C^3, C^5).

4h: yield 84%, $T_{decomp.}$ 247 °C. ^{1}H NMR, δ: 2.81 (s, 3H), 3.15 (m, 2H), 3.42 (m, 4H), 3.58 (m, 2H). ^{13}C NMR, δ: 40.33, 47.35, 52.85, 125.08 (C^4), 144.99 (C^3, C^5).

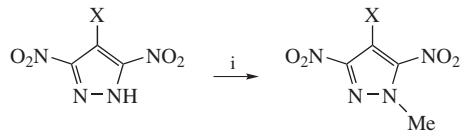
For the synthesis of compound **4a** from carbamate **9**, see Online Supplementary Materials.



Scheme 2 *Reagents and conditions*: i, HNR′R″ (3–10 equiv.) in H_2O, room temperature, 10 h, then 20% H_2SO_4; ii, RSH (1.2 equiv.)/NaOH (2 equiv.) in H_2O, room temperature, 3 h, then 20% H_2SO_4; iii, $NaHCO_3$ (2.5 equiv.) in H_2O, 80–90 °C, 9 h.

step in all these reactions is the formation of the corresponding pyrazolate-anion, the substitution in which is the second step leading to the final products. It is worth noting that nucleophilic substitution within the anionic (pyrazolate) species could not be predictable *a priori*.

At the same time, in spite of its intrinsic low basicity, trinitropyrazole **1** could be N-methylated with dimethyl sulfate under very mild conditions. The reaction proceeds smoothly in water at ~20 °C in the presence of $NaHCO_3$ giving rise to another all-carbon nitrated 1-methyl-3,4,5-trinitro-1*H*-pyrazole **7** (*cf.* lit.[2]) (Scheme 3).¶ Compound **7**, being less soluble in water than **1**, precipitates during the preparation of **1**.



Scheme 3 *Reagents and conditions*: i, Me_2SO_4 (1.5 equiv.)–$NaHCO_3$ (2 equiv.), H_2O, room temperature, 7 h.

§ *Synthesis of 3,5-dinitro-4-SR-1*H*-pyrazoles* **5a–f** *(general procedure).* To the solution of trinitropyrazole **1** (0.61 g, 3 mmol) in water (10 ml), NaOH (0.24 g, 6 mmol) was added, and the mixture was stirred for 10 min, then the appropriate thiol (3.6 mmol) was slowly added. The stirring was continued for 3 h at room temperature, then the mixture was acidified with 20% H_2SO_4 to pH 1. The precipitate formed was filtered off, dried and crystallized from EtOH–H_2O.

5a: yield 70%, mp 92–93 °C. ^{1}H NMR, δ: 1.15 (t, 3H), 2.95 (q, 2H). ^{13}C NMR, δ: 14.45, 28.85, 107.54 (C^4), 151.62 (C^3, C^5).

5b: yield 98%, mp 155–156 °C. ^{1}H NMR, δ: 7.35 (m, 5H). ^{13}C NMR, δ: 105.13 (C^4), 127.05, 128.15, 129.33, 133.82, 151.58 (C^3, C^5).

5c: yield 91%, mp 136–137 °C. ^{1}H NMR, δ: 7.17 (d, 2H), 7.45 (d, 2H). ^{13}C NMR, δ: 103.81 (C^4), 119.80, 129.83, 132.02, 133.92, 152.10 (C^3, C^5).

5d: yield 85%, mp 138–139 °C. ^{1}H NMR, δ: 7.15 (d, 2H), 7.45 (d, 2H). ^{13}C NMR, δ: 103.88 (C^4), 119.88, 129.90, 132.02, 133.81, 151.91 (C^3, C^5).

5e: yield 95%, mp 166–167 °C. ^{1}H NMR, δ: 4.23 (s, 2H), 7.15 (d, 2H), 7.39 (d, 2H). ^{13}C NMR, δ: 38.19, 105.77 (C^4), 128.40, 130.68, 131.15, 136.00, 152.32 (C^3, C^5).

5f: yield 78%, mp 114–115 °C. ^{1}H NMR, δ: 3.72 (s, 2H). ^{13}C NMR, δ: 36.13, 106.30 (C^4), 151.90 (C^3, C^5), 170.34.

¶ For the synthesis and characteristics of compounds **6–8**, see Online Supplementary Materials.

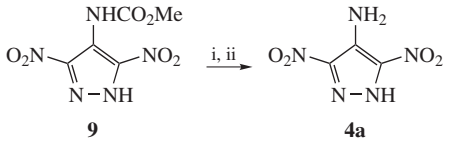
The experimental data demonstrate that electrophilicity of trinitropyrazole **1** is so great that its reactions with nucleophiles occur under extremely mild conditions.

The mentioned recent paper[2] reports that 'drastic conditions are required to provoke 4-NO_2 displacement' which is in contradiction with our present results. Our colleagues would attribute such a 'poor' reactivity of 4-NO_2 to the experimentally (X-ray) discovered non-coplanarity of this nitro group with the rest of the system. However, such a statement seems unlikely as it is well known that non-coplanarity of aromatic nitro group is usually the true reason for its nucleofugacity, since the formation of *ipso*-σ-complex between the nucleophile and the nitro-(hetero)arene, which is the limiting stage in S_NAr reactions, proceeds at higher rates with such substrates.[5]

The extended explanations on the unusual reactivity of trinitropyrazole **1** based on the structural and theoretical methods will be published soon.

Due to the high rate of NH proton exchange in the solutions of products **3**, **4** and **5**, their ^{13}C NMR spectra contain only two carbon signals assigned to C^4 and $C^{3,5}$ atoms of the pyrazole ring. Additional proofs of the structures were found during NMR study of compound **8** which was synthesized by N-methylation of compound **4b**. The application of HMBC spectroscopy allows one to observe the long distance ^{1}H–^{13}C coupling constant between the protons of N*H*Me and carbon atoms C^3 (δ 140.80 ppm) and C^5 (δ 133.82 ppm). These data, together with the chemical shift of C^4 (δ 130.87 ppm) and the absence of spin-coupling interaction of NHMe with N^{1}Me in the NOESY spectrum unambiguously show that the NHMe fragment is attached to the 4-position of the pyrazole ring of the product **8**. This means that in the parent compound **4b** this group was also at the 4-position.

The structure of **4a** was confirmed by its independent synthesis through alkali hydrolysis of carbamate **9**[6,7] (Scheme 4).‡



Scheme 4 *Reagents and conditions*: i, KOH (3 equiv.)/H_2O, 70–90 °C, 7 h; ii, 20% H_2SO_4.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2010.09.003.

References

1 I. L. Dalinger, G. P. Popova, I. A. Vatsadze, T. K. Shkineva and S. A. Shevelev, *Izv. Akad. Nauk, Ser. Khim*., 2009, 2120 (*Russ. Chem. Bull., Int. Ed*., 2009, **58**, 2185).

2 G. Herve, C. Roussel and H. Graindorge, *Angew. Chem. Int. Ed*., 2010, **49**, 3177.

3 J. Catalan, J. L. Abband and J. Elguero, *Adv. Heterocycl. Chem*., 1987, **41**, 187.

4 A. A. Zaitsev, I. L. Dalinger and S. A. Shevelev, *Usp. Khim.*, 2009, **78**, 643 (*Russ. Chem. Rev*., 2009, **78**, 589).

5 (*a*) F. Benedetti, D. Marshall, Ch. Stirling and Y. Lend, *J. Chem., Soc*., *Chem. Commun*., 1982, 918; (*b*) O. V. Serushkina, M. D. Dutov, V. N. Solkan and S. A. Shevelev, *Izv. Akad. Nauk, Ser. Khim*., 2001, 2297 (*Russ. Chem. Bull., Int. Ed.*, 2001, **50**, 2406); (*c*) S. A. Shevelev, I. L. Dalinger and T. I. Cherkasova, *Tetrahedron Lett.*, 2001, **42**, 8539; (*d*) V. V. Rozhkov, A. M. Kuvshinov, V. I. Gulevskaya, I. I. Chervin and S. A. Shevelev, *Synthesis*, 1999, 2065.

6 V. M. Vinogradov, T. I. Cherkasova, I. L. Dalinger and S. A. Shevelev, *Izv. Akad. Nauk, Ser. Khim*., 1993, 1616 (*Russ. Chem. Bull.*, 1993, **42**, 1552).

7 I. L. Dalinger, T. I. Cherkasova and S. A. Shevelev, *Mendeleev Commun*., 1997, 58.

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