Synthesis of 2,5-disubstituted pyrazolyl-1,3,4-oxadiazoles by the Huisgen reaction*

T. K. Shkineva, O. V. Serushkina, I. A. Vatsadze, T. E. Khoranyan, and I. L. Dalinger★

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 119991 Moscow, Russian Federation. E-mail: dalinger@ioc.ac.ru

We developed an approach to the synthesis of 2,5-disubstituted pyrazole-containing 1,3,4-oxadiazoles by acylation of 5-(nitropyrazolyl)tetrazoles with alkyl, aryl, and hetaryl acyl chlorides with subsequent recyclization of the intermediate *N*-acyltetrazoles into 1,3,4-oxadiazoles and studied nitration of the obtained 2-aryl-5-(nitropyrazolyl)-1,3,4-oxadiazoles.

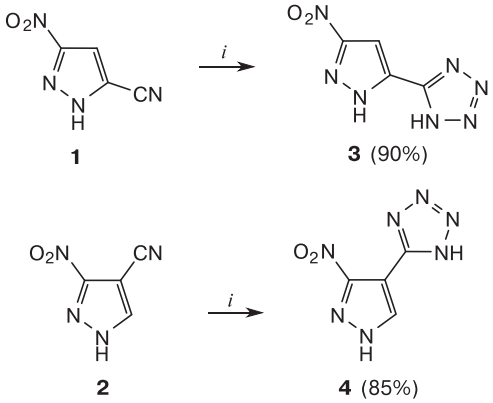
Key words: 1,3,4-oxadiazole, nitro group, nitropyrazole, Huisgen reaction, hybrid molecules.

Oxadiazoles, in particular, their 1,3,4-regioisomers, have a wide range of applications from materials science[1—3] to explosives[4,5] and biologically active compounds.[6,7] Recently, 1,3,4-oxadiazole derivatives have been found to exhibit antitumor,[8—10] antiviral,[11,12] antiinflammatory,[13] analgesic,[13] antibacterial,[14] antiparasitic,[15] and fungicidal activity.[16] Therefore, the development of approaches to the structural modification of 1,3,4-oxadiazole derivatives using various functional groups or structural fragments in order to improve their physicochemical or pharmacological properties continues to be relevant. One of the approaches to such modification is the design of hybrid molecules, a combinations of several heterocycles of the same or different types, which possess new properties expanding areas of their application.

A pyrazole fragment is often present in biologically active compounds,[17] components of dyes and luminophores,[18] energetic materials.[19—22] The present work is a continuation of our research aimed at developing methods for the synthesis and studying the reactivity of hybrid heteronuclear compounds consisting of the nitropyrazole ring bonded with a polynitrogen heterocycle[23—27] and is devoted to the development of efficient methods for the synthesis of 5-(nitropyrazolyl)-1,3,4-oxadiazole derivatives. It should be noted that nitro derivatives of pyrazole-containing 1,3,4-oxadiazoles are very rare; however, both promising biologically active substances[28,29] and thermally stable high-energy compounds have been found among them.[30—32]

We started our study by looking for the possibility of forming a 1,3,4-oxadiazole ring from nitropyrazole derivatives. One of the traditional methods for the synthesis of 1,3,4-oxadiazoles is the reaction of the corresponding tetrazoles with carboxylic acid chlorides,[4,33—36] also known as the Huisgen reaction.[4,36] This method is used relatively seldom, probably due to the small number of available and stable tetrazoles. Earlier, we have developed an efficient method for the preparation of pyrazole-substituted tetrazoles by treatment of cyanopyrazoles with the $[Et_3NH^+N_3^-]$ system in refluxing toluene (Scheme 1).[37] In particular, this

Scheme 1



Reagents and conditions: *i*. 1) NaN_3, $Et_3N \cdot HCl$, toluene, 110 °C, 8 h (for **3**) or 10 h (for **4**); 2) HCl.

* Dedicated to the Academician of the Russian Academy of Sciences V. A. Tartakovsky on the occasion of his 90th birthday.

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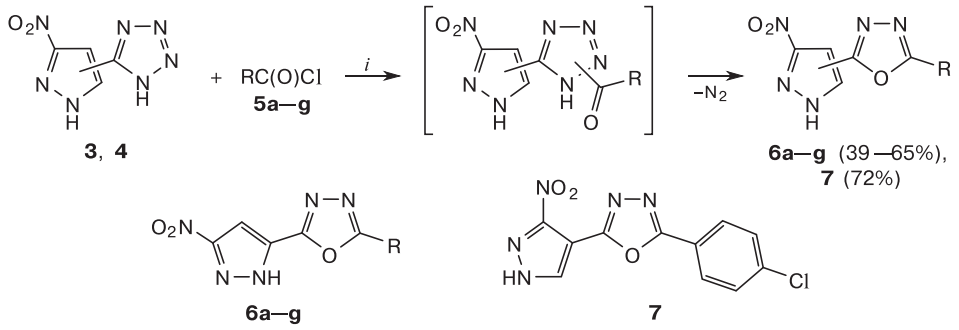
Scheme 2



6: R = Me (**a**), 4-MeC_6H_4 (**b**), 4-$MeOC_6H_4$ (s), 3,5-$(MeO)_2C_6H_3$ (**d**), 4-ClC_6H_4 (**e**), 3-$F_3CC_6H_4$ (**f**), 3,5-$(NO_2)_2C_6H_3$ (**g**)

Reagents and conditions: *i*. 1) NEt_3, $C_2H_2Cl_4$; 2) 110 °C.

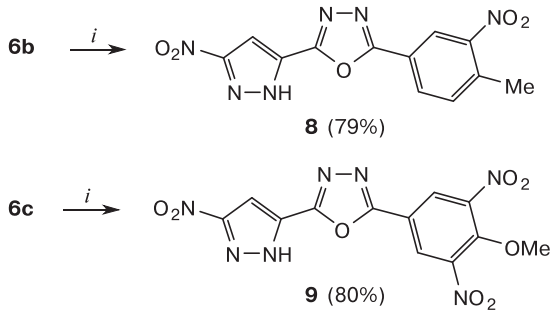
method was applied to nitriles **1** and **2** to obtain tetrazoles **3** and **4** in high yields. Note that this method turned out to be more efficient for the synthesis of the known tetrazole **3** than that proposed earlier.[38]

Having at our disposal NH-unsubstituted 5-(nitropyrazolyl)tetrazoles, it seemed reasonable to study their reaction with of alkyl and aryl carboxylic acid chlorides **5a—g** under the Huisgen reaction conditions. We found that pyrazolyltetrazoles **3** and **4** in tetrachloroethane in the presence of NEt_3 as a base undergo acylation with carboxylic acid chlorides, including aromatic acids containing both donor and acceptor substituents. Subsequent thermolysis of intermediately formed *N*-acyltetrazoles at 110 °C for 3—9 h gave 2-aryl-5-(nitropyrazolyl)-1,3,4-oxadiazoles **6a—g** and **7** in 40—77% yield (Scheme 2).

In addition to the traditional use of nitro compounds as high-energy substances, in recent years great efforts have been made to study the biological activity of nitroaromatic and heteroaromatic compounds.[20,39—42] The nitro group in such molecules has the ability to be bioactivated, for example, by enzymatic or one-electron reduction or by interaction with cellular nucleophiles.[43] Nitro compounds are important intermediate products in organic synthesis, since a significant activating and directing effect of the nitro group in the structure of aryl and hetaryl compounds on the course of their chemical transformations increases the synthetic possibilities for further functionalization of these compounds.[44—46] At the same time, the nitration of pyrazole-containing 1,3,4-oxadiazoles is practically unstudied: to the best of our knowledge, a single example of the nitration of bispyrazolyl-1,3,4-oxadiazoles has recently been described.[30] We studied the possibility of introducing additional nitro groups in the resulting 2-aryloxadiazoles using compounds **6b,c,e,g** and **7** (Schemes 3 and 4).

Treatment of oxadiazole **6b** containing a donor substituent at *para*-position of the benzene ring with a mixture of concentrated H_2SO_4 and HNO_3, widely used for the synthesis of nitro derivatives of pyrazoles,[20,23,25,26,47] at room temperaturee for 24 h results in the electrophilic attack at only one position of the aryl substituent to form *m*-nitroaryl derivative **8** (see Scheme 3). The nitration of oxadiazole **6c** with a *para*-methoxy group in the aryl substituent under the same conditions leads to the introduction of two nitro groups simultaneously with the formation of the 3,5-dinitroaryl derivative **9** (see Scheme 3).

Scheme 3

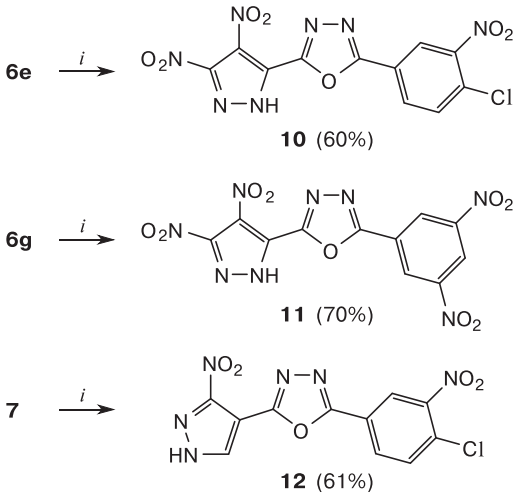


Reagents and conditions: *i*. HNO_3, H_2SO_4, 20 °C, 24 h.

Raising the reaction temperature to 80 °C allows to nitrate oxadiazoles **6e,g** and **7** containing electron-withdrawing substituents in the aryl ring already within 4 h, with the unsubstituted C(4) atom of the pyrazole substituent being additionally nitrated (see Scheme 4). In the case of compound **6e**, which contains a weak electron-withdrawing substituent at *para*-position of the aromatic ring, the nitration occurs at both position 3 of the aryl substituent and the unsubstituted C(4) atom

of the pyrazole ring, resulting in 3,4-dinitropyrazolyl-3-nitroaryloxadiazole **10**. In the case of compound **6g**, the aryl substituent is deactivated to nitration by two *meta*-arranged electron-withdrawing nitro groups, therefore, only the C(4) position of the pyrazole ring undergoes nitration, which leads to 3,4-dinitropyrazolyloxadiazole **11**. In the case of compound **7**, only the aromatic substituent undergoes nitration, with no additional nitration of the pyrazole substituent taking place, since the most active position 4 of the pyrazole ring under the nitration conditions is occupied by an electron-withdrawing oxadiazole substituent, which additionally deactivates position 5, which is significantly less active towards electrophilic nitration.

Scheme 4

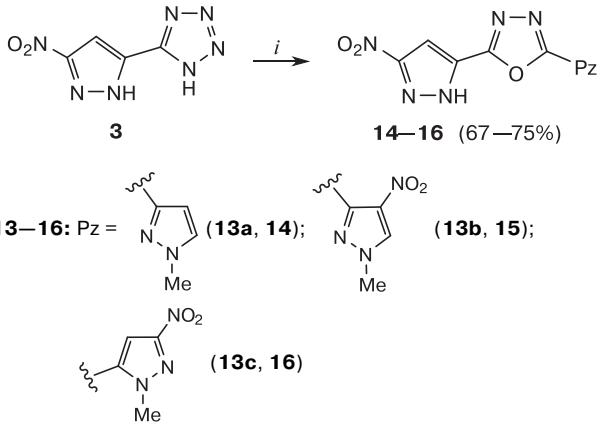


Reagents and conditions: *i*. HNO_3, H_2SO_4, 80 °C, 4 h.

It should be noted that the nitration under these conditions of compounds **6b,c** with donor substituents in the aryl ring leads to a difficult-to-separate mixture of water-soluble compounds, which, according to ^{13}C NMR spectroscopy, do not contain the oxadiazole ring. The problems concerning the destruction of the 1,3,4-oxadiazole ring by nitration and the formation of water-soluble products are described in the recently published work.[30]

Attempts to prepare 2,5-bis(pyrazolyl)-1,3,4-oxadiazoles by the Huisgen reaction using heterocyclic carboxylic acid chlorides showed that the reaction proceeds only with *N*-substituted pyrazolecarboxylic acid chlorides. The acylation of pyrazolyltetrazole **3** with chlorides **13a—c** in tetrachloroethane in the presence of NEt_3 with subsequent heating to 110 °C gave bis(pyrazolyl)oxadiazoles **14—16** in good yields (Scheme 5).

Scheme 5



Reagents and conditions: 1) PzC(O)Cl (**13a—c**), NEt_3, $C_2H_2Cl_4$; 2) 110 °C.

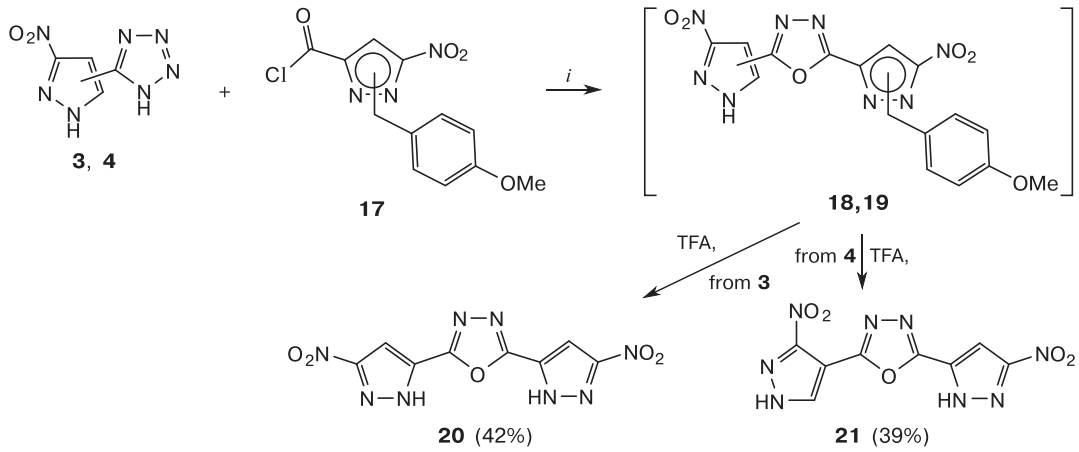
To obtain completely *N*-unsubstituted bis(pyrazolyl)-1,3,4-oxadiazoles, we decided to use pyrazolecarboxylic acid chloride containing an easily removable protective group at the N(1) atom of the pyrazole ring. In fact, the Huisgen reaction of tetrazoles **3** and **4** with acyl chloride **17** under our conditions led to the intermediate oxadiazoles **18** and **19** containing a *para*-methoxybenzyl protecting group. The removal of the protecting group by reflux of oxadiazoles **18** and **19** in trifluoroacetic acid for 3.5 h gave the corresponding tricycles **20** and **21** (Scheme 6).

The structures of oxadiazoles **6—12**, **14—16**, **20**, and **21** were confirmed by IR and multinuclear NMR spectroscopy, high resolution mass spectrometry or elemental analysis.

In the assignment of signals for the pyrazole ring, we used the well-known regularities in the pyrazoles series.[23,46,47] The assignment of signals in the ^{13}C NMR spectra was carried out on the basis of the rule that the chemical shifts of carbon atoms in nitropyrazoles are arranged in the following sequence: $\delta(C(3)=N(sp^2)) > \delta(C(5)—N(sp^3)) > \delta(C(4))$, while the signal for the carbon atom bonded to the nitro group is strongly broadened due to the quadrupole $^{13}C—^{14}N$ relaxation, which facilitates its identification. The ^{13}C NMR spectra of the obtained unsymmetrically substituted compounds exhibit two signals for the 1,3,4-oxadiazole ring, with the signal for the carbon atom bound with the aryl substituent being located in the lower field (δ_C 161—165) than that for the carbon atom bound with the pyrazole substituent (δ_C 154—158). The introduction of additional nitro groups in both the aryl and the pyrazole substituent has almost no effect on this regularity.

In conclusion, we have developed a general method for the synthesis of unsymmetrical hybrid pyrazole-

Scheme 6



Reagents and conditions: *i*. 1) NEt_3, $C_2H_2Cl_4$; 2) 110 °C.

containing 2,5-disubstituted 1,3,4-oxadiazoles based on 5-(nitropyrazolyl)tetrazoles. The nitration of the obtained 2-aryl-5-(nitropyrazolyl)-1,3,4-oxadiazoles was studied. It was shown that the direction of nitration and the number of simultaneously introduced nitro groups strongly depend on the nature of substituents in the aryl ring, the presence of a free position 4 in the pyrazole ring, and the nitration temperature. As a result, the products containing one or two nitro groups more than the starting compounds were obtained.

Experimental

IR spectra were recorded on a Bruker Alpha Fourier-transform spectrometer in KBr pellets. ^1H, ^{13}C, and ^{14}N NMR spectra were recorded on a BrukerAM-300 instrument (300.13 (^1H), 75.47 (^{13}C), and 21.69 MHz (^{14}N)) in DMSO-d_6 (unless otherwise stated) at 299 K. Chemical shifts for ^1H and ^{13}C nuclei are given relative to $SiMe_4$, for ^{14}N nuclei, relative to $MeNO_2$. Electrospray ionization high-resolution mass spectra were recorded on a Bruker MicroOTOFII instrument. Elemental analysis was performed on a PerkinElmer SeriesII 2400 analyzer. Melting points of compounds were determined by Kofler method on a Boetius hot stage (heating rate 4 K min^{-1}) and were not corrected. Reaction progress and purity of obtained compounds were monitored by TLC on Merck Silicagel 60 F_{254} plates.

Acetyl chloride (**5a**) and benzoyl chlorides **5b,c,e—g** were commercially available. Tetrazole **3**,[37] nitrile **2**,[48] 3,5-dimethoxybenzoyl chloride (**5d**),[49] 1-methyl-3-pyrazolecarboxylic acid,[50] 1-methyl-4-nitro-3-pyrazolecarboxylic acid,[51] 1-methyl-3-nitro-5-pyrazolecarboxylic acid,[51] and *N*-(4-methoxybenzyl)-3(5)-nitro-5(3)-pyrazole-1*H*-carboxylic acids[52] were synthesized by known procedures.

5-(3-Nitro-1*H*-pyrazol-4-yl)tetrazole (4). A mixture of cyanopyrazole **2** (6.9 g, 0.05 mol), NaN_3 (4.23 g, 0.065 mol), triethylamine hydrochloride (8.94 g, 0.065 mol), and toluene (150 mL) was refluxed for 10 h and cooled, followed by the addition of water with stirring until complete dissolution of the precipitate (200—500 mL). The aqueous layer was separated and acidified with HCl to pH 1—2. The precipitate formed was collected by filtration, washed with cold water, and dried in air. The filtrate was extracted with EtOAc (3×50 mL), the organic layer was dried with Na_2SO_4. The evaporation of the solvent *in vacuo* gave an additional portion of the product. Both precipitates were combined and dried in air. The yield was 7.69 g (85%), m.p. 237—239 °C (with decomp.) (EtOH) (*cf.* Ref. 38: m.p. 225—226 °C). IR, ν/cm^{-1}: 3224 (s), 3103 (s), 2959 (m), 2852 (m), 2726 (m), 2645 (m), 1753 (w), 1641 (m), 1537 (s, NO_2), 1520 (m), 1379 (s, NO_2), 1328 (m), 1238 (w), 1204 (w), 1133 (m), 1105 (m), 1064 (m), 997 (w), 853 (m), 829 (s), 791 (m), 747 (m), 709 (w), 651 (w), 499 (w). ^1H NMR, δ: 14.62 (br.s, 1 H, NH); 8.63 (s, 1 H, H(5) Pz). ^{13}C NMR, δ: 152.6 (C(5) of tetrazole); 147.1 (br.s, C(3) Pz); 134.4 (C(5)H Pz); 101.3 (C(4) Pz). ^{14}N NMR, δ: −21.40 (NO_2). MS, *m/z*: 181 $[M]^+$. Found (%): C, 26.68; H, 1.58; N, 53.81. $C_4H_3N_7O_2$. Calculated (%): C, 26.53; H, 1.67; N, 54.14.

Synthesis of pyrazolyl-1,3,4-oxadiazoles 6a—g and 7 (general procedure). Triethylamine (0.54 mL, 3.9 mmol) was added dropwise to a suspension of tetrazole **3** or **4** (0.54 g, 3 mmol) in tetrachloroethane (5 mL) with stirring, followed by the addition in one portion of the corresponding carboxylic acid chloride **5a—g** (3.3 mmol). The reaction mixture was slowly (~1 h) heated to 100—110 °C, kept at this temperature for 3.5 h in the synthesis of compounds **6a—d,g** or 9 h in the synthesis of compounds **6e,f**, and cooled. The precipitate formed was collected by filtration, washed with 5% aqueous HCl (4 mL) and water (5 mL), dried in air.

2-Methyl-5-(3-nitro-1*H*-pyrazol-5-yl)-1,3,4-oxadiazole (6a). The yield was 49%, m.p. 252—254 °C (EtOH—MeCN, 2 : 1). IR, ν/cm^{-1}: 3138 (s), 1641 (m), 1574 (s), 1541 (v.s, NO_2), 1411 (s), 1356 (s, NO_2), 1330 (s, NO_2), 1215 (m), 1182 (m), 990 (s), 900 (m), 826 (s), 729 (w), 502 (w).

^{1}H NMR, δ: 15.49 (s, 1 H, NH Pz); 7.65 (s, 1 H, H(4) Pz); 2.61 (s, 3 H, Me). ^{13}C NMR, δ: 164.5 (C(2) of oxadiazole); 156.2 (br.s, C(3) Pz); 155.8 (C(5) of oxadiazole); 130.3 (C(5) Pz); 102.5 (C(4)H Pz); 10.6 (Me). Found (%): C, 36.75; H, 2.49; N, 35.63. $C_6H_5N_5O_3$. Calculated (%): C, 36.93; H, 2.58; N, 35.89.

2-(4-Methylphenyl)-5-(3-nitro-1*H*-pyrazol-5-yl)-1,3,4-oxadiazole (6b). The yield was 39%, m.p. 269—271 °C (EtOH). IR, ν/cm^{-1}: 3150 (m), 3105 (m), 2902 (m), 1612 (m), 1542 (v.s, NO_2), 1497 (m), 1407 (s), 1363 (s, NO_2), 1326 (s), 1185 (w), 1015 (m), 992 (m), 826 (s), 735 (m), 501 (w). ^{1}H NMR, δ: 8.01 (d, 2 H, Ph, J = 8.1 Hz); 7.80 (s, 1 H, H(4) Pz); 7.46 (d, 2 H, Ph, J = 8.0 Hz); 2.41 (s, 3 H, Me). ^{13}C NMR, δ: 164.3 (C(2) of oxadiazole); 155.6 (br.s, C(3) Pz); 155.4 (C(5) of oxadiazole); 142.8; 130.0 (2 CH Ph); 129.9; (C(5) Pz); 126.8 (2 CH Ph); 120.0; 102.9 (C(4)H Pz); 21.7 (Me). MS, found: m/z 272.0784 $[M + H]^+$; calculated for $C_{12}H_{10}N_5O_3$: 272.0778.

2-(4-Methoxyphenyl)-5-(3-nitro-1*H*-pyrazol-5-yl)-1,3,4-oxadiazole (6c). The yield was 60%, m.p. 302—304 °C (EtOH). IR, ν/cm^{-1}: 3087 (m), 1609 (m), 1543 (s, NO_2), 1496 (s), 1326 (s, NO_2), 1257 (s), 1172 (m), 1019 (s), 832 (m), 625 (w). ^{1}H NMR, δ: 8.06 (d, 2 H, Ph, J = 8.6 Hz); 7.79 (s, 1 H, H(4) Pz); 7.19 (d, 2 H, Ph, J = 8.8 Hz); 3.87 (s, 3 H, OMe). ^{13}C NMR, δ: 164.2 (C(2) of oxadiazole); 162.4 (C(4) Ph); 156.3 (br.s, C(3) Pz); 155.2 (C(5) of oxadiazole); 130.3 (C(5) Pz); 128.8 (2 CH Ph); 115.0; 114.9 (2 CH Ph); 102.8 (C(4)H Pz); 55.6 (OMe). MS, found: m/z 288.0733 $[M + H]^+$; calculated for $C_{12}H_{10}N_5O_4$: 288.0727.

2-(3,5-Dimethoxyphenyl)-5-(3-nitro-1*H*-pyrazol-5-yl)-1,3,4-oxadiazole (6d). The yield was 65%, m.p. 273—275 °C (EtOH). IR, ν/cm^{-1}: 3437 (m), 3150 (w), 1604 (s), 1544 (v.s, NO_2), 1462 (s), 1428 (m), 1345 (s), 1331 (s), 1312 (s, NO_2), 1208 (s), 1165 (v.s), 1065 (m), 1022 (m), 989 (m), 921 (w), 826 (m), 738 (w). ^{1}H NMR, δ: 15.53 (br.s, 1 H, NH Pz); 7.87 (s, 1 H, H(4) Pz); 7.24 (s, 2 H, Ph); 6.78 (s, 1 H, Ph); 3.86 (s, 6 H, OMe). ^{13}C NMR, δ: 164.0 (C(2) of oxadiazole); 161.0 (C(3,5) Ph); 156.3 (br.s, C(3) Pz); 155.7 (C(5) of oxadiazole); 130.1 (C(5) Pz); 124.2 (C(1) Ph); 104.6 (2 CH Ph); 104.3 (CH Ph); 103.1 (C(4)H Pz); 55.6 (OMe). MS, found: m/z 318.0842 $[M + H]^+$; calculated for $C_{13}H_{12}N_5O_5$: 318.0833.

2-(4-Chlorophenyl)-5-(3-nitro-1*H*-pyrazol-5-yl)-1,3,4-oxadiazole (6e). The yield was 57%, m.p. 302—304 °C (EtOH). IR, ν/cm^{-1}: 3144 (m), 1603 (m), 1545 (v.s, NO_2), 1488 (m), 1411 (m), 1347 (s, NO_2), 1327 (m), 1222 (m), 1096 (m), 989 (m), 846 (m), 739 (m), 424 (w). ^{1}H NMR, δ: 8.14 (d, 2 H, Ph, J = 8.2 Hz); 7.76 (s, 1 H, H(4) Pz); 7.72 (d, 2 H, Ph, J = 8.3 Hz). ^{13}C NMR, δ: 163.6 (C(2) of oxadiazole); 156.1 (br.s, C(3) Pz); 156.0 (C(5) of oxadiazole); 137.4; 131.1 (C(5) Pz); 129.7 (2 CH Ph); 128.7 (2 CH Ph); 121.7; 103.0 (C(4)H Pz). MS, found: m/z 292.0231 $[M(^{35}Cl) + H]^+$; calculated for $C_{11}H_7(^{35}Cl)N_5O_3$: 292.0232.

5-(3-Nitro-1*H*-pyrazol-5-yl)-2-(3-trifluoromethylphenyl)-1,3,4-oxadiazole (6f). The yield was 57%, m.p. 207—209 °C (EtOH). IR, ν/cm^{-1}: 1632 (w), 1538 (v.s, NO_2), 1467 (m), 1408 (m), 1364 (m), 1330 (s, NO_2), 1286 (v.s), 1188 (s), 1132 (s), 1069 (w), 996 (m), 939 (w), 819 (m), 740 (m), 699 (m), 510 (w). ^{1}H NMR, δ: 8.44—8.40 (m, 2 H, H Ph); 8.06 (d, 1 H, Ph, J = 7.8 Hz); 7.93—7.88 (m, 2 H, Ph); 7.91 (s, 1 H, H(5) Pz). ^{13}C NMR, δ: 163.0 (C(2) of oxadiazole); 156.2 (br.s, C(3) Pz); 156.1 (C(5) of oxadiazole); 130.9 (CH Ph); 130.7 (CH Ph); 130.3 (q, $\underline{C}CF_3$, $^2J_{CF}$ = 32.6 Hz); 130.0 (C(5) Pz); 128.9 (q, CH Ph, $^3J_{CF}$ = 3.4 Hz); 123.8 (C Ph); 123.6 (q, CF_3, $^1J_{CF}$ = 272.6 Hz); 123.3 (q, CH Ph, $^3J_{CF}$ = 3.4 Hz); 103.3 (C(4)H Pz). MS, found: m/z 326.0492 $[M + H]^+$; calculated for $C_{12}H_7F_3N_5O_3$: 326.0496.

2-(3,5-Dinitrophenyl)-5-(3-nitro-1*H*-pyrazol-5-yl)-1,3,4-oxadiazole (6g). The yield was 48%, m.p. 254—256 °C (EtOH—MeCN, 1 : 1). IR, ν/cm^{-1}: 3122 (w), 3085 (w), 1629 (w), 1541 (v.s, NO_2), 1344 (v.s, NO_2), 1225 (w), 1147 (w), 1083 (w), 998 (w), 924 (w), 728 (m), 446 (w). ^{1}H NMR, δ: 9.16 (s, 1 H, H Ph); 9.15 (s, 1 H, Ph); 9.04 (s, 1 H, Ph); 8.03 (s, 1 H, H(4) Pz). ^{13}C NMR, δ: 161.4 (C(2) of oxadiazole); 156.7 (C(5) of oxadiazole); 156.6 (br.s, C(3) Pz); 148.9 (C(3,5) Ph); 129.8 (C(5) Pz); 126.6 (2 CH Ph); 125.7 (C(1) Ph); 121.4 (CH Ph); 103.8 (C(4)H Pz). ^{14}N NMR, δ: −15.07 (NO_2). Found (%): C, 38.20; H, 1.39; N, 28.03. $C_{11}H_5N_7O_7$ Calculated (%): C, 38.05; H, 1.45; N, 28.24.

2-(4-Chlorophenyl)-5-(3-nitro-1*H*-pyrazol-4-yl)-1,3,4-oxadiazole (7). The yield was 72%, m.p. 273—275 °C (EtOH—MeCN, 1 : 1). IR, ν/cm^{-1}: 3227 (s), 3132 (m), 1604 (m), 1544 (v.s, NO_2), 1481 (s), 1388 (v.s, NO_2), 1332 (s), 1177 (w), 1091 (m), 1058 (m), 1010 (w), 961 (w), 880 (w), 832 (v.s), 761 (m), 740 (s), 653 (w), 534 (w), 503 (m). ^{1}H NMR, δ: 8.84 (s, 1 H, H(5) Pz); 8.06 (d, 2 H, Ph, J = 8.2 Hz); 7.71 (d, 2 H, Ph, J = 8.3 Hz). ^{13}C NMR, δ: 164.4 (C(2) of oxadiazole); 157.1 (C(5) of oxadiazole); 152.5 (br.s, C(3) Pz); 137.0; 135.0 (C(5)H Pz); 129.6 (2 CH Ph); 128.3 (2 CH Ph); 121.8; 100.3 (C(4) Pz). MS, found: m/z 292.0228 $[M(^{35}Cl) + H]^+$, 294.0203 $[M(^{37}Cl) + H]^+$; calculated for $C_{11}H_7(^{35}Cl)N_5O_3$: 292.0232; for $C_{11}H_7(^{37}Cl)N_5O_3$: 294.0203. MS, found: m/z 290.0094 $[M(^{35}Cl) - H]^-$, 292.0069 $[M(^{37}Cl) - H]^-$; calculated for $C_{11}H_5(^{35}Cl)N_5O_3$: 290.0086; for $C_{11}H_5(^{37}Cl)N_5O_3$: 292.0058.

Nitration of oxadiazoles 6b,c,e,g and 7 (general procedure). A solution of oxadiazole **6b,c,e,g** or **7** (0.75 mmol) in concentrated H_2SO_4 (5 mL) and HNO_3 (d = 1.5 g cm^{-3}, 0.8 mL) was stirred for 24 h at 20 °C in the case of compounds **6b,c** or 4 h at 80 °C in the case of compounds **6e,g** and **7**. The mixture was poured into ice-cold water (25 mL), the precipitate formed was collected by filtration, washed with water, and dried in air.

2-(4-Methyl-3-nitrophenyl)-5-(3-nitro-1*H*-pyrazol-5-yl)-1,3,4-oxadiazole (8). The yield was 79%, m.p. 247—249 °C (EtOH—MeCN, 3 : 1). IR, ν/cm^{-1}: 3142 (w), 1627 (m), 1522 (v.s, NO_2), 1409 (m), 1355 (s, NO_2), 1324 (m), 1193 (w), 1027 (w), 997 (m), 906 (w), 825 (m), 733 (m), 707 (w). ^{1}H NMR, δ: 8.64 (s, 1 H, Ph); 8.32 (d, 1 H, Ph, J = 8.0 Hz); 7.84 (s, 1 H, H(4) Pz); 7.80 (d, 1 H, Ph, J = 8.1 Hz); 2.64 (s, 3 H, Me). ^{13}C NMR, δ: 162.6 (C(2) of oxadiazole); 156.1 (br.s, C(3) Pz); 156.0 (C(5) of oxadiazole); 149.3; 137.3; 134.3 (CH Ph); 130.8 (CH Ph); 130.0 (C(5) Pz); 122.6 (CH Ph); 121.9; 103.3 (C(4)H Pz); 19.8 (Me). ^{14}N NMR, δ: −19.24 (NO_2). Found (%): C, 44.12; H, 2.67; N, 25.65. $C_{12}H_8N_6O_5 \cdot 0.5H_2O$. Calculated (%): C, 44.31; H, 2.79; N, 25.84.

2-(4-Methoxy-3,5-dinitrophenyl)-5-(3-nitro-1*H*-pyrazol-5-yl)-1,3,4-oxadiazole (9). The yield was 80%, m.p. 215—217 °C (MeCN). IR, ν/cm^{-1}: 3303 (s), 1629 (m), 1535 (v.s, NO_2), 1478 (m), 1408 (m), 1355 (s, NO_2), 1300 (m), 1205 (w), 994 (w), 968 (m), 828 (w), 724 (m). ^{1}H NMR, δ: 8.94 (s, 2 H, Ph); 7.93 (s, 1 H, H(4) Pz); 4.05 (s, 3 H, OMe). ^{13}C NMR, δ: 161.2 (C(2) of oxadiazole); 156.3 (br.s, C(3) Pz); 156.4 (C(5) of oxadiazole); 148.8; 144.9; 128.0 (C(5) Pz); 127.4 (2 CH Ph); 118.9; 103.6 (C(4)H Pz); 64.7 (OMe). ^{14}N NMR, δ: −18.08 (NO_2). Found (%): C, 38.33; H, 1.97; N, 25.73. $C_{12}H_7N_7O_8$. Calculated (%): C, 38.21; H, 1.87; N, 25.99.

2-(4-Chloro-3-nitrophenyl)-5-(3,4-dinitro-1*H*-pyrazol-5-yl)-1,3,4-oxadiazole (10). The yield was 60%, m.p. 188—190 °C (EtOH—H_2O, 5 : 1). IR, ν/cm^{-1}: 3554 (m), 3440 (m), 1615 (m), 1563 (s, NO_2), 1538 (v.s, NO_2), 1468 (m), 1429 (m), 1358 (s, NO_2), 1335 (s, NO_2), 1206 (w), 1052 (w), 1038 (w), 953 (w), 815 (w), 740 (w), 510 (w). ^{1}H NMR, δ: 8.67 (s, 1 H, Ph); 8.30 (d, 1 H, Ph, J = 8.3 Hz); 8.07 (d, 1 H, Ph, J = 8.4 Hz). ^{13}C NMR, δ: 162.4 (C(2) of oxadiazole); 155.8 (C(5) of oxadiazole); 148.3 (br.s, C(3) Pz); 148.0; 133.4 (CH Ph); 131.5 (CH Ph); 129.1; 127.6 (C(5) Pz); 125.9 (br.s, C(4) Pz); 123.9 (CH Ph); 122.9. ^{14}N NMR, δ: −24.98 (NO_2). Found (%): C, 33.01; H, 1.40; N, 24.65. $C_{11}H_4N_7O_7 \cdot H_2O$. Calculated (%): C, 33.06; H, 1.51; N, 24.53.

5-(3,4-Dinitro-1*H*-pyrazol-5-yl)-2-(3,5-dinitrophenyl)-1,3,4-oxadiazole (11). The yield was 70%, m.p. 153—155 °C (CH_2ClCH_2Cl). IR, ν/cm^{-1}: 3093 (m), 1706 (v.s), 1629 (w), 1545 (v.s, NO_2), 1471 (m), 1417 (w), 1350 (v.s, NO_2), 1285 (s), 1183 (m), 1079 (w), 923 (m), 820 (w), 726 (s), 698 (m), 535 (w). ^{1}H NMR, δ: 9.02 (s, 1 H, Ph); 8.90 (s, 1 H, Ph); 8.89 (s, 1 H, Ph). ^{13}C NMR, δ: 163.9 (C(2) of oxadiazole); 156.9 (C(5) of oxadiazole); 148.3 (C(3,5) Ph); 145.5 (br.s, C(3) Pz); 134.0; 131.5 (C(5) Pz); 128.9 (2 CH Ph); 126.5 (br.s, C(4) Pz); 122.1 (CH Ph). ^{14}N NMR, δ: −18.97 (NO_2); −25.66 (NO_2). Found (%): C, 33.58; H, 0.95; N, 28.36. $C_{11}H_4N_8O_9$. Calculated (%): C, 33.69; H, 1.03; N, 28.57.

2-(4-Chloro-3-nitrophenyl)-5-(3-nitro-1*H*-pyrazol-4-yl)-1,3,4-oxadiazole (12). The yield was 61%, m.p. 250—251 °C (EtOH—MeCN, 1 : 2). IR, ν/cm^{-1}: 3128 (m), 1623 (s), 1538 (v.s, NO_2), 1392 (m), 1344 (s, NO_2), 1257 (w), 1061 (m), 850 (w), 830 (m), 735 (m). ^{1}H NMR, δ: 14.70 (br.s, 1 H, NH Pz); 8.88 (s, 1 H, H(5) Pz); 8.67 (d, 1 H, Ph, J = 1.4 Hz); 8.31 (dd, 1 H, Ph, J = 8.5 Hz, J = 1.6 Hz); 8.05 (d, 1 H, Ph, J = 8.5 Hz). ^{13}C NMR, δ: 162.0 (C(2) of oxadiazole); 157.7 (C(5) of oxadiazole); 152.6 (br.s, C(3) Pz); 148.1; 135.2; 133.2 (CH Ph); 131.3 (CH Ph); 128.6 (C(5)H Pz); 123.5 (CH Ph); 123.2; 100.1 (C(4) Pz). ^{14}N NMR, δ: −14.89 (NO_2); −22.11 (NO_2). Found (%): C, 39.08; H, 1.52; N, 24.72. $C_{11}H_5ClN_6O_5$. Calculated (%): C, 39.25; H, 1.50; N, 24.96.

Synthesis of pyrazolecarboxylic acid chlorides 13a—c and 17 (general procedure). Oxalyl chloride (9.56 mmol) was added dropwise to a solution of the corresponding carboxylic acid (6.37 mmol) in anhydrous CH_2Cl_2 (25 mL) and anhydrous DMF (0.1 mL) with stirring at room temperature. The mixture was stirred until complete dissolution of the starting acid (from 2 to 6 h), the solvent was evaporated *in vacuo*. The obtained acyl chlorides were used without additional purification.

Synthesis of bispyrazolyl-1,3,4-oxadiazoles 14—16 (general procedure). Triethylamine (0.54 mL, 3.9 mmol) was added dropwise to a suspension of tetrazole **3** (0.54 g, 3 mmol) in tetrachloroethane (5 mL) with stirring, followed by the addition in one portion of the corresponding carboxylic acid chloride **13a—c** (3.3 mmol). The reaction mixture was slowly (~1 h) heated to 100—110 °C, kept at this temperature for 4 h, and cooled. In the case of product **14**, the precipitate formed was collected by filtration, washed with 5% aqueous HCl (4 mL) and water (5 mL), and dried in air. In the case of products **15** and **16**, the solvent was evaporated *in vacuo*, the dry residue was suspended in 5% aqueous HCl (5 mL), stirred for 30 min at 30 °C, the precipitate was collected by filtration, washed with H_2O, and dried in air.

2-(1-Methyl-1*H*-pyrazol-3-yl)-5-(3-nitro-1*H*-pyrazol-5-yl)-1,3,4-oxadiazole (14). The yield was 67%, m.p. 307—309 °C (EtOH—MeCN, 1 : 1). IR, ν/cm^{-1}: 3127 (v.s), 1604 (s), 1549 (v.s, NO_2), 1459 (m), 1403 (m), 1345 (s, NO_2), 1249 (m), 1207 (w), 1094 (w), 993 (m), 928 (m), 879 (m), 827 (m), 790 (m), 747 (w), 444 (w). ^{1}H NMR, δ: 7.99 (d, 2 H, H(5) Pz, J = 1.6 Hz); 7.73 (s, 1 H, H(4′) Pz); 6.98 (d, 1 H, H(4) Pz, J = 1.7 Hz); 4.00 (s, 3 H, NMe). ^{13}C NMR, δ: 160.1 (C(2) of oxadiazole); 156.0 (br.s, C(3′) Pz); 155.2 (C(5) of oxadiazole); 135.4; 130.4 (C(5)H Pz); 130.1; 106.7 (C(4)H Pz); 102.9 (C(4′)H Pz); 21.7 (Me). MS, found: *m/z* 262.0683 $[M + H]^+$; calculated for $C_9H_8N_7O_3$: 262.0683.

2-(1-Methyl-4-nitro-1*H*-pyrazol-3-yl)-5-(3-nitro-1*H*-pyrazol-5-yl)-1,3,4-oxadiazole (15). The yield was 68%, m.p. 231—233 °C (EtOH). IR, ν/cm^{-1}: 3138 (s), 2907 (m), 1628 (w), 1542 (v.s, NO_2), 1436 (m), 1354 (s, NO_2), 1337 (s, NO_2), 1252 (w), 1079 (w), 1021 (w), 992 (w), 856 (w), 826 (m), 747 (w), 500 (w). ^{1}H NMR, δ: 9.17 (s, 1 H, H(5) Pz); 7.77 (s, 1 H, H(4′) Pz); 4.06 (s, 3 H, NMe). ^{13}C NMR, δ: 156.8 (C(2) of oxadiazole); 156.0 (C(3) Pz and C(5) of oxadiazole); 156.0 (br.s, C(3′) Pz); 134.0 (C(5)H Pz); 133.4 (br.s, C(4) Pz); 129.9 (C(5′) Pz); 103.4 (C(4′)H Pz); 40.5 (Me). ^{14}N NMR, δ: −21.46 (NO_2). MS, found: *m/z* 307.0529 $[M + H]^+$; calculated for $C_9H_7N_8O_5$: 307.0534.

2-(1-Methyl-3-nitro-1*H*-pyrazol-5-yl)-5-(3-nitro-1*H*-pyrazol-5-yl)-1,3,4-oxadiazole (16). The yield was 75%, m.p. 236—238 °C (EtOH). IR, ν/cm^{-1}: 3246 (s), 1615 (s), 1544 (v.s, NO_2), 1481 (m), 1404 (s), 1376 (s), 1334 (s, NO_2), 1294 (s), 1252 (w), 1192 (m), 1128 (m), 1065 (m), 994 (m), 937 (m), 825 (s), 736 (m), 424 (w). ^{1}H NMR, δ: 8.88 (s, 1 H, Pz); 7.82 (s, 1 H, Pz); 4.36 (s, 3 H, NMe). ^{13}C NMR, δ: 156.1 (br.s, C(3′) Pz); 156.0 (C(3) Pz); 155.5 (C(2) of oxadiazole); 154.1 (C(5) of oxadiazole); 129.9 (C(5′) Pz); 129.7 (C(5) Pz); 105.3 (C(4)H Pz); 103.7 (C(4′)H Pz); 41.2 (Me). ^{14}N NMR, δ: −24.68 (NO_2). MS, found: *m/z* 307.0534 $[M + H]^+$; calculated for $C_9H_7N_8O_5$: 307.0534.

Synthesis of bispyrazolyl-1,3,4-оксадиazoles 20 and 21 (general procedure). Triethylamine (0.63 mL, 4.5 mmol) was added dropwise to a suspension of tetrazole **3** or **4** (0.51 g, 2.8 mmol) in tetrachloroethane (8 mL) with stirring, followed by the addition in one portion of acyl chloride **17** (0.90 g, 3.4 mmol). The mixture was slowly heated to 100—110 °C

(~1 h) and kept at this temperature for 4 h. The solvent was evaporated *in vacuo*, a 5% aqueous HCl (10 mL) was added to the resulting dense oil. After stirring for 1 h at 30 °C, the precipitate formed was collected by filtration, washed with water, and dried in air. The resulting intermediate products **18** or **19** were suspended in CF_3CO_2H (20 mL), the mixture was refluxed for 3.5 h and cooled. In the case of product **18**, the precipitate formed was collected by filtration, washed with water, and dried in air. In the case of product **19**, ice-cold water (80 mL) was added to the reaction mixture, the precipitate formed was collected by filtration, washed with water, and dried in air.

2,5-Bis(3-nitro-1*H*-pyrazol-5-yl)-1,3,4-oxadiazole (20). The yield was 42%, m.p. 315—316 °C (TFA). IR, ν/cm^{-1}: 3175 (m), 3115 (s), 2926 (m), 1626 (m), 1552 (v.s, NO_2), 1456 (w), 1401 (m), 1344 (s, NO_2), 1213 (m), 1172 (m), 1099 (w), 997 (m), 933 (w), 873 (m), 826 (m), 768 (w), 427 (w). ^{1}H NMR, δ: 15.69 (s, 1 H, NH Pz); 7.76 (s, 1 H, H(4) Pz). ^{13}C NMR, δ: 156.0 (br.s, C(3) Pz and C(2(5)) of oxadiazole); 129.9 (C(5) Pz); 103.4 (C(4)H Pz). ^{14}N NMR, δ: −17.52 (NO_2). MS, found: *m/z* 293.0380 $[M + H]^+$; calculated for $C_8H_5N_8O_5$: 293.0377.

2-(3-Nitro-1*H*-pyrazol-4-yl)-5-(3-nitro-1*H*-pyrazol-5-yl)-1,3,4-oxadiazole (21). The yield was 39%, m.p. 315—316 °C (TFA). IR, ν/cm^{-1}: 3158 (m), 3005 (w), 2911 (w), 2862 (w), 1637 (m), 1544 (v.s, NO_2), 1407 (s), 1386 (s, NO_2), 1347 (m), 1300 (m), 1213 (w), 1184 (m), 1096 (w), 1067 (m), 1025 (m), 991 (w), 825 (s), 741 (m), 482 (w). ^{1}H NMR, δ: 15.63 (s, 1 H, NH Pz); 14.73 (s, 1 H, NH Pz); 8.81 (s, 1 H, H(5) Pz); 7.68 (s, 1 H, H(4′) Pz). ^{13}C NMR, δ: 157.2 (C(2) of oxadiazole); 156.0 (br.s, C(3′) Pz and C(5) of oxadiazole); 152.6 (C(3) Pz); 135.5 (C(5)H Pz); 129.6 (C(5′) Pz); 103.1 (C(4′)H Pz); 99.8 (C(4) Pz). ^{14}N NMR, δ: −22.57 (NO_2). MS, found: *m/z* 293.0381 $[M + H]^+$; calculated for $C_8H_5N_8O_5$: 293.0377.

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