Vicarious nucleophilic amination of five-membered 4,6-dinitrobenzoheterocycles

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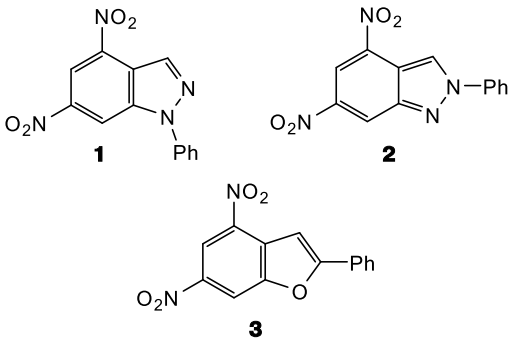
Reactions of isomeric 4,6-dinitro-1- and 4,6-dinitro-2-phenylindazoles, as well as 4,6-dinitro-2-phenylbenzo[*b*]furan, with various aminating agents were studied under the vicarious nucleophilic substitution conditions. It was found that depending on the aminating system, the starting compounds undergo either selective mono-amination at position 7 or double amination.

Key words: amination, benzoheterocycles, vicarious nucleophilic substitution of hydrogen, aromatic nitro compounds, *ortho*-nitroamines.

Aromatic *ortho*-nitroamines and their derivatives, *ortho*-diamines, are convenient precursors for a wide range of benzannulated heterocycles (benzofuroxanes, benzotriazoles, benzimidazoles, *etc*.). One of the main approaches to these derivative (besides nitration of arylamines) is nucleophilic amination of nitroarenes. For example, it was shown earlier[1] that 2-aryl-4,6-dinitroindoles can be aminated at position 7 under the conditions of vicarious nucleophilic substitution of hydrogen (VNS) by treatment with 1,1,1-trimethylhydrazinium iodide (TMHI) in the presence of Bu^{t}OK. This method was also used to aminate mono- and dinitrobenzenes.[2]

The literature data[3—9] on amination of aromatic and heteroaromatic nitro compounds under the VNS conditions are quite ample. The list of aminating agents included, in particular, sulfenyl amides,[3] 4-amino-1,2,4-triazole,[4] 1,1,1-trimethylhydrazinium iodide,[2] O-methylhydroxylamine,[5] and some others. In most cases, the reactions are carried out in the presence of an excess of a strong base (for example, Bu^{t}OK) in aprotic dipolar solvents (DMSO, DMF) at a reduced temperature. In addition, the use of hydroxylamine hydrochloride in the presence of KOH in EtOH was described for the amination of nitro compounds derived from benzene,[6] naphthalene,[7] benzothiazole,[8] and benzothiadiazole.[9] In these cases, as a rule, the reactions proceeded regioselectively with the introduction of one amino group into the aromatic ring.

In the present work, we studied the reactions of isomeric 4,6-dinitro-1- and 4,6-dinitro-2-phenylindazoles (**1** and **2**), as well as 4,6-dinitro-2-phenylbenzo[*b*]furan (**3**), with various aminating agents. The choice of the objects for research is substantiated by the valuable properties of many benzofuran and especially indazole derivatives. For example, an indazole fragment is contained in numerous biologically active compounds, it is a part of some alkaloids.[10—13]



It was found that the reaction does not take place when 4-amino-1,2,4-triazole is used as an aminating agent and results in the recovery of the corresponding starting dinitro compounds. The reaction with *O*-methylhydroxylamine in the presence of Bu^{t}OK gives only destruction products of the starting compounds; varying the reaction conditions (temperature, solvent, the use of copper(I) halides as catalysts) did not lead to the desired result. Monoamino derivatives **4** and **5** were obtained in good yields only when $[Me_3NNH_2]I$ (TMHI) was used as an aminating agent in the presence of Bu^{t}OK (Scheme 1).

The direction of the nucleophilic attack was established based on spectral data. Thus, a cross peak corresponding to the interaction of spatially close protons of the amino group and the *ortho*-protons of the *N*-phenyl substituent is observed in the $^1H—^1H$ NOESY NMR spectrum of compound **4**, which unambiguously confirms the formation of the 7-amino derivative.

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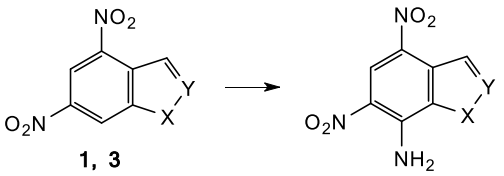
Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 2, pp. 0390—0393, February, 2020.

Scheme 1

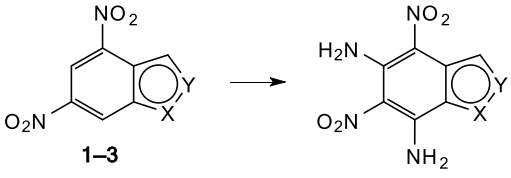


Compound	X	Y	Product	Yield (%)
1	NPh	N	**4**	84
3	O	CPh	**5**	85

Reagents and conditions: $[Me_3NNH_2]I$, Bu^tOK, DMSO, 20 °C.

An unexpected result was obtained in the reaction of dinitroindazoles **1** and **2**, as well as dinitrobenzofuran **3**, with an excess of hydroxylamine hydrochloride and KOH as a base in EtOH at 20—30 °C. The TLC monitoring showed that the complete conversion of the starting compounds was observed already after 1 h and in each case a single product was formed, namely, 5,7-diamino-4,6-dinitro derivative **6**, **7**, or **8**, respectively, which were isolated in high yield (Scheme 2).

Scheme 2



Compound	X	Y	Product	Yield (%)
1	NPh	N	**6**	87
2	N	NPh	**7**	98
3	O	CPh	**8**	91

Reagents and conditions: $NH_2OH \cdot HCl$, KOH, EtOH, 20—30 °C.

The structures of diamines **6—8** were established using a combination of physicochemical methods (1D and 2D polynuclear NMR spectroscopy, IR spectroscopy, mass spectrometry, elemental analysis, and X-ray diffraction). The ^1H NMR spectra of compounds **6—8** showed the signals for phenyl substituents and heterocyclic fragments, as well as for two amino groups (in the region of δ 7.5—11.0). In the case of compound **6**, the signals for the NH_2 protons appear at δ 7.5 and 9.5 as two broadened singlets, while three signals (at δ 9.5, 9.8, and 10.9) with relative intensities of 2 : 1 : 1 corresponding to two amino groups show up in the spectrum of diamine **7**, *i.e.*, the protons of one of the amino groups are nonequivalent. This position of the signals is probably due to strong intra- and intermolecular interactions, which was later confirmed by X-ray diffraction. The data of 2D heteronuclear NMR correlation spectroscopy (HSQC HMBC) allowed us to assign all the hydrogen and carbon atoms of compound **7** and to conclude that both amino groups are in the benzene ring. The ^{14}N NMR spectrum of diamine **7** contains two signals for nitro groups. Compounds **6** and **8** have an extremely low solubility in most common solvents, which made it impossible to record even 1D ^{13}C NMR spectra for them. In the IR spectra, one can identify the absorption bands of the amino groups involved in the formation of associates (3160—3280 and 3350—3430 cm^{-1}), as well as for the nitro groups involved in hydrogen bonding (1250—1280 and 1600—1620 cm^{-1}). According to the results of elemental analysis, compound **7** forms a monohydrate and compound **8** forms a dihydrate (crystallization water was detected in both cases), while compound **6** does not contain any associated solvents.

The X-ray diffraction data for compounds **7** and **8** showed that bond lengths and bond angles in both molecules are typical of the corresponding fragments of similar compounds. In both crystal structures, the molecules are in almost planar conformations (Fig. 1). The torsion angles between the mean planes of the heterocyclic and the phenyl rings are 2.6° (for compound **7**) and 3.1

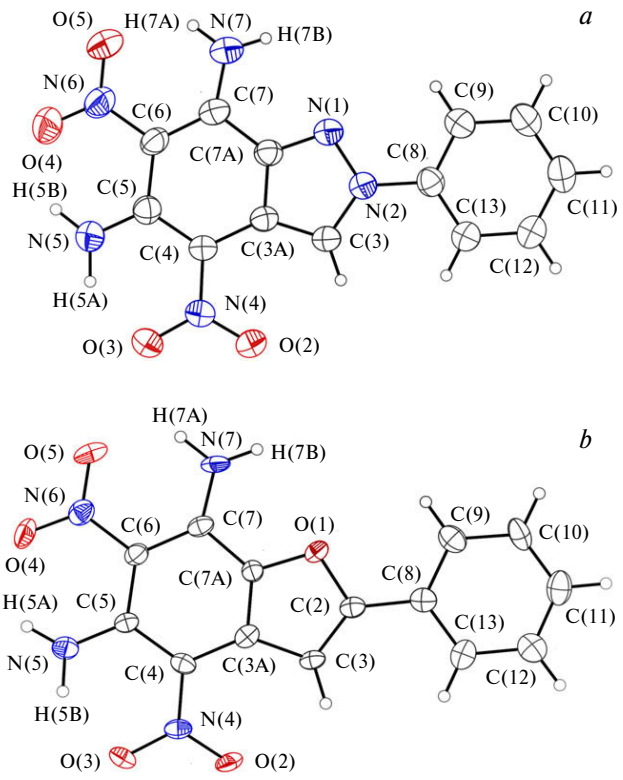


Fig. 1. General view of molecule **7** (*a*) and one of the crystallographically independent molecules **8** (*b*) in the crystal according to the X-ray diffraction data in the representation of atoms as thermal ellipsoids (p = 50%).

and 3.4° (for two crystallographically independent molecules of **8**). The hydrogen atoms of the amino groups are involved into intramolecular hydrogen bonds with the oxygen atoms of the nitro groups, as well as with the nitrogen (**7**) and oxygen atoms (**8**) of the heterocycle. The presence of these intramolecular hydrogen bonds leads to the absence of intermolecular hydrogen contacts, and the structural fragments in the crystal packing of both compounds show π-stacking and other weak non-specific intermolecular interactions.

Note that this result of amination was unexpected, since the introduction of two amino groups into the dinitrobenzene fragment using this aminating agent was not previously described. Even in the case of highly electrophilic substrates, such as 1,3,5-trinitrobenzene[6] and 4,6-dinitrobenzofurazan,[14] only monoamine derivatives are usually formed. The only exception is 4,6-dinitrobenzofuroxan: its reaction with the $NH_2OH \cdot HCl$—KOH—EtOH system under similar conditions leads to 5,7-diamino-4,6-dinitrobenzofuroxan.[15] As for the isomeric dinitroindazoles and, especially, dinitrobenzofuran studied in this work, they cannot be considered as highly electrophilic compounds taking into account the π-amphoteric nature of the pyrazole ring.

All the attempts to obtain monoamino derivatives at a lower temperature (−15—10 °C) led to the formation of a complex mixture, in which, according to the ^{1}H NMR spectral data, the starting dinitroindazoles **1** or **2**, dinitrodiamines **6** or **7**, as well as two more compounds in each, presumably, isomeric 5- and 7-amino derivatives, were present. This fact indicates that the rates of introduction of the first and the second amino groups are very close, which results in the impossibility to isolate monoamino derivatives.

In conclusion, we studied the reaction of isomeric 4,6-dinitro-1- and 4,6-dinitro-2-phenylindazoles, as well as of 4,6-dinitro-2-phenylbenzo[*b*]furan, with various aminating agents under the conditions of vicarious nucleophilic substitution. It was found that either selective monoamination (at position 7) or double amination of the starting 4,6-dinitrobicycles occurs depending on the choice of the amination system.

Experimental

Melting points were measured on a Stuart SMP20 instrument. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC-200 (^{1}H 200 MHz, ^{13}C 50 MHz) and Bruker AM-300 (^{1}H, 300 MHz; ^{13}C, 75 MHz) spectrometers. All the experiments were carried out according to standard Bruker procedures. Chemical shifts are given relative to Me_4Si (^{1}H and ^{13}C) and CH_3NO_2 (^{14}N). NMR spectra were recorded in DMSO-d_6. IR spectra were recorded on a Bruker Alpha spectrometer, samples were prepared in KBr pellets. The reaction progress and the purity of compounds were monitored by TLC on Silica gel 60 F254 plates (Merk). Compounds **1**,[16] **2**,[17] **3**,[18] and TMHI[2] were synthesized according to the described procedures.

Synthesis of compounds 4 and 5 (general procedure). Potassium *tert*-butoxide (0.34 g, 3 mmol) was added to a solution of compound **1** or **3** (1.5 mmol) and TMHI (0.6 g, 3 mmol) in DMSO (20 mL). The reaction mixture was stirred for 2 h at room temperature, poured into water (100 mL), and acidified with HCl to pH 4. The precipitate was collected by filtration, in the case of compound **4** it was washed with hot EtOH and dried in air. In the case of compound **5**, the product was purified by column chromatography (SiO_2—toluene).

7-Amino-4,6-dinitro-1-phenyl-1*H*-indazole (4). The yield was 84%. M.p. 213—215 °C. ^{1}H NMR, δ: 7.50 (s, 2 H, NH_2); 7.65—7.75 (m, 5 H, Ph); 8.71 (s, 1 H, H(3)); 8.88 (s, 1 H, H(5)). ^{13}C NMR, δ: 119.6, 119.7, 123.5, 126.6, 128.6, 129.8, 129.9, 130.1, 134.2, 138.1, 138.7. Found (%): C, 52.37; H, 3.18; N, 23.23. $C_{13}H_9N_5O_4$. Calculated (%): C, 52.18; H, 3.03; N, 23.40.

7-Amino-4,6-dinitro-2-phenylbenzo[*b*]furan (5). The yield was 45%. M.p. > 300 °C. ^{1}H NMR, δ: 7.56 (m, 3 H, Ph); 7.85 (s, 1 H, H(3)); 8.21 (d, 2 H, Ph, J = 7.1 Hz); 8.59 (br.s, 2 H, NH_2); 8.83 (s, 1 H, H(5)). Found (%): C, 56.63; H, 3.46; N, 13.80. $C_{14}H_9N_3O_5$. Calculated (%): C, 56.19; H, 3.03; N, 14.04.

Synthesis of compounds 6—8 (general procedure). A solution of KOH (2.9 g, 51.8 mmol) in MeOH (20 mL) was added dropwise to a suspension of compound **1, 2**, or **3** (0.57 g, 2 mmol) and $NH_2OH \cdot HCl$ (1.18 g, 17.2 mmol) in EtOH (30 mL) at 20 °C. The reaction mixture was stirred for 1—2 h (TLC), poured into water (300 mL), and acidified with HCl to pH 5. The precipitate was collected by filtration and dried in air.

5,7-Diamino-4,6-dinitro-1-phenyl-1*H*-indazole (6). The yield was 87%. M.p. 318—320 °C. IR, ν/cm^{-1}: 1288 (NO_2), 1600 (NO_2), 3284 (NH_2), 3432 (NH_2). ^{1}H NMR, δ: 7.55 (br.s, 2 H, NH_2); 7.65 (m, 5 H, Ph); 8.57 (s, 1 H, H(3)); 9.5 (br.s, 2 H, NH_2). MS, *m/z*: 314 $[M]^+$. Found (%): C, 50.09; H, 3.45; N, 26.51. $C_{13}H_{10}N_6O_4$. Calculated (%): C, 49.69; H, 3.21; N, 26.74.

5,7-Diamino-4,6-dinitro-2-phenyl-2*H*-indazole (7). The yield was 98% (monohydrate). M.p. 276—278 °C. ^{1}H NMR, δ: 7.47 (t, 1 H, *p*-Ph, J = 7.6 Hz); 7.6 (t, 2 H, *m*-Ph, J = 7.8 Hz); 8.15 (d, 2 H, *o*-Ph, J = 7.8 Hz); 9.00 (s, 1 H, H(3)); 9.55 (br.s, 2 H, NH_2); 9.80, 10.85 (both br.s, 2 H, NH_2). ^{13}C NMR, δ: 110.3 (C(5)), 116.8 (C(7)), 117.0 (C(3a)), 119.9 (*o*-C_{Ph}), 123.4 (C(3)), 128.2 (*p*-C_{Ph}), 129.6 (*m*-C_{Ph}), 135.2 (C(4)), 138.9 (*ipso*-C_{Ph}), 147.8 (C(6)), 148.1 (C(7a)). ^{14}N NMR, δ: −12.74, −19.27 (NO_2). IR, ν/cm^{-1}: 1252 (NO_2), 1284 (NO_2), 1624 (NO_2), 3176 (NH_2), 3356 (NH_2). MS, *m/z*: 314 $[M]^+$. Found (%): C, 46.50; H, 3.49; N, 25.10. $C_{13}H_{12}N_6O_5$. Calculated (%): C, 46.99; H, 3.64; N, 25.29.

5,7-Diamino-4,6-dinitro-2-phenylbenzo[*b*]furan (8). The yield was 91% (dihydrate). M.p. 273—275 °C. IR, ν/cm^{-1}: 1280 (NO_2), 1576 (NO_2), 1624 (NO_2), 3292 (NH_2), 3444 (NH_2). ^{1}H NMR, δ: 7.50 (m, 3 H, Ph); 7.80 (s, 1 H, H(3)); 8.20 (m, 2 H, Ph); 9.10 (s, 2 H NH_2); 9.95 (s, 2 H, NH_2). Found (%): C, 48.31; H, 3.98; N, 16.20. $C_{14}H_{14}N_4O_7$. Calculated (%): C, 48.00; H, 4.03; N, 15.99.

X-ray diffraction studies of compound 7 were carried out on a Bruker SMART 1000 CCD diffractometer (λ(Mo-Kα) = = 0.71072 Å, ω-scan technique, 2θ < 60°). Red crystals $C_{13}H_{10}N_6O_4$ at 296 K: a monoclinic crystal system, space group $P2_1/n$, a = 7.2170(5), b = 23.8805(15), c = 8.1508(5) Å, β = 111.4891(13)°, V = 1307.11(15) Å^3, Z = 4 (Z' = 1), d_{calc} = = 1.597 g cm^{-3}. Unit cell parameters and intensities of 3794 independent reflections (R_{int} = 0.0303) out of 11217 collected were used to determine and refine the structure. The structure was solved by the direct method and refined by the full-matrix

least-squares method in the anisotropic approximation. Hydrogen atoms bonded to nitrogen atoms were localized and refined isotropically. The positions of the remaining hydrogen atoms were calculated geometrically and refined using the riding model. The final R factors: $R_1 = 0.0456$ (for 2309 reflections with $I > 2\sigma(I)$), $wR_2 = 0.1226$, and GOOF = 1.027.

X-ray diffraction studies of compound 8 were carried out on a Bruker Apex II diffractometer (λ(Mo-Kα) = 0.71072 Å, ω-scan technique, $2\theta < 60°$). Dark red crystals $C_{14}H_{10}N_4O_5$ (and solvent) at 120 K, orthorhombic, space group $P2_12_12_1$, a = 6.9828(9), b = 17.551(2), c = 24.942(3) Å, V = 3056.7(7) Å^3, Z = 8 (Z' = 2). Intensities of 8908 independent reflections (R_{int} = 0.1703) out of 35572 collected were used to determine and refine the structure. The structure was solved by the direct method and refined by the full-matrix least-squares method in the anisotropic approximation. Hydrogen atoms of amino groups were found from difference Fourier synthesis; the positions of the remaining hydrogen atoms were calculated. The positions of all hydrogen atoms were refined using the riding model. The contribution to diffraction from the disordered solvent was implicitly modeled using the SQUEEZE procedure implemented in the PLATON software package.[19] The final R factors: R_1 = 0.0767 (for 4226 reflections with $I > 2\sigma(I)$), wR_2 = 0.1891, and GOOF = 1.074.

All the calculations were performed using the SHELXT software package;[20] the SHELXL software package[21] was used for refinement. The full structural data were deposited with the Cambridge Crystallographic Data Center, CCDC 1914801 (**8**) and 1914802 (**7**).

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Received September 3, 2019;
accepted October 1, 2019