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Elena Chugunova [1,*], Almir Gazizov [1], Daut Islamov [1], Victoria Matveeva [1], Alexander Burilov [1], Nurgali Akylbekov [2], Alexey Dobrynin [1], Rakhmetulla Zhapparbergenov [2], Nurbol Appazov [2,3], Beauty K. Chabuka [4], Kimberley Christopher [4], Daria I. Tonkoglazova [4] and Igor Alabugin [1,4]

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Abstract: We report an unusual transformation where a transient formation of a nitrene moiety initiates a sequence of steps where leading to a remote oxidative C-H functionalization (R-CH_3 to R-$CH_2OC(O)R'$) and concomitant reduction of the nitrene into an amino group. No external oxidants or reductants are needed for this formal molecular com-proportionation. Detected and isolated intermediates and computational analysis suggest that the process occurs with pyrazole ring opening and recyclization.

Keywords: furoxan; 1*H*-pyrazole; nitrene; fragmentation; cyclization

1. Introduction

In continuation of our efforts to search for potent anticancer and antimicrobial agents [1–4], we were interested in synthesizing a previously unknown bis-heterocyclic pyrazolo-furoxan fusion. Pyrazole-based compounds poses antimicrobial, antipyretic, anti-inflammatory and analgesic effects [5–8]. Furoxan ring-containing molecules exhibit anti-tuberculosis [9], antitumor [10], anti-inflammatory [11], antiaggregant [12], etc. biological activity. For target compounds synthesis we planned to use one of the known methods for obtaining a furoxan cycle – thermolysis of α-nitroazides (Scheme 1) [13–19] However, when we applied these reaction conditions, the outcome was unexpected. The observed transformation involved a remote methyl group and proceeded as a redox disproportionation where this group was oxidized into a CH_2OAc moiety while the azido group was reduced into the amine. Interestingly, the nitro group, which could potentially serve as a relay between the two reacted functionalities, remained unchanged. Considering this surprising outcome, we have explored this new conformation in more detail and wish to report the results of this investigation in this work.

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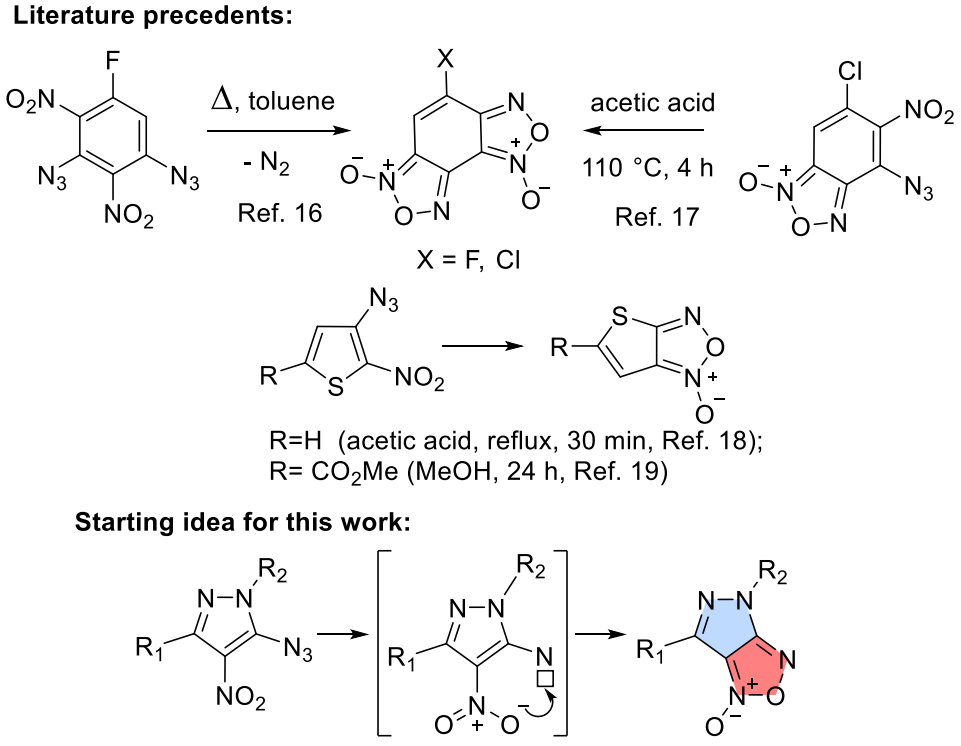

Scheme 1. The original goal of this work: fusion of two dinitrogen heterocycles, pyrazole and furoxan.

The high energy stored in the azide functionality makes it a powerful tool for many organic transformations [20,21]. In addition, the N_3-group can be considered as a convenient amine surrogate, i.e., a form of amine protection, as this group can be easily installed into a molecule and converted into corresponding NH_2 later in the synthetic sequence. Several reductive strategies for azide-to-amine transformations include the use of strong reducing agents such as $LiAlH_4$ [22], $NaBH_4$ [23], $Zn(BH_4)_2$ [24]. The search for milder conditions led to the development of sulfide chemistry [25,26] or copper(I) catalysis [27]. However, Staudinger reaction with the use of phosphine or phosphite reagents remains the most frequent choice for this reduction [28–31]. Nevertheless, each of these approaches has its disadvantages, including poor group tolerance, additional synthesis of ligands, or phosphorus(V) waste.

On the other hand, C–H activation in aliphatic functional groups remains challenging and usually requires oxidative conditions. Furthermore, direct esterification of C–H bonds is often limited by the nature of substrates [32,33]. Several oxidative acetoxylation protocols with the in situ generation of hypervalent iodine species have been described [34,35]. The combination of copper- [36,37] or palladium-catalysts [38–42] with external oxidants or electrochemical oxidation [43] also provided a useful tool for AcO-group insertion into alkane moiety. However, these approaches are either incompatible with sensitive functional groups (e.g., unprotected amines) or demand the presence of directing groups. Using acetic acid itself for C–H acetoxylation is unusual and conceptually appealing.

2. Results and Discussion

Synthesis of reactants and analysis of products. We started by preparing 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole **2** from edaravone **1**, a medication used to treat stroke and amyotrophic lateral sclerosis [44,45] (Scheme 2) according to the literature method [46]. It was reported that nitration of compound **2** with concentrated nitric acid in acetic anhydride led to nitration at the 4th position of the pyrazole ring with the formation of 5-chloro-3-methyl-4-nitro-1-phenyl-1*H*-pyrazole [46]. When we

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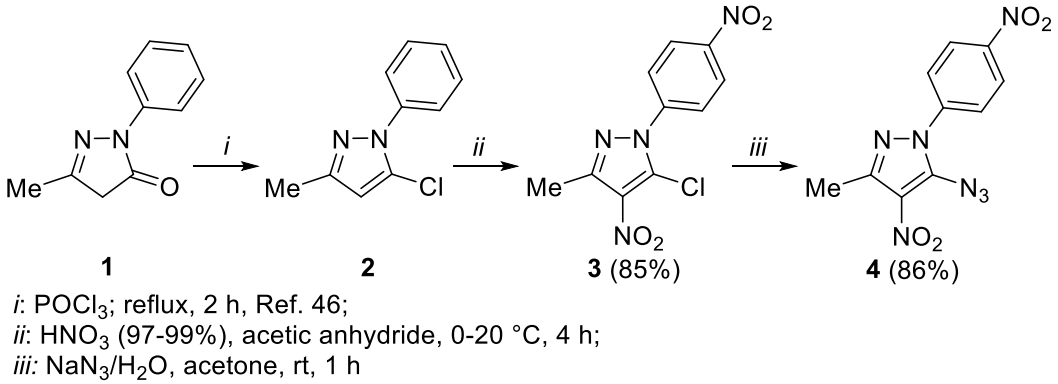
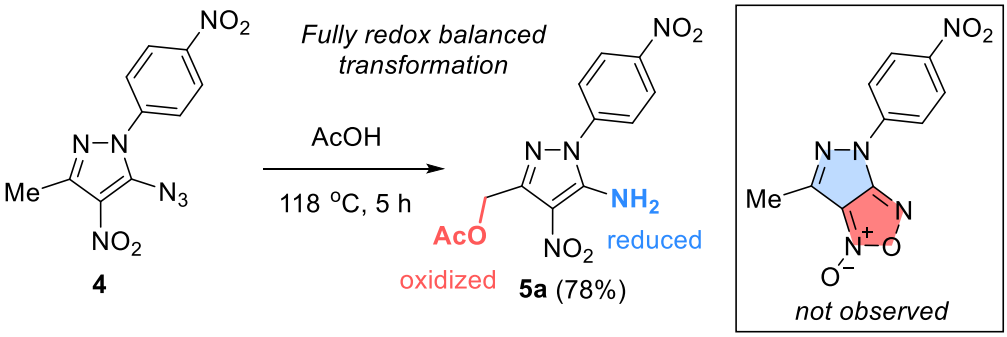
used fuming nitric acid (97-99%) it resulted in incorporation of the additional nitro group at the *para*-position of the phenyl group, allowing us to obtain compound **3**.

Reaction of 5-chloro-3-methyl-4-nitro-1-(4-nitrophenyl)-1*H*-pyrazole **3** with sodium azide resulted in the facile replacement of chlorine by the azido group. We have shown earlier that the presence of adjacent azide and nitro groups usually leads to cyclization to the furoxan ring upon refluxing in high-boiling solvents [16,17]. In some cases, this reaction proceeds spontaneously at the stage of azide preparation [47].



Scheme 2. Reaction of edaravone **1** with $POCl_3$, following nitration and azidation with formation of 5-azido-3-methyl-4-nitro-1-(4-nitrophenyl)-1*H*-pyrazole **4.**

However, to our surprise, thermolysis of *o*-azidonitro derivative **4** in acetic acid led to 5-amino-4-nitro-1-(4-nitrophenyl)-1*H*-pyrazol-3-yl)methyl acetate **5a**, instead of the expected cyclization product furoxan. The new product is formed as a result of the reduction of the azido group to amino group and the oxidative conversion of the methyl group to an CH_2OAc moiety (Scheme 3). Aminopyrazole derivatives are widely used in organic synthesis as convenient starting reagents for obtaining new annelated heterocycles, which may be of interest as potentially physiologically active compounds [48]. For example, 4-amino-pyrazole-3-carboxylic esters are used as intermediates for the synthesis of Sildenafil (Viagra) and Allopurinol [49].



Scheme 3. Unexpected redox disproportionation of α-nitroazide **4.**

The reaction of azide **4** with propionic, butyric acids and butanol leads to similar products **5b-d.** In all cases, compound **6** was isolated as a by-product in trace amounts.

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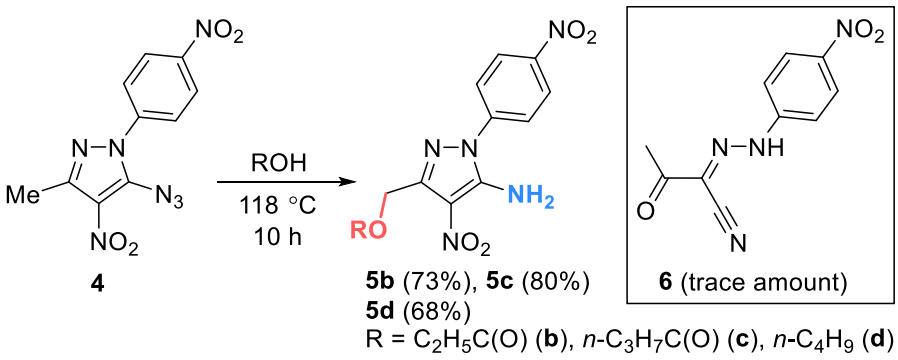

Scheme 4. Reaction of nitroazide **4** with selected carboxylic acids and butanol.

The structures of compounds **3**, **5a**, and **6** were confirmed by X-Ray Analysis (Figure S13,S14 and Figure 1). Bihetaryl scaffold of **5a** is twisted due to steric repulsion in *ortho*-positions (Figure 1, A). Interplanar and torsion angles between *p*-nitro-phenylene and pyrazole rings are 37.91º and 36.37º, respectively. Acetoxy-group lies in "*gauche*"-conformation to diaza-cycle (torsion angle C10C9C12O13 59.42º) where the acceptor C-O bond aligns with the donor heterocycle π-system. Interestingly, NH_2 substituent participates in both intra- and intermolecular hydrogen bonding with oxygens of NO_2 and C=O groups, respectively.

Hydrazide **6** has a completely planar structure with two cross-conjugated fragments at the NH-moiety (Figure 1, B). A lone pair of the NH nitrogen can participate in conjugation with both substituents, and as a result, the central N-atom is sp^2-hybridized. The sum of valence angles at the NH nitrogen equals 360.0º.

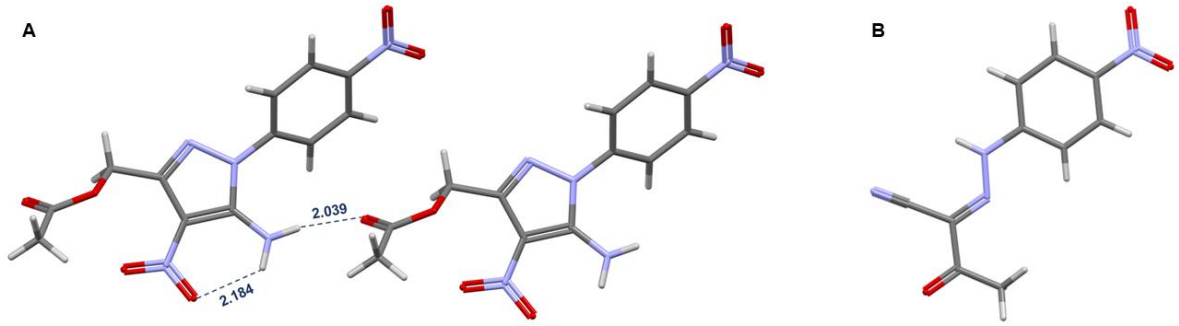

Figure 1. (**A**) – fragment of crystal packing of compound **5a,** (**B**) – molecular structure of compound **6.**

Possible mechanism. Considering that this process involves a metal-free C–H activation at relatively mild conditions, its mechanism is intrinsically interesting at it may pave the way to similar C–H activations of a broader range of substrates. The key step is likely to be the formation of the nitro-substituted nitrene. Aryl nitrenes are capable of complex transformations including a variety of ring expansions, fragmentations, and bond insertions [50–53]. Singlet aryl nitrenes can also be trapped by reactions with internal nucleophiles [54–56]. Although Ph-nitrene is known to be a triplet (~15 kcal/mol lower than the open-shell singlet state), the singlet/triplet gap in pyrazol nitrene has not been studied.

Once the pyrazole nitrene **7** is formed, it can potentially react in several ways. Direct intramolecular attack of an oxygen from the nitro-group leads to neutral bicyclic species **8**, which can be converted into **9** by protonation. Alternatively, pyrrole nitrogen can increase electron density at the nitrene via resonance, facilitating protonation with the formation of a nitrenium ion (not shown) which may also cyclize with the formation of fused bicyclic cation **9**. When **9** is formed, the mechanistic path can diverge. Here, we have considered two possibilities. First, intramolecular

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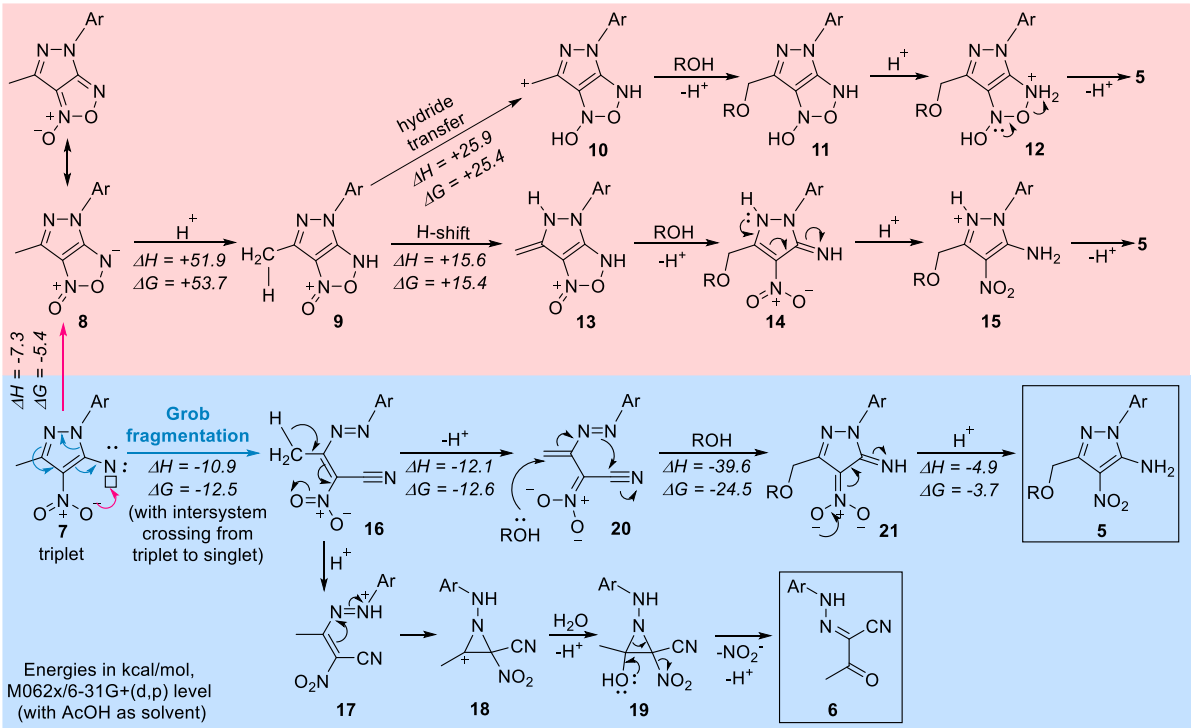
activation of methyl substituent by electron-deficient oxygen in **9** may enable hydride transfer, allowing for the formation of a stabilized carbocation **10**. The nucleophilic attack of ROH at the cationic carbon, followed by proton transfer and the furoxan ring opening, would form the final product **5**. An interesting feature of this path would be that nitrene would provide transient activation of the nitro group, rendering it an even stronger hydride acceptor. However, computational analysis at the M062x/6-31+G (d,p) level (with AcOH as solvent) suggested that the barrier for such hydride shift is prohibitively large (67 kcal/mol) and the carbocationic intermediate **10** is nearly 25 kcal/mol higher in energy than **9.**

In an alternative intramolecular activation path, prototropic tautomerization of cation **9** in acidic media would lead to the dearomatizing methyl-methylene tautomeric transformation **9→13**. ROH attack on alkene fragment can synchronously open the furoxan ring and unmask the nitro and imine groups of **14**. Subsequent proton transfers reestablish aromaticity with the formation of pyrazole **15**. Deprotonation of **15** would lead to the observed product **5**. We consider this path unfavorable due to the >15 kcal/mol penalty for the loss of aromaticity in **13**. Furthermore, the formation of the key precursor, i.e., the bicyclic cation **9** by protonation of neutral **8** by acetic acid is also predicted to be >50 kcal/mol uphill.

Based on these considerations and the formation of an acyclic side product **6**, we explored the possibility of ring opening as the first step in the reaction sequence. Here, we were guided by the literature precedent as 5-azidopyrazoles are known to undergo ring opening processes with the formation of cyano-group after nitrogen loss upon heating [57,58]. Furthermore, our attempts to optimize the singlet state of nitrene **7** led to its barrierless Grob fragmentation with the formation of acyclic nitrile **16**.

Protonation of intermediate **16** can lead to the formation of hydrazonium cation **17** which may undergo cyclization to N-amino-substituted aziridine cation **18**. Due to hybridization effects [59] and inverse α-effect [60–62], such cations are expected to be quite reactive and should undergo quick capture by an external nucleophile (**18→19**). Collapse of amino acetal with the concomitant aziridine ring opening in **19** relieves the transient strain. Hydrazine lone pair then assists in elimination of the NO_2 group to reestablish conjugation and, after deprotonation, forms the isolated byproduct **6**.

Furthermore, the same intermediate **16** can undergo isomerization into alkene **20** which after nucleophilic addition of ROH can undergo a 5-exo-trig ring closure that recreates the heterocyclic moiety. Protonation of the cyclic nitronate **21** is coupled with aromatization and formation of the final product **5.**



Scheme 5. Suggested mechanism for the formation of unusual products in the attempted synthesis of pyrazole/furoxan hybrid. Pathways discarded from the computational evidence are shown at the red background. The suggested plausible path is shown in blue.

In conclusion, we report an interesting "redox-balanced" transformation where two functional groups separated in space undergo simultaneous redox transformations in the opposite directions: the Me group is oxidized while the nitrene moiety is reduced. The absence of usual furoxan products in this case can be attributed to the combination of two factors: the lower aromaticity of pyrazole relative to benzene [63,64] and accumulation of strain upon fusion of the two five-membered rings [65]. The interplay of electronic effects due to the presence of multiple nitrogen atoms in pyrazole activates the fast Grob fragmentation into functionally rich acyclic nitro nitrile 16 which can recyclize after prototropic isomerization and Michael-like addition of AcOH.

3. Materials and Methods

Chemistry

IR spectra were recorded as emulsion in vaseline oil (sample concentration 0.25%) on a Tensor 37 Vertex 70 RAM II spectrometer (Bruker Optik GmbH, Germany) in the range 400–4000 cm^{-1}; given are the most intense absorption bands. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AVANCE 400 spectrometer (Bruker BioSpin, Rheinstetten, Germany) operating at 400 MHz (for ^{1}H NMR) and 101 MHz (for ^{13}C NMR) and on Brucker spectrometers AVANCE*III*-500 (Bruker BioSpin, Rheinstetten, Germany) operating at 500.1 MHz for ^{1}Hat 303 K and 126 MHz (for ^{13}C NMR). Chemical shifts were measured in δ (ppm) with reference to the solvent (δ = 7.27 ppm and 77.00 ppm for $CDCl_3$, δ = 2.06 ppm and 28.94 ppm for $(CD_3)_2CO$ for ^{1}H and ^{13}C NMR, respectively). Electrospray ionization (ESI) mass spectra were obtained on an Amazon X mass spectrometer from Bruker Daltonics (Bremen, Germany) with an ion trap. The measurements were carried out in the mode of recording negative ions in the m/z range from 100 to 2000. Elemental analysis was performed on a CHNS-O Elemental Analyser EuroEA3028-HT-OM (EuroVector S.p.A., Milan, Italy) with an accuracy ±0.4% for C, H, Cl and N. The melting point was determined in glass capillaries on a Stuart SMP 10 instrument (Keison Products, Chelmsford, UK). The progress of reactions and the purity of product were monitored by TLC on Sorbfil UV-254 plates (Sorbpolimer, Krasnodar, Russia); the chromatograms were developed under UV light.

X-ray crystallography data. The data set for the single crystal **3** and **6** were collected on a Bruker Quest diffractometer using graphite monochromated MoKα (0.71073 Å) radiation and ω-scan rotation. Data collection: images were indexed, integrated, and scaled using the APEX2 [66] data reduction package and corrected for absorption using SADABS [67]. The structure **3** were solved by the direct methods and refined using SHELX [68]. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were calculated on idealized positions and refined as riding atoms. The X-ray analysis was performed on the equipment of Spectral-Analytical Center of FRC Kazan Scientific Center of RAS.

Crystallographic data for compound **3**: $C_{10}H_7ClN_4O_4$, *M* 282.65, monoclinic, $P2_1/c$, *a* 3.7604(1), *b* 32.2193(11), *c* 9.0673(3) Å,*β*93.985(1)°, *V* 1095.92(6) $Å^3$, *Z* 4, D_{calcd} 1.713g·cm^{-3}, μ(Mo-Kα) 0.367 mm^{-1}, F(000) 576, (θ 1.3- 27.9°, completeness 99.9%), T 100(2) K, orange prism, (0.11 x 0.17 x 0.56) mm^3,transmission 0.6946 - 0.7456, 39950 measured reflections, 2597 independent (R_{int} 0.044), 173 parameters, R_1 = 0.0367 (for 2379 observed $I > 2\sigma(I)$) , wR_2 = 0.1435 (all data), GOOF 1.05, largest diff. peak and hole 0.50 and -0.40 e.A^{-3}. CCDC number 2299127.

Crystallographic data for compound **6**: $C_{10}H_8N_4O_3$, *M* 232.20, monoclinic, $P2_1/n$, *a* 7.0578(14), *b* 13.434(3), *c* 11.160(2) Å,*β* 96.736(6)°, *V* 1050.8(4) $Å^3$, *Z* 4, D_{calcd} 1.468g·cm^{-3}, μ(Mo-Kα) 0.113 mm^{-1}, F(000) 480, (θ 2.4 - 27.9°, completeness 99.8%), T 162(2) K, orange needle, (0.04 x 0.05 x 0.15) mm^3, transmission 0 0.6291 - 0.7456, 39950 measured reflections, 23472 independent (R_{int} 0.273), 155 parameters, R_1 = 0.0852 (for 1013 observed $I > 2\sigma(I)$) , wR_2 = 0.2504 (all data), GOOF 0.941, largest diff. peak and hole 0.31 and -0.28 e.A^{-3}. CCDC number 2299128.

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The data set for the single crystal **5a** were collected on a Rigaku Synergy S instrument (Rigaku Oxford diffraction, Tokyo, Japan) with a HyPix detector and a PhotonJet microfocus X-ray tube using Cu Kα (1.54184 Å) radiation at a low temperature. Images were indexed and integrated using the CrysAlisPro data reduction package. Data were corrected for systematic errors and absorption using the ABSPACK module: numerical absorption correction based on Gaussian integration over a multifaceted crystal model and empirical absorption correction based on spherical harmonics according to the point group symmetry using equivalent reflections. The GRAL module was used for the analysis of systematic absences and space group determination. The structure was solved by direct methods using SHELXT [69] and refined by the full-matrix least-squares on F2 using SHELXL [70]. Non-hydrogen atoms were refined anisotropically. The hydrogen atoms were inserted at the calculated positions and refined as riding atoms. The figures were generated using the Mercury v4.1 [71] program. Crystals were obtained by the slow evaporation method.

Crystallographic data for compound **5a**: $C_{12}H_{11}N_5O_6$ (M =321.26 g/mol): triclinic, space group P-1 (no. 2), a = 7.7774(2) Å, b = 9.7999(2) Å, c = 9.96110(10) Å, α = 102.833(2)°, β = 111.543(2)°, γ = 92.620(2)°, V = 681.72(3) Å^3, Z = 2, T = 110.0(5) K, μ(Cu Kα) = 1.107 mm^{-1}, $Dcalc$ = 1.565 g/cm^3, 7375 reflections measured (9.348° ≤ 2Θ ≤ 153.212°), 2745 unique (R_{int} = 0.0229, R_{sigma} = 0.0227) which were used in all calculations. The final R_1 was 0.0347 (I > 2σ(I)) and wR_2 was 0.0938 (all data). CCDC number 2294752.

CCDC 2299127, 2299128, 2294752 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.uk).

5-Chloro-3-methyl-4-nitro-1-(4-nitrophenyl)-1*H*-pyrazole (3). Acetic anhydride (6 mL) was added to 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole **2** (0.44 g, 2.3 mmol), reaction mixture was cooled to 0 °C and then fuming nitric acid (97–99%, 4 mL) was added dropwise. Reaction mixture was stirred at room temperature for 4 h, then poured over crushed ice. The obtained precipitate was filtered off, washed with cold water (100 mL) and dried under vacuum (0.06 mm Hg) at 40 °C to constant weight. Crude product was recrystallized from acetone to give target compound. Yellow powder, yield 0.55 g (85%), m.p.: 148–150 °C. IR (ν, cm^{-1}): 1346 (NO_2 symm), 1530 (NO_2 asymm). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.41 (d, J = 8.6 Hz, 2H), 7.83 (d, J = 8.6 Hz, 2H), 2.64 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 148.7, 147.9, 141.7, 131.2, 128.2, 126.0, 125.0, 14.7. Anal. calcd (%) for $C_{10}H_7ClN_4O_4$: C, 42.50; H, 2.50; Cl, 12.54; N, 19.82. Found: C, 42.54; H, 2.48; Cl, 12.53; N, 19.85.

5-Azido-3-methyl-4-nitro-1-(4-nitrophenyl)-1*H*-pyrazole (4). To a solution of 5-chloro-3-methyl-4-nitro-1-(4-nitrophenyl)-1*H*-pyrazole **3** (0.50 g, 1.8 mmol) in acetone (5 mL) at room temperature was added a solution of sodium azide (0.15 g, 2.3 mmol) in 1 mL of water. The reaction mixture was stirred for 1 h (the reaction was monitored by thin layer chromatography, eluent: toluene – ethylacetate (2:1, v/v)). After completion of the reaction, the solvent was removed under reduced pressure, washed with cold water and dried in vacuum (0.06 mm Hg) at 40 °C to constant weight. Light brown powder, yield 0.45 g (86%), m.p.: 104–106 °C. IR (ν, cm^{-1}): 1349 (NO_2 symm), 1557 (NO_2 asymm), 2151 (N_3). ^{1}H NMR (500 MHz, Acetone-d_6): δ = 8.40–8.43 (m, 2H), 8.07–8.11 (m, 2H), 2.55 (s, 3H). ^{13}C NMR (101 MHz, Acetone-d_6): δ = 147.9, 147.6, 142.5, 138.5, 126.2, 125.2, 125.1, 14.4. Anal. calcd (%) for $C_{10}H_7N_7O_4$: C, 41.53; H, 2.44; N, 33.90. Found: C, 41.58; H, 2.47; N, 33.87.

Synthesis of compounds 5a-d (general method). 5-Azido-3-methyl-4-nitro-1-(4-nitrophenyl)-1*H*-pyrazole **4** (0.1 g, 0.34 mmol) was heated in 3 mL of acid/butanol at 118 °C for 5 h (for acetic acid) or 10 h (for propionic, butyric acids and butanol). Then solvent was removed under reduced pressure. In case of propionic, butyric acids and butanol crude product was purified by column chromatography on silica gel (eluent: toluene – ethylacetate (10:1, v/v)) to give the target compound (the side-product **6** was isolated in trace amount).

5-Amino-4-nitro-1-(4-nitrophenyl)-1*H*-pyrazol-3-yl)methyl acetate (5a). Gray pearlescent solid (0.08 g) was obtained in 78% yield. M.p.: 198–199 °C. IR (ν, cm^{-1}): 1346 (NO_2 symm), 1599 (NO_2 asymm), 1637 (CO), 1721 (C=O), 3408 (NH_2). ^{1}H NMR (400 MHz, Acetone-d_6): δ = 8.46 (d, J = 9.0 Hz, 2H), 7.99 (d, J = 9.0 Hz, 2H), 7.35 (br.s, 2H), 5.33 (s, 2H), 2.08 (s, 3H). ^{13}C NMR (101 MHz, Acetone-d_6):

δ = 169.6, 147.1, 144.7, 142.3, 125.1, 124.9, 116.9, 58.7, 19.6. Anal. calcd (%) for $C_{12}H_{11}N_5O_6$: C, 44.87; H, 3.45; N, 21.80. Found: C, 44.83; H, 3.52; N, 21.85. ESI, m/z for $C_{12}H_{11}N_5O_6$: 319.99 [M-H]$^-$.

(5-Amino-4-nitro-1-(4-nitrophenyl)-1*H*-pyrazol-3-yl)methyl propionate (5b). Orange oil, yield 0.085 g (73%). IR (ν, cm^{-1}): 1347 (NO_2 symm), 1598 (NO_2 asymm), 1635 (CO), 1738 (C=O), 3430 (NH_2). ^{1}H NMR (400 MHz, Acetone-d_6): δ = 8.38–8.42 (m, 2H), 7.91–7.97 (m, 2H), 7.36 (br.s, 2H), 5.31 (s, 2H), 2.38 (q, *J* = 7.6 Hz, 2H), 1.11 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, Acetone-d_6): δ = 173.9, 147.9, 145.7, 143.1, 125.9(4), 125.9(1), 125.6, 117.7, 59.5, 27.7, 9.4. Anal. calcd (%) for $C_{13}H_{13}N_5O_6$: C, 46.57; H, 3.91; N, 20.89. Found: C, 46.72; H, 4.02; N, 20.92. ESI, m/z for $C_{13}H_{13}N_5O_6$: 334.04 [M-H]$^-$.

(5-Amino-4-nitro-1-(4-nitrophenyl)-1*H*-pyrazol-3-yl)methyl butyrate (5c). Orange oil, yield 0.096 g (80%). IR (ν, cm^{-1}): 1347 (NO_2 symm), 1598 (NO_2 asymm), 1634 (CO), 1734 (C=O), 3434 (NH_2). ^{1}H NMR (600 MHz, Acetone-d_6): δ = 8.42–8.48 (m, 2H), 7.95–8.01 (m, 2H), 7.36 (br.s, 2H), 5.33 (s, 2H), 2.35 (t, *J* = 7.4 Hz, 2H), 1.65 (q, *J* = 7.4 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, Acetone-d_6): δ = 173.1, 148.0, 147.9, 145.7, 143.2, 125.9(5), 125.8(9), 125.7, 59.4, 36.3, 19.1, 13.8. Anal. calcd (%) for $C_{14}H_{15}N_5O_6$: C, 48.14; H, 4.33; N, 20.05. Found: C, 48.20; H, 4.37; N, 20.01. ESI, m/z for $C_{14}H_{15}N_5O_6$: 348.05 [M-H]$^-$.

3-(Butoxymethyl)-4-nitro-1-(4-nitrophenyl)-1*H*-pyrazol-5-amine (5d). Orange oil, yield 0.075 g (68%). IR (ν, cm^{-1}): 1346 (NO_2 symm), 1598 (NO_2 asymm), 1634 (CO), 1702 (C=O), 3430 (NH_2). ^{1}H NMR (400 MHz, Acetone-d_6): δ = 8.41–8.45 (m, 2H), 7.94–7.99 (m, 2H), 7.29 (br.s, 2H), 4.68 (s, 2H), 3.59 (t, *J* = 6.5 Hz, 2H), 1.62–1.53 (m, 2H), 1.48–1.32 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Acetone-d_6): δ = 147.9, 147.7(4), 147.6(8), 143.4, 125.9, 125.6, 117.9, 71.3, 65.9, 32.5, 19.9, 14.1. Anal. calcd (%) for $C_{14}H_{17}N_5O_5$: C, 50.15; H, 5.11; N, 20.89. Found: C, 50.23; H, 5.17; N, 20.82. ESI,) m/z for $C_{14}H_{17}N_5O_5$: 334.08 [M-H]$^-$.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, p. 2-3 – experimental section; Figures S1–S12 (p. 4-9) – copies of NMR spectra of all synthesized compounds; S13-S14 (p. 10) – the X-ray diffraction data of compound **3**; p. 11-18 – computational data; p. 19 – references for computational data.

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