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Nucleophilic substitution in 1-methyl-3,4,5-trinitro-1*H*-pyrazole

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1-Methyl-3,4,5-trinitropyrazole in reaction with thiols, phenols, oximes, ammonia, amines and NH-azoles gives substitution products of the 5-positioned nitro group.

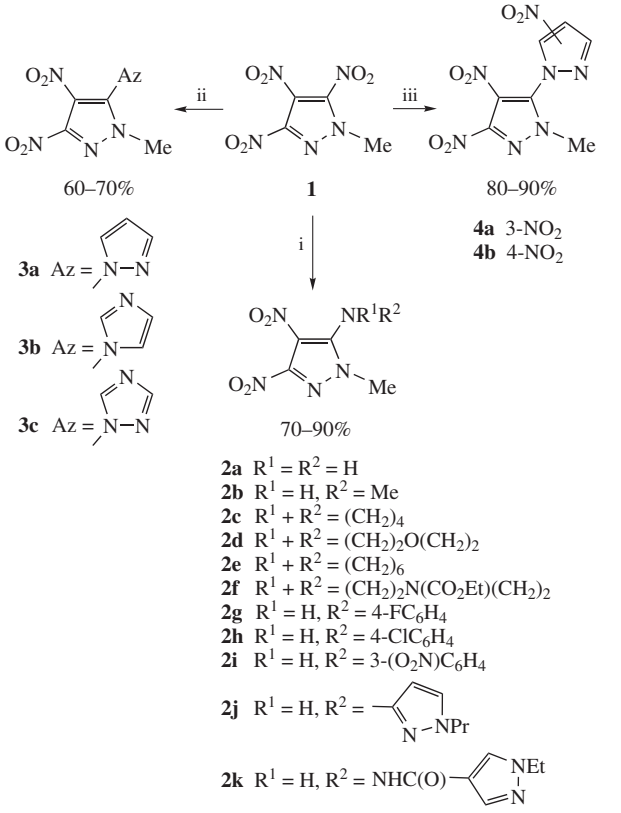
Reactions of 3,4,5-trinitro-1*H*-pyrazole (TNP) with nucleophiles affords the substitution products of the 4-positioned nitro group of the pyrazole moiety,[1,2] the process occurring *via* the intermediate formation of 3,4,5-trinitropyrazolate anion. These findings stimulated us to study the reactivity of N-substituted TNP derivative, 1-methyl-3,4,5-trinitro-1*H*-pyrazole (MTNP), which is unable to form the respective N-anion.[1]

Here we have found that MTNP **1** in reactions with S-, N- and O-nucleophiles behaves completely different compared to TNP and the nucleophilic substitution proceeds regiospecifically at the 5-position.

The list of N-nucleophiles chosen for the study of MTNP reactivity includes ammonia, various amino compounds and NH-azoles (Scheme 1). The reactions were carried out in methanol at room temperature using two equivalents of the appropriate nucleophile. Using these conditions, we isolated products **2** in 60–90% yields. The full conversion of the starting compounds was achieved in 2 h in the case of amino compounds. For the completion of the reactions with NH-azoles, much longer time was required, in some cases up to 48 h. This fact could be explained by the very low basisity of these reactants (pK_{BH^+} for alkylpyrazoles, 3.04–2.48; for 2-methyl-4-nitroimidazole, 0.86; for 1,2,4-triazole, 2.45).[3] The azole-containing products **3** are formed in 60–80% yields.

The least basic nitropyrazoles used in our experiments (pK_{BH^+} for 4-nitropyrazole, –2.0; for 3-nitropyrazole, –4.66)[3] did not react with MTNP in the absence of a base assisting the transformation of these azoles into the more nucleophilic anions (pK_a for nitropyrazoles ~ 9.6–9.8).[3] Thus, the reactions of MTNP with nitropyrazoles in the presence of 1 equiv. of NaOH in aqueous acetonitrile accomplish in 1 h affording the products **4a**,**b** in 80–90% yield (Scheme 1).†

The anionic forms of O- and S-nucleophiles react with MTNP much easier than that of N-nucleophiles (Scheme 2).‡ Phenols, among them those containing one and two nitro groups, as well as oximes in the presence of 1 equiv. of NaOH were used as O-nucleophiles. The reactions were carried out in aqueous acetonitrile at room temperature. Under these conditions the full conversions were achieved in 1 h, and the yields of products **5** and **6** were about 70–85%.



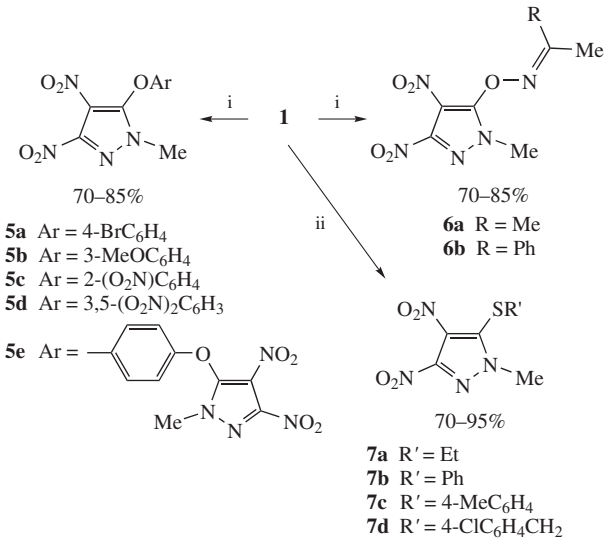
Scheme 1 *Reagents and conditions*: i, NHR^1R^2 (2 equiv.), MeOH, room temperature, 1–2 h; ii, AzH (2 equiv.), MeOH, room temperature, 48 h; iii, 3(4)-nitropyrazole (1 equiv.)/NaOH (1 equiv.), H_2O/MeCN, room temperature, 1 h.

Strongly nucleophilic thiolates react with MTNP **1** at room temperature very rapidly, the reactions being complete in 15 min

† *Synthesis of compounds* **2** *and* **3** *(general procedure)*. 4 mmol of corresponding amine or NH-azole (in case of **2a**,**b** 10 mmol NH_3 and $MeNH_2$ as 24% and 40% aqueous solutions, respectively) was added to the solution of pyrazole **1** (2.0 mmol) in MeOH (10 ml), and the reaction mixture was left for 2 h in case of amines and 48 h in case of azoles at room temperature. The resulting mixture was kept at 0–5 °C, the precipitate formed was filtered off, dried *in vacuo* over P_2O_5 and crystallized from MeOH–H_2O.

Synthesis of 1-methyl-5-(nitropyrazolyl)-3,4-dinitropyrazoles **4** *(general procedure)*. The appropriate nitropyrazole (2 mmol) was added to the solution of NaOH (2 mmol) in water (3 ml) and the mixture was stirred for 10 min, then solution of pyrazole **1** (2 mmol) in MeCN (10 ml) was added and the reaction mixture was left for 1 h at ambient temperature. The solvent was then removed *in vacuo*, and the residue was extracted with $CHCl_3$ (3×5 ml). The organic layer was separated and dried over $MgSO_4$, the solvent was removed *in vacuo*, and the residue was crystallized from light petroleum (**4a**) or chromatographed on silica (eluent $CHCl_3$, R_f 0.35) (**4b**).

For characteristics of compounds **2a–k**, **3a–c** and **4a**,**b**, see Online Supplementary Materials.



Scheme 2 *Reagents and conditions*: i, RC(Me)NOH or ArOH (or 4-HOC_6H_4OH in case of **5e**) (1 equiv.)/NaOH (1 equiv.), H_2O/MeCN, room temperature, 1 h; ii, R′SH (1 equiv.)/NaOH (1 equiv.), H_2O/MeCN, room temperature, 15 min.

giving the products in up to 95% yields. In the case of ethanethiol the reaction even needed the external cooling.

The structures of products **2–7** were established based on ^{1}H and ^{13}C NMR spectra using correlation HMBC, HSQC and NOESY experiments, and additionally were confirmed by IR, mass spectra and elemental analysis. All products have characteristic of NO_2 group IR bands. All mass spectra show molecular ions peaks $[M]^+$.

The characteristic feature of ^{1}H NMR spectra of products **2–7** is the position of N–Me signal, δ 3.60–4.00, compared to isomeric 4-substituted *N*-methyl-3,5-dinitropyrazoles where the signals have $\delta \geqslant 4.15$ ppm (see refs. 1, 4–6). Moreover, the additional characteristic parameter in the spectra of compounds **2–7** is the existence of high field signal C^4–NO_2 as well as two low field signals assigned to C^3 and C^5, one of them (C^3–NO_2) being broadened.

The additional prove of the structure of compound **2b** was made using two-dimensional NMR techniques HMBC and NOESY. In HMBS spectrum the long-range ^{1}H–^{13}C spin coupling for C^5 (δ 147.50 ppm) is observed not only for NH*Me* group but also for the protons of N^1–Me fragment. Furthermore, the NOESY experiment shows the interaction of NH*Me* protons with those of N^1–Me group. This is possible only in the case when NHMe group is at the 5-position of the pyrazole ring.

In conclusion, we have found that reactivity of MTNP towards nucleophiles obeys the general rule[5,7] of the nucleophilic substitution in the 1-R-4-R′-3,5-dinitropyrazoles, *i.e.*, the regiospecific substitution of 5-positioned nitro group takes place. Such a result was confirmed by quantum chemical calculations which explains the difference in activation energies by the difference in positive charges at 3- and 5-positions.[5]

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2011.04.012.

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‡ *Synthesis of 5-aryloxy-, 5-alkylideneaminoxy- and 5-sulfanyl-1-methyl-3,4-dinitropyrazoles* **5a–e**, **6a**,**b** *and* **7a–d** *(general procedure).* The appropriate phenol, oxime or thiol (2 mmol) was added to the solution of NaOH (2 mmol) in water (3 ml) and the mixture with stirred for 10 min. Then solution of pyrazole **1** (2 mmol) in MeCN (10 ml) was added (in case of **5e**, 4 mmol of NaOH and 4 mmol of pyrazole **1**) and the reaction mixture was left for 1 h in case of phenols and oximes or 15 min in case of thiols at ambient temperature. The solvent was then removed *in vacuo*, and the residue was filtered off and dried. Products **5d**,**e** precipitated in the reaction mixture were isolated by simple filtration. All compounds were crystallized from MeOH–H_2O.

For characteristics of compounds **5a–e**, **6a**,**b** and **7a–d**, see Online Supplementary Materials.